Effect of invasive tests during pregnancy on perinatal transmission of hepatitis B infection: a scoping review

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Summary

Prenatal and intrapartum invasive tests are possible mechanisms of mother to child transmission (MTCT) of hepatitis B virus (HBV). The viral activity can affect the MTCT risk after invasive tests, but the evidence is scarce. This scoping review discussed the effects of prenatal or intrapartum invasive tests on the risk of HBV MTCT. The risk of MTCT after amniocentesis was low among hepatitis B infected pregnant individuals with negative hepatitis B e antigen (HBeAg) statuses or HBV DNA < 7 $\log_{10}$ IU/mL, and comparable to those that did not undergo prenatal invasive tests. Amniocentesis could increase the risk of MTCT among women with seropositive HBeAg statuses or HBV DNA ≥ 7 $\log_{10}$ IU/mL, but there were no MTCT among these women who received antiviral treatment. Data on CVS, cordocentesis and intrapartum invasive tests were insufficient to conclude their effects on MTCT. We also reviewed 50 international clinical practice guidelines. Most of them did not have recommendations on the management of hepatitis B infected pregnant individuals requiring prenatal or intrapartum invasive tests and significant discrepancies existed among the remaining guidelines. A workflow and two pragmatic approaches were discussed to assist clinical management. Furthermore, we would like to encourage future research to provide comprehensive data on the factors influencing the MTCT rate (such as maternal HBV DNA viral load and HBeAg status, availability and timing of neonatal birth dose immunizations, transplacental or transamniotic invasive tests, complications of the invasive tests and the use of antiviral prophylaxis).

Keywords: Amniocentesis; Chorionic villus sampling; Cordocentesis; Immunisation; Immunoprophylaxis failure; Scalp blood sampling; Scalp electrode; Vaccination; Vertical transmission

Introduction

Hepatitis B virus (HBV) infection remains a global threat. It is estimated that 254 million people were chronically infected, and 1.1 million people died because of complications from HBV in 2022.[1] Mother to child transmission (MTCT) is the predominant route of HBV transmission. Neonatal active and passive immunization is the most cost-effective strategy to prevent MTCT.[2] However, immunoprophylaxis failure can occur in some infants despite timely neonatal immunization.[3] Prenatal and intrapartum invasive tests such as chorionic villous sampling (CVS), amniocentesis, cordocentesis, intrapartum scalp blood sampling or scalp electrode application are possible mechanisms for in-utero infection by exposing the fetus to maternal blood habouring HBV during pregnancy and labour, thus increasing the risk of MTCT.[4] Earlier observational studies suggest that prenatal invasive procedures would not increase the risk of MTCT.[5] However, more recent cohort studies find conflicting results, in which amniocentesis increases the risk of MTCT in women with high viral load.[6,7] Information on the effect of intrapartum invasive test on MTCT is scarce.

Many guidelines are available to assist obstetricians and clinicians to optimally manage hepatitis B infected individuals during pregnancy, so as to prevent MTCT and achieve the World Health Organization's goal to eradicate HBV by 2030.[8] Most available guidelines suggest discussing with the women and balancing the risk and benefit of prenatal invasive tests but the content for discussion is not clearly defined, and little is mentioned on intrapartum invasive test. Quantification of hepatitis B viral load has now become a standard of care to guide the utilisation of antiviral prophylaxis during pregnancy.[9–12] Since viral activity may potentiate the effect of these invasive tests on the risk of MTCT, this scoping review aims to discuss the effects of prenatal or intrapartum invasive test on the risk of MTCT in women with different hepatitis B e antigen (HBeAg) status and HBV DNA levels. We believe this information is crucial to facilitate the discussions between obstetricians and hepatitis B infected pregnant women, on balancing the need of invasive tests and

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the risk of MTCT. We also review the current statements from international guidelines on prenatal and intrapartum invasive test and proposed our recommendations.

Methods

Search strategy and selection criteria

A scoping review was performed according to a priori protocol, which was registered in the International prospective register of systematic reviews (PROSPERO) on 22nd May, 2024 (registration number: CRD42024545775). It was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Review (PRISMA-ScR) checklist. MEDLINE, EMBASE, and the Cochrane Library were searched electronically, with no start date to 1 June, 2024, utilizing a combination of the key words: pregnancy, hepatitis, invasive, chorionic villous sampling, amniocentesis, cordocentesis, scalp blood and scalp electrode. There was no restriction in language. Studies must describe the rate of MTCT after prenatal or intrapartum invasive tests. We excluded abstracts, studies with duplicated data, and studies that reported less than five cases. Ethical approval was not required as this study retrieved data from published studies. Another systematic search was performed on five electronic data bases (CINAHL, Embase, Medline, Web of Science, Cochrane Library) using the keywords of 'hepatitis', 'guideline', 'recommendation', 'consensus' and 'pregnancy' to identify clinical practice guidelines published after 2018, on the use of prenatal and intrapartum invasive test among hepatitis B infected pregnant women. Extended search was performed from the references, clinical practice guidelines or recommendation documents that specifically described invasive tests in the title were included with no restriction on the timing of publications.

The title and abstract were screened for articles fulfilling the criteria. Full-text review of these articles was performed. Reference lists of relevant articles were searched manually for additional reports. Two reviewers (K.W.C. and T.S.T.A) performed the selection of articles and extracted the data independently. Any inconsistencies were resolved by a third reviewer (M.T.Y.S.). The quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS). Attempts to contact the authors were made when appropriate.

Data synthesis

Data on the type of prenatal and intrapartum invasive test, maternal HBeAg status, maternal HBV DNA, timing of neonatal HBV vaccine and hepatitis B immunoglobulin (HBIG), timing of neonatal testing for HBV markers were extracted. The MTCT rate and p-values from relevant statistical analyses ($p < 0.05$ was considered statistically significant) were recorded.

Reporting on HBV DNA levels

HBV DNA levels can be reported as IU/mL or copies/mL. The World Health Organization (WHO) recommended the conversion factor of 1IU/mL ~ 5.3 copies/mL. However, it has been noted that the conversion could vary depending on the methodology utilized by the DNA platforms, for example, with the use of an in-house PCR technique. Thus, direct conversion with the WHO recommended conversion factor may affect the precision of data interpretation.[2] To maintain accuracy from the original studies, we reported HBV DNA levels in IU/mL wherever possible, and copies/mL was utilized if it was the sole unit stated and conversion factor was not provided in the study.

Role of the funding source

There was no funding source for this study.

Results

Study selection and characteristics

The search identified 320 articles, of which 312 were excluded based on the title or abstract. Eight full-text articles were assessed and seven were finally eligible for inclusion (Fig. 1).[6,7,13–17] The characteristics of the included studies are shown in Table 1.

Supplementary Table S1 shows the quality of the included studies. Of the seven studies, one was prospective and six were retrospective studies. There was no randomized controlled trial. The study quality was good in three studies and fair in four studies. Three studies compared the MTCT rate between hepatitis B infected pregnant women with and without amniocentesis.[6,7,17] The remaining four described the rate of MTCT after CVS, amniocentesis and cordocentesis among hepatitis B infected pregnant women.[13–16] In total, there were 1126 prenatal invasive tests (1 CVS, 1119 amniocentesis, and 6 cordocentesis) and another 1721 women did not receive any invasive tests. No study evaluated the risk of MTCT after intrapartum scalp blood sampling or scalp electrode insertion. MTCT was defined as positive hepatitis B surface antigen (HBsAg) at 7 months after birth or later except the study by Grosheide et al. which included subjects with positive HBsAg at 3 and 6 months after delivery.[13] Two studies did not provide sufficient information to confirm all infants received adequate neonatal immunization.[13,14] The overall rate of MTCT within the included cohorts ranged from 0% to 16.7%. Information on the HBV DNA level, approach of amniocentesis/cordocentesis, appearance of amniotic fluid and bleeding from punctured placenta/uterine wall was available in four, four, five and three studies, respectively.

MTCT rates among women who received prenatal invasive tests

Table 2 shows the effect of HBeAg status, HBV DNA levels and use of antiviral therapy on the rate of MTCT

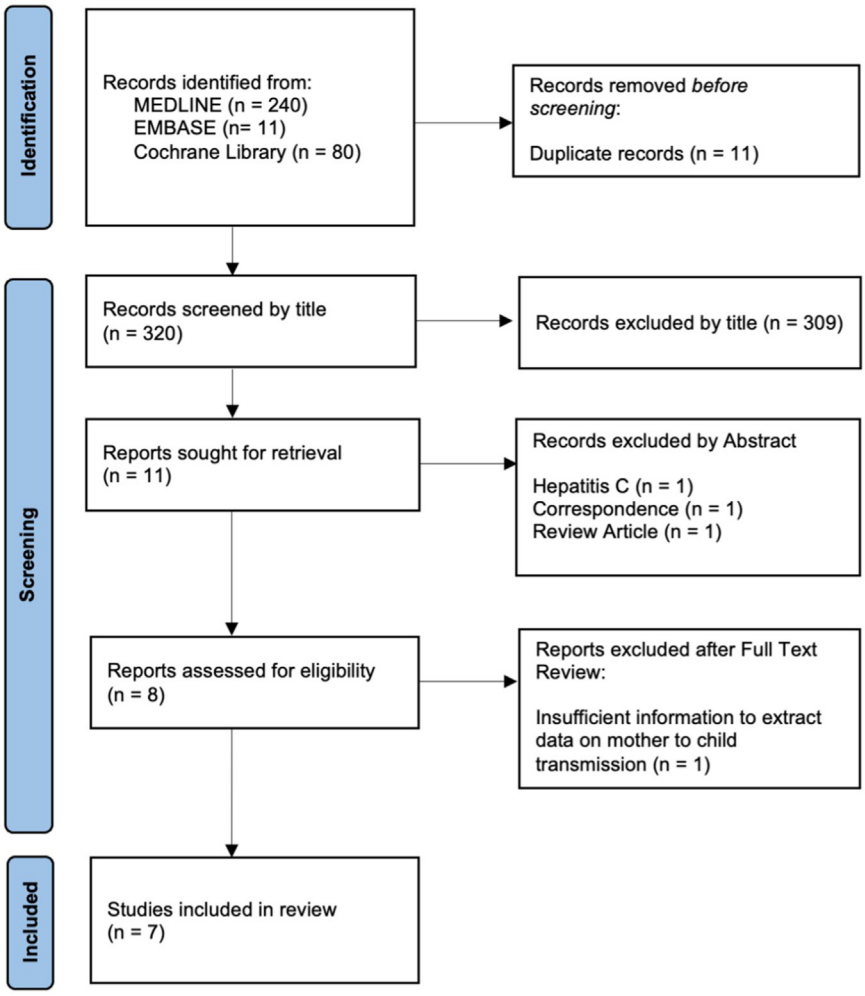

Fig. 1: PRISMA flow diagram.

following prenatal invasive tests. Table 3 shows the effect of transplacental approach, post-procedural bleeding, and appearance of amniotic fluid on the rate of MTCT following amniocentesis/cordocentesis.

HBeAg status on MTCT rates

HBeAg status was available in 7 studies consisting of 2847 women. The proportion of positive HBeAg within the included cohorts ranged from 4.8% to 53.6%. Among HBeAg negative women, the MTCT rate was 0.0% after CVS (1 study, n = 0/1)[13] and cordocentesis (1 study, n = 0/4).[16] The MTCT rate after amniocentesis ranged from 0.0% (4 studies, n = 0/148)[7,13–15] to 0.4% (1 study, n = 3/735)[17] and 2.4% (1 study, n = 1/41).[6]

Among HBeAg positive women, the MTCT rate after cordocentesis was 50.0% (1 study, n = 1/2).[16] The rate of MTCT after amniocentesis varied from 0.0% (2 studies, n = 0/3),[13,15] 1.8% (1 study, n = 2/111),[17] 8.2% (1 study, n = 4/49),[7] 13.6% (1 study, n = 3/22),[6] to 30.0% (1 study, n = 3/10).[14]

The MTCT rate after amniocentesis was higher in HBeAg positive women than HBeAg negative women in two studies (8.2%, n = 4/49 vs 0.0%, n = 0/94, p = 0.013; 30.0%, n = 3/10 vs 0.0%, n = 0/22, p = 0.024)[7,14] but this significance was not demonstrated in other studies (1.8%, n = 2/111 vs 0.4%, n = 3/735, p = 0.131; 13.6%, n = 3/22 vs 2.4%, n = 1/41, p = 0.118).[6,17] Two studies reported no MTCT among three HBeAg positive women as well as 32 HBeAg negative women.[13,15]

Effect of HBV DNA levels and MTCT rates

HBV DNA level was mentioned in 4 studies. Yi et al. was the only study that reported viral loads in copies/mL rather than IU/mL. The rate of MTCT after amniocentesis was 0.0% (n = 0/40), 5.9% (n = 1/17) and 50.0% (n = 3/6) when HBV DNA levels were <500 copies/mL,

Author year title	Country	Study design study period	Study population (inclusion and exclusion description, definition of mother to child transmission, neonatal vaccination, basic demographics)
Grosheide et al. 1994 Early invasive prenatal diagnosis in HBsAg-positive women	Netherland	Two centers Retrospective cohort 1982–1989	Inclusion • HBsAg positive pregnant women Exclusion • N/A Definition of mother to child transmission • Infants positive for HBsAg at 3 months and afterwards ? all infants received HBIG and HBV vaccines Overall basic demographics (n = 15) • No mother to child transmission • 2 (13.3%) HBeAg positive 14 amniocentesis • 2 (14.3%) HBeAg positive • No transplacental amniocentesis • No blood in the amniotic fluid 1 CVS • No HBeAg positive
Ko et al. 1994 Amniocentesis in mothers who are hepatitis B virus carriers does not expose the infant to an increased risk of hepatitis B virus infection.	Taiwan	Retrospective cohort	Inclusion • HBsAg positive pregnant women Exclusion • N/A Definition of mother to child transmission • Infants positive for HBsAg at 3 months to 5 years ? all infants received HBIG and HBV vaccines Overall basic demographics, amniocentesis (n = 32) • 3 (9.4%) mother to child transmission rate • 10 (31.3%) HBeAg positive • 9 (28.1%) transplacental • 4 (12.5%) Postprocedural bleeding
Alexander et al. 1999 Risk of hepatitis B transmission after amniocentesis in chronic hepatitis B carriers.	USA	Single-center Prospective cohort 1990–1995	Inclusion • HBsAg positive pregnant women Exclusion • N/A Definition of mother to child transmission • Infants positive for HBsAg at 9–15 months All infants received HBIG and HBV vaccines Overall basic demographics, amniocentesis (n = 21) • No mother to child transmission rate • 1 (4.8%) HBeAg positive • No bloody amniotic fluid

(Table 1 continues on next page)

500–6.99 $\log_{10}$ copies/mL and ≥ 7 $\log_{10}$ copies/mL, respectively.[6] Amniocentesis in women with HBV DNA ≥500 copies/mL and ≥7 $\log_{10}$ copies/mL were associated with an increased risk of MTCT, when compared to HBV DNA <500 copies/mL (17.4%, n = 4/23 vs 0.0%, n = 0/40, p = 0.015) and <7 $\log_{10}$ copies/mL (50.0%, n = 3/6 vs 1.8%, n = 1/57, p = 0.002), respectively.

Two studies reported MTCT rate after amniocentesis using the HBV DNA cut-offs of 200,000 IU/mL (i.e. 5.3 $\log_{10}$ IU/mL) and 7 $\log_{10}$ IU/mL, respectively. No significant difference was demonstrated in the rate of MTCT after amniocentesis when maternal HBV DNA >200,000 IU/mL was compared to ≤200,000 IU/mL (1.3%, n = 1/78 vs 0.5%, n = 4/768, p = 0.384).[17] However, another study showed a significantly higher MTCT rate among women with higher viral loads when the cut-off of 7 $\log_{10}$ IU/mL was used (10.8%, n = 4/37 vs 0.0%, n = 0/106, p = 0.004).[7]

Only one study reported on MTCT following cordocentesis. The MTCT rate ranged from 0.0% (n = 0/5) when HBV DNA <200,000 IU/mL to 100.0% (n = 1/1) when HBV DNA ≥200,000 IU/mL.[16]

Use of antiviral prophylaxis and MTCT rates

Four studies provided information on antiviral therapy during pregnancy. Yi et al. excluded all women treated with antiviral therapy 6 months before and during pregnancy from their study. Two studies compared the rate of

Author year title	Country	Study design study period	Study population (inclusion and exclusion description, definition of mother to child transmission, neonatal vaccination, basic demographics)
(Continued from previous page)			
Yi et al. 2014 Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers.	China	Single-center Retrospective cohort 2008–2012	Inclusion • HBsAg positive pregnant women Exclusion criteria • Co-infection with either HCV, HDV, HIV or toxoplasma gondii • Noncompliant with regular prenatal care after 12 weeks of gestation • Maternal HBV DNA levels not monitored Definition of mother to child transmission • Infants positive for HBsAg at 7–12 months All infants received HBIG and HBV vaccines Overall basic demographics (n = 261) • 9 (3.4%) mother to child transmission rate • 140 (53.6%) HBeAg positive • 141 (54.0%) DNA ≥500 copies/mL • 73 (28.0%) DNA ≥10,000,000 copies/mL • No maternal antiviral 63 had amniocentesis • 22 (34.9%) HBeAg positive • 23 (36.5%) HBV DNA ≥500 copies/ml • No bloody amniotic fluid 198 without amniocentesis • 118 (59.6%) HBeAg positive • 118 (59.6%) HBV DNA ≥500 copies/ml
Han et al. 2019 Mother-to-child transmission of hepatitis B virus after amniocentesis: A retrospective matched cohort study.	China	Single-center Retrospective cohort 2009–2016	Inclusion • HBsAg positive pregnant women Exclusion criteria • Coinfection with HCV, HDV, or HIV • Long-term use of glucocorticoid drugs or immunomodulators • HBsAg positive father Definition of mother to child transmission • Infants positive for HBsAg and/HBV DNA at 7–12 months All infants received HBIG and HBV vaccines Overall basic demographics (n = 748) • 7 (0.9%) mother to child transmission rate • 237 (31.7%) HBeAg positive • 187 (25%) HBV DNA > 7 log10 IU/mL • 80 (10.7%) received antiviral 143 had amniocentesis • 49 (34.3%) HBeAg positive • 37 (25.9%) HBV DNA >10,000,000 IU/mL • 15 (10.5%) received antiviral (Four prior to pregnancy, seven at 0–11 weeks before amniocentesis, four 1–4 weeks after amniocentesis • 13 (9.1%) transplacental • 14 (9.8%) post-procedure bleeding from placenta/uterine wall • No signs of gross bloodstaining of amniotic fluid 605 without amniocentesis • 188 (31.1%) HBeAg positive • 150 (24.8%) HBV DNA >10,000,000 IU/mL • 65 (10.7%) received antiviral (20 prior to pregnancy, 45 after pregnancy)

(Table 1 continues on next page)

MTCT between antiviral users and non-users. The use of antiviral therapy did not result in a significant difference in the MTCT rate after invasive tests, and this observation persisted even when HBeAg positive status or viral load ≥ 7 $\log_{10}$ IU/mL were taken into consideration (2 studies, $p > 0.05$).[7,17] However, it is worth noting that among women who received antivirals, no MTCT occurred after prenatal invasive tests across three different studies (amniocentesis: 2 studies, n = 0/128; cordocentesis: 1 study, n = 0/1), even among women with positive HBeAg statuses (0.0%, 2 studies, n = 0/59) or viral load levels ≥ 7 $\log_{10}$ IU/mL (0.0%, 2 studies, n = 0/16).[7,16,17] The timing of antiviral therapy commencement (before or after invasive test) did not affect the rate of MTCT.[7,16,17]

Author year title	Country	Study design study period	Study population (inclusion and exclusion description, definition of mother to child transmission, neonatal vaccination, basic demographics)
(Continued from previous page)			
Han et al. 2021 Risk of mother-to-child transmission of hepatitis B virus after fetal blood sampling: a report of six cases.	China	Single center Retrospective cohort 2015–2016	Inclusion • HBsAg positive pregnant women Exclusion • N/A Definition of mother to child transmission • Infants positive for HBsAg and/HBV DNA at 12–38 months All infants received HBIG and HBV vaccines Overall basic demographics, cordocentesis (n = 6) • 1 (16.7%) mother to child transmission rate • 2 (33.3%) HBeAg positive • 1 (16.7%) HBV DNA >200,000 IU/mL • 1 (16.7%) received antiviral (before procedure) • 1 (16.7%) Post-procedure bleeding from placenta/uterine wall • 1 (16.7%) transplacental
Du et al. 2024 Risk of mother-to-child transmission after amniocentesis in pregnant women with hepatitis B virus: a retrospective cohort study.	China	Single center Retrospective cohort 2019	Inclusion • HBsAg positive pregnant women Exclusion • Coinfection with HAV, HCV, syphilis, or HIV • Miscarriage • Termination of pregnancy • Stillbirth • Twin • Multiple pregnancy • Infant death within 6 months of birth • Loss of follow- up information Definition of mother to child transmission • Infants positive for HBsAg and negative for HBsAb at 1–6 months after completion of vaccination All infants received HBIG and HBV vaccines Overall basic demographics (n = 1764) • 9 (0.5%) mother to child transmission rate • 320 (18.1%) HBeAg positive • 185 (10.5%) HBV DNA >200,000 IU/mL • 267 (15.1%) received antiviral 846 had amniocentesis • 111 (13.1%) HBeAg positive • 78 (9.2%) HBV DNA >200,000 IU/mL • 113 (13.4%) received antiviral • 31 (3.7%) bloody or brown amniotic fluid 918 without amniocentesis • 209 (22.8%) HBeAg positive • 107 (11.7%) HBV DNA >200,000 IU/mL • 154 (16.8%) received antiviral

Table 1: **Characteristics of included studies reporting mother to child transmission rate after prenatal invasive test.**

Effect of transplacental approach to MTCT rates

The approach of prenatal invasive tests was reported in 4 studies. MTCT was observed in 7.7% (1 study, n = 1/13)[7] and 11.1% (1 study, n = 1/9)[14] after transplacental amniocentesis and 100% (1 study, n = 1/1) after transplacental cordocentesis.[16]

For transamniotic approach, the MTCT rate ranged from 0.0% (1 study, n = 0/14)[13] to 2.3% (1 study, n = 3/130)[7] and 8.7% (1 study, n = 2/23)[14] after amniocentesis, and was 0.0% (1 study, n = 0/5) after cordocentesis.[16]

No MTCT was demonstrated in 98 transamniotic and eight transplacental amniocentesis in women with HBV DNA < 7 $\log_{10}$ IU/mL.[7] The approach of invasive tests did not alter the risk of MTCT (two studies, $p > 0.05$),[7,13] even among women with HBV DNA ≥ 7 $\log_{10}$ IU/mL ($p > 0.05$).[7]

Effect of post-procedural bleeding and appearance of amniotic fluid on MTCT rates

Three studies reported on post-procedural bleeding from the punctured placenta or uterine wall.

The MTCT rates in cases with reported bleeding were 0.0% (1 study, n = 0/4)[14] and 7.1% (1 study, n = 1/14)[7] for amniocentesis and 100.0% (1 study, n = 1/1)[16]

	Overall	HBeAg negative	HBeAg positive	HBV DNA level	On antiviral therapy	No antiviral therapy
Amniocentesis						
Grosheide et al. 1994	0/14 (0.0%)	0/12 (0.0%)	0/2 (0.0%)	–	–	–
Ko et al. 1994	3/32 (9.4%)	0/22 (0.0%)[b]	3/10 (30.0%)[b]	–	–	–
Alexander et al. 1999	0/21 (0.0%)	0/20 (0.0%)	0/1 (0.0%)	–	–	–
Yi et al. 2014	4/63 (6.3%)	1/41 (2.4%)	3/22 (13.6%)	<500 copies/mL 0/40 (0.0%)[d,e] ≥500 copies/mL 4/23 (17.4%)[a,d] 500 copies/mL–6.99 log_{10} copies/mL 1/17 (5.9%)[e] ≥7 log_{10} copies/mL 3/6 (50.0%)[a,e]	0/0 (0.0%)	4/63 (6.3%) <500 copies/mL 0/40 (0.0%)[d,e] ≥500 copies/mL 4/23 (17.4%)[a,d] 500 copies/mL–6.99 log_{10} copies/mL 1/17 (5.9%)[e] ≥7 log_{10} copies/mL 3/6 (50.0%)[a,e]
Han et al. 2019	4/143 (2.8%)[a]	0/94 (0.0%)[b]	4/49 (8.2%)[a,b]	<7 log_{10} IU/mL 0/106 (0.0%)[c] ≥7 log_{10} IU/mL 4/37 (10.8%)[a,c]	0/15 (0.0%) HBV DNA ≥ 7 log_{10} IU/mL 0/9 (0.0%) Started before pregnancy 0/4 (0.0%) Started before amniocentesis 0/7 (0.0%) Started after amniocentesis 0/4 (0.0%)	4/128 (3.1%)[a] HBV DNA ≥ 7 log_{10} IU/mL 4/28 (14.3%)[a]
Du et al. 2024	5/846 (0.6%)	3/735 (0.4%)	2/111 (1.8%)	≤200,000 IU/mL 4/768 (0.5%) >200,000 IU/mL 1/78 (1.3%) ≥7 log_{10} IU/mL 0/14 (0.0%)	0/113 (0.0%) HBeAg positive 0/58 (0.0%) HBV DNA >200,000 IU/mL 0/65 (0.0%) HBV DNA ≥ 7 log_{10} IU/mL 0/7 (0.0%) Started after amniocentesis 0/113 (0.0%)	5/733 (0.7%) HBeAg positive 2/53 (3.8%) HBV DNA >200,000 IU/mL 1/13 (7.7%) HBV DNA ≥ 7 log_{10} IU/mL 0/7 (0.0%)
Chorionic villous sampling						
Grosheide et al. 1994	0/1 (0.0%)	0/1 (0.0%)	0/0 (0.0%)	–	–	–
Cordocentesis						
Han et al. 2021	1/6 (16.7%)	0/4 (0.0%)	1/2 (50.0%)	<200,000 IU/mL 0/5 (0.0%) ≥200,000 IU/mL 1/1 (100.0%)	0/1 (0.0%) Started before cordocentesis 0/1 (0.0%)	1/5 (20.0%)
No prenatal invasive tests						
Yi et al. 2014	5/198 (2.5%)	0/80 (0.0%)	5/118 (4.2%)	<500 copies/mL 0/80 (0.0%) ≥500 copies/mL 5/118 (4.2%)[a] 500 copies/mL–6.99 log_{10} copies/mL 2/51 (3.9%) ≥7 log_{10} copies/mL 3/67 (4.5%)[a]	0/0 (0.0%)	5/198 (2.5%) <500 copies/mL 0/80 (0.0%) ≥500 copies/mL 5/118 (4.2%) 500 copies/mL–6.99 log_{10} copies/mL 2/51 (3.9%) ≥7 log_{10} copies/mL 3/67 (4.5%)
Han et al. 2019	3/605 (0.5%)[a]	0/417 (0.0%)[b]	3/188 (1.6%)[a,b]	<7 log_{10} IU/mL 0/455 (0.0%)[c] ≥7 log_{10} IU/mL 3/150 (2.0%)[a,c]	0/65 (0.0%) HBV DNA ≥ 7 log_{10} IU/mL 0/35 (0.0%)	3/540 (0.6%)[a] HBV DNA ≥ 7 log_{10} IU/mL 3/115 (2.6%)[a]
Du et al. 2024	4/918 (0.4%)	2/709 (0.3%)	2/209 (1.0%)	≤200,000 IU/mL 3/811 (0.4%) >200,000 IU/mL 1/107 (0.9%) ≥7 log_{10} IU/mL 0/22 (0.0%)	1/154 (0.6%)	3/764 (0.4%)

[a]Comparison between women with and without amniocentesis in the study showed statistical significance $p < 0.05$. [b]Comparison between HBeAg positive and HBeAg negative women in the study showed statistical significance $p < 0.05$. [c]Comparison between maternal HBV DNA <7 log_{10} IU/mL and ≥7 log_{10} IU/mL in the study showed statistical significance $p < 0.05$. [d]Comparison between maternal HBV DNA <500 copies/mL and ≥500 copies/mL in the study showed statistical significance $p < 0.05$. [e]Comparison between maternal HBV DNA <7 log_{10} copies/mL and ≥7 log_{10} copies/mL in the study showed statistical significance $p < 0.05$.

Table 2: **The effect of HBeAg status, HBV DNA levels and use of antiviral therapy on the rate of mother to child transmission following prenatal invasive tests.**

	Transplacental approach	Transamniotic approach	Post-procedural bleeding from punctured placenta/uterine wall	No post-procedural bleeding from punctured placenta/uterine wall	Bloody/brown amniotic fluid	No bloody/ brown amniotic fluid
Amniocentesis						
Grosheide et al. 1994	0/0 (0.0%)	0/14 (0.0%)	–	–	0/0 (0.0%)	0/14 (0.0%)
Ko et al. 1994	1/9 (11.1%)	2/23 (8.7%)	0/4 (0.0%)	3/28 (10.7%)	–	–
Alexander et al. 1999	–	–	–	–	0/0 (0.0%)	0/21 (0.0%)
Yi et al. 2014	–	–	–	–	0/0 (0.0%)	4/63 (6.3%)
Han et al. 2019	1/13 (7.7%) HBV DNA < 7 log_{10} IU/mL 0/8 (0.0%) HBV DNA ≥ 7 log_{10} IU/mL 1/5 (20.0%)	3/130 (2.3%) HBV DNA < 7 log_{10} IU/mL 0/98 (0.0%) HBV DNA ≥ 7 log_{10} IU/mL 3/32 (9.4%)	1/14 (7.1%) HBV DNA < 7 log_{10} IU/mL 0/7 (0.0%) HBV DNA ≥ 7 log_{10} IU/mL 1/4 (25.0%)	3/129 (2.3%)	0/0 (0.0%)	4/143 (2.8%)
Du et al. 2024	–	–	–	–	2/31 (6.5%)[a]	3/815 (0.4%)[a]
Cordocentesis						
Han et al. 2021	1/1 (100.0%) ≥200,000 IU/mL 1/1 (100.0%)	0/5 (0.0%)	1/1 (100.0%) ≥200,000 IU/mL 1/1 (100.0%)	0/5 (0.0%)	–	–

[a]Comparison between amniocentesis with and without bloody/brown amniotic fluid in the study showed statistical significance p < 0.05.

Table 3: **The effect of post-procedural bleeding, appearance of amniotic fluid and transplacental approach on the rate of mother to child transmission following amniocentesis/ cordocentesis.**

for cordocentesis. On the other hand, the MTCT rates in cases with no reported bleeding were 2.3% (1 study, n = 3/129)[7] and 10.7% (1 study, n = 3/28)[14] for amniocentesis and 0.0% (n = 0/5)[16] for cordocentesis. Post-procedural bleeding did not increase the risk of MTCT (p > 0.05).[7,14]

No MTCT was observed following amniocentesis with post-procedural bleeding among women with viral load < 7 log_{10} IU/mL (1 study, amniocentesis, n = 0/7).[7] Among women with HBV DNA ≥ 7 log_{10} IU/mL, the MTCT rate with post-procedural bleeding was 25.0% for amniocentesis (1 study, n = 1/4) and 100.0% for cordocentesis (1 study, n = 1/1).[7,16]

Five studies reported on bloody/brown amniotic fluid. MTCT was observed in 6.5% of pregnancies after amniocentesis with bloody/brown amniotic fluid (1 study, n = 2/31).[17] The rates of MTCT without bloody/ brown amniotic fluid were 0.0% (2 studies, n = 0/36),[13,15] 0.4% (1 studies, n = 3/815),[17] 2.8% (1 studies, n = 4/ 143)[7] and 6.3% (1 studies, n = 4/63).[6]

Studies comparing MTCT between women with and without amniocentesis

Han et al. revealed an increased risk of MTCT following amniocentesis among women with HBeAg positive statuses (8.2%, n = 4/49 vs 1.6%, n = 3/188, p = 0.016) and HBV DNA ≥ 7 log_{10} IU/mL (10.8%, n = 4/37 vs 2.0%, n = 3/150, p = 0.011), compared to those without amniocentesis.[7] This elevated risk of MTCT among HBeAg positive women was not demonstrated in the other two studies.[6,17] Yi et al. found that amniocentesis increased the risk of MTCT among women with HBV DNA ≥500 copies/mL (17.4%, n = 4/23 vs 4.2%, n = 5/ 118, p = 0.039) and ≥7 log_{10} copies/mL (50.0%, n = 3/6 vs 4.5%, n = 3/67, p = 0.006), compared with women without amniocentesis.[6] However, Du et al. did not find an increased risk of MTCT after amniocentesis in women with HBV DNA >200,000 IU/mL or ≥7 log_{10} IU/mL, compared to those that did not undergo amniocentesis.[17] Among women not on antiviral treatment, amniocentesis increased the risk of MTCT in one study (3.1%, n = 4/128 vs 0.6%, n = 3/540, p = 0.010)[7] but this association was not noted in the other two studies.[6,17] The risks of MTCT among HBeAg negative, HBV DNA < 7 log_{10} IU/mL and antiviral users were comparable with and without amniocentesis.[6,7,17]

Review on clinical practice guidelines

A systematic search identified 50 guidelines (Supplementary Table S2).[9,10,18–45,46–64] Only 9 (18%), 16 (32%), 3 (6%) and 5 (10%) discussed the effect of CVS, amniocentesis, cordocentesis and intrapartum invasive test on MTCT respectively. For CVS, the recommendations ranged from to avoid (n = 1), avoid in women with high viral load (n = 1), increase risk of MTCT (n = 1), increase risk of MTCT in women with high viral load (n = 1), consider antiviral treatment in women with high viral load (n = 1), suggest amniocentesis in view of limited evidence (n = 1), and discuss and balance the risk and benefit of invasive test (n = 3). For amniocentesis, the recommendations ranged from to avoid (n = 1), avoid in women with high viral load (n = 1), consider antiviral treatment in women with high viral load (n = 1), increase risk of MTCT in women with high viral load (n = 3), discuss and balance the risk and benefit of invasive test (n = 10). In addition, four guidelines suggested to avoid transplacental amniocentesis. High viral load was defined in nine guidelines

using different cut-offs, 5.3 $\log_{10}$ IU/mL in two, 7 $\log_{10}$ IU/mL in two and 7 $\log_{10}$ copies/mL in six. For cordocentesis, the recommendations ranged from increased risk of MTCT (n = 1) and to discuss and balance the risk and benefit of invasive test (n = 2). For intrapartum invasive tests, recommendations ranged from to avoid (n = 3) and not contraindicated (n = 2).

Discussion

Our results suggested that the risk of MTCT after amniocentesis was low in women with negative HBeAg statuses or HBV DNA < 7 $\log_{10}$ IU/mL, and comparable to those that did not undergo prenatal invasive tests. However, amniocentesis could potentially increase the risk of MTCT among hepatitis B infected pregnant individuals with seropositive HBeAg statuses or HBV DNA ≥ 7 $\log_{10}$ IU/mL, as demonstrated by the higher MTCT rates when compared to i) HBeAg negative status or HBV DNA < 7 $\log_{10}$ IU/mL in women that had amniocentesis, and ii) HBeAg positive status or HBV DNA ≥ 7 $\log_{10}$ IU/mL in women without amniocentesis. To note, no cases of MTCT were reported following transplacental amniocentesis or amniocentesis with post-procedural bleeding in women with negative HBeAg statuses or HBV DNA < 7 $\log_{10}$ IU/mL, as well as among women with positive HBeAg statuses or viral load levels ≥ 7 $\log_{10}$ IU/mL but received antiviral treatment. However, the small number of cases limited our conclusion on these determining factors and further evaluation is required on the deleterious and protective effects in women with positive HBeAg statuses or viral load levels ≥ 7 $\log_{10}$ IU/mL. Data on CVS, cordocentesis and intrapartum invasive tests were insufficient, therefore we could not conclude their effects on MTCT. Many international guidelines, including the World Health Organizations', did not have recommendations on the management of hepatitis B infected pregnant individuals requiring prenatal or intrapartum invasive test. For other guidelines, the recommendations varied significantly.

In-utero infection could result in persistent neonatal HBV infection despite neonatal vaccine and HBIG. Placental infection, prenatal invasive tests and intrapartum HBV exposure are possible mechanisms of in-utero infection.[4] Theoretically, CVS, amniocentesis and cordocentesis can all result in mixing of fetal and maternal blood and therefore HBV in-utero infection could occur.[65,66] The possible increased risk of MTCT after amniocentesis among positive HBeAg women indicated that the degree of viral replication is a potentiating factor. This echoed with the observations of increasing MTCT rates among women with active viral replication, via other mechanisms leading to in-utero infection such as germline and placental infection.[4] Earlier observational cohort studies failed to demonstrate the increased risk of MTCT following amniocentesis.[5,13–15] These studies had small sample sizes, lack HBV DNA quantification and a control group (HBV infected women without amniocentesis), which could lead to selection bias and were unable to give individual risk estimates in women with different degrees of viral replication. A majority of the existing guidelines did not discuss the effect of prenatal and intrapartum invasive tests on MTCT. Other guidelines suggested discussing and balancing the risk and benefit of invasive tests without giving clear contents. The viral load to define risk of MTCT after amniocentesis varied among guidelines.

This study was performed using a structured search strategy and predefined eligibility criteria. We attempted to cover prenatal and intrapartum invasive tests, and summarized the best available evidence in the literature. Our study had several limitations. First, there were extreme paucity of data on CVS and cordocentesis regarding the risk of MTCT, probably owing to the concern of a higher chance of fetal–maternal haemorrhage then transmission of HBV compared with amniocentesis. Cordocentesis was also associated with a higher risk of procedural-related miscarriage. Therefore, clinicians may favour amniocentesis to aid prenatal diagnosis for pregnant women with HBV. Second, the effect of intrapartum invasive tests on MTCT remains unclear. 32% women may continue to have a high viral load of >200,000 IU/mL at labour, despite maternal antiviral treatment started from 30 to 32 weeks of gestation.[67] Although timely neonatal immunization at birth could neutralize transient peripartum HBV exposure, intrapartum invasive tests could still increase the risk of MTCT. We are not expecting any high-quality evidence on intrapartum invasive tests in the near future to guide recommendations, especially with the anticipated lower utilization of fetal scalp blood sampling due to its potential harm on Apgar score at 5 min.[68] Lacking concrete data on CVS, cordocentesis and invasive intrapartum tests could affect clinician decision making. For example, clinicians may withhold intrapartum invasive procedures and lower the threshold for Caesarean delivery due to a concern of fetal wellbeing. On the other hand, clinicians may fail to recognize the increased risk of MTCT following these invasive tests, leading to suboptimal counselling and MTCT as a result of inadequate antiviral prophylaxis. Third, only observational studies were available which could introduce confounding, publication and selection bias. Small sample size among women with active viral activity could affect the validity of our findings. Furthermore, inadequate information from included studies, on the approach of amniocentesis (transplacental vs transamniotic), post-procedural bleeding and the use of antiviral treatment restricted our further analysis regarding the influence of these factors on MTCT, especially in women with positive HBeAg statuses or HBV DNA ≥ 7 $\log_{10}$ IU/mL. Fourth, the use of

copies/mL to report viral load limited conversion and merging of the data. The viral load threshold of 7 $\log_{10}$ IU/mL was also arbitrary and different clinical guidelines used different cut-offs. More data are needed to establish the appropriate viral load cut-off to identify women at risk of MTCT after invasive tests. Finally, we could not confirm the protective effect of antiviral treatment on MTCT among women with active viral replication and the optimal interval between initiating antiviral treatment and undergoing invasive tests require further evaluation. Despite these limitations, our data shed some light on the effect of invasive tests during pregnancy to MTCT.

Conducting a clinical trial and randomizing women to invasive tests is difficult as the choice of these tests are often personalized. Emulating a randomized controlled trial utilizing observational data could be possible to evaluate the causal effect of particular interventions.[69] The risk of MTCT could be further influenced by many other factors, such as maternal HBV DNA viral load and HBeAg status, mode of delivery, use of antenatal antiviral prophylaxis, availability and timing of both neonatal birth dose vaccine and HBIG. Other determining factors specifically related to the invasive tests include the method (CVS, amniocentesis, cordocentesis, fetal scalp blood sampling, or the use of fetal scalp electrodes), timing (gestational age, prenatal or intrapartum), approach (transplacental or transamniotic), complications of the invasive tests (post-procedural bleeding from the punctured placenta or uterine wall or blood stained amniotic fluid sample), and the use of antiviral prophylaxis (timing of initiation in relation to the invasive procedures). Information on these determining factors were limited in the literature and further evaluation is vital. Therefore, we recommend future research focusing on the evaluation of risk factors of MTCT to provide these comprehensive data. Then, an emulated randomized controlled trial or individual patient data meta-analysis should be utilised to identify the risk factors, viral load threshold associated with increased risks of MTCT after invasive tests, and to guide the need of antenatal antiviral prophylaxis for at risk women.

In light of the absence of robust evidence, we utilized our findings and suggested a clinical algorithm for hepatitis B infected pregnant individuals requiring prenatal or intrapartum invasive tests (Fig. 2). For amniocentesis, a transamniotic approach should be employed as in other women without HBV infection.[19] It is generally accepted that amniocentesis would not increase the risk of MTCT in women with a low viral load or seronegative HBeAg status while women with high

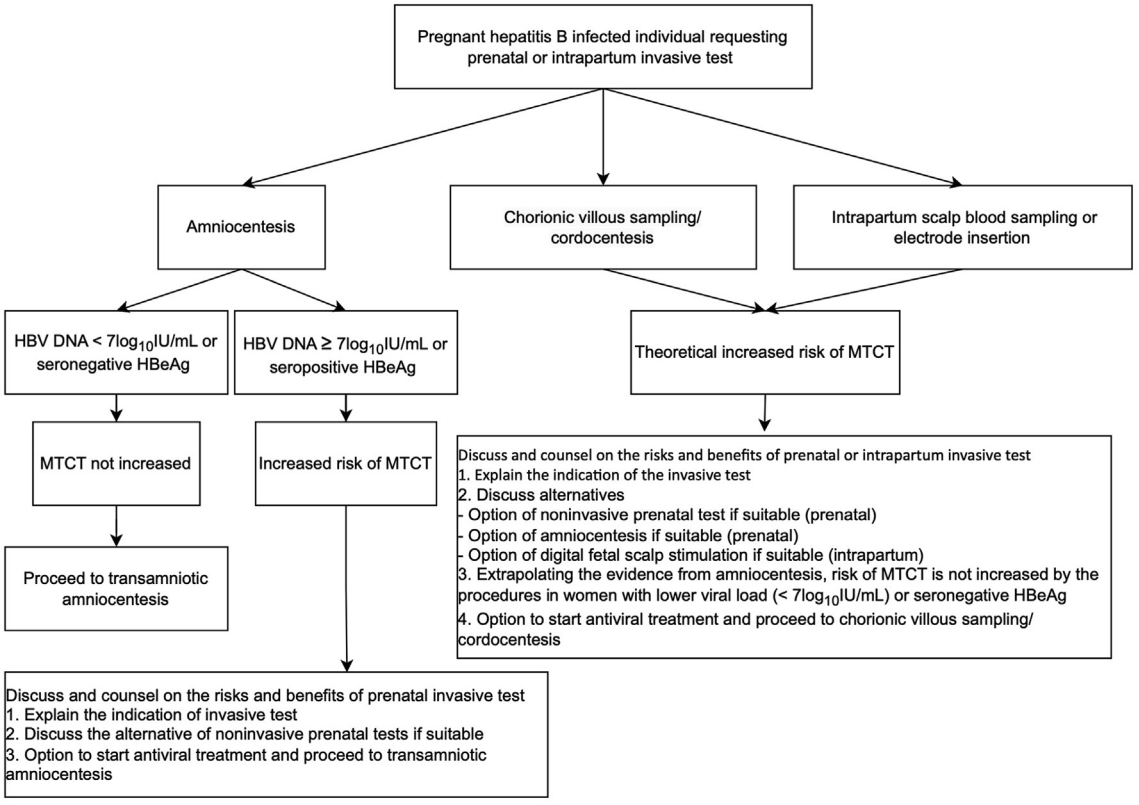

Fig. 2: Clinical algorithms in pregnant hepatitis B infected individual requiring prenatal or intrapartum invasive test.

viral load ≥ 7 $\log_{10}$ IU/mL or seropositive HBeAg status should be counselled about the increased risk of MTCT and the benefit of amniocentesis.

For CVS, cordocentesis, fetal scalp blood sampling, and the use of fetal scalp electrodes, there is a theoretical but undetermined risk of in-utero infection after these procedures. These procedures should also be best avoided if an alternative is available.

For woman considering an invasive test but with an indetermined or increased risk of MTCT, she should be thoroughly counselled and this should include: i) the indication of the invasive test: prenatal invasive tests offer essential genetic information of the pregnancy and often guide the decision on termination of pregnancy and peripartum management. Intrapartum invasive tests can be used to determine the well-being of the fetus and allow labour to progress, or the need for imminent delivery in the case of fetal distress. ii) the alternatives of invasive tests: noninvasive prenatal testing could reduce the need of diagnostic prenatal invasive test in women having positive aneuploidy screening by conventional test.[70] Demonstration of an acceleration of fetal heart rate after a digital fetal scalp stimulation in women with a suspicious intrapartum tracing on cardiotocogram can reduce the necessity for fetal scalp blood sampling.[71] iii) The risk of MTCT: women should be counselled about the data scarcity concerning the risk of MTCT with some invasive procedures. In principle, by extrapolating the evidence from amniocentesis, the risk of MTCT after invasive test is smaller in women with a lower viral load or on antiviral treatment. If the women finally choose to undergo the prenatal invasive test, the option of starting tenofovir disoproxil fumarate (TDF) to decrease the maternal viral load with or without delaying the test should be discussed, depending on the urgency of the scenario as some countries may have a legal gestational limit for termination of pregnancy, should this be needed. The optimal timing to start TDF would depend on the timing of the invasive procedure which typically occurs between 11^{+0} and 13^{+6} weeks for CVS and after 15^{+0} weeks for amniocentesis.

In fact, women with seropositive HBeAg statuses or HBV DNA levels >200,000 IU/mL are already eligible for antenatal antiviral prophylaxis to reduce the risk of MTCT, irrespective of the need of invasive tests during pregnancy. A pragmatic approach would be earlier assessment of HBV DNA levels or HBeAg status during the first or early second trimester of pregnancy. Advancing the initiation of antiviral prophylaxis from third trimester to early second trimester of pregnancy could achieve a higher suppression of viral load at delivery and lower the risk of MTCT.[72,73] In low- and middle-income countries accounting for the majority of the HBV burden, risk stratification by HBeAg status or HBV DNA levels may not be feasible due to logistic or financial constraints. Another compromised approach suggested by WHO is to offer antenatal TDF to all hepatitis B infected pregnant women, which may be a cost-effective strategy to reduce MTCT in these countries.[12,74,75] Since preterm birth is also common in low- and middle-income countries, starting antiviral treatment from second trimester (for example 14–20 weeks) may avoid no or shortened antiviral treatment as a result of preterm birth. Both approaches could also tackle the issue of MTCT after invasive tests since women at risk would be given antiviral prophylaxis to reduce the viral load from early pregnancy to the time of invasive tests. Maternal TDF treatment from early pregnancy is well tolerated by the mother without evidence of teratogenicity.[73]

Hepatitis B infection still poses a tremendous burden globally and progress towards achieving elimination of HBV by 2030 remains unsatisfactory. We found that amniocentesis potentially increases the risk of MTCT in women with seropositive HBeAg statuses or viral load ≥ 7 $\log_{10}$ IU/mL, but the risk might be ameliorated by antenatal antiviral therapy. However, most guidelines lack comprehensive management suggestions for women requiring invasive tests and significant variations exist among recommendations from national guidelines, thus missing the opportunity to further minimize the risk of MTCT. Our review on the current literature, together with the suggested clinical algorithm and two pragmatic approaches, can address current gaps in clinical practice and set research priorities. Stakeholders can also utilize our findings when formulating future guidelines.

More data is required to investigate the virological (HBV DNA, HBeAg status) and clinical factors influencing HBV MTCT after invasive tests. The approach of earlier initiation and wider application of antiviral prophylaxis may cover women undergoing invasive tests and reduce the MTCT rate, but its clinical impact and feasibility need further evaluation.

Contributors

KWC conceived the study. KWC and TSTA accessed, verified and analysed the data. KWC wrote the first draft of the paper. All authors critically revised the drafts of the paper. All authors had full access to the data of the study, read, approved the final manuscript and responsible for the decision to submit the manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of interests

All authors declare no conflicts of interests.

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Nil.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103039.

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