The ethics of overruling parental refusal of neonatal hepatitis B vaccination for babies born to mothers with hepatitis B virus infection

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Clinical vignette: A term newborn baby, Sara, is born by normal vaginal delivery following an uncomplicated pregnancy. Sara's mother has chronic asymptomatic hepatitis B virus (HBV) infection with positive HB surface antigen, low viral load, HB e antigen negative and anti-HBe positive. Sara's mother is not on treatment for HBV. Despite extensive discussion, the family hold a fixed belief that vaccinations are harmful and refuse the birth dose of HBV vaccine. Should clinicians involve social services and pursue legal avenues to allow vaccination of Sara against parental wishes?

Vaccine hesitancy represents one of the WHO's Top Ten Threats to Global Health and is likely to be a significant obstacle to future COVID-19 vaccination programmes.[1,2] Most childhood immunisations serve to reduce a future risk of illness if exposure subsequently occurs to (sometimes rare) transmissible diseases. However, for babies born to mothers who have HBV infection, a known exposure has occurred to a vaccine-preventable infection during birth with immediate risk of vertical acquisition of a potentially life-limiting chronic infection.[3–7] When a woman with HBV refuses the birth dose of HBV vaccine for her baby, infectious diseases and safeguarding teams are asked to provide opinions on whether this crosses the threshold for triggering child protection mechanisms.[8,9] Such discussions are sometimes urgently held in the first hours after birth, compounding an already challenging situation. Some populations have both high prevalence of chronic HBV infection and high rates of vaccine hesitancy (Figure).[10,11] Nevertheless, the incidence of families with HBV infection refusing HBV vaccination for their babies is unknown, the scenario is not yet addressed in guidelines, and legal precedent is scarce.[4,5,8,9] Here we focus on ethical arguments for and against referring families to social services and over-ruling parental refusal in the child's best interests.[12,13]

Where families with HBV have concerns about vaccination the topic should be broached early in pregnancy by obstetric and hepatology teams as soon as maternal HBV is identified with appropriate counselling and support for the family.[4,14] Good relationships between the

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family and healthcare professionals are needed to enable provision of relevant and clear information in the family's preferred language at an appropriate point in pregnancy. It is critical to elicit and address the family's specific concerns and barriers to vaccine acceptance, including safety fears, stigma within their communities, language barriers, and denial of the diagnosis.[15–17] A clear plan should be made antenatally for all pregnant women with HBV including the family's decision regarding neonatal vaccination.[14] Where the family's concerns regarding HBV vaccine have not been allayed, antenatal involvement of public health, neonatal, and paediatric infectious diseases teams enables further dialogue, continuity of care when the baby is born, and ensures that every attempt has been made to address concerns before considering mechanisms to overrule parental refusal.

A critical factor in decision-making is the actual risk of acquisition of hepatitis B infection and the subsequent risk of harm to the baby. There is a spectrum of infectivity: the risk of vertical transmission without intervention may be as high as 90% in mothers with detectable HBe-antigen or 5-40% where there is low viral load, presence of maternal anti-HBe-antibody and no expression of HBe-antigen.[3–5,7,18,19] Acquisition of this bloodborne virus is associated with up to 90% risk of chronic infection if acquired perinatally.[3–5,20] It is estimated that 20-40% of persons who become chronically infected during childhood without treatment will develop life-threatening complications or die from HBV-related cirrhosis or liver cancer (although antiviral therapy for HBV can be associated with approximately a 50% reduction in risk of death).[3–5,14,17,18,20–24] HBV vaccination at birth followed by completion of a full vaccination course is highly effective (>95% seroprotection in infants) and together with guideline-dependent use of hepatitis B immunoglobulin is the mainstay of international guidance for prevention of vertical transmission.[4,5,7,25] Meta-analysis of four randomised controlled trials of HBV vaccination alone at birth vs placebo or no intervention in high HBV prevalence settings with predominantly HBeAg positive or unknown mothers showed 72% risk reduction of HBV infection.[5,19,25–27] Effectiveness of HBV vaccination programs against hepatocellular

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carcinoma (60% decrease in incidence) and death due to fulminant liver failure (76% decrease) or chronic liver disease (92% decrease) has been shown in long-term studies since vaccine introduction in Taiwan.[19,28–30] The importance of the urgent and timely administration of the birth dose as soon as possible after birth (and within 24 hours) in preventing perinatal HBV transmission is recognised in national and international recommendations, and is a target area in the WHO strategy for elimination of hepatitis B as a major public health threat by 2030.[4,5,16,17,19,31,32] Vaccine effectiveness decreases after 24 hours, although there is still some effect up to 7 days after birth.[4,5] The HBV vaccine has an excellent and well-established safety profile with minimal adverse reactions and a risk of anaphylaxis among vaccine recipients of 1.1 per million vaccine doses.[4,5,17,19,33–35] In high infectivity scenarios adjunctive antiviral therapy during pregnancy can also reduce the risk of vertical transmission, although it does not negate the need for vaccination.[3,5,36–40] The need for subsequent doses of HBV vaccination to sustain full seroprotection, including against subsequent horizontal transmission from family members with HBV and in other settings, highlights the importance of maintaining a good long-term relationship and clear communication with affected families. UK data show that prior to the introduction of the universal HBV vaccination in late 2017, 1 in 4 babies for whom HBV vaccination was indicated to prevent vertical transmission did not receive three doses by their first birthday.[41]

The mandate for overruling parental refusal is clearer in high infectivity scenarios, whilst in other cases (such as the introductory clinical vignette) it may be harder to gain consensus amongst health and social care professionals. There are interesting parallels and some key differences when considering the risk to infants of acquiring HIV from their mothers (Table 1). HIV is another vertically transmissible chronic viral infection without a cure with safe and effective interventions to prevent mother-to-child transmission.[42,43] Here we consider the arguments first in favour and then against referring families to social services and the courts where a mother has HBV infection and is at lower risk of vertical transmission to the baby, as in Sara's situation in the introductory vignette.

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In favour of overruling

The UK ethical and legal framework for protecting children's health requires that medical interventions be offered and applied to promote the 'best interests' of the child, who of course in this scenario are not able to express their own opinion. "Best Interests" is what maximises the expected utility to the child. This can be expressed as the [value of benefits x probability of benefits] – [value of harms x probability of harms] compared to available alternatives. Given the massive expected disutility of chronic HBV to the child and the extremely low risk of adverse events from the HBV vaccine, it is clear that it would be in Sara's interests to receive her neonatal HBV vaccine even if the probability of infection were low.

One possible justification for permitting non-vaccination might be on consequentialist or utilitarian grounds (ie an act is morally right if it generates the best consequences or maximises the total amount of good for all). According to both these moral theories, one must consider not only the utility to the child but the utility to all parties affected, which include parents and society (Table 2). It might be argued that harm done to the parents by forcing vaccination through a Child Protection Order is significant, as would be the indirect harms of potentially increasing publicity for the anti-vaccine movement. There are also the threats to public health of chronic HBV and subsequent horizontal transmission which need to be included in favour of enforcing vaccination. In the current scenario there is a high degree of certainty about the expected disutility to the child from not being vaccinated whereas there is much less certainty around the degree of disutility following coerced vaccination. Hence even consequentialist and utilitarian analyses are likely to favour overruling the family's decision not to vaccinate.

A different ethical framework draws on the so-called 'Harm Principle'. This principle justifies overruling parents if they are making decisions that significantly harm their child. There is a

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grey zone (the 'Zone of Parental Discretion') where parents have liberty to exercise judgement when it would not significantly harm their child.[22,23] However, risk of chronic HBV is likely to be considered a significant harm by current societal and medical standards (Table 1), meaning that non-vaccination arguably lies outside the zone of parental discretion.

Against overruling

It would be in Sara's best interests for her to have the neonatal vaccine and to have a reduced risk of acquiring chronic HBV. However, it would also be in her best interests to have the rest of her childhood vaccines. While much of society believes that vaccines are a good thing (both for individual children and for the community) we have not chosen to mandate them in the UK. Furthermore, there are many situations where parents make suboptimal decisions (for example about their children's diet, exercise, schooling) without state intervention.[10] Health professionals do not overrule parents every time that they are making unwise choices.

The key difference with the case that we are considering is that the absolute acute risk to the child is much higher and has a safe, effective and easily administered single intervention. However, there is both medical and moral uncertainty about the risks of transmission and the full consequences of intervention against parental wishes. There is heterogeneity in the clinical course and medical uncertainty as shown by the wide confidence intervals around perinatal transmission and risks of life-threatening complications. If Sara were to acquire HBV, she may clear the infection, or develop chronic HBV. If she develops chronic infection she may or may not develop liver disease or cancer. The number of newborns that you need to immunise (Number Needed to Treat – NNT) to a prevent a case of cirrhosis, hepatocellular carcinoma, or death is estimated to be between 7 and 110, although the risk of these outcomes may decrease with antiviral treatment and there are additional harms from HBV to self and others. As you cannot predict whether Sara is one of the children that will benefit from this preventative intervention and the timescale for developing serious

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complications is over many years, moral uncertainty is introduced. There is no question that it is justified to immunise Sara, and that it is justified to strongly encourage her parents to accede to immunisation. The question is whether the risk of harm to Sara is sufficiently high that it is justified to use the blunt tool of the law to enforce treatment. In the case scenario, a minimum of 6 families (and possibly as many as 110 or more) would have social services involvement and the possibility of a court order generated unnecessarily for one child to benefit (by having cirrhosis, liver cancer, or death prevented). That potentially has considerable negative psychological impact for those families as well as engendering distrust in health professionals and thus possible disengagement with health services.

Conclusion

The ethical challenge of neonatal hepatitis immunisation is that there is, at present, no consensus about whether the risk in low infectivity scenarios is sufficiently high to overrule parental refusal, although some cases have gone to court (Table 1).[8,9] Precedent for overruling parental refusal for medical interventions to prevent mother-to-child transmission of HIV in high resource settings is well-established (Table 1).[42,43] There are strong ethical arguments in favour of neonatal hepatitis B immunisation to prevent vertical transmission. Parents should be strongly encouraged to consent to immunisation. Where a pregnant woman has HBV and does not wish for immunisation of their baby when born, there should be urgent multidisciplinary consultation to establish the risk of transmission and long-term harm to the child as well as to continue the dialogue regarding the child's best interests in being vaccinated (Figure 2). Where there is a high risk of transmission and serious illness, parental refusal should not be accepted. Urgent input from social services and referral to a court is ethically warranted. In cases where there is a lower risk of transmission, there can be uncertainty about what the absolute risk is to the child and whether this is sufficient to warrant court referral. Perception and interpretation of risk and NNT varies substantially.[12,44] National and international guidance on the appropriate threshold and publicly available anonymised legal judgments would help ensure consistent ethical decision-making. We

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suggest involvement of clinical ethics committees and seeking second opinions from other specialist centres with a low threshold for initiating child protection referrals and legal avenues (Figure 2). Where concerns have not been allayed before birth and a consensus decision has not been achieved the process will need to be accelerated with early involvement of safeguarding teams to enable intervention in a timely manner if it is indicated. A number of research priorities could help better inform conversations with families (Box/Panel) and it's crucial that a range of stakeholders including patient HBV advocacy organisations, public health specialists, infectious diseases clinicians, paediatricians, social workers, ethicists and the general public are involved in ongoing discussions around the tension between parental autonomy and the child's best interests.

Authorship statement:

RB, SP, DFK, AJP, JS and DW conceived the work. RB, JS and DW drafted the work. EPKP obtained the data and plotted Figure 1. All authors revised the work for important intellectual content.

Declaration of interests:

AJP is Chair of UK Dept. Health and Social Care's (DHSC) Joint Committee on Vaccination & Immunisation (JCVI), an NIHR Senior Investigator, and is a member of the WHO's SAGE. The views expressed in this article do not necessarily represent the views of DHSC, JCVI, NIHR or WHO. AB reports personal fees from Sanofi Pasteur and from Seqirus, outside the submitted work; RB, DFK, SP, GTW, EPKP, HB, AT, SM, AB, MR, JS and DW have no conflicts of interest.

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LEGENDS:

FIGURE 1: Hepatitis B prevalence and vaccine safety confidence data for Europe. Data extracted for the 22 countries for which data on both vaccine confidence and modelled hepatitis B prevalence are available from references [10,11]. Countries with either <75% agreement that vaccines are safe or with Hepatitis B prevalence >1% (ECDC criteria for high HBV endemicity countries) are labelled, alongside the UK (which does not meet these criteria).[45]

FIGURE 2: Proposed dialogue process for managing scenarios where a pregnant woman with HBV has concerns about vaccinating her baby when born.
IU=International Units

TABLE 1: A comparison of disease, treatment, prevention, and legal characteristics related to vertical transmission of hepatitis B and HIV.
ART=Antiretroviral therapy, IQR=Interquartile Range, RCT=Randomised Controlled Trial.
[#]UK Case Law 2019 – pending publication of judgement in British and Irish Legal Information Institute (https://www.bailii.org/), personal communication A Banerjee.

TABLE 2: Consideration of the costs and benefits in a utilitarian or consequentialist ethical analysis where child protection or legal mechanisms are used to mandate hepatitis B vaccination for the newborn of a mother with chronic HBV infection

BOX/PANEL: Research and policy priorities regarding the ethics of overruling neonatal hepatitis B vaccine refusal

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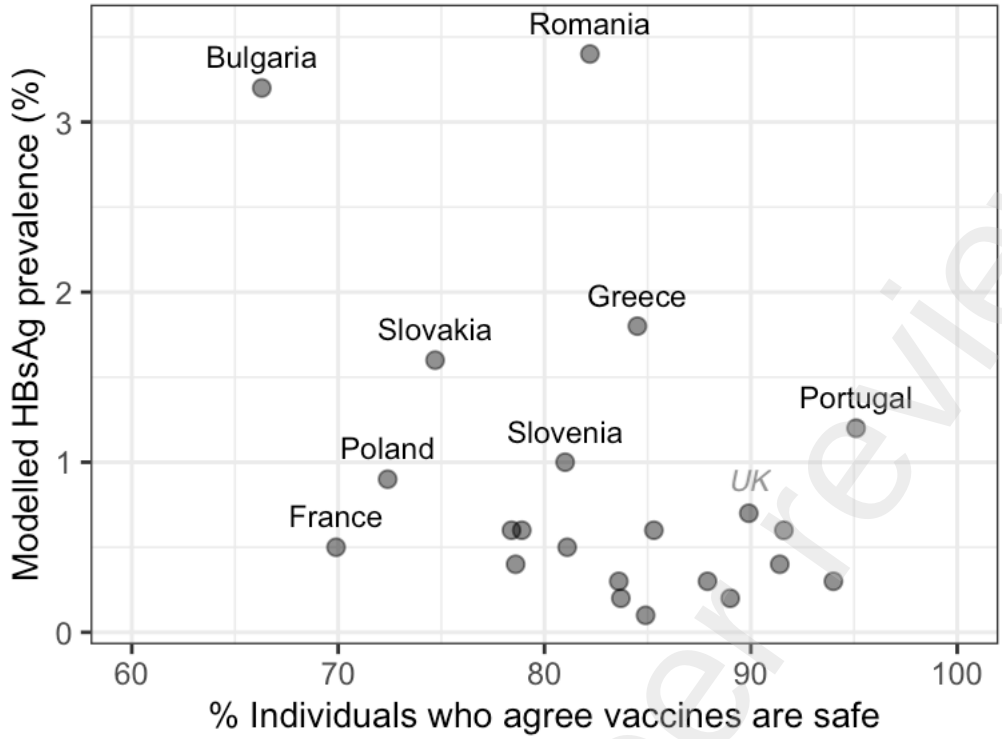
398 FIGURE 1:



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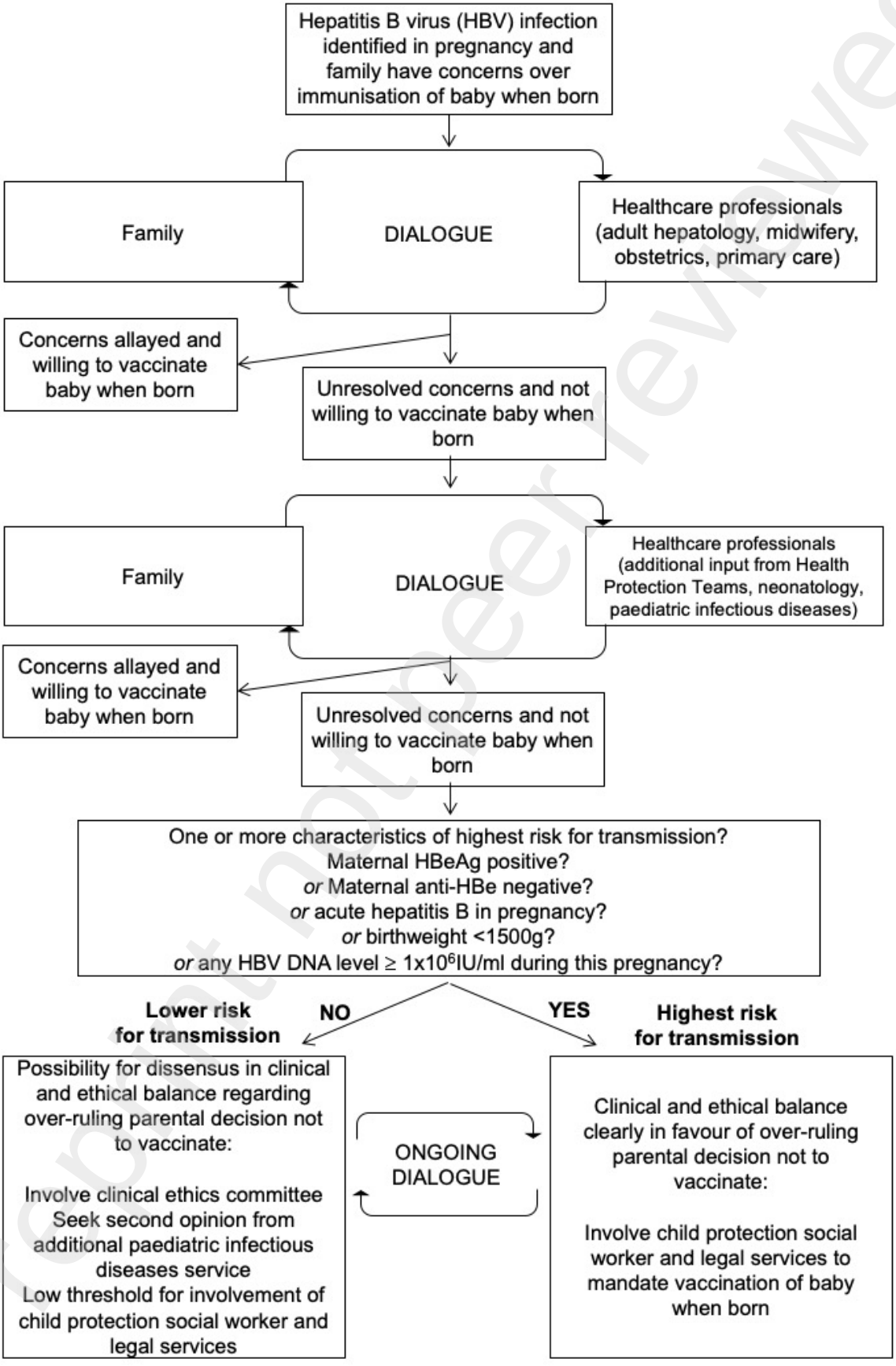
400 FIGURE 2:



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402 TABLE 1:

		Hepatitis B	HIV
Disease characteristics	**Vertical transmission rates**	Without intervention: 5% to 40% for HBeAg-negative mothers and 70% to 90% for HBeAg-positive mothers.[3,19]	Without intervention: 14-48% [46]
	Key factors related to infectivity	Viral load, HBeAg, and anti-HBe status	Viral load
	Potential for chronic infection if acquired perinatally	80-90%[5]	100%
	Potentially fatal	20-40% of persons who become chronically infected during childhood will develop life-threatening complications or die from cirrhosis or liver cancer[3–5,14,17,18,20–24] Risk ratio for death from RCTs of antiviral therapy vs no treatment in adults: 0.45 (95%CI 0.16-1.3) [23]	8% first AIDS-defining event and 3% mortality rate amongst children with perinatally-acquired HIV initiating ART in middle- and high-income countries.[47]
Treatment characteristics	**Specific medical treatment**	Yes	Yes
	Widely available medical cure	No	No
	Plausible that treatment would improve over a newly infected child's lifetime	Yes	Yes
Prevention characteristics	**Effective vaccine**	Within 24 h of birth, followed by at least two more doses within 6–12 months is 90-95% effective[3]	No
	Interventions to prevent vertical transmission	HBV treatment in pregnancy for higher viral load scenarios [5,37–39] Full course of Hepatitis B vaccination for newborn including birth dose Passive immunisation with Hepatitis B immunoglobulin at birth (guidelines vary)[4,5]	Maternal ART in pregnancy Consider C-section if detectable viral load ART for the neonate Risk assessment for breast feeding[48]
	Recommended time critical window for intervention after birth	As soon as possible after birth (and no later than 24 hours)[4]	Very soon after birth, certainly within 4 hours.[48]
	Vaccine uptake (Median, IQR for vaccination rates by local authority in UK)	86.4% (78.3-100) for three doses of HBV vaccine by first birthday where mother has HBV[41]	N/A
Legal context	**Precedent for state intervention if family refuse interventions to prevent vertical transmission**	Yes [8,9,#]	Yes [42]

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404 TABLE 2:

Benefits to baby	**Costs to baby**
Decreased risk of acquiring vertically transmitted hepatitis B	"generally well-tolerated and the most common adverse reactions are soreness and redness at the injection site. Other reactions that have been reported but may not be causally related include fever, rash, malaise and an influenza-like syndrome, arthritis, arthralgia, myalgia and abnormal liver function tests." [4]
Decreased risk of acquiring horizontally transmitted hepatitis B later in life	Impact on early maternal bonding and establishment of breast feeding due to associated stress
Decreased lifetime risk of developing liver failure, cirrhosis, hepatocellular carcinoma	Potential for development of challenging long-term dynamics within the family related to decisions and actions taken at birth.
Decreased anxiety associated with chronic HBV infection and possibility of life-threatening outcome.	Potential for altered patterns of health-seeking behaviours and impact on future interactions with health care professionals.
Decreased risk of needing to take chronic medications to treat hepatitis B, which have more adverse effects than vaccination.	
Decreased risk of having potentially stigmatising chronic viral infection[15]	
Decreased risk of needing to consider hepatitis B infection and occupational health consideration when making educational and career choices[15]	
Decreased risk of challenges obtaining health or life insurance or having hepatitis B-related medical expenses.[15]	
Decreased risk of needing to attend medical outpatients and have blood tests to monitor hepatitis B infection over lifetime	
Benefits to parents	**Costs to parents**
Potentially reduced need for long-term medical appointments, reduced associated costs	Impact on early maternal bonding and establishment of breast feeding due to stress associated with discussions of child protection or legal measures
Avoidance of guilt if baby contracts HBV at birth	Potential for development of challenging long-term dynamics within the family related to decisions and actions taken at birth.
Relief and reassurance that child is protected against HBV into adult life if completes full course of vaccination	Development of distrust and antagonistic relationship with health care and social work professionals
	Detrimental impact on mental health and stigma issues
Benefits to society	**Costs to society**
Decreased risk of onward transmission of hepatitis B to others (e.g. future sexual partners)	State social work and legal resources finite with many children in need
Exercising state's role to act in child's best interest	Risk of entrenching vaccine hesitancy and antagonistic relationships with the state.

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BOX/PANEL:

Contemporary data to inform discussions with families:

- Updated systematic reviews and meta-analyses on:
    - Risk of vertical transmission in different infectivity scenarios in clinical practice (viral load, HBe antigen and anti-HBe status, birth weight, gestational age, clinical stage of HBV infection in pregnancy) with combinations of interventions to prevent vertical transmission (HBV vaccine [birth dose followed by complete or incomplete course of vaccination], HBV immunoglobulin at birth, antiviral therapy in pregnancy)
    - Long-term outcomes on cirrhosis, hepatocellular carcinoma, and death for perinatally acquired HBV infection in era of treatment for HBV
- Provision of parent information leaflets in extended range of languages.

Exploration of underlying reasons behind HBV vaccine hesitancy

- Qualitative research with those affected by HBV and HBV advocacy organisations to systematically explore concerns regarding vertical transmission and vaccination

Quantifying the problem:

- Retrospective and prospective data collection on number of referrals to social services for this scenario.
- Publication of anonymised legal judgements where referrals have reached court.

Evaluating the policy and global landscape:

- Review of national and international clinical guidance and legal status of this scenario.

Quantifying dissensus amongst health professionals:

- Surveys of clinical practice and attitudes towards state intervention in low and high infectivity scenarios amongst obstetric, neonatal, public health and infectious diseases clinicians.

Societal perspectives

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- Exploration of perceptions of general public around acceptable levels of risk to which parents can expose their children

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