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Brief report

Ethical issues in preventing mother-to-child transmission of hepatitis B by immunisation

David Isaacs[a,b,*], Henry A. Kilham[a,b], Shirley Alexander[a], Nick Wood[a], Adam Buckmaster[c,d], Jenny Royle[e]

[a] Clinical Ethics Advisory Group, Children's Hospital at Westmead, Westmead, NSW, 2145, Australia
[b] University of Sydney, NSW, 2006, Australia
[c] Department of Paediatrics, Gosford Hospital, Gosford, NSW, 2250, Australia
[d] University of Newcastle, Newcastle, NSW, 2300, Australia
[e] Immunisation Advisory Service, Royal Children's Hospital, Parkville, Vic, 3052, Australia

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ABSTRACT

Without intervention, a pregnant woman who is a chronic hepatitis B carrier is at risk of transmitting hepatitis B and of her infant becoming a chronic carrier and having a significantly increased lifetime risk of developing liver cancer or cirrhosis. Hepatitis B vaccine and immunoglobulin reduce the risk of the baby becoming a carrier, but with only a short window period after birth to deliver this potentially life-saving intervention. We reviewed the evidence on the magnitude of the risk. If the carrier mother is *e* antigen positive (highly infective), the calculated risk to the infant without intervention is 75.2%, reduced to 6.0% by giving vaccine and immunoglobulin at birth. If the mother is surface antigen positive but *e* antigen negative, the risk to the infant without intervention is 10.3%, reduced to 1.0% by giving vaccine and immunoglobulin. If vaccine is accepted but immunoglobulin refused, as for example by some Jehovah's Witnesses, the risk to babies of *e* antigen positive mothers is reduced to 21.0% and to babies of *e* antigen negative mothers to 2.6%. These figures can be used to inform parents and as a possible basis for child protection proceedings if parents decline vaccine and/or immunoglobulin. We argue from the perspective of the best interests of the child that the severity of the condition justifies initiating child protection proceedings whenever a baby is born to a hepatitis B carrier mother and, despite concerted attempts to persuade them, the parents refuse vaccine and/or immunoglobulin.

1. Introduction

Immunising babies against hepatitis B is not without controversy. Some have argued that routine immunisation against hepatitis B in a population where hepatitis B is rare does not address a substantial public health danger and, because hepatitis B is acquired mainly through intravenous drug use or sexual contact, should be deferred until the individual can make an informed decision [1]. Nevertheless, many countries with a low incidence of hepatitis B give routine hepatitis B immunisation in infancy to protect the child against any later risk of acquiring hepatitis B [2,3] and there is evidence that such immunity lasts at least 10 years and probably longer [2]. In Australia, a neonatal birth dose of hepatitis B vaccine is routinely given to all babies plus three further doses in infancy [3]. In addition, there is universal antenatal screening for hepatitis B surface antigen (HBsAg) and infants born to HBsAg positive mothers are routinely given both vaccine and immunoglobulin as soon as possible after birth [3].

We have argued before that routine childhood immunisations should not be mandatory in a population where there is a high voluntary uptake and no immediate danger of epidemics, but intervention may be justified in cases where we know with practical certainty that parents' failure to immunise puts their own child or other children at high risk of severe illness [4]. In this paper we use the best available evidence to calculate the risk that a child of a mother who is a chronic carrier will acquire hepatitis B at birth, with or without the interventions of vaccine and/or immunoglobulin, and we discuss the ethical implications.

2. Methods

We reviewed the literature on rates of mother-to-child hepatitis B transmission by searching The Cochrane Neonatal Group Controlled Trials Register, The Cochrane Hepato-Biliary Group Con-

* Corresponding author at: Clinical Ethics Advisory Group, Children's Hospital at Westmead, Westmead, NSW, 2145, Australia. Tel.: +61 298453414; fax: +61 298453421.
E-mail address: davidi@chw.edu.au (D. Isaacs).

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trolled Trials Register, The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, and EMBASE for trials of neonatal hepatitis B vaccine with or without immunoglobulin compared to placebo in infants of hepatitis B carrier mothers and by searching MEDLINE and EMBASE for papers that reported rates of mother-to-infant transmission from hepatitis B *e* antigen positive and negative mothers. We attempted to differentiate rates of neonatal infection when carrier mothers who were surface antigen positive were also *e* antigen positive (high infectivity) or *e* antigen negative (low infectivity). We searched MEDLINE and EMBASE for papers that defined infectivity in terms of maternal viral load. We calculated the rates of mother-to-child hepatitis B transmission without intervention from the rates in the placebo groups in clinical trials and from papers that reported transmission rates before vaccine or immunoglobulin were available.

3. Results

With regard to efficacy of vaccine and/or immunoglobulin, we found 135 intervention trials and three meta-analyses, but after excluding non-randomised studies and inappropriate reviews, we found 29 relevant randomised controlled trials, one Cochrane systematic review [5] and one systematic review by the same authors that reported the same data [6].

Many studies included both *e* antigen positive and *e* antigen negative mothers but did not report mother-to-child transmission rates separately for *e* antigen positive and *e* antigen negative mothers. We calculated rates of transmission without intervention using only those intervention studies or reports of the natural history that clearly reported an adequate distinction between *e* antigen positive and *e* antigen negative mothers. The rate of mother-to-child hepatitis B transmission from *e* antigen positive mothers without intervention was reported in 8 studies [7–14] the range was 73–95% and the mean 75.2% (138 of 182 cases). We used this figure to calculate risks (see Table 1).

One study examined risk of transmission relative to maternal viral load [11], but used techniques that are no longer in use, while another small study reported only three infected babies [15]. We were unable to quantify risk based on current methods of measuring maternal viral load, although the risk of transmission clearly increases with increasing maternal viral load.

Compared with placebo or no intervention, vaccination reduced the transmission of hepatitis B from a surface antigen positive mother (*e* antigen status in studies was often unknown or unspecified) to her infant (relative risk 0.28, 95% confidence interval 0.20–0.40; four trials). There was no significant difference in hepatitis B incidence between recombinant vaccine and plasma derived vaccine (1.00, 0.71–1.42; four trials) and between high dose versus low dose vaccine (plasma derived vaccine 0.97, 0.55–1.68, three trials; recombinant vaccine 0.78, 0.31–1.94, one trial), so our calculations on the effectiveness of vaccine are based on all vaccine trials combined. Using the figure of 72% for vaccine efficacy, if mother is *e* antigen positive, vaccine alone would reduce the risk of transmission of hepatitis B from 75.2% to 21.0% (see Table 1).

Vaccine plus hepatitis B immunoglobulin reduced hepatitis B transmission from a surface antigen positive mother by 92% compared with placebo or no intervention (0.08, 0.03–0.17; three trials) [11,13,14]. If mother is *e* antigen positive, vaccine plus hepatitis B immunoglobulin will reduce the risk to her baby of contracting chronic hepatitis B by 92%, from 75.2% to 6.0% (see Table 1).

The risk of transmission to a baby whose carrier mother is known to be *e* antigen negative, based on only one study [16], is 3 of 29 or 10.3%. This risk can be expected to be reduced by 92% to 1.0% using vaccine and immunoglobulin, or by 72% to 2.6% using vaccine alone (see Table 1).

Rarely a parent declines vaccine but accepts immunoglobulin alone. Only one trial compared hepatitis B immunoglobulin alone with placebo and found a relative risk of 0.50 (95% CI 0.41–0.60) [16]. Compared with vaccine, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (RR 0.54, 95% CI 0.41–0.73, 10 trials) [6]. We estimated the efficacy of immunoglobulin alone as 50%.

4. Discussion

In 1985, Blumberg and Fox predicted that the novel ability to detect hepatitis B carriers and the development of an effective vaccine would solve some problems but would raise new ethical and medical questions, something they called the Daedalus effect ("when a problem is solved it often raises others") [17].

The predicted risk to chronic carriers is based on historical data. In a study from Taiwan, 54.3% of men who were chronic carriers of hepatitis B died from cirrhosis or liver cancer, compared with only 1.5% of non-carriers [18]. The risk is lower for women who are chronic carriers and may be different in industrialised countries, while outcomes may be better with current and emerging therapies against hepatitis B [19]. There are scanty recent data on outcome for carriers infected at birth [19].

Routine hepatitis B immunisation commencing at birth in a population with a low risk of hepatitis B such as Australia is not without controversy [1]. Individual risk of acquiring hepatitis B generally does not arise until adolescent and early adult years, from sexual activity or needle-sharing, so some have argued that immunisation should be deferred to adolescence, when the child is competent to make an informed choice about being immunised against hepatitis B [1]. Arguments for neonatal or infant programmes are based on individual benefit (administering the vaccine at the time of greatest risk of transmission if mother is a carrier) and population benefits including herd immunity and the fact that higher levels of immunisation will be achieved by immunising in infancy compared with immunising in adolescence. There is evidence for enduring immunity after infant immunisation [2]. When a parent who is known to be hepatitis B surface antigen negative refuses a birth dose of hepatitis B vaccine for her newborn baby, the risk to the baby of acquiring hepatitis B before adolescence is negligible.

Where a mother is a hepatitis B carrier, however, the risk to the infant of becoming a chronic carrier is increased. Chronic carriers are at high risk of developing cirrhosis or liver cancer, although the magnitude of the risk in an industrialised country is debatable. Also, a chronic carrier is probably at risk of anxiety about their uncertain prognosis. Use of vaccine and immunoglobulin together greatly decreases the risk of transmission, and ethical concerns only arise if one or both of these preventative interventions is refused by parents. Refusal of treatment is unusual; when it occurs it is often in the context of a strong belief system, such as vehement anti-vaccination advocates. This can result in a non-negotiable situation, with strong medical science pitted against parents who believe equally strongly in dangers of vaccines and possibly in irreparable harm to their child.

In general, parents are in the best position to decide what should happen to their infants and parental autonomy is an extremely important ethical principle. Our argument for over-riding parental decisions on immunisation when mother is a chronic carrier is from the perspective of the best interests of the child. An argument from herd immunity, to protect others against infection if the infant becomes a carrier, is not a strong argument in any country, because there are other ways of preventing transmission of infection, and particularly not in Australia where most of the population is already protected by universal infant hepatitis B immunisation.

Table 1
Calculated risk to infant of acquiring hepatitis B at birth from carrier mother depending on mother's serological status and intervention.

Mother's hepatitis B status	Risk to infant with no intervention	Risk if infant receives vaccine and immunoglobulin at birth	Risk if infant receives vaccine alone at birth	Risk if infant receives immunoglobulin alone at birth
e antigen positive	75.2%	6.0%	21.0%	37.6%
e antigen negative	10.3%	1.0%	2.6%	5.0%

An important aspect of any discussion is knowledge of the magnitude of risk. We found data on risk were not readily accessible. Below, we try to quantify the level of risk for different scenarios.

Overall we consider that there are four likely scenarios in terms of conflict:

(i) Mother is s antigen positive and *e* antigen positive and the parents refuse vaccine (and usually refuse immunoglobulin also)
(ii) Mother is s antigen positive and *e* antigen negative and the parents refuse vaccine (and usually refuse immunoglobulin also)
(iii) Mother is s antigen positive and *e* antigen positive and the parents refuse immunoglobulin
(iv) Mother is s antigen positive and *e* antigen positive and the parents refuse immunoglobulin.

The risk in each of these situations is described in Table 1.

As paediatricians, we feel a responsibility to consider and to advocate for the best interests of the baby. In rare circumstances, when we judge that a child is significantly endangered by his or her parents' decision, this will mean seeking to over-ride the parents [20,21]. Essentially, it is an expression of the fact that a majority community view is to protect individuals, in this case infants, who are not currently able to decide for themselves, even where this goes against usual conventions of parental autonomy. We argue that any of the above four situations constitutes a child protection issue.

The American Academy of Pediatrics Committee on Bioethics recommends that all legal interventions apply equally whenever children are endangered or harmed, without exemptions based on parental religious beliefs. They argue against "the stringent application of medical neglect laws when children do not receive recommended immunisations". However, they do support mandatory mass vaccinations in epidemics and they do not consider the unusual situation we describe when there is an increased risk of harm to an individual infant because of exposure to maternal hepatitis B [20]. A subsequent report from the same committee on responding to parents who refuse immunisation of their child argues from the perspective of the best interests of the child, while acknowledging that parents and physicians may not always agree on what constitutes the best interest of an individual child. This report argues that the parents' decision should be respected unless the child is put at serious risk of harm [21]. Dawson concurs that parental decision-making about vaccination may be over-ridden when the objective risk is high [22].

When there are competing ethical principles, parental autonomy versus the best interests of the infant, the level of risk is an important aspect of deciding whether or not to intervene. A high risk of a severe outcome probably justifies intervention but if the risk is negligible or very low, the parents' autonomy should probably be pre-eminent. The question of 'just how much risk' justifies legal action is debatable. For example, if a Jehovah's Witness mother is hepatitis B surface antigen positive and e antigen negative, the risk to the baby of 10.3% can be reduced to 2.6% with vaccine alone. If the parents accept vaccine but refuse immunoglobulin it could be argued that the additional benefit provided by enforcing the administration of immunoglobulin is out-weighed by the infringement of parental autonomy. Alternatively, it could be argued that the baby's best interests outweigh the infringement of parental autonomy. In a recent case in Australia, mother was *e* antigen negative and the parents refused vaccine and immunoglobulin. The paediatricians involved argued for child care proceedings to protect the best interests of the child while the obstetricians argued from parental autonomy that their decision not to immunise should be respected. Involvement of the Courts is traumatic but allows an independent assessment of the situation.

There have been very few cases in Australia where parents have refused vaccine or immunoglobulin to protect their newborn baby of a carrier mother against hepatitis B, and there is no legal consensus on what level of risk justifies intervention to protect the child. We have involved child protection services in the state of New South Wales on two occasions when insoluble conflict has arisen. (i) Involved the lowest risk situation and (ii) of an *e* antigen negative mother whose parents refused vaccine and immunoglobulin (baseline risk 10.3% reducible to 1%). The other case concerned a Jehovah's Witness *e* antigen positive carrier mother and her partner who, despite extensive discussion, refused immunoglobulin but not vaccine for their newborn baby. The Jehovah's Witness website, the Watchtower, [23] states that most Jehovah's Witnesses do not consider immunoglobulin to be a prohibited blood product but some extreme believers will refuse it. We took into consideration that a child given immunoglobulin is considered by some Jehovah's Witnesses to have been damaged. It is well established that the community at large accept legal measures to override parental autonomy where a Jehovah's Witness child requires life-saving treatment such as blood transfusion. We argued that in this case, the risk to the infant of becoming a carrier could be reduced from 75.2% to 21% with vaccine alone, but that a 21% risk, instead of a 6% risk using vaccine and immunoglobulin, represented an unacceptably high risk. The Court ruled on both occasions that the best interests of the child were predominant, that the benefits of vaccine and immunoglobulin far outweighed any risks, and the Court authorised medical staff to give vaccine and immunoglobulin [24].

Obviously, problems are best avoided if possible. Early recognition and discussion may resolve issues, but occasionally views are too polarised. The mechanics of giving vaccine and immunoglobulin against parental wishes can be fraught and, although we make every conscious attempt to negotiate in a non-threatening way, we were involved in one situation where the parents absconded with their baby in defiance of a Court order [24] and another where the parents changed maternity hospital covertly in an attempt to avoid the recommended intervention.

In conclusion, we do not believe that immunisations need to be compulsory when high coverage rates can be achieved voluntarily without compulsion [3,25]. If a mother who is not a hepatitis B carrier (or whose carrier status is unknown in a low-risk situation) elects not to have her baby immunised with hepatitis B vaccine at birth, attempted rational persuasion is reasonable, but coercion is not justifiable. However, we believe that being a chronic carrier from birth carries a high risk of reduced life expectancy from cirrhosis or liver cancer and at the least is likely to cause the carrier significant anxiety. We argue that the medical profession has a duty to protect children from their parents' beliefs if those endanger the child to an unacceptable degree and that even a 2% increased risk

of such a severe outcome is unacceptably high. When medical and nursing staff judge that a situation justifies intervention but the parents disagree and no solution can be negotiated, we suggest the Courts should be asked to adjudicate. We maintain we should inform the Court of the risks and benefits of the intervention, the parents can make their case and the Court should decide whether the level of risk without intervention and the degree of benefit from intervention justifies mandatory treatment.

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