At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain

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Abstract

We evaluated the immunogenicity of hepatitis B (HB) vaccine in UniJect, a pre-filled, non-reusable injection device, stored at tropical temperatures for up to one month and used to give the first dose of HB vaccine to newborns. Infants in Tabanan district, Bali, Indonesia, were given their first dose of HB vaccine with UniJect stored out of the cold chain, UniJect stored in the cold chain; or standard syringe, needle and multidose vial stored in the cold chain. Subsequent doses were given by usual means and blood samples drawn 4–6 weeks after the third dose. No significant differences were found in seroconversion rates or geometric mean titres of HB surface antibody between the three groups. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Hepatitis B vaccine; Cold chain; Newborn

1. Introduction

In 1992, the World Health Organization (WHO) recommended universal childhood immunisation against hepatitis B (HB) [1]. HB vaccine is relatively heat stable and undergoes only a small loss in potency when stored for two to six months at 37°C [2–4]. The World Health Organization considers HB vaccine to be a candidate for use beyond the cold chain under certain conditions because of its thermal stability and vulnerability to damage due to freezing during storage and transport [5]. This strategy could increase immunisation coverage in areas not reached by the cold chain.

Studies in China have shown that the immunogenicity of HB vaccine in humans is retained when stored at ambient temperatures for up to 3 months [6]. However, concerns about improper syringe and needle reuse, lack of supervision, and jeopardising cold chain practices for heat-sensitive vaccines have discouraged widespread implementation of HB immunisation beyond the cold chain.

To overcome these obstacles, a recent study in Indonesia used a pre-filled single-use injection device for outreach immunisation beyond the cold chain [7]. The device, called UniJect\textsuperscript{\textregistered}, was stored at ambient temperatures for up to one month in midwives’ homes and used during home visits to deliver the first dose of HB vaccine to infants within a few days of birth. The field acceptability study found that use of UniJect outside the cold chain simplified logistics, minimised vaccine wastage, and facilitated speed and efficiency of immunisation during home visits [7].

Concurrently, a serological study was conducted to evaluate the immunogenicity of an infant dose of HB
vaccine in UniJect taken out of the cold chain for periods of up to one month. This paper describes the results of this study.

2. Methods

2.1. Study sites and personnel

The study was conducted from January to September, 1996 in sites participating in the Indonesian Ministry of Health’s Healthy Start for Child Survival Project on the island of Bali. Approximately 50 rural villages in Tabanan district were included in the study. Trained village midwives in this area routinely vaccinate newborn infants with HB vaccine during home visits. During the study, these midwives used UniJect or standard disposable syringes with multidose vials for at-birth HB immunisation. All at-birth immunisations were given in the homes of newborn infants. The study was funded by the Australian Agency for International Development (AusAID) and managed by the Indonesian Ministry of Health, the Macfarlane Burnet Centre for Medical Research (MBC), and the Program for Appropriate Technology in Health (PATH). Ethical approval for the study was given by the Indonesian Ministry of Health.

2.2. Study procedures

Study participants were healthy infants scheduled to receive their first HB immunisation within the first week of life. Signed consent was obtained from guardians of all participants. Each infant was assigned to one of the three study groups, on a geographic basis. Eight sub-district health centres outside the major town (Tabanan) were selected on the basis that more women were likely to give birth at home than in the town. Between five and eight villages served by participating health centres were randomly allocated to one of the study groups. Each participating health centre included villages in each of the three study groups.

- Group 1: Birth dose with HB-filled UniJect stored out of the cold chain for up to one month.
- Group 2: Birth dose with HB-filled UniJect stored within the cold chain.
- Group 3: Control group — birth dose with standard disposable syringe and 10-dose vial of HB vaccine stored in the cold chain (2–8°C).

Maternal anti-HBs positivity rates (an indicator of prior HB infection and subsequent immunity) in the three groups were comparable — Group 1 (16/98, 16.3%), Group 2 (16/89, 18.0%) and Group 3 11/59, 18.6%).

The sample size was calculated assuming that the expected proportion of infants who achieve protective levels of antibody following a primary course of HB vaccine (seroprotection — defined as levels of anti-HBs equal to or greater than 10 mIU/ml at 4 weeks post-third dose), is approximately 90%. With 95% level of confidence and 80% power, equal groups of 60 subjects would allow the detection of a 25% change in the rate of seroprotection, equivalent to a relative risk of 0.75. The same sample size will allow comparison of geometric mean titres (GMT) between groups. Assuming a standard deviation of GMT of 2.5, the study would be able to detect a minimum difference of GMT of 1.25.

All three groups received the second dose of HB vaccine at approximately 9 weeks (range = 6–15 weeks, S.D. = 1.3) and the third dose at approximately 18 weeks (range = 10–27 weeks, S.D. = 1.7), according to standard Indonesian immunisation procedures at monthly integrated health posts using standard sterilisable needles and plastic syringes, and 10-dose vaccine vials. This was done in order to model the most feasible vaccine delivery options. The benefits of UniJect relate primarily to outreach delivery of the first dose of HB vaccine. Its use for subsequent doses was not a practical option or under consideration in Indonesia, where clinic attendance rates for second and third HB vaccine doses are high. We wanted to evaluate the ways in which Uniject might actually be used for infant immunisation in Indonesia i.e., for the birth dose, with subsequent doses given in maternal and child health clinics using multi-dose vaccine vials and standard needles and syringes. The vaccine used for all groups was plasma derived and produced by the Korean Green Cross Corporation. A single dose consisted of 5 μg of HBsAg protein contained in 0.5 ml.

Four to six weeks after the final HB vaccine dose, a blood collection team returned to each local health centre to collect a 3 ml blood sample by venipuncture from each infant participant. At the same time, a 5 ml blood sample was collected from the infant’s mother to establish her HB serostatus, including for HBe antigen. Serum samples were separated and frozen on the day of collection and stored until analysis. Samples were tested for HB surface antigen, surface antibody, and core antibody by radioimmunoassay (AusriaII, Ausab, and Corab, respectively, Abbott Laboratories, Illinois, USA). Testing was performed at the Laboratorium Hepatika, Lombok, Indonesia with technical assistance from MBC and the Victorian Infectious Diseases Reference Laboratory in Melbourne, Australia. Data analysis and standard statistical measures were calculated using EpiInfo 6.04 software (EpiInfo, Version 6 — Centres for Disease
2.3. Injection equipment and vaccines

UniJect is a plastic disposable injection device, pre-filled with a single dose of medication (Fig. 1). The medication is enclosed in a sealed blister, and a permanent needle is attached. UniJect is designed to prevent reuse. The UniJect devices were pre-filled to deliver 0.5 ml of HB vaccine and manufactured with 23-gauge, 20 mm needles. UniJect is activated by pushing the needle cap toward the body of the device, opening the fluid path between the needle and the blister. The cap is then removed, the needle inserted into the subject, and the dose is delivered by squeezing the blister until it collapses. UniJects were stored in a specially designed, sturdy carrier. This is fitted with a cardboard disposal box for used UniJects, which was incinerated and replaced monthly.

The control group received at-birth HB vaccine with a 3 ml disposable syringe, and detachable 23 gauge, 25 mm needle. All study participants received their second and third doses of HB vaccine with standard 3 ml sterilisable plastic syringes fitted with detachable 23-gauge, 25 mm needles.

Standard 10-dose vials were used for the control group at birth and for the second and third doses for all participants. Bulk HB vaccine from the Korean Green Cross Corporation was filled into UniJect devices by Perum Bio Farma (Bandung, Indonesia). The vaccine was subject to standard release testing procedures, after filling into UniJect devices.

2.4. Out-of-the-cold-chain storage of UniJect

In Group 1 villages, midwives stored vaccine-filled UniJects under ambient conditions in their homes for up to one month. The devices were kept under normal cold chain conditions as they were distributed from Bio Farma to national, provincial, and district storage facilities, and finally to local health centres. Once a month, the midwives visited the nearest health centre and picked up a supply of vaccine in UniJect devices. Training emphasised the importance of keeping the carrier containing the vaccines away from heat or direct sunlight. To determine whether vaccine had been exposed to excessively high temperatures, each outreach carrier was fitted with a threshold heat indicator that changes colour upon exposure to 49°C or greater temperatures. Midwives and health centre coordinators were advised to monitor the heat indicators and discontinue vaccination with any devices associated with a heat indicator that had changed colour.

3. Results

The proportion of enrolled children from whom a blood sample was obtained in each of the three study groups was similar — for group 1 98/103 (95%), group 2 89/98 (91%) and group 3 59/66 (89%) — a total of 246 out of 267 initially enrolled.

Table 1
Seroconversion by study group

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of infants</th>
<th>Anti HBs ≥ 1 mIU/ml</th>
<th>Anti HBs ≥ 10 mIU/ml</th>
<th>95% CI (Anti HBs ≥ 10 mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UniJect, non-cold chain</td>
<td>93</td>
<td>91 (97.8%)</td>
<td>82 (88.2%)</td>
<td>79.8–97.3</td>
</tr>
<tr>
<td>UniJect, cold chain</td>
<td>83</td>
<td>79 (95.2%)</td>
<td>77 (92.8%)</td>
<td>84.9–97.3</td>
</tr>
<tr>
<td>Control: syringe, cold chain</td>
<td>57</td>
<td>56 (98.2%)</td>
<td>54 (94.7%)</td>
<td>85.4–98.9</td>
</tr>
<tr>
<td>Total</td>
<td>233</td>
<td>226 (97.0%)</td>
<td>213 (91.4%)</td>
<td>87.1–94.7</td>
</tr>
<tr>
<td>p = 0.48</td>
<td></td>
<td>p = 0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Uniject</td>
<td>176</td>
<td>170 (96.6%)</td>
<td>159 (90.3%)</td>
<td>85.0–94.3</td>
</tr>
<tr>
<td>Control</td>
<td>57</td>
<td>56 (98.2%)</td>
<td>54 (94.7%)</td>
<td>85.4–98.9</td>
</tr>
<tr>
<td>p = 0.85</td>
<td></td>
<td>p = 0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cold chain</td>
<td>140</td>
<td>135 (96.4%)</td>
<td>131 (93.6%)</td>
<td>88.1–97.0</td>
</tr>
<tr>
<td>Non-cold chain</td>
<td>93</td>
<td>91 (97.8%)</td>
<td>82 (88.2%)</td>
<td>79.8–93.9</td>
</tr>
<tr>
<td>p = 0.82</td>
<td></td>
<td>p = 0.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Anti HBs level above 1 mIU/ml, the manufacturer’s specified lower limit of detection.
Vaccine outreach beyond the cold chain could substantially improve vaccination coverage and timeliness for more than 50% of the world’s babies who are delivered at home by midwives or traditional birth attendants, and who do not have access to vaccines in the cold chain when deliveries take place. Perinatal transmission of HB occurs mainly in poor countries where delivery commonly takes place outside health care facilities with the capacity to store vaccines in a reliable cold chain.

Administration of the first dose of HB vaccine soon after birth is particularly important in areas such as Indonesia and many other parts of East and South East Asia, where a substantial proportion of chronic HB carriage results from mother to infant transmission, usually at the time of birth. We have shown in previous studies that a 3 dose course of HB vaccine commencing with a first dose given at home within 7 days of birth in Indonesia, reduces carrier rates in children by more than 50% compared with a 3 dose course, in which, the first dose is delivered more than 7 days after birth (1.4 and 3.0%, respectively) [8]. In highly endemic areas, administration of the first dose as soon as possible after birth is, thus, more important for HB vaccine than for any other vaccine. This is because of the high rate of chronic infection — around 90% — which follows perinatal infection, compared with a chronic infection rate of less than 10% following HB infection in late childhood, adolescence or adulthood. HB vaccine alone (without HB immune globulin) commencing within 24–48 h of birth, is around 90% effective in preventing perinatal infection [9].

The Indonesian government has now adopted national policies of home visits by health workers to all newborn, and first dose HB vaccination soon after birth. However, at-home immunisation with standard syringes and multidose vials could result in high vaccine wastage rates and/or poor compliance with safe injection practices. The availability of thermostable HB vaccine in a safe single dose presentation that can be kept in the homes of local community health workers and given at or shortly after delivery significantly increases global HB immunisation capabilities, enabling more practical outreach opportunities, immunisation in remote areas, and reducing cost of transport/distribution, dependence on ice and insulated vaccine carriers [5]. In addition, compared with the usual multidose vials, vaccine wastage can be dramatically reduced.

Home visits by health care workers to mothers and their newborn have other benefits apart from timely administration of HB vaccine. Such early postnatal contact between health care workers, mothers and infants can enable delivery of other vaccines (such as tetanus toxoid for mothers), micronutrient supplemen-

### 3.1. Seroconversion

Two hundred and thirty-three children met the requirements for inclusion in the analysis of seroconversion (sufficient serum for testing and at least 28 days between third dose of HB vaccine and blood sampling). Of these 233 children, 226 (97%) had detectable HB surface antibody (anti HBs > 1 mIU/ml), and 213 (91.4%) had levels traditionally defined as protective (anti HBs ≥ 10 mIU/ml). No significant difference in seroconversion rate between the three study groups was found using either cut-off, as shown in Table 1.

### 3.2. Geometric mean titre

GMT of anti HBs expressed in milli International Units per ml (mIU/ml) was calculated for 217 children for whom sufficient serum was available for testing, the blood sample was collected at least 28 days after the third dose of HB vaccine, HB core antibody was negative, and whose mothers were HBsAg negative. No significant differences in GMT were detected between any of the comparison groups, as shown in Table 2.

### 4. Discussion

WHO and other authorities currently recommend that HB vaccine be stored at 2–8°C. However, the ability to deliver vaccines beyond the cold chain could significantly increase vaccine coverage, especially for those vaccines for which immunisation at or near birth is beneficial. Provision of vaccine in multi-dose vials and under refrigerated conditions is impractical where cold storage is not available, and where only single doses of relatively expensive vaccines will be used.

#### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>GMT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniject, non-cold chain</td>
<td>87</td>
<td>288</td>
<td>179–464</td>
</tr>
<tr>
<td>Uniject, cold chain</td>
<td>75</td>
<td>312</td>
<td>215–450</td>
</tr>
<tr>
<td>Control: syringe, cold chain</td>
<td>55</td>
<td>376</td>
<td>230–614</td>
</tr>
<tr>
<td>All Uniject</td>
<td>162</td>
<td>299</td>
<td>219–407</td>
</tr>
<tr>
<td>Control</td>
<td>55</td>
<td>376</td>
<td>230–614</td>
</tr>
<tr>
<td>All cold chain</td>
<td>130</td>
<td>338</td>
<td>250–455</td>
</tr>
<tr>
<td>Non-cold chain</td>
<td>87</td>
<td>288</td>
<td>179–464</td>
</tr>
</tbody>
</table>

*p = 0.73

*p = 0.53

*p = 0.56

None of the heat indicators suggested exposure to a temperature of 49°C or higher.
tation (iron/folate, vitamin A and iodine) health education (in such matters as umbilical cord care and promotion of early and exclusive breast-feeding), and identification and special care of low birthweight infants [7].

A pre-filled, single-use injection device would still require cold storage at national and regional distribution centres, thus requiring either increased storage space at these levels or more frequent distribution of smaller vaccine quantities. This relatively minor disadvantage of the single dose presentation needs to be weighed against the advantages of more effective and safe prevention of the HB chronic carrier state. A study using a World Bank model [10] to evaluate the cost of interventions per disability adjusted life year concluded that providing a HB vaccine birth dose with UniJect is roughly 20% more cost effective than immunisation with a standard syringe at 6 weeks of age [11].

While the heat stability of HB vaccine has been established through invitro laboratory testing and in a single field study in China, this study confirmed heat stability under actual service delivery conditions in which a new safe injection device was utilised. Our study demonstrates a lack of any statistically significant difference in immunogenicity between standard cold chain storage for all three HB vaccine doses and storage outside the cold chain at ambient conditions for up to one month in a tropical setting for the first HB vaccine dose. This finding has important implications for immunisation programs. Delivery of HB vaccine outside the cold chain, especially in conjunction with a single-use injection device, could extend immunisation coverage, timeliness, effectiveness and safety.

Acknowledgements

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References