

# Improving birth dose coverage of hepatitis B vaccine

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**Abstract** Administration of a birth dose of hepatitis B vaccine (HepB vaccine) to neonates is recommended to prevent mother-to-infant transmission and chronic infection with the hepatitis B virus (HBV). Although manufacturers recommend HepB vaccine distribution and storage at 2–8 °C, recognition of the heat stability of hepatitis B surface antigen stimulated research into its use after storage at, or exposure to, ambient or high temperatures. Storage of HepB vaccine at ambient temperatures would enable birth dosing for neonates delivered at home in remote areas or at health posts lacking refrigeration. This article reviews the current evidence on the thermostability of HepB vaccine when stored outside the cold chain (OCC). The reports reviewed show that the vaccines studied were safe and effective whether stored cold or OCC. Field and laboratory data also verifies the retained potency of the vaccine after exposure to heat. The attachment of a highly stable variety of a vaccine vial monitor (measuring cumulative exposure to heat) on many HepB vaccines strongly supports policies allowing their storage OCC, when this will benefit birth dose coverage. We recommend that this strategy be introduced to improve birth dose coverage, especially in rural and remote areas. Concurrent monitoring and evaluation should be undertaken to affirm the safe implementation of this strategy, and assess its cost, feasibility and effect on reducing HBV infection rates. Meanwhile, release of manufacturer data verifying the potency of currently available HepB vaccines after exposure to heat will increase confidence in the use of vaccine vial monitors as a managerial tool during storage of HepB vaccine OCC.

**Keywords** Hepatitis B vaccines/supply and distribution; Drug storage/methods; Drug stability (*source: MeSH, NLM*).

**Mots clés** Vaccin antihépatite B/ressources et distribution; Conservation médicament/méthodes; Stabilité médicament (*source: MeSH, INSERM*).

**Palabras clave** Vacunas contra hepatitis B/provisión y distribución; Almacenaje de medicamentos/métodos; Estabilidad de medicamentos (*fuentes: DeCS, BIREME*).

## Arabic

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Voir page 70 le résumé en français. En la página 70 figura un resumen en español.

## Introduction

The earliest effective formulation of hepatitis B (HepB) vaccine was developed by Krugman et al. in the late 1960s.<sup>1,2</sup> Although the first commercial formulations of plasma-derived HepB vaccine were produced by largely chemical methods,<sup>3</sup> an alternative process developed by Prince et al. used a flash-heat inactivation method, which was far cheaper and yielded a vaccine of greater potency.<sup>2</sup>

The immunogenic component of all HepB vaccines is the 22 nm hepatitis B surface antigen (HBsAg) protein, which has extraordinary conformational integrity due to highly stable disulfide bridges between its cysteine residues. This fact, and the use of heat in the production process used by Prince, suggested that these vaccines might be heat stable,

enabling their storage outside the chain of refrigeration (outside the cold chain; OCC) normally required for vaccines used in the Expanded Programme on Immunization (EPI). This programme provides life-saving vaccination against at least six diseases for infants and young children all over the world.

Storage of HepB vaccine OCC has long been advocated to improve availability of a birth dose for infants born in remote areas where refrigeration is not available. Birth dosing can prevent most perinatal infections with hepatitis B virus (HBV), but is currently unavailable to many infants in developing nations because of the difficulty of keeping vials at the manufacturers' recommended temperature of 2–8 °C.<sup>4</sup>

Indonesia allows OCC storage of HepB vaccine for the birth dose — but

other nations seem reluctant to follow suit — and WHO does not yet unequivocally support such a strategy. This is presumably because of limited reported experience with vaccines used in this way, and the reluctance of manufacturers to support use of their products outside the conditions under which they were licensed. WHO guidelines on the introduction of HepB vaccine recommend storage of 2–8 °C<sup>5</sup> but according to another WHO publication, some vaccines, especially hepatitis B, can be taken OCC if a vaccine vial monitor (VVM) is properly used to monitor heat exposure.<sup>6</sup> VVMs are small labels with a heat-sensitive central square that changes gradually from white to black upon exposure to heat or light.<sup>7</sup> They are placed on vaccine vials by manufacturers before shipping. Most HepB vaccines procured

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by the United Nations Children's Fund (UNICEF) are now shipped with a VVM on each vial.

To assist decision-makers considering use of OCC storage in nations where this will improve access to the birth dose of HepB vaccine, we present the available data on the immunogenicity and potency of HepB vaccines exposed to heat, and discuss the associated benefits, risks and possible costs of this strategy and the alternatives.

## Literature search strategy

Research published since 1980 on the administration of heat-treated or heat-exposed HepB vaccine was sought using Medline, Embase, and a second Medline search through the *New England Journal of Medicine*. Finally, a search of the Cochrane Collaboration's systematic reviews was undertaken. The keywords were "hepatitis B", "HBsAg", "hepatitis B vaccine", "heat stability", "heat", "heat tolerance", "thermostability" and "heat exposure" in various combinations. For summaries of unpublished literature, we also referred to published reviews of vaccine thermostability<sup>8</sup> and HepB vaccines in clinical practice,<sup>9</sup> and overviews of the introduction of immunization against HBV.<sup>5</sup> We also gained information through email contact with experts in the field, including Dr Craig Shapiro and Dr Mark Kane (formerly at the US Centers for Disease Control), Dr David West (formerly of the Merck Laboratories in Virginia, USA), Dr Joseph Torresi (University of Melbourne, Australia) and Dr Alfred Prince (New York Blood Center, USA). For information on VVMs, we referred to published documents from WHO and the sole manufacturer, TEMPTIME Corporation (formerly Lifelines, Morris Plains, New Jersey, USA), all of which are in the public domain.

## Review of the literature

Five studies (four published, one in press) were identified; three were field-based and two conducted in a controlled setting. In the field studies, only the first dose of HepB vaccine was kept OCC at ambient temperatures, whereas in the controlled studies all three doses were exposed to defined temperatures. The three field studies used plasma-derived vaccines, whilst the controlled studies used a recombinant-DNA vaccine. The

five studies, and the available manufacturer data, are summarized below and in Table 1 and Table 2.

### Study one

In 1991, the first field study of HepB vaccine stored OCC was conducted in Long-An County, Guangxi, southern China.<sup>10, 11</sup> The study used a 10 µg plasma-derived vaccine produced at the Beijing Institute of Serum and Vaccine and reported by the manufacturer to be stable for up to 3 months at 35 °C. In the study location, over 80% of births occurred at home, attended by village midwives or doctors. In one group of infants ( $n = 358$ ), the first dose of vaccine was stored for up to 3 months at ambient temperature (15–30 °C) and administered by the birth attendant. In the other group ( $n = 232$ ), the first dose had been refrigerated and was administered by the village doctor within 72 h of delivery. The second and third doses were given routinely at ages 1–2 and 5–8 months.

Infants were tested for antibody to HBsAg (anti-HBs) and HBsAg 12 months after the third dose. The prevalence of any anti-HBs was 81.6% in the OCC group and 81.9% in the refrigeration group. Maternal HBsAg rates were 15.4% and 20.7%, respectively. There was no difference between HBsAg rates amongst vaccinated infants in the OCC and refrigeration groups (1.1% vs 2.2%). All HBsAg-positive (HBsAg+) infants were delivered by HBsAg+ mothers. The estimated protective efficacy of vaccination (the percent reduction in HBsAg attributable to vaccination amongst infants exposed to HBV) was similar at 84.5% and 77.8%, respectively in the two groups. This is the only study of HepB vaccine OCC to include this indicator.

Despite certain limitations (relatively low vaccine immunogenicity and a lack of temperature data), this study concluded that the HepB vaccine stored OCC in semi-tropical conditions for up to 3 months can remain both immunogenic and protective.

### Study two

A 1996 study in Bali, Indonesia, evaluated the immunogenicity of three doses of a 5 µg, Korean, plasma-derived HepB vaccine in three groups of infants.<sup>12</sup> In the first group ( $n = 66$ ), all doses were stored cold in 10-dose vials, and administered at birth, 9 weeks and 18 weeks.

In group two ( $n = 98$ ), the first dose was packaged in a pre-filled, single-dose injection device, again stored cold. In group three ( $n = 103$ ), these devices for the birth dose were stored at ambient temperature (averaging 27 °C in a similar study<sup>13</sup> for periods of up to a month. For groups two and three, the second and third doses were stored and administered as for group one. Vaccines stored OCC were monitored to ensure they did not exceed temperatures of  $\geq 49$  °C.

Serum for follow-up analysis was available for 217 infants, and was taken 4–6 weeks after the third dose. There was no difference in the prevalence of a protective level of anti-HBs ( $\geq 10$  mIU/ml) between the groups (Table 1), nor between the geometric mean titre (GMT) of antibody in the OCC (288 mIU/ml) and combined cold chain (338 mIU/ml) groups ( $P = 0.56$ ). In addition, the vaccine used lost only 1% of its potency (method of testing not stated) after 1 month OCC, in comparison to the same formulation of vaccine stored cold.<sup>13</sup>

Rates of maternal anti-HBs were similar amongst the three groups (range 16.3–18.6%), but the titre of anti-HBs amongst the mothers was not reported. Lower levels of anti-HBs titres amongst mothers of group three infants might explain the slightly lower rate of protective anti-HBs (Table 1) and GMT in this group.

This study again suggested that the first dose of HepB vaccine can be stored OCC at tropical temperatures without losing its potency, or the potential of three doses to induce protective levels of antibody.

### Study three

In the most recent field study, our own work<sup>14</sup> in Viet Nam compared the immunogenicity of three doses of a local plasma-derived vaccine in infants who received three doses stored cold ( $n = 358$ ) or for whom the first dose was stored OCC for up to 1 month ( $n = 748$ ). Serum was collected at age 9–18 months, and the vaccine was protective in 80.3% of all infants in the OCC group. There were no differences in the prevalence of a protective level of antibody or GMT between the groups of infants (Table 1).

### Study four

A controlled study<sup>15</sup> compared the anti-HBs response of 58 healthy, HBV-seronegative volunteers (average age

Table 1. Immunogenicity and protective efficacy of hepatitis B vaccine stored outside the cold chain (OCC)

Report and type of vaccine used	Group	How doses stored	No. followed up	Anti-HBs $\geq 10$ mIU/ml (%) <sup>a</sup>	GMT	Protective efficacy (%)
<b>Study 1</b> Anonymous (1991) <sup>10</sup> 10 µg plasma-derived	1	At 4–8 °C	232	81.9 <sup>a</sup>	NA	77.8
	2	First dose OCC (15–30 °C) for up to 3 months, doses two and three at 4–8 °C	358	81.6 <sup>a</sup>	NA	84.5
<b>Study 2</b> Otto et al. (1999) <sup>12</sup> 5 µg plasma-derived	1	At 2–8 °C, in 10 dose vials, for all doses	55	94.7	376	NA
	2	At 2–8 °C, first dose in pre-filled, single-dose injection devices, doses two and three in 10-dose vials	75	92.8	312	NA
	3	First dose in pre-filled, single-dose injection devices, OCC for up to 1 month; doses two and three in 10-dose vials at 2–8 °C	87	88.2	288	NA
<b>Study 3</b> Hipgrave et al. <sup>14</sup> 2.5 µg plasma-derived	1	At 2–8 °C, in two dose vials, for all doses	358	77.9	135	NA
	2	First dose OCC (20–35 °C) for up to 1 month, doses two and three at 2–8 °C	748	83.0 <sup>b</sup>	113	NA
<b>Study 4</b> Just & Berger (1988) <sup>15</sup> 20 µg recombinant	1	At 4 °C	31	100	2054	NA
	2	All 3 doses exposed to 37 °C for one week	27	97	3392	NA
<b>Study 5</b> Van Damme et al. (1992) <sup>16</sup> 20 µg recombinant	1	At 4 °C	33	100	10,359	NA
	2	All 3 doses exposed to 45 °C for one week	39	95	6,813	NA
	3	All 3 doses exposed to 37 °C for one month	37	100	5,937	NA

GMT = geometric mean titre, NA = not available.

<sup>a</sup> As Study 1 did not measure titre, percentages refer to presence of any anti-HBs.

<sup>b</sup> This figure is an average of those protected after receipt of a birth dose stored OCC for 1–14 days (83.6%) and 15–31 days (82.7%).

22.5 years, but no other details given). Twenty-seven participants received three 20 µg doses of the yeast-derived Engerix-B vaccine (Smith-Kline Biologicals, Belgium) exposed to a temperature of 37 °C for 1 week, at 0, 1 and 6 months; 31 received three doses stored at 4 °C according to the same schedule. No serious adverse reactions or between-group differences in side-effects were reported. There was no significant difference in the rates of protection (above 95% for all groups) and GMTs between the groups, and results were similar to other studies of this vaccine (Table 1).

### Study five

The second controlled study<sup>16</sup> compared the antibody responses of three groups of healthy adult recipients of HepB vaccine (aged 18–30 years, matched for average age and sex). The first group received three 20 µg doses of Engerix-B stored at 4 °C, at 0, 1 and 6 months. The second group received the same vaccine

exposed to 45 °C for 1 week for each dose, and the third group received the same vaccine stored at 37 °C for 1 month for each dose, according to the same schedule. No other details regarding the recipients were provided; in particular, as for study four, differences in obesity, a known influence on response to HepB vaccine,<sup>17</sup> were not reported. There were no differences in the very high rates of protection, GMT or side-effect profiles between groups, and no serious adverse reactions. GMTs were again similar to other studies of this vaccine.

### Manufacturers' data

According to data from vaccine manufacturers summarized in a 1998 WHO paper<sup>8</sup> the upper limit of HepB vaccine's shelf life if stored at 2–8 °C has not been determined, but seems to be many years. The manufacturer of Engerix-B considers it to be stable for 30 days at 20–25 °C, 1 week at 37 °C, and 3 days at 45 °C, with corresponding calculated

half-lives of 9 months, 31 and 13 days. The product information accompanying Engerix-B also quotes study four.<sup>15</sup>

Table 2 shows animal test data from other manufacturers of HepB vaccine.<sup>8</sup> The only outlier (which cannot be checked as the source is not in the public domain) has a vaccine half-life of only 7 days at 36–40 °C. It is important to note that, except where stated, the test parameters in Table 2 do not refer to maintenance of 100% potency, unlike the studies reviewed above where the potency (in terms of human immunogenicity) of heat exposed vaccine was maintained in each case.

### Vaccine vial monitors

Most manufacturers supplying HepB vaccine through UNICEF procurement channels now place VVMs on monovalent formulations. These were not available when the studies reviewed above were undertaken.

Table 2. Stability of several types of hepatitis B vaccine according to immunogenicity tests on animals

Vaccine type	Parameter used to assess vaccine	Storage temperature (°C)			
		2–8	20–26	36–40	45
Plasma-derived	Longest storage without significant loss of potency	24 months	12 months	3 months	ND
Plasma-derived	Remaining potency after specified time	100% at 24 months	70% at 24 months	70% at 24 months	ND
Plasma-derived	Longest storage with relative potency upper confidence interval >1 <sup>a</sup>	44 months	ND	ND	ND
Plasma-derived	Half-life <sup>b</sup>	>3 years	4 months	7 days	ND
Recombinant	Longest storage with relative potency upper confidence interval >1	53 months	12 months	7 months	1 months
	Half-life	ND	9 months	1 months	3 days

Adapted from Galazka et al.<sup>8</sup> ND = no data available.

<sup>a</sup> Refers to potency in comparison to vaccine stored for shorter periods of time or at 2–8 °C for the same period of time.

<sup>b</sup> Half-life: time at which 50% of original vaccine potency lost.

Four VVMs are produced with different temperature stability characteristics. The variety applied to HepB vaccines is the VVM30. At 37 °C (the WHO standard for assessing VVM stability) the behaviour of the VVM30 is normally distributed around a median of 26.25 days, with a standard deviation of 1.875 days; that is 5% will reach the end-point by 22.5 days at 37 °C, 95% before 30 days and 5% after day 30. This range was specifically calibrated so that VVM30s reach their end-point when cumulative temperature exposure does not exceed the range within which, according to existing data, HepB vaccine potency seems to be maintained. The end-point is reached earlier at higher ambient temperatures.<sup>18</sup>

## Discussion

To change practices relating to storage of HepB vaccines in order to improve rates of birth dosing requires not only scientific justification, but also an appraisal of the benefits likely to arise, the monitoring and evaluation required and the associated risks, costs and difficulties. It should also be considered alongside other options for achieving the same end.

### Overview of the data

The data presented support relaxation of the WHO policy on storing HepB vaccine at 2–8 °C,<sup>5</sup> and are consistent with the known heat stability of the HBsAg. There is no difference in the frequency or strength of antibody response after immunization with HepB vaccine stored

cold, OCC for dose one, or with all three doses exposed to fixed high temperatures. Measured vaccine potency is also maintained after prolonged exposure to high temperatures.

### VVMs, and the need for manufacturer data

Many nations have introduced HepB vaccines with VVMs. At present, only Indonesia is implementing an OCC strategy to improve rates of birth dosing, but pilot projects are in progress in Viet Nam and China.

The reluctance of countries to allow OCC storage of HepB vaccine might be because manufacturers do not currently provide stability data on their products. In addition, unlike the data for oral polio vaccine,<sup>19</sup> we could find no published data linking VVM status and HepB vaccine potency. The fact that manufacturers apply a VVM30 to their vaccines suggests that they have this data but are reluctant to affirm that VVM status is a proxy for vaccine potency, perhaps because vaccine licensing conditions stipulate refrigeration. To reduce confusion and instil confidence in use of VVMs as recommended by WHO,<sup>6</sup> the product literature accompanying each HepB vaccine should at least include a summary of its retained potency at various temperatures.

### Proposed changes in policy and practice

WHO publications should be consistent in their recommendations on how HepB vaccines should be stored. Countries with

low birth-dose coverage should attempt to improve it by allowing storage of vials of HepB vaccine OCC, where this can be appropriately monitored.

OCC storage of HepB vaccine must be appropriately prepared and supervised by trained personnel, and deferred in nations or areas unable to oversee its safe and effective implementation. Health staff and logisticians should be oriented as to the implementation, benefits, and limitations of the strategy. Vials should be stored in a secure, dry area, and out of direct sunlight. Arrangements for destruction of vials with a VVM indicating excessive heat exposure should be in place.

Ideally, a coordinated programme of evaluation should accompany introduction of this strategy, with indicators relating to both the process of its implementation, and outcomes, such as rates of birth dosing, coverage with three doses of vaccine and decreasing HBsAg seroprevalence, as well as the incidence of adverse events. When evaluating declines in HBsAg seroprevalence, it would be interesting to group infants by the exact day of life on which they receive the birth dose, variously defined as within 24 h<sup>5</sup> or 7 days<sup>20</sup> of delivery, to provide more data on the relative importance of its timing on the prevention of perinatal infection, as there is little published data on this.

### The potential public health benefit

The potential effect of increased HepB vaccine birth dosing will be greatest in nations in the WHO Western Pacific Region, many of which have only added

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this vaccine to their EPI since 2000. This region, which includes China, the lower Mekong and Pacific Island nations, has 28% of the world's population but half the world's deaths caused by HBV. The birth cohort is 26 million and at least 30% of infants are born at home or in health facilities with limited access to refrigerated vaccines. Assuming a low-range overall risk of perinatal HBV infection of 3%<sup>4</sup> — 70–90% of which become chronic<sup>21–23</sup> and 25% of which result in subsequent HBV-related death<sup>23</sup> — up to 52 650 such deaths per year could be avoided in this region alone, if a birth dose of HepB vaccine were available for infants born in areas lacking a cold chain. Moreover, increasing the rate of birth dosing should reduce the risk of drop out from the first to the third doses of the vaccine, further reducing vulnerability to HBV infection.

### Other options for improving rates of birth dosing with HepB vaccine

An increase in the proportion of women delivering in facilities with refrigeration or in the number of facilities with refrigerators might also increase birth dosing with vaccine stored cold. Both are longer-term possibilities complementary to the OCC strategy, and should be encouraged alongside introduction of the WHO multidose vial policy,<sup>24</sup> which has the potential to make all EPI vaccines available on a daily basis. Motivating mothers to deliver in health facilities with refrigeration, however, requires costly and systemic improvements in access to such facilities and the management and quality of services offered, along with extensive advocacy.<sup>25</sup> Expanding the cold chain involves start-up and recurrent costs in hardware and training that, depending on wastage rates, almost certainly outweigh those associated with taking even single-dose vials of HepB vaccine OCC for birth dosing where needed.<sup>20</sup> In addition, this option needs very close supervision, as with inexperienced hands at grass roots level there is the risk of freezing this vaccine,<sup>26</sup> rendering ineffective the potentially critical post-exposure birth dose of HepB vaccine amongst infants of carrier mothers.

Other alternatives include allowing community-level refrigeration in local shops — although there is the risk of

vaccine freezing — or collection of a refrigerated vial of vaccine by health staff after each birth is reported. Our field studies suggest, however, that not only is this system unreliable (requiring timely notification of the birth, availability of transport and motivation of all involved), but also that the costs associated with collecting and transporting the vaccine are usually borne by the infant's family, discouraging uptake. We and others (Dr M Creati, Public Health Association of Australia conference, Cairns, August 2004) have also identified reluctance of EPI staff to release vials of HepB vaccine to midwives in such circumstances.

### Risks, costs and difficulties associated with the OCC strategy

There is a risk of confusion in allowing OCC storage for one dose of one vaccine but maintaining the cold chain for all others. This risk was found to be small in the one trial in which it was assessed (albeit for HepB vaccine in pre-filled, single-dose injection devices;<sup>15</sup>) and can be kept to a minimum with adequate policy support, appropriate staff training and public advocacy.

There is also the risk of vaccination with heat-affected vaccine, but this will decrease as familiarity with VVMs increases. A related risk is that OCC storage might result in high rates of costly vaccine wastage if VVMs frequently reach the point at which discarding the vial is indicated. This might be problematic in very hot nations as the VVM30 end-point is reached earlier at high temperatures.<sup>18</sup> It might also be important if countries are using multidose vials of HepB vaccine or expensive varieties such as single-doses in pre-filled injection devices. HepB vaccine in these devices comes labelled with a VVM30,<sup>27</sup> is simple to use,<sup>28</sup> and its different appearance seems to reduce the risk that EPI staff will take other vaccines OCC in error.<sup>13</sup> As HepB vaccine is costly, wastage of doses in pre-filled, single-dose injection devices, multidose vials or indeed any formulation, and the effect of this on EPI budgets, should also be included in future evaluations of the vaccine stored OCC. Such an evaluation in Indonesia recently concluded that even with HepB vaccine in pre-filled, single-dose injection devices, the OCC strategy is economically justified.<sup>20</sup>

Costs will be incurred in the introduction of the OCC strategy, but

experience suggests that they are small. As in Indonesia,<sup>13, 20</sup> our pilot introduction of the OCC strategy in Viet Nam and China required no more than a 4 h orientation of health centre staff that was added to their regular monthly meeting, and a level of additional monitoring that was no greater than should be routine. Costs were offset by various indirect savings and direct benefits<sup>13, 20</sup> — an improved rate of formal health service contact for infants delivered at home provides an opportunity for many maternal and neonatal health services. Thus introduction of the policy has been a cost-effective way to enhance oversight of broader health practices, appreciated by all at grass roots level.

Finally, experiences in Indonesia suggest that difficulties in introducing the OCC strategy relate more to overcoming health worker reluctance arising from prior teaching, unfamiliarity with VVMs and EPI staff refusal to cede responsibility for vaccination to midwives, than to any practical or financial difficulty. These difficulties again highlight the need for a clear and consistent policy at both the local and international level at the time of the strategy's introduction.

### Conclusion

All neonates should receive a birth dose of the HepB vaccine within the first few hours of life, regardless of the availability of refrigeration, in situations in which there is: an assured supply of vaccine and replacement of spoiled or expired vials; monitoring of adverse events following immunization; and supervision of health staff. Many countries with high rates of chronic HBV infection currently receive HepB vaccine free from the Vaccine Fund. Such nations should allow OCC storage of HepB vaccine for birth dosing wherever possible, to gain experience in meeting all possible challenges and verify for themselves the benefits of an OCC strategy, before this support ends. ■

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## Résumé

### Amélioration de la couverture vaccinale contre l'hépatite B des nourrissons

Il est recommandé d'administrer aux nourrissons dès leur naissance une dose de vaccin contre l'hépatite B (vaccin HepB) afin de prévenir une éventuelle transmission de la mère à l'enfant et l'infection chronique par le virus de l'hépatite B (VHB). Bien que les fabricants préconisent de maintenir le vaccin HepB à une température de 2 à 8 °C pendant sa distribution et sa conservation, la mise en évidence de la stabilité thermique des antigènes de surface du virus de l'hépatite B a encouragé les recherches sur les possibilités d'utiliser ce vaccin après un stockage ou une exposition à une température supérieure ou égale à l'ambiante. La possibilité de stocker le vaccin HepB à la température ambiante permettrait son administration à la naissance aux nourrissons à domicile dans le cas des zones reculées ou dans des postes de santé non équipés d'un réfrigérateur. Le présent article examine les éléments actuellement disponibles au sujet de la stabilité thermique de ce vaccin en cas de rupture de la chaîne du froid pendant sa conservation. D'après les rapports examinés, les vaccins étudiés étaient sans risque et efficaces, qu'ils aient été stockés au froid ou en dehors de la chaîne du froid. Les résultats d'études

sur le terrain et en laboratoire confirment également que le HepB conserve son activité vaccinale après une exposition à la chaleur. Les résultats de la fixation sur de nombreuses doses de vaccin HepB de divers dispositifs très stables de contrôle de l'activité (mesurant l'exposition cumulée à la chaleur) viennent fortement étayer les politiques autorisant la conservation de ce vaccin en dehors de la chaîne du froid, lorsque cette disposition favorise une meilleure couverture vaccinale des nouveaux-nés. La mise en place de cette pratique est donc recommandée afin d'étendre la couverture vaccinale des nouveaux-nés, notamment dans les zones rurales et éloignées. Il convient d'entreprendre en parallèle un suivi et une évaluation pour confirmer l'absence de risque de cette disposition et estimer son coût, sa faisabilité et son effet sur la baisse des taux d'infection par le VHB. Entre temps, la publication par les fabricants de données confirmant l'activité des vaccins HepB actuellement disponibles après une exposition à la chaleur pourrait renforcer la confiance dans l'utilisation d'étiquettes de contrôle de l'activité comme outil de gestion pour la conservation de ce vaccin en dehors de la chaîne du froid.

## Resumen

### Mejora de la cobertura con dosis de nacimiento de la vacuna contra la hepatitis B

Se recomienda administrar una dosis de nacimiento de la vacuna contra la hepatitis B (vacuna HepB) a los recién nacidos para evitar la transmisión de la madre al niño del virus de la hepatitis B (VHB) y la infección crónica consiguiente. Aunque los fabricantes recomiendan distribuir y almacenar las vacunas HepB a 2 - 8 °C, el descubrimiento de la termoestabilidad del antígeno de superficie del virus de la hepatitis B llevó a investigar su posible utilización tras su almacenamiento o exposición a temperaturas ambientales o altas. El almacenamiento de la vacuna HepB a temperatura ambiente permitiría administrar la dosis de nacimiento a los recién nacidos en su hogar en las zonas remotas o en puestos de salud carentes de sistemas de refrigeración. En este artículo se analiza la evidencia disponible sobre la termoestabilidad de la vacuna HepB almacenada fuera de la cadena de frío. Los informes examinados revelan que las vacunas estudiadas eran seguras y eficaces tanto si se almacenaban bajo refrigeración como en caso contrario. Los datos obtenidos sobre el terreno y en laboratorio corroboran que la

vacuna conserva su actividad tras la exposición al calor. La inclusión de una modalidad altamente estable de sensor de control de la vacuna (que mide la exposición acumulativa al calor) en muchas vacunas HepB es una poderosa razón adicional en favor de la política de permitir su almacenamiento al margen de la cadena de frío cuando ello redunde en beneficio de la cobertura de la dosis de nacimiento. Recomendamos que se aplique esta estrategia para mejorar dicha cobertura, especialmente en las zonas rurales y remotas. Es necesario emprender actividades simultáneas de vigilancia y evaluación para garantizar una aplicación segura de esa estrategia y evaluar su costo, viabilidad y efecto de reducción de las tasas de infección por el VHB. Mientras tanto, la publicación de los datos de los fabricantes sobre la conservación de la actividad de las vacunas HepB actualmente disponibles tras su exposición al calor aumentará la confianza en los sensores de control como instrumento de gestión durante el almacenamiento de la vacuna HepB al margen de la cadena de frío.

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