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Hepatitis B vaccine stored outside the cold chain setting: a pilot study in rural Lao PDR

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Abstract

Background: Hepatitis B vaccine birth dose (HepB-BD) was introduced in Lao People's Democratic Republic (Lao-PDR) to prevent perinatal hepatitis B virus transmission. HepB-BD, which is labeled for storage between 2 and 8 °C, is not available at all health facilities, because

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Alejandro Ramirez-Gonzalez was involved in the conception/design of the study, protocol development, interpretation of the data, and critical revisions of the article.

Kathleen Wannemuehler was involved in the conception/design of the study, analysis and interpretation of the data, and critical revisions of the article.

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Karen Hennessey was involved in the conception/design of the study, interpretation of the data, and critical revisions of the article.

Minal K. Patel was involved in the conception/design of the study, field implementation, analysis and interpretation of the data, and critical revisions of the article.

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Declaration of interests

Authors have no conflicts of interest.

of some lack of functional cold chain; however, previous studies show that HepB-BD is stable if stored outside the cold chain (OCC). A pilot study was conducted in Lao-PDR to evaluate impact of OCC policy on HepB-BD coverage.

Methods: During the six month pilot, HepB-BD was stored OCC for up to 28 days in two intervention districts and stored in cold chain in two comparison districts. In the intervention districts, healthcare workers were educated about HepB-BD and OCC storage. A post-pilot survey compared HepB-BD coverage among children born during the pilot (aged 2–8 months) and children born 1 year before (aged 14–20 months).

Findings: In the intervention districts, 388 children aged 2–8 months and 371 children aged 14–20 months were enrolled in the survey; in the comparison districts, 190 children aged 2–8 months and 184 children aged 14–20 months were enrolled. Compared with the pre-pilot cohort, a 27% median increase in HepB-BD (interquartile range [IQR] 58%, $p < 0.0001$) occurred in the pilot cohort in the intervention districts, compared with a 0% median change (IQR 25%, $p = 0.03$) in comparison districts. No adverse reactions were reported.

Interpretation: OCC storage improved HepB-BD coverage with no increase in adverse reactions. Findings can guide Lao-PDR on implementation and scale-up options of OCC policy.

Keywords

Hepatitis B virus; Lao People’s Democratic Republic; Hepatitis B vaccine; Hepatitis B vaccine birth dose; Outside the cold chain

1. Introduction

Hepatitis B virus (HBV) infection is a major cause of chronic liver disease and causes an estimated 785,000 deaths annually [1]. In endemic countries, HBV infection is commonly transmitted from mother-to-child at birth or during early childhood [2]. This has implications for disease prevention because risk for developing chronic HBV infection varies inversely with age: approximately 90% of infants infected during the first year of life develop chronic infection, compared with 30% of children infected between ages 1 and 4 years and fewer than 5% of persons infected as adults [3]. Timely administration of hepatitis B vaccine birth dose (HepB-BD), a dose given within 24 h of birth, plus at least 2 additional doses of vaccine prevents perinatal HBV infection in 85% to 90% of infants born to chronically infected mothers [3].

Lao People’s Democratic Republic (Lao-PDR), one of the world’s least developed countries, is considered highly endemic for HBV, with an estimated 8% prevalence of chronic HBV infection [4]. Because of the large disease burden, hepatitis B vaccine (HepB) was introduced in Lao-PDR in 2001 as part of a quadrivalent diphtheria-tetanus-pertussis-hepatitis B vaccine; HepB-BD was introduced in a phased approach from 2004 to 2008. The current vaccination schedule is HepB-BD within 7 days of birth, followed by 3 doses of pentavalent diphtheria-tetanus-pertussis-Haemophilus influenza b-hepatitis B vaccine at 6, 10, 14 weeks of age. HepB-BD coverage has been improving slowly (Fig. 1), but remains one of the lowest in the Western Pacific Region. Reasons for low coverage include: (1) only 37% of deliveries (home or health facility) are attended by a skilled birth attendant (SBA);

(2) access to health care is challenging because of terrain and marginalized populations; and (3) inadequate cold chain capacity in many health facilities makes vaccine storage difficult [5].

One strategy for improving Lao-PDR's HepB-BD coverage is to take advantage of HepB vaccine's heat-tolerance and store the vaccine outside the cold chain (OCC). An OCC strategy allows for *off-label* storage and transport of vaccines outside the traditional 2 °C to 8 °C for limited periods, under monitored and controlled conditions, as appropriate to the stability of the antigen and provided the vaccine vial is labeled with a vaccine vial monitor (VVM). This management is different from storage in a controlled temperature chain (CTC) which refers to *on-label* use of vaccine outside 2 °C to 8 °C [6]. Multiple studies have shown that HepB vaccine retains effectiveness when stored at 37 °C for 1 month [7-13]. Although OCC is currently an off-label use of the vaccine, the World Health Organization (WHO) Regional Office for the Western Pacific endorses use of HepB vaccine OCC if approved by national regulatory authorities [14]. A pilot project was conducted to determine feasibility and impact of implementing an OCC policy for HepB-BD storage in Lao-PDR.

2. Methods

2.1. Human subjects' rights and ethics

We obtained informed consent from caregivers. Study protocol was approved by the Lao-PDR Ministry of Health and the Ethics Review Committee at the WHO Regional Office for the Western Pacific. CDC's role did not constitute engagement in human subjects research and did not require review by the CDC Institutional Review Board.

2.2. Site selection and characteristics

On the basis of low reported HepB-BD coverage (7–11% in 2011), two districts in Bolikhamxay province (Viengthon and Bolikhanh) were selected to participate in the 6-month OCC pilot. In these intervention districts, 11 of 12 health centers were selected; one was excluded because of difficult access. Neighboring districts in Khammouane province (Nakai and Bualapha) were chosen as comparison districts because of similar annual birth rates and reported HepB-BD coverage (5–11% in 2011) to the intervention districts. In the comparison districts, 13 of 16 health centers were selected; three were excluded because of difficult access.

Each health center provides services to approximately 4–16 villages. Each village is classified according to service delivery characteristics, as fixed, outreach, or mobile, depending on travel time and distance from the health facility to the village. Fixed villages either have a health facility within the boundaries of the village or one located a few kilometers from the village. Outreach villages are located more than a few kilometers away from a health facility; a roundtrip visit to the village from the health facility can be done in one day. Mobile villages are far from health facilities; a roundtrip visit to the village from the health facility requires healthcare workers to stay overnight. Intervention health facilities served 15 fixed, 30 outreach, and 23 mobile villages, compared with comparison health facilities, which served 13 fixed, 29 outreach, and 80 mobile villages.

2.3. Intervention description

During the pilot study, healthcare workers in intervention districts were trained to store two-dose monovalent HepB vaccine vials (Shanvac®-B, Shantha Biotechnics Private Ltd., India) in ambient temperatures for up to 28 days. Even if a health center had a functioning refrigerator, workers were instructed to keep HepB vaccine OCC. Health center staff were instructed to only use one dose of the two-dose vial, except in the case of twins, to maintain consistency with the national multidose vial policy which only allows multiuse of a vial that has been stored as per the label. After 28 days, unused HepB vaccine was discarded. In the comparison districts, HepB vaccine was stored according to standard cold chain procedures.

Healthcare workers from intervention districts participated in a half-day training, which provided an overview of HBV burden and transmission, importance of timely HepB-BD, instructions on storing HepB-BD OCC, when to discard vaccine, logistics of monthly vaccine pick-up, and how to document vaccine administration and wastage. No additional logistical or supply chain support outside standard immunization programme support was provided.

2.4. Assessment

Monthly, we administered a standard questionnaire to the senior healthcare worker at all enrolled health centers in both arms either in person or by phone. Health centers were monitored for adverse events following immunization (AEFI), OCC acceptance among staff and parents, HepB-BD storage and handling practices, and stock out information. VVMs on all vials were evaluated. Temperature LogTags® were placed with the vaccine vials in both arms to record temperature every 35 min.

From October to November 2013, a final survey was conducted. The study was designed to evaluate differences in the change in coverage between intervention and control arms. Change in village-level HepB-BD coverage was estimated by subtracting coverage in 14–20 month olds (those born before pilot) from coverage in 2–8 month olds (those born during pilot) in each village. A sample of 14 villages per arm achieves 90% power to detect a 10% difference from 10% to 20% with an $\alpha = 0.05$, assuming a standard deviation of 10% and a normal distribution, using a two-sided Wilcoxon test assuming a normal distribution.

All villages within the health facility's catchment area were eligible for sampling. Because we expected improvement to be related to village classification, we defined three strata (fixed, outreach, mobile). In each stratum, we chose 15 villages (except in the comparison arm, because only 13 fixed villages existed) by systematic random sampling. All children from ages 2–8 months and 14–20 months were eligible to participate. In each selected village, enumerators conducted a census to search for all eligible children, including those deceased. Consenting caregivers were given a questionnaire, which collected demographic data, birth details, and vaccination history. For HepB-BD, if written history (i.e., vaccination card) was unavailable, we obtained vaccination history based on caregiver recall. For other vaccinations, only written history was collected. Teams also reviewed vaccination registers at the village's primary health center and attempted to obtain vaccination data on all children

identified, as well as children reportedly living in the village who were not found on visit day.

2.5. Data analysis

Monthly monitoring data were entered and stored in Microsoft Access 2010 (Seattle, WA) and was analyzed in SAS v9·3 (Cary, NC). Frequencies and proportions were calculated for dichotomous variables of interest; median and interquartile ranges (IQR) were calculated for temperature data.

Final survey data were entered and stored in EpiInfo 7 (Atlanta, GA) and was analyzed in SAS v9·3 (Cary, NC). During data cleaning, if vaccination dates by register and card were discrepant, register data were considered more accurate. Recall data were used if they were the only data available. For each cohort in each arm, proportions were calculated for various demographic and population characteristics. HepB-BD was defined as any dose given before age 6 weeks (age of first pentavalent vaccine). Children who died on their birth date were excluded. To assess change in HepB-BD coverage, only villages that had at least one child in each age cohort were analyzed. In each arm, village HepB-BD coverage was calculated for each cohort; the median of all village HepB-BD coverage is presented by cohort and arm. The difference in coverage between cohorts by village was calculated; this is the median percent change. The Wilcoxon signed-rank test was used to assess if the median percent change was significantly different from no change. Percent change for all villages in the intervention arm was compared with percent change for all villages in the comparison arm using the two-sided Wilcoxon two-sample test. For analysis of secondary objectives completed at the child-level, such as evaluating change in HepB-BD as a function of birth location and village classification, we accounted for village-level cluster using survey methods and report the second-order Rao-Scott χ^2 p-values.

2.6. Role of the funding source

Funding for this study was provided by WHO; WHO staff participated in design and implementation.

3. Results

3.1. Process evaluation

All 11 intervention health facilities were monitored monthly; all 11 had refrigerators, though they were not always functional. Of the 13 comparison health facilities, nine (69%) had refrigerators and were assessed. Four comparison health facilities lacked refrigerators and were visited once to obtain baseline data, but repeat visits were not conducted because HepB-BD was not provided.

No AEFI were reported in either study arm following HepB-BD administration. In the intervention arm, all health facilities properly stored HepB-BD OCC; no other vaccine was stored OCC. No difficulties with OCC storage were reported; staff reported no confusion regarding which vaccines were stored OCC or concerns about safety of keeping the vaccine OCC. Staff reported that no parents expressed concern that vaccine was stored OCC. In the

intervention arm, no VVMs for HepB-BD stored OCC reached the discard point before the 28-day limit.

In the intervention arm, the median temperature the vaccine was exposed to was 27 °C (25–75% IQR 25.3–28.7 °C). No freezing temperatures were observed, and temperatures above 37 °C were rare (0.1% of the recorded time points). In the comparison arm, the median temperature the vaccine was exposed to was 4.6 °C (25–75% IQR 2.5–18.2 °C). Exposure to temperatures below 2 °C was frequent (16.5% of recorded time points).

3.2. Evaluation survey

In the intervention arm, 44 villages (15 fixed, 15 outreach, and 14 mobile) were visited; one selected mobile village was excluded because of security issues. Among these villages, 388 children aged 2–8 months (median 5.4 months) and 371 children aged 14–20 months (median 17 months) were identified. In the comparison arm, 43 villages (13 fixed, 15 outreach, and 15 mobile) were visited; 190 children aged 2–8 months (median 5.1 months) and 184 children aged 14–20 months (median 17.2 months) were identified. All caregivers provided consent to participate. Children in the intervention and comparison village were different with respect to ethnicity, maternal education, and location of birth. (Table 1)

To compare change in village HepB-BD coverage, three villages in the intervention arm (1 fixed, 2 outreach) and three villages in the comparison arm (2 fixed, 1 outreach) were excluded because they only had children born in one age cohort and no change could be calculated. In the intervention arm, median village HepB-BD coverage was 33% (25–75% IQR 20–69%) in the 2–8 month olds and 0% (25–75% IQR 0–20%) in the 14–20 month olds. In the comparison arm, median village HepB-BD coverage was 0% (25–75% IQR 0–29%) in 2–8 month olds and 0% (25–75% IQR 0–0%) in 14–20 month olds. In the intervention arm, median change in village HepB-BD coverage was 27% (IQR 58%) compared with median change of 0% (IQR 25%) in the comparison arm (Wilcoxon *p*-value = 0.004) (Fig. 2). There was no significant difference in median change in Bacillus Calmette–Guérin (BCG) vaccination between intervention and comparison arms (Wilcoxon p = 0.67).

The median change in HepB-BD coverage was further analyzed by village classification and study arm, using the signed-rank test (Fig. 3). In the intervention arm, a significant improvement occurred among the fixed villages (median change 57% [IQR 39%], $p = 0.002$), outreach villages (median change 27% [IQR 19%], $p = 0.03$), and mobile villages (median change 6% [IQR 20%], $p = 0.04$). In the comparison arm, significant improvement occurred only among fixed villages (median change 33% [IQR 60%], $p = 0.03$); no significant improvement occurred among outreach villages (median change 0% [IQR 20%], $p = 0{\cdot}84$) or mobile villages (median change 0% [17%], $p = 0{\cdot}13$).

Analysis by place of birth, in the intervention villages, intervention children were more likely than pre-intervention children to receive HepB-BD if they were born in a health facility, for all three types of villages. Coverage was also higher for intervention children born at home in the fixed villages ($p = 0.006$) (Table 2). In the comparison villages, a significant improvement occurred in HepB-BD receipt among intervention children born in

health facilities overall, but there was no association between HepB-BD receipt for those born at home or for those born in health facilities when stratified by village type. In the intervention arm, no difference occurred among intervention and pre-intervention children in the timing of HepB-BD: 127 (87%) of 146, 2–8 month olds received HepB-BD within 24 h, compared with 38 (88%) of 42, 14–20 month olds (χ^2 $p = 0{\cdot}57$). In the comparison arm, more children born during the intervention received the dose within 24 h: 41 of 44, 2–8 month olds received HepB-BD within 24 h, compared with 8 (44%) of 18, 14–20 month olds (χ^2 $p < 0.0001$).

4. Discussion

HepB-BD coverage improved during this study with HepB-BD stored in an OCC setting. No AEFI were reported, and healthcare worker acceptance of the OCC strategy was high. If similar improvements in HepB-BD coverage were obtained with expansion of the use of HepB-BD in OCC to the rest of Lao-PDR, future morbidity and mortality from chronic HBV could be decreased significantly. Additionally, using HepB-BD in OCC could alleviate the burden on cold chain and decrease exposure of the vaccine to freezing temperatures, as was seen in the comparison arm of this study. Several studies have documented the exposure of HepB vaccine to freezing temperatures either during improper storage or during poorly monitored transport, which can render the vaccine ineffective [10-12].

We saw an improvement of coverage in both arms, with greater improvement in the intervention arm and improvement in the comparison arm occurring only in fixed facility (less remote) villages. We attribute the improvement in coverage in the comparison arm to the Hawthorne effect and the increased number of births in health facilities. Monthly inquiries were made about the status of HepB-BD vaccination in comparison arm health facilities and might have resulted in healthcare workers vaccinating children more diligently, particularly those born in health facilities. Additionally, improvement could also have been the result of an increased number of births in health facilities that occurred in comparison villages during the pilot period, as birth location has been shown to be related to birth dose administration [15]. The improvement in HepB-BD coverage is unlikely to be the result of general improvements in the immunization program, because no change in BCG coverage occurred.

The pilot allowed health facilities in the intervention arm to provide vaccine continuously, established a consistent system for stock replenishment, and made it easier for healthcare workers to bring vaccine to the home during deliveries and postnatal visits. In the intervention arm, newborns were more likely to receive vaccine if they were born in a health facility. Storing vaccine OCC allowed health facilities that did not have functioning cold chain to vaccinate newborns daily. All health facilities in the intervention arm had refrigerators before the pilot; one would expect minimal coverage improvement from an OCC strategy. However, before the pilot, when refrigerators were not functioning, HepB-BD stopped being available. Storage of vaccine OCC allowed health facilities to maintain the supply despite problems with broken or unpowered refrigerators. We did not expect much improvement among home births, though we did see that HepB-BD coverage improved among home births in fixed villages located near health facilities, suggesting that use of

HepB-BD vaccine during postnatal outreach visits increased. Vaccinating the unreached newborns will require a variety of strategies in addition to vaccine storage OCC, such as increasing health facility delivery rates, ensuring all babies born in health facilities are vaccinated in a timely manner, and tracking pregnancies for postnatal outreach [2].

This study has several limitations. Populations in each arm were different with respect to ethnicity, maternal education, and birth location, which could have affected results. Because of access challenges, several health facilities were not enrolled; this could have potentially inflated the improvement seen, because these health facilities were unlikely to have provided HepB-BD during the study. Several selected villages only had children from one age group, which made a comparison impossible. Some villages only had a small number of children born; small changes in the number of children born and vaccinated could have led to large changes in coverage. Additionally, some secondary analyses had small sample sizes and potentially were under-powered to detect a difference. Although 95% of the HepB-BD vaccination data was documented by written records, 5% was based on recall, which could have been unreliable. Finally, we did not conduct training in the comparison villages, so we were unable to determine if the improvements were the result of training, use of OCC itself, or both.

Because of the high prevalence of chronic HBV in Lao-PDR and multiple barriers to HepB-BD administration, finding innovative ways to increase coverage is critically important. In addition to efforts already implemented in Lao-PDR, OCC storage has the potential to provide access to HepB-BD in areas without cold chain; however, sustainability of this type of pilot can be challenging. Three months after the pilot, 45% of intervention health facilities had a stock-out of HepB vaccine compared with 0% during the pilot; this could be due to non-functional cold chain preventing the storage of vaccine, or problems with obtaining vaccine. Before scaling-up, improved supply chain and logistics, other improved immunization programme management, and strengthening of related aspects of the broader health system will need to be established. System problems such as stockouts or failure to understand OCC could make this program ineffective.

Ideally, HepB vaccine will be labeled for use in CTC; WHO is encouraging manufacturers to pursue relabeling though manufacturers might not see the cost-benefit. Lao-PDR and other countries with similar access issues are eager for a HepB-BD vaccine that can be used in CTC. While the global community awaits relabeling, findings from this pilot should be used to guide a scale-up of an OCC program in Lao-PDR and could provide guidance to similar settings so that more children have access to a HepB-BD.

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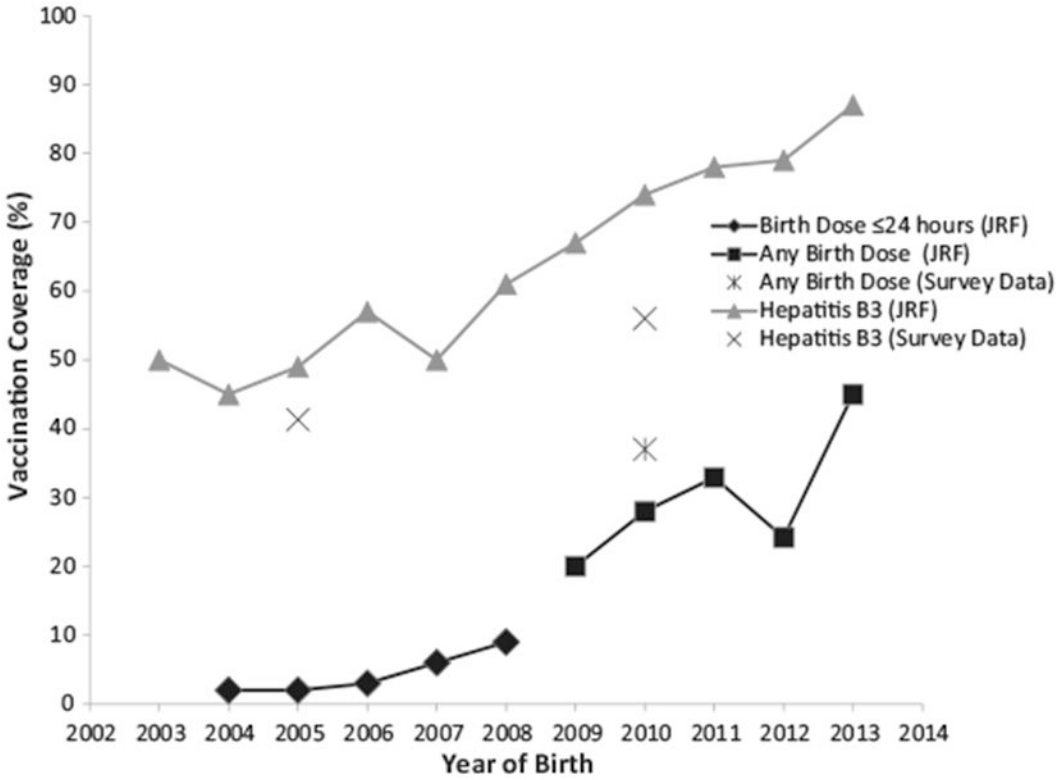

Fig. 1.

Hepatitis B vaccination coverage for Lao-PDR, 2003–2013. Data sources: WHO/UNICEF Joint Reporting Form (JRF), Lao PDR Multiple Indicator Cluster Survey 2006, Lao Social Indicator Survey 2011–2012.

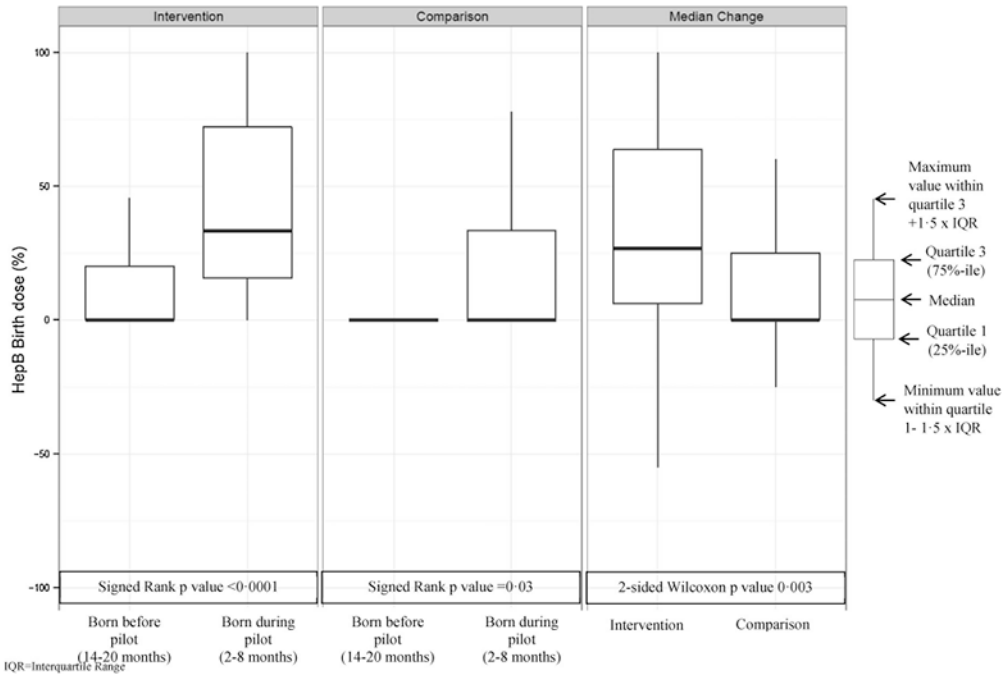

Fig. 2.

Box plots describing the change in hepatitis B birth dose coverage for each village between 14–20 month olds and 2–8 month olds in the intervention and comparison arms as part of the outside cold chain pilot, Lao-PDR, 2013. IQR = Interquartile Range.

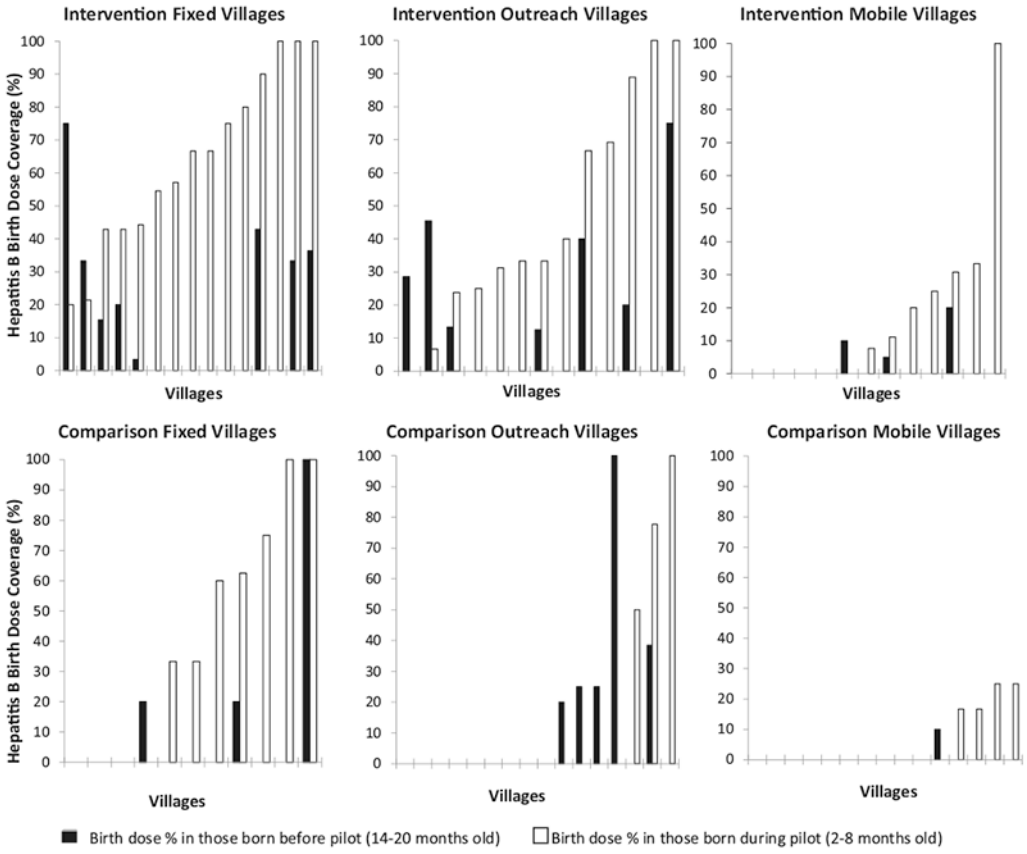

Fig. 3.

Hepatitis B birth dose coverage (%) in each type of village (fixed, outreach, mobile) in each arm (intervention versus comparison) evaluated in the final survey among children born before the pilot (14–20 months of age) and during the pilot (2–8 months of age), Lao-PDR, 2013. Each pair of bars shows the coverage before and during the pilot study in a selected village. If the bar is missing, this means that coverage was 0%. Villages that had only children in one age group are excluded due to the inability to assess the change in coverage.

Table 1

Characteristics of children participating in the final survey as part of the outside cold chain pilot study, Lao-PDR, 2013[a]

	Intervention						Comparison					
	Before pilot[b]			During pilot[c]			Before pilot[b]			During pilot[c]		
	Total	*n*	%	Total	*n*	%	Total	*n*	%	Total	*n*	%
Male	371	203	55	388	164	42	184	90	49	190	99	52
Ethnic group												
Lao	329	133	40	347	117	34	175	71	41	186	73	39
Khmu	329	70	21	347	71	20	175	100	57	186	104	56
Hmong	329	125	38	347	159	46	175	0	0	186	0	0
Other	329	1	0	347	0	0	175	4	2	186	9	5
Village classification												
Fixed	371	172	46	388	166	43	184	51	28	190	54	28
Outreach	371	107	29	388	122	31	184	70	38	190	67	35
Mobile	371	92	25	388	100	26	184	63	34	190	69	36
Deceased	369	8	2	388	13	3	184	4	2	190	6	3
Highest level of maternal education completed												
None	329	78	24	347	95	27	175	106	61	186	112	60
Primary school	329	174	53	347	167	48	175	55	31	186	49	26
Secondary school	329	69	21	347	79	23	175	12	7	186	24	13
Post-secondary	329	8	2	347	6	2	175	2	1	186	1	1
Religion												
Buddhist	329	130	40	347	115	33	174	62	36	186	62	33
Animist	329	188	57	347	219	63	174	112	64	186	123	66
Christian	329	11	3	347	13	4	174	0	0	186	0	0
Birth history												
Born at health facility	329	147	45	347	146	42	175	19	11	186	41	22
Born at home with SBA	329	6	2	347	4	1	175	19	11	186	22	12
Born at home without SBA	329	176	53	347	197	57	175	137	78	186	123	66
Children with written vaccination data (card or register)	370	350	95	385	364	95	184	177	96	190	176	93
Any hepatitis B birth dose	362	42	12	378	146	39	177	18	10	187	44	24

[a] Three children in the 2–8 month cohort and 1 child in the 14–20 month cohort died on date of birth and are excluded as they were not eligible for vaccination.

[b] Before Pilot = Born one year prior to pilot implementation (14–20 month olds).

[c] During Pilot = Born during pilot implementation (2–8 month olds).

Table 2

Hepatitis B birth dose (HepB-BD) coverage (%) by birth location and village classification, Lao-PDR, 2013.

	Intervention							Comparison						
	Before pilot[a]			During pilot[b]				Before pilot[a]			During pilot[b]			
	# of newborns receiving HepB-BD	Total # of births	HepB-BD coverage (%)	# of newborns receiving HepB-BD	Total # of births	HepB-BD coverage (%)	χ^2 p value[c]	# of newborns receiving HepB-BD	Total # of births	HepB-BD coverage (%)	# of newborns receiving HepB-BD	Total # of births	HepB-BD coverage (%)	χ^2 p value[c]
Health facility birth														
Fixed	15	66	23	56	67	84	**<0·0001**	5	10	50	19	22	86	0·09
Outreach	17	65	26	41	56	73	**<0·0001**	1	3	33	8	12	67	0·29
Mobile	2	14	14	12	21	57	**<0·0001**	1	5	20	3	7	43	0·25
Total	34	145	23	109	144	76	**<0·0001**	7	18	39	30	41	73	**0·04**
Home birth														
Fixed	1	71	1	24	80	30	**0·0006**	3	38	8	8	32	25	0·12
Outreach	1	36	3	4	48	8	0·37	8	64	13	5	52	10	0·67
Mobile	1	68	1	2	65	3	0·65	0	48	0	1	58	2	–
Total	3	175	2	30	193	16	**0·004**	11	150	7	14	142	10	0·53

[a] Before Pilot = Born one year prior to pilot implementation (14–20 month olds).

[b] During Pilot = Born during pilot implementation (2–8 month olds).

[c] Second order Rao-Scott χ^2 accounting for clustering.