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Research article

# Vaccine temperature management in Lao People's Democratic Republic: A nationwide cross-sectional study

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## HIGHLIGHTS

- The Lao PDR has suffered several outbreaks of vaccine-preventable diseases.
- This study investigated the cold chain during vaccine transport to health centres.
- Vaccines were exposed to suboptimal conditions during transit from central to health centres and at storage at all levels.
- Vaccine storage temperature fluctuated in some health centres.
- Deficiencies in cold chain management may contribute to outbreaks of vaccine-preventable diseases.

## ARTICLE INFO

*Keywords:*
Cold chain
Expanded program on immunization
National immunization program

## ABSTRACT

*Objective:* The objective of the study was to evaluate the duration and frequency of vaccine exposure to suboptimal temperatures during transit from the central vaccine storage in the capital to health centers in Lao PDR.
*Methods:* Temperature data loggers traveled from the capital to the health centre storages (146) with the vaccines to monitor the vaccine temperature nationwide. One health centre per district was selected using a simple random sampling method for the first round of temperature monitoring. One health centre was selected from every forty-nine high risk districts monitor the trend of vaccine temperature at the health centre storage and during outreach sessions in several districts. Vaccines and temperature data loggers were transported using the normal vaccination transportation.
*Findings:* Overall, the vaccines were exposed to temperatures >8 °C for an average of 1648 min, equivalent to 9.0% of the observational period, and to temperatures <0 °C for an average of 184 min, equivalent to 1.35% of the study period. The proportion of exposure to temperatures >8 °C was the highest during the transit from the capital to the province. The proportion of exposure to temperatures <0 °C was the highest during storage at district level. Examined by region, vaccines in the northern provinces had higher risk of exposure to temperatures >8 °C; however, the risk of exposure to temperatures <0 °C was scattered nationwide. Moreover, some health centers showed fluctuations in storage temperature.
*Conclusions:* Challenges associated with cold chain management, and the resulting deterioration of vaccines, might account for outbreaks of vaccine-preventable diseases. The government should examine and invest in suitable technologies and approaches to ensure consistency in cold chain management.

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## 1. Introduction

Vaccination is among the most effective public health interventions to reduce child mortality, and the Expanded program on Immunization (EPI) improved access to vaccines [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12].

The EPI was introduced in 1979 in Lao People's Democratic Republic (PDR), which is a land-linked country bordering Myanmar, Cambodia, China, Thailand, and Vietnam and is largely mountainous with the Mekong River running through from north to south [8, 13, 14]. The country suffered several outbreaks of vaccine-preventable diseases, such as diphtheria and measles, despite improved vaccination coverage [14, 15, 16, 17]. Some studies reported that seroprevalence or seroprotection rates of these diseases were low [14, 15, 16, 18]. Proposed explanations included low immunization coverage, reduced response to vaccines in individuals due to immune deficiencies, suboptimal nutritional status, and parasite infestation [14, 16, 18, 19]. In addition, some authors also suggested that challenges in cold chain management might have affected vaccine effectiveness [14, 15, 16, 18, 19].

Cold chain management is required to guarantee quality and safety of vaccines [10, 11, 20]. For example, vaccines need to be kept within a specified temperature range from production to delivery, which tend to take place in different countries [21]. Figure 1 shows a typical cold chain system [22]. Temperatures outside the recommended range can damage the vaccines; all childhood vaccines, except oral polio vaccines, should be kept at 2–8 °C. However, assessments conducted by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) in 2008 and 2011 showed that only a few countries met the minimum standards of cold chain management [23]. In Lao PDR, there are three levels of cold chain management. The first level is overseen by the National Immunization Program (NIP) is located in Vientiane, the capital of the country (primary vaccine storage facility). During distribution, the vaccines are transported from the capital to the regional or provincial storage facilities, which are considered "intermediate" vaccine stores. From there, they are dispatched to district storage facilities and then, to relevant health centers where immunization services are provided either on site or during outreach sessions. Outreach sessions occur four or five times per year, depending on the accessibility of villages. In 2008 and 2009, a study conducted in 8 health centres in two provinces (Savannakhet and Luang Namtha) showed significant cold chain weaknesses from provincial level downwards [24]. Another study conducted in 10 health centers in two provinces (Saravan and Xayabouly) in 2016 still identified storage in districts and during transit to health centers as key remaining challenges in cold chain management in the country [20]. Nevertheless, as several outbreaks of vaccine-preventable diseases have occurred in different parts of the country, a further examination of cold chain management nationwide is warranted.

The aim of this study was to evaluate the duration and frequency of vaccine exposure to suboptimal temperatures (temperatures <0 or >8 °C) during transit from the primary vaccine storage facility to health centers nationwide in Lao PDR.

## 2. Methods

### 2.1. Study sites

In Lao PDR, there are 17 provinces and 1 municipality, and districts are the following administrative units (146 districts according to the data provided by NIP), and villages are the most peripheral administrative units. One health center per district was selected for this study using a simple random sampling method for the first round of temperature monitoring to monitor vaccine temperature throughout from central storage to the selected health centre storages (Figure 1).

The Ministry of Health of Lao PDR has identified 49 high-risk districts based on the immunization coverage of third dose of diphtheria-pertussis-tetanus in 2016. One health center was selected from every 49 high-risk districts using a simple random sampling method for the second round temperature monitoring to record vaccine temperature at the health centre storage and during the outreach sessions in several districts.

### 2.2. Temperature monitoring (from NIP to health centers)

A temperature data logger (USB Temperature data logger; Model number MJ-UDL-11, Sato Shouji Inc., Japan, temperature range: from -20 to 70 degrees Celsius) was pre-set up to measure and record vaccine temperature every 5 min. These temperature data loggers were placed in the vaccine cold boxes/carriers and stayed with vaccines throughout transit from the central storage to the health centers. Another temperature data logger (Model number CTL-01PDF, CUSTOM ™, Japan, temperature range: from -30 to 70 degrees Celsius) was pre-set up to measure and record the ambient temperature every 30 min; the ambient temperature data loggers traveled with the vaccines placed outside the cold chain equipment throughout the study period. A monitoring form was attached with the vaccines and temperature data loggers to record events, such as arrival and departure date of vaccines and means of

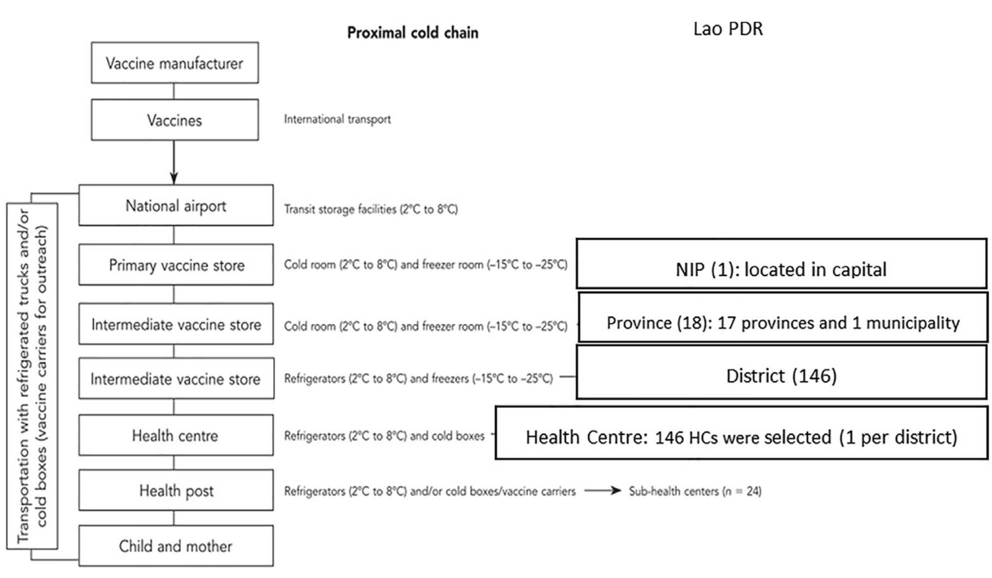


Figure 1. Cold chain system.

transport. These forms were filled out by the provincial and district EPI officers, and the health center staff. Vaccines, temperature loggers and, monitoring forms were distributed from 2-3/2017 using the normal vaccination transportation and arrived at the selected health centers from 2-4/2017.

### 2.3. Temperature monitoring (at health center/outreach)

Temperature data loggers (USB Temperature data logger; Model number MJ-UDL-11, Sato Shouji Inc., Japan, temperature range: from -20 to 70 degrees Celsius) which were pre-set up to measure and record vaccine temperature every 5 min were, distributed to 49 high-risk districts from 5/2017 and traveled to 1 health center in each district to monitor the temperature of the vaccines at the health center storage and during the outreach sessions.

### 2.4. Data analysis

The temperature data loggers were sent back from the health centers, and delivered to the National Immunization Program office using the normal vaccination transportation in reverse from 4-8/2017. All data were downloaded from each device into an Excel spreadsheet or a PDF file. Data from the monitoring forms were entered into an Excel spreadsheet.

Descriptive analyses were used to calculate cumulative time and proportion of the vaccines in the cold chain system exposed to temperatures <0 °C or >8 °C for the following three conditions for each temperature logger [20, 25]:

i. from departure from the NIP offices to arrival at the health center,
ii. during transit, and
iii. during storage at different administrative levels.

The average cumulative times and proportion were calculated for all temperature data loggers (Table 1).

The average proportions and the cumulative times were calculated for each province as well (Table 2).

As the exact time of departure and arrival were not recorded in this study, duration of transportation was calculated as follows:

i. from central to provincial level: starting from the time the logger recorded a temperature below 8 °C for the first time on the day of departure from the central level until 23:59 of the day of arrival at the province, or starting at 8 am on the departure day, if the logger did not reach a temperature below 8 °C on the departure day;
ii. from province to district level: from 8 am on the day of departure from province to 12:00 pm on the day of arrival; and
iii. from district to health center: from 8 am on the day of departure to 12:00 pm on the day of arrival.

Duration of storage was calculated when the loggers and vaccines were not transported, according to the same definitions. For the Champasak and Attapue provinces, where departure dates were missing after the central departure date, the temperatures were calculated for the week. The temperatures were plotted to examine temperature exposure trends at the health centers storage and during outreach sessions.

### 2.5. Ethical consideration

No ethical clearance or informed consent was required since this study did not involve any intervention or interaction with human participants. Authorization to conduct this study was granted by the Ministry of Health and the Provincial Health Departments [10, 20].

## 3. Results

Out of 146 data loggers, 141, which recorded vaccine temperature, and 129, which recorded ambient temperature, were returned to the NIP. Out of the returned loggers, 127 loggers were accompanied by monitoring forms. Data from 127 pairs of loggers (loggers which monitored/recorded vaccine temperature and those which monitored/recorded ambient temperature) were used for analysis.

Figure 2 shows examples of the trends of temperature from two districts.

Overall, the vaccines were exposed to temperatures >8 °C for an average of 1648 min, equivalent to 9.0% of the observational period, and to temperatures <0 °C for an average of 184 min, equivalent to 1.35% of the study period (Table1, Figure 3). In addition, the vaccines were exposed to temperatures >8 °C for an average of 760 min, equivalent to 2.3% of the time spent in stock in province and transit from province to district facilities, and 399 min (2.3%) during stock in district, transit from district storage to health centers and stock in health centres (Table1, Figure 3). The vaccines were exposed to temperatures <0 °C for an average of 72 min, equivalent to 0.40% of

**Table 1.** Times that vaccines spent at suboptimal temperatures.

| N = 127 | Average observation period (minutes) <min, max> | Average cumulative time (minutes) spent at <min, max> | | Average % of observation period spent at <min, max> | |
|---|---|---|---|---|---|
| | | >8 °C | <0 °C | >8 °C | <0 °C |
| From NIP to HC | 18041 <2005, 85920> | 1648 <0, 24315> | 184 <0, 3705> | 9.0 <0, 60.6> | 1.35 <0, 13.93> |
| transit (NIP→province) | 3289 <330, 49455> | 301 <0, 2055> | 11 <0, 340> | 2.4 <0, 42.8> | 0.07 <0, 2.48> |
| From province to district | 9412 <480, 81360> | 760 <0, 24010> | 72 <0, 3705> | 2.3 <0, 33.4> | 0.40 <0, 9.30> |
| stock in province | 5707 <480, 42240> | 166 <0, 5890> | 48 <0, 3705> | 1.0 <0, 31.7> | 0.10 <0, 9.30> |
| transit (province→district) | 1659 <240, 81360> | 391 <0, 24010> | 21 <0, 740> | 0.9 <0, 28.0> | 0.21 <0, 3.81> |
| From district to HC | 3917 <720, 73440> | 399 <0, 6930> | 73 <0, 1440> | 2.3 <0, 26.0> | 0.50 <0, 13.93> |
| stock in district | 2529 <480, 42960> | 184 <0, 4080> | 43 <0, 1440> | 1.1 <0, 21.7> | 0.40 <0, 13.94> |
| transit (district→HC) | 1002 <0, 33360> | 147 <0, 4560> | 26 <0, 1130> | 0.9 <0, 23.4> | 0.13 <0, 12.27> |
| stock in HC | 720 | 198 <0, 720> | 14 <0, 525> | 1.6 <0, 20.9> | 0.12 <0, 6.57> |

**Table 2.** Times that vaccines spent at suboptimal temperatures (provinces).

| | Observed/total districts | Average observation period | Average cumulative time (minutes) spent at | | Average % of observation period spent at | |
|---|---|---|---|---|---|---|
| | 127/141 | | >8 °C | <0 °C | >8 °C | <0 °C |
| Attapu | 5/5 | 9309 | 158 | 0 | 1.70 | 0 |
| Bokeo | 4/4 | 11579 | 1259 | 319 | 12.52 | 3.06 |
| Bolikhamxai | 5/7 | 6902 | 742 | 133 | 10.43 | 1.97 |
| Champasak | 10/10 | 9271 | 169 | 246 | 1.82 | 2.65 |
| Houaphan | 8/9 | 49924 | 9898 | 104 | 26.45 | 0.79 |
| Khammouan | 10/10 | 19749 | 466 | 62 | 2.71 | 0.31 |
| Louang Namtha | 4/4 | 18500 | 296 | 196 | 1.69 | 1.30 |
| Louangphrabang | 10/12 | 20496 | 2649 | 112 | 9.65 | 0.22 |
| Oudoumxai | 7/7 | 54967 | 3287 | 957 | 6.76 | 2.13 |
| Phoungsali | 6/7 | 9452 | 2605 | 125 | 29.22 | 1.16 |
| Saravan | 7/8 | 8736 | 224 | 168 | 2.57 | 1.94 |
| Savannakhet | 13/14 | 7708 | 336 | 190 | 4.80 | 2.05 |
| Vientiane (prov) | 11/11 | 19320 | 450 | 90 | 2.03 | 0.48 |
| Vientiane (municipality) | 5/7 | 27102 | 500 | 17 | 2.17 | 0.09 |
| Xekong | 3/4 | 7888 | 698 | 0 | 8.33 | 0 |
| Xayaboury | 10/11 | 7727 | 1680 | 126 | 21.37 | 1.96 |
| Xaisamboun | 3/5 | 14220 | 1397 | 627 | 9.86 | 4.20 |
| Xiengkhoang | 6/7 | 16803 | 1934 | 142 | 11.61 | 0.99 |

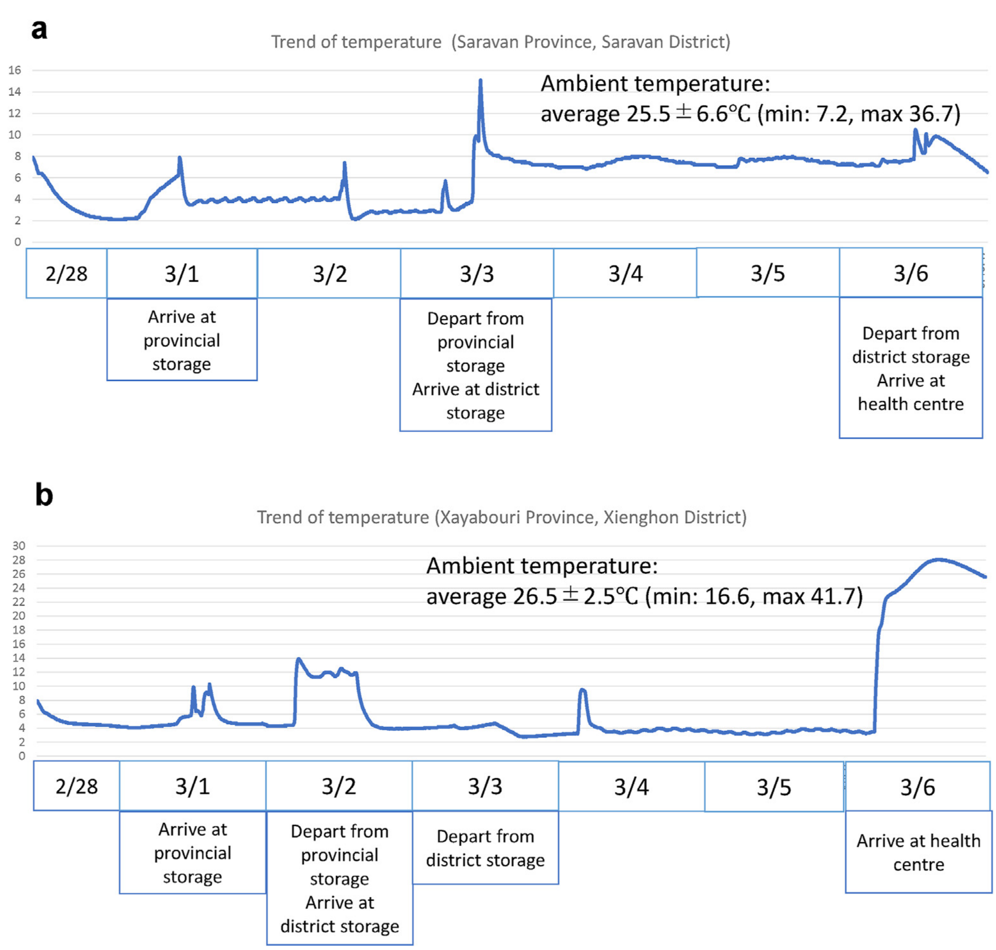


**Figure 2.** Trend of cold chain temperature (from NIP to HC).

stock in province and transit time from province to district, and an average of 73 min, equivalent to0.50% of the time in stock in district, transit from district to health center and stock in health centres (Table 1, Figure 3).

The vaccines were exposed to temperatures >8 °C during 2.4% of transit time from the NIP offices to the province, which was the longest proportion of transportation time spent in non-optimum temperature during transit (Figure 4). The vaccines were exposed to temperatures

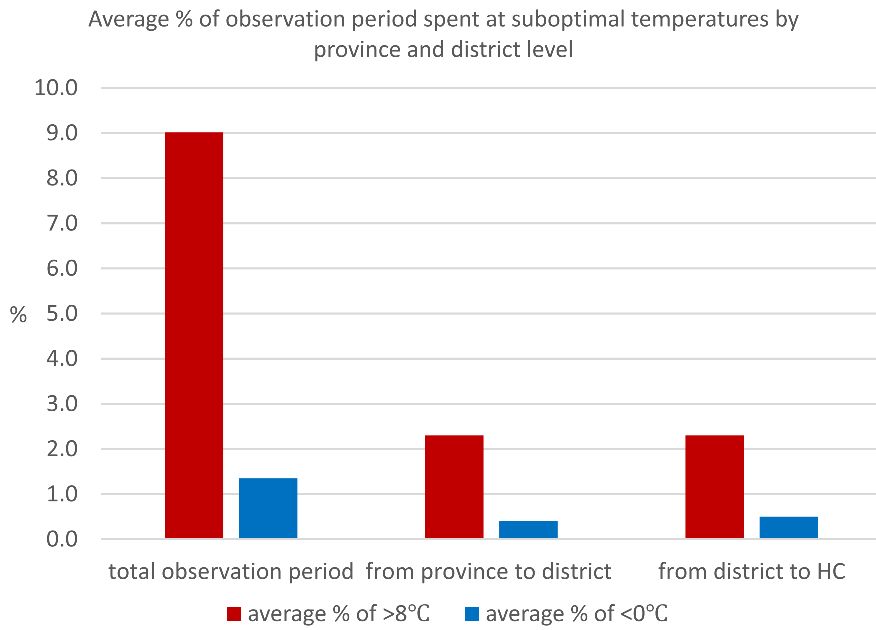


**Figure 3.** Average proportion of observation period spent at suboptimal temperatures.

<0 °C during 0.4% of the time spent in the district storage, which was the highest proportion of time the vaccines spent in non-optimum temperature during storage (Figure 4).

The average proportion of exposure by province to the temperature >8 °C was grouped into three groups and marked in the map: ≥20% of exposure (red), >20%, and ≥10% of exposure (orange), <10% of exposure (green) and the provinces with >1% of the exposure to the temperature <0 °C were marked with blue in the map. The provinces where vaccines were exposed to temperatures >8 °C were based in northern part (Table 2, Figure 5). However, the provinces with >1% of exposing <0 °C had no particular geographical distribution (Table 2, Figure 5).

All data loggers came back to the NIP from 49 health centers in high-risk districts; however, the date of health center arrival, name of the health center, date of outreach sessions, and date of travel back to the NIP were not recorded in more than half of the monitoring forms. Out of 49 data loggers distributed for high-risk districts, eight districts confirmed that data loggers were taken during the outreach and five confirmed occasionally took them to outreach. Figure 6 shows the fluctuating, 2-week temperature trend from two health centers from which data were available.

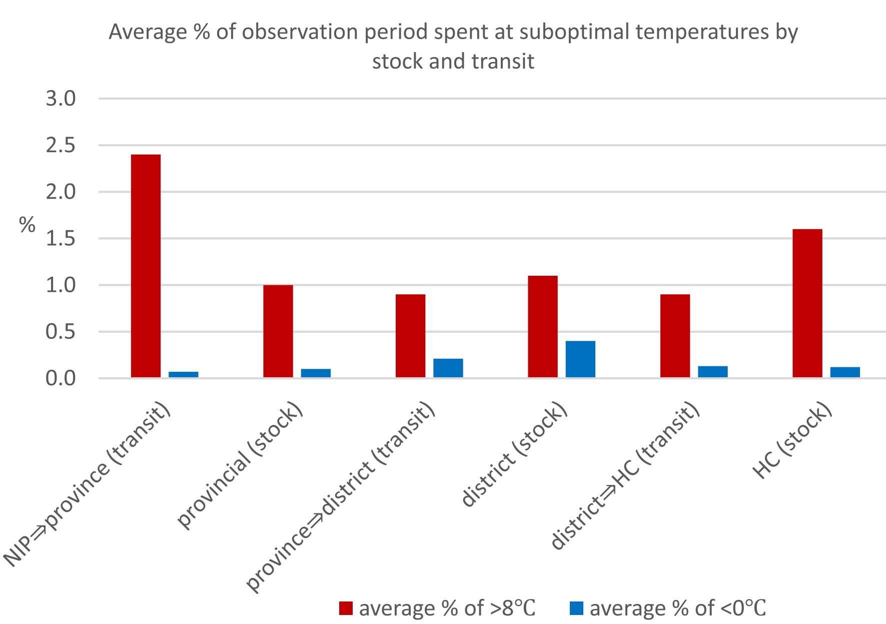


**Figure 4.** Average proportion of observation period spent at suboptimal temperatures by stock and transit.

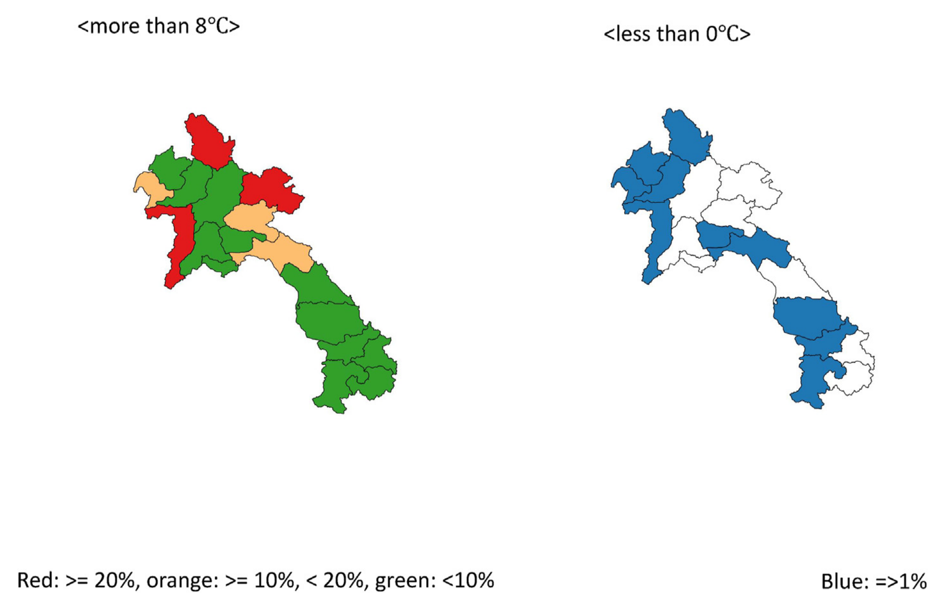


**Figure 5.** Average proportion of observational period spent at suboptimal temperatures by provinces.

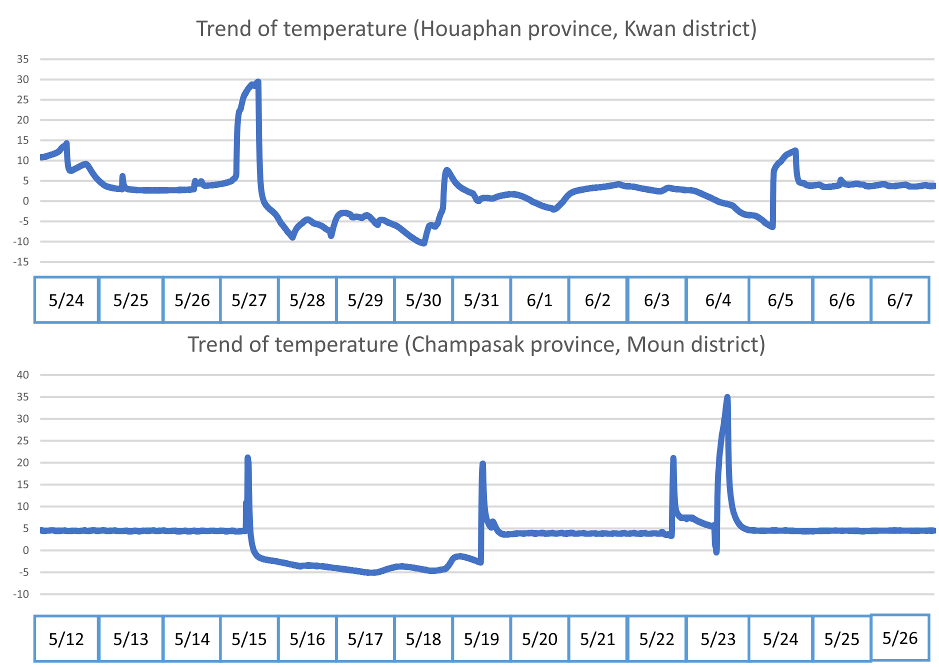


**Figure 6.** Trend of cold chain temperature (HC/outreach).

## 4. Discussion

The vaccines were exposed to temperatures >8 °C by an average of 1648 min, which was 9.0% of the observation period, and to temperatures below 0 °C by the average of 184 min, which was 1.35% of the observation period in Lao PDR. The proportion of exposure to temperatures >8 °C was the highest during the transit from NIP to the province. The proportion of exposure to temperatures <0 °C was the highest during storage at district facilities. Examined by region, vaccines in the northern provinces had higher risk of exposure to temperatures >8 °C; however, the risk of exposure to temperatures <0 °C was scattered nationwide. Moreover, some health centers showed fluctuations in storage temperature.

Two studies have been conducted to date in Lao PDR to evaluate cold chain management: the first, done by the UNICEF in 2008 and 2009, followed by the previous study, which conducted in 2016. The study by the UNICEF covered the central level storage in the capital and two provinces (two districts per province and four centers per district). The study in 2016 covered the central level storage, two provinces, one district per province, and five health centers per district [20]. The study in 2008–2009 showed significant cold chain weakness below the provincial level [24]. For example, the vaccines were exposed to temperatures >8 °C for 7% of the total recorded time, and to temperatures <0 °C for >18% of the time spent at the provincial storage in Luang Namtha province [24]. The study in 2016 showed that the challenge of storing vaccines in optimum temperatures remained at the district storage and during transit, despite improvements at the provincial level [20]. For example, the vaccines were exposed to temperatures >8 °C for >80% of the total recorded time at the district storage in Saravan province, and to <0 °C for >50% of the recorded time at the district storage in Xayabouly province.

This present study is the first nationwide study to monitor cold chain management and showed challenges remained equally at the province and district levels and likely at the health centers and during outreach activities. In addition, transit from the NIP offices to the provinces had the highest risk of exposure to temperatures >8 °C, and northern provinces were more at risk of exposure to temperatures >8 °C than other regions.

Ashok et al. showed 9–20% of cold chain equipment in the studied facilities in ten countries maintained sub-zero conditions more than 24 h and 12–13% of cold chain equipment maintained >8 °C more than five days [26]. A study from India in 2012 showed that vaccines were exposed to >8 °C for 14.3%, 13.2%, 8.23% and 14.7% in state, regional, district and peripheral health facilities of their combined storage times respectively and exposed to <0 °C for 1.5%, 0.2%, 0.6% and 10.5% [27].

Common causes of exposure to temperatures >8 °C during transport were inappropriate coolant packs, duration of transit exceeding the container's cold life, troubles with vehicle (e.g., breakdown, refrigerator system breakdown), and exposure to sunlight [28]. Our findings showed the range of travel time (observation period) was wide, which suggests that cold chain management should be flexible enough to respond to changes en route and differences in distances traveled.

This study showed that the highest proportion of exposure to temperatures <0 °C was observed at the district storage; however, this risk was distributed evenly nationwide. Common causes of exposure to temperatures <0 °C during storage included inappropriate equipment installation (e.g., too close to the freezer room), incorrect thermostat adjustment, and placing the vaccines in cold spots. Healthcare workers should be trained to prevent these avoidable errors [28].

A break in the cold chain affects quality of the vaccines and may lead to loss of potency [14, 29].

Overheating and freezing can damage vaccines [29]. Heat-stable vaccines should be protected from extreme heat spikes [29]. Hachiya et al. found inconsistent seroprevalence between measles and rubella in a nationwide study on anti-measles IgG and anti-rubella IgG seroprevalence after supplementary immunization activities using measles and rubella combination vaccine [15]. A reason proposed for this inconsistency was weak cold chain management, which would affect the measles component of the vaccine, particularly, since it is more heat-sensitive than the rubella component of the vaccine [15]. In fact, the measles vaccine is one of the unstable vaccines available, which requires an uninterrupted cold chain and protection from light throughout transport and storage and should be used within 4 h after it has been reconstituted [27, 30]. The WHO guidelines state that the potency of a vaccine may be compromised if a vaccine is frozen at a temperature below -0.5 °C for 60 min or more; further, a vaccine might become compromised after being heated at a temperature above 8.0 °C for 10 h or more [23]. This study showed the average cumulative time of the vaccines exposure to >8 °C was more than 1 day with a wide range of the duration, which suggests that a break in the cold chain can happen anytime between dispatch from the central storage facility until delivery to patients.

The EPI has contributed to a reduction in child mortality, which is why it is important to address the cold chain management challenges to ensure consistency in vaccine quality across the program [31]. However, challenges grow as the number of new vaccines increases [26, 31]. Innovative vaccine preservation technologies or approaches are now available for countries to choose the most suitable options for their regions, depending on specific challenges and improvements required [31, 32]. Those technologies include innovative cold chain equipment such as solar direct-drive refrigerators, long-term passive cold boxes, and equipment with user-independent freeze prevention or temperature monitoring and control devices that allow staff to take appropriate error-response actions on-site [26, 32]. The use of a controlled temperature chain, which allows the vaccines to keep at temperatures of up to 40 °C for up to 4 days during immunization campaigns, could be an option for some vaccines [33, 34]. Outsourcing of cold chain management to private sector might also be an option in some cases [23]. However, outsourcing would require investment of resources and political will to improve cold chain management, which might be difficult to achieve. Nevertheless, it is a small cost compared to potential consequences of vaccine failures. In addition, given the global stakeholders' commitment to funding and procuring vaccines, ensuring timely and sufficient funding for cold chain management should be considered a priority [26].

This study has several limitations. First, the precise arrival and departure times of the data loggers were not recorded due to resource limitations, which meant training for health personnel in provinces, districts, and at health centers was insufficient. As a result, the estimated duration of transit and storage might be inaccurate. Second, this was a single, cross-sectional study conducted mainly during dry months, which means its generalizability is limited. Cold chain management might be more difficult during the rainy season. Third, no shake test was conducted at the end of the observation period, and the potency of vaccines was not assessed [25]. Lastly, the type of vaccine boxes/carriers and the number of ice packs placed in the boxes/carriers were not monitored were not monitored and quality and quantity of cold chain equipment or adherence to national protocol to cold chain management were not examined. Comprehensive cold chain evaluation, including accounting for human resource and equipment quality, should be conducted.

## 5. Conclusion

The study was the first nationwide examination of cold chain management in Lao PDR to shed light on the overall temperature management. It showed that challenges to maintain vaccines at constant, optimum temperatures remained, equally, at provincial and district levels, as well as at health centers and during outreach activities. Challenges associated with cold chain management, and the resulting deterioration of vaccines, might account for outbreaks of vaccine-preventable diseases. The government should examine and invest in suitable technologies and approaches to ensure consistency in cold chain management.

## Declarations

### *Author contribution statement*

Tomomi Kitamura and Masahiko Hachiya: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Masataro Norizuki: Conceived and designed the experiments.

Hironori Okabayashi: Conceived and designed the experiments; Performed the experiments.

Shinsuke Miyano and Munehito Machida: Conceived and designed the experiments; Performed the experiments; Wrote the paper.

Viraneth Bouakhasith, Kongxay Phounphenghack, Chansay Pathammavong and Anonh Xeuatvongsa: Performed the experiments.

Akiko Kobayashi: Analyzed and interpreted the data; Wrote the paper.

Yoshio Mori, Makoto Takeda, Masaya Sugiyama and Masashi Mizokami: Analyzed and interpreted the data.

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### *Data availability statement*

Data will be made available on request.

## *Declaration of interests statement*

The authors declare no conflict of interest.

## *Additional information*

No additional information is available for this paper.

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