Cold chain temperature monitoring in Vietnam

Monitoring ambient and cold chain temperatures during delivery of human papillomavirus vaccine

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Introduction

This study was undertaken as part of the Optimize project. Optimize is a collaboration between the World Health Organization (WHO) and PATH to help identify innovative approaches to creating a vaccine supply chain that is flexible and robust enough to handle increasing volumes of more costly new vaccines. Optimize is a five-year project funded by the Bill & Melinda Gates Foundation.

To accomplish this study, Optimize collaborated with PATH's Cervical Cancer Project in Vietnam. Human papillomavirus (HPV) vaccine is intended to prevent cervical cancer. A two-year HPV vaccine demonstration project is being conducted to demonstrate how existing delivery systems can be adapted to successfully provide HPV vaccine to young adolescent girls. The HPV vaccine is a strong candidate for out of the cold chain (OCC) use given its characteristics of high-heat stability and freeze sensitivity.[1,2]

There have been a number of studies both in the field[3,4,5] and laboratory[6,7,8] evaluating the effectiveness of vaccines that are kept OCC for a defined period of time. In the northern region of Vietnam, studies were conducted in rural districts in the late 1990s and again in 2005 to evaluate the delivery of hepatitis B vaccine birth dose using OCC storage strategies.[9,10] A research paper on GARDASIL® (Merck & Co., Inc, Whitehouse Station, NJ, USA) HPV vaccine showed this product to be extremely stable—for periods of 130 months or longer at 25ºC. At higher temperatures of 37º to 42ºC, the vaccine maintained more than 50% of its potency for several months.[1] Furthermore, the storage and handling information for GARDASIL® includes the statement that it can be out of refrigeration (at temperatures at or below 25°C/71°F) for a total time of not more than 72 hours.[10] Also, though not used in this particular study, published data on the stability of a different HPV vaccine, Cervarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium), show that the product is stable for up to three years when stored at 2º to 8ºC with simulated cold chain breaks of either one week at 37ºC or four weeks at 25ºC.[2]

Generally there are three common reasons for taking vaccines OCC: 1) to provide ready access for health workers to vaccines for time-sensitive administration (such as birth dose); 2) to ease cost and efforts of outreach trips; 3) to prevent exposure to freezing temperatures that can occur in vaccine carriers.

The vaccines used in the HPV vaccine project were approved and licensed by the government of Vietnam prior to the study.

Objective

The primary objective of this temperature monitoring study was to gather ambient temperature data during different HPV vaccine delivery strategies and in multiple geographic settings and seasons. These data will be compared to the known heat stability profile of the HPV vaccine to further the international dialogue on the appropriateness of OCC HPV vaccine delivery strategies. A secondary objective was to collect data about temperatures inside the cold chain (ICC) during storage and transport of HPV vaccines.

Methods

The temperature surveys were conducted during the delivery of second and third doses of the HPV vaccine at project sites in Vietnam. Main vaccination sessions for the second dose were held from January 12–20, followed by "mop-up" sessions (vaccinations administered to eligible girls not present at the main vaccination session) from February 2–5 in 2009. Main vaccination sessions for the third dose were conducted from May 2−19, followed by mop-up sessions from June 2–6, in 2009.

Small temperature recording devices were attached to the interior and exterior of vaccine carriers at the time of vaccine pick-up at the district health centers and transported to project communes by commune health workers or district health workers for vaccination sessions at schools and commune health centers (CHCs). The temperature recorders were kept with the vaccines at all times until the vaccines were returned to the district level. The person in charge of vaccine transport and delivery documented the date, time, and location of each place that the vaccine was stored and delivered. When the vaccines were returned to the district stores, the recorders were removed and returned to the local PATH office for download and analysis.

The temperature loggers used were model Trix-8 from LogTag Temperature Recorders based in Auckland, New Zealand. Slightly larger than a credit card, these devices record temperature, date and time at predetermined intervals. Recording accuracy is ±0.5°C, and they were programmed to automatically record temperature readings every 15 minutes while in use. Data were downloaded through use of LogTag software and a LogTag interface cradle. These data were exported into Microsoft Excel for analysis.

Photo: PATH

Study Sites

The data for this survey were collected from a variety of communes in four HPV vaccine demonstration project districts in two provinces, Thanh Hoa in Northern Vietnam and Can Tho in the South. The sample was purposive—collecting data from project sites that represented urban (Binh Thuy and Ninh Kieu districts in Can Tho), rural (Nong Cong district in Thanh Hoa), and mountainous areas (Quan Hoa district in Thanh Hoa). See Table 1 for a list of the study sites and their characteristics.

Table 1. Selected study sites.

	Can Tho province		Thanh Hoa province	
	Urban		Rural	Mountainous
	Binh Thuy	Ninh Kieu	Nong Cong	Quan Hoa
Far from district	Thoi An Dong	Hung Loi	Minh Nghia, Te Loi	Trung Son, Hien Chung
Near to district	Bui Huu Nghia	An Binh	Cong Binh, Tan Phuc	Hoi Xuan, Nam Tien

In Vietnam, weather patterns vary considerably from north to south and from coastal or delta areas to mountainous regions. In the south the weather is warm with little seasonal variation. For example, in Can Tho monthly average temperature ranges from 25ºC in January to 28ºC in May.[12] However, in the north temperatures are hot in the summer and cool in the winter—in Thanh Hoa City average monthly temperature ranges from 17ºC in January to 29ºC in July.[12] In the northern mountainous regions the temperatures again vary from season to season but do not reach quite as high as in the low-elevation areas.

Results

The data generated by the electronic temperature data recorders show that during the temperature recording periods the ambient temperatures never exceeded 36ºC. In addition, we learned from the parallel measurement of temperatures ICC that there is a risk of exposing vaccines to temperatures below the recommended limit during storage and transport.

Tables 2 and 3 present temperature results during vaccine transport and administration for second and third dose vaccination sessions, respectively. Variables reported include average and range of duration of outreach days, mean and range of temperatures both ICC and OCC, and average number of vaccine vials used per session. The results are stratified by HPV vaccination dose (second dose or third dose) and district.

Table 2. Information from main HPV vaccination sessions, second dose (January 12–20, 2009).

Province	Can Tho		Thanh Hoa	
District	Ninh Kieu (2 teams)	Binh Thuy (2 teams)	Nong Cong (4 teams)	Quan Hoa† (4 teams)
Average duration of outreach day*, minutes	180	270	268	95
Range of outreach day, min–max minutes	45–240	180–525	120–465	30–180
Ambient temperature during transport, °C min–max/(mean)	19.4–25.5 (23.3)	22.4–26.1 (24.4)	12.2–22.9 (15.87)	7.6–23.0 (16.1)
Ambient (OCC) temperature during sessions, °C min–max/(mean)	20–26.9 (22.9)	19.4–24.0 (21.4)	11.9–22.4 (17.6)	8.6–14.0 (10.7)

Province	Can Tho		Thanh Hoa	
District	**Ninh Kieu (2 teams)**	**Binh Thuy (2 teams)**	**Nong Cong (4 teams)**	**Quan Hoa† (4 teams)**
ICC temperatures during transport, °C min–max/(mean)	0.3–24.2 (6.5)	4.8–12.4 (8.0)	1.2–23.1 (9.0)	0.7–11.2 (3.4)
ICC temperature during vaccination sessions, °C min–max/(mean)	0.2–17 (4.2)	1.5–12.6 (5.9)	0.7–22.6 (9.5)	1.1–3.1 (1.9)
Average number of used vaccine vials per session	72.5	33	21.1	18.8

* Outreach day is the length of time from loading vaccines in carriers until return to refrigerator.
† Nam Dong commune in Quan Hoa had a misplaced temperature monitor and was omitted from analysis for OCC readings.

Table 3. Information from main HPV vaccination sessions, third dose (May 2–19, 2009).

Province	Can Tho		Thanh Hoa	
District	**Ninh Kieu (2 teams)**	**Binh Thuy (2 teams)**	**Nong Cong (4 teams)**	**Quan Hoa (4 teams)**
Average duration of outreach day*, minutes	187.5	135	144.4	123.8
Range of outreach day, min–max minutes	90–225	15–180	90–435	75–195
Ambient temperature during transport, °C min–max/(mean)	27.0–30.4 (28.4)	27.3–31.0 (28.3)	25.9–30.4 (27.5)	21.0–29.9 (24.0)
Ambient temperature during sessions, °C min–max/(mean)	26.2–31.6 (28.4)	25.7–28.9 (26.2)	24.2–31.8 (27.1)	22.2–26.6 (24.2)
ICC temperatures during transport, °C min–max/(mean)	2.2–28.7 (11.4)	2.9–27.4 (10.1)	0.4–31.0 (10.5)	3.5–20.5 (8.1)
ICC temperature during vaccination sessions, °C min–max/(mean)	4.0–9.3 (5.7)	1.3–18.5 (5.4)	1.8–31.8 (10.0)	3.2–10.9 (5.3)
Average number of used vaccine vials per session	52	19.4	21.1	18.8

Mop-up sessions in a subset of communes were similarly evaluated (Tables 4 and 5), but kept separate from the main vaccination sessions presented in Tables 2 and 3 to prevent these smaller sessions from skewing data from the main vaccination sessions.

Table 4. Information from mop-up sessions, second dose (February 2–5, 2009).

Province	Can Tho	Thanh Hoa
District	**Ninh Kieu (2 teams)**	**Nong Cong (1 team)**
Average duration of outreach day, minutes	112.5	60
Range of outreach duration, minutes	45–180	n/a
Ambient temperature during transport, °C min–max/(mean)	23.9–24.8 (24.3)	17.1–19.3 (17.9)

Province	Can Tho	Thanh Hoa
District	**Ninh Kieu (2 teams)**	**Nong Cong (1 team)**
Ambient temperatures during vaccination sessions, °C min–max/(mean)	24.2–25.5 (24.9)	11.9–14.9 (13.3)
ICC temperatures during transport, °C min–max/(mean)	0.6–4.4 (2.6)	3.8–16.9 (5.4)
ICC temperatures during vaccination sessions, °C min–max/(mean)	0.4–5.6 (3.9)	1.7–3.3 (2.5)
Average number of used vaccine vials at the end of outreach day	4	8

Table 5. Information from mop-up sessions, third dose (June 2–6, 2009).

Province	Can Tho	Thanh Hoa
District	**Ninh Kieu (1 team, 1 session)**	**Binh Thuy (1 team, 2 sessions)**
Average duration of outreach day, minutes	570	300
Range of outreach day length, minutes	n/a	60–540
Ambient temperature during transport, °C min–max/(mean)	24.9–27.8 (26.6)	30.1–30.1 (30.1)
Ambient temperatures during vaccination sessions, °C min–max/(mean)	26.7–28.8 (27.3)	29.1–30.1 (29.5)
ICC temperatures during transport, °C min–max/(mean)	1.7–24.8 (11.0)	5.3–5.3 (5.3)
ICC temperatures during vaccination sessions, °C min–max/(mean)	1.4–8.1 (3.4)	2.4–5.5 (3.3)
Average number of used vaccine vials at the end of outreach day	10	3.5

As mentioned above, some CHCs equipped with refrigerators and district cold stores left temperature monitors attached overnight to monitor ICC and OCC temperatures during storage. The highest temperature recording on the loggers was 35.8ºC, recorded outside of the immunization study period. The data is presented for second-dose vaccinations in Table 6 and third-dose vaccinations in Table 7.

Table 6. Ambient and cold chain temperatures of HPV vaccines stored overnight (January 12–February 5, 2009).

Province	Can Tho		Thanh Hoa
District	**Binh Thuy (2 teams)**	**Ninh Kieu (1 team)**	**Quan Hoa (1 team)**
Average ambient temperature during storage, °C	23.2	26.8	13.6
Ambient temperature range during storage, °C	19.0–30.9	20.7–31.1	7.6–16.5

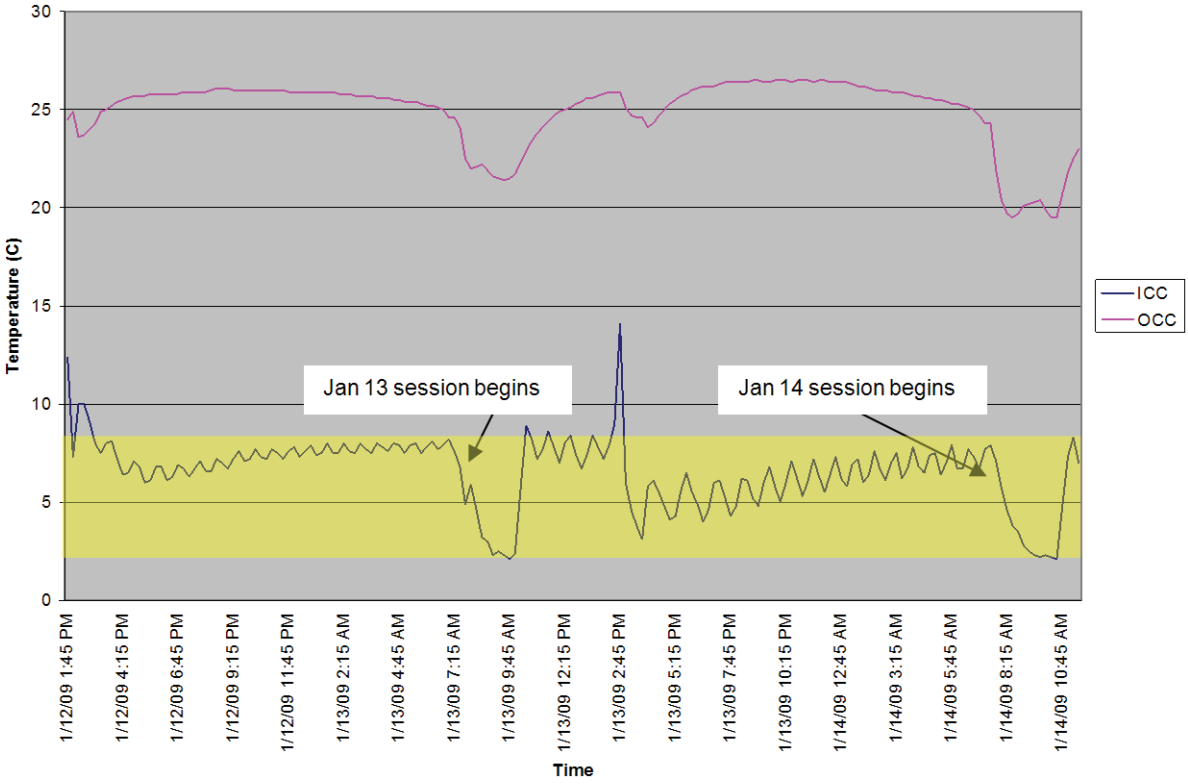
Province	Can Tho		Thanh Hoa
Average ICC temperature during storage, °C	3.8	5.5	1.5
ICC temperature range during storage, °C	-3.4–9.1	3–8.6	0.6–4.9

Table 7. Ambient and cold chain temperature of HPV vaccines stored overnight (May 2–June 6, 2009).

Province	Can Tho	Thanh Hoa	
District	**Binh Thuy (2 teams)**	**Nong Cong (1 team)**	**Quan Hoa (1 team)**
Average ambient temperature during storage, °C	30.4	26.4	23.3
Ambient temperature range during storage, °C	21.1–31.9	24.4–31.3	19.8–31.7
Average ICC temperature during storage, °C	5.1	10.5	4.7
ICC temperature range during storage, °C	-0.1–22.2	0.1–25.4	3.5–5.6

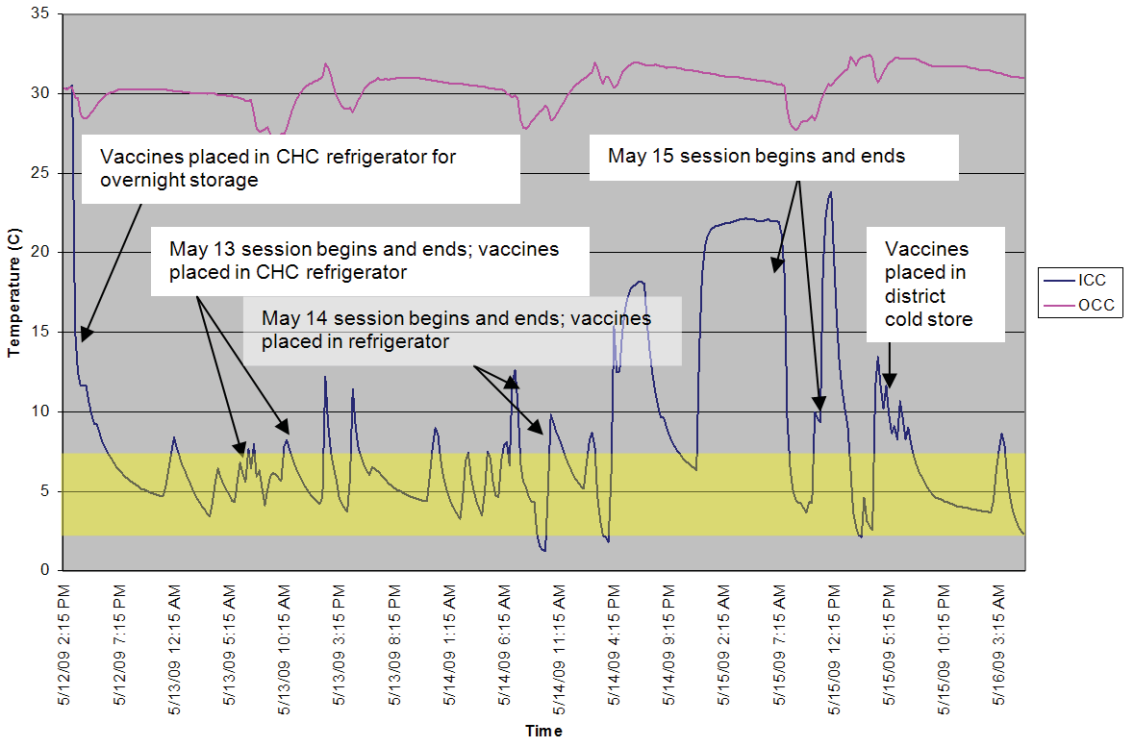
Figures 1 through 6 are illustrative examples of ICC and OCC temperatures recorded over the course of the main vaccination sessions.

Figure 1. Data comparing ICC temperatures and OCC temperatures for HPV vaccine transport and storage during second dose vaccination sessions in Bui Huu Nghia commune (Binh Thuy district, Can Tho province).



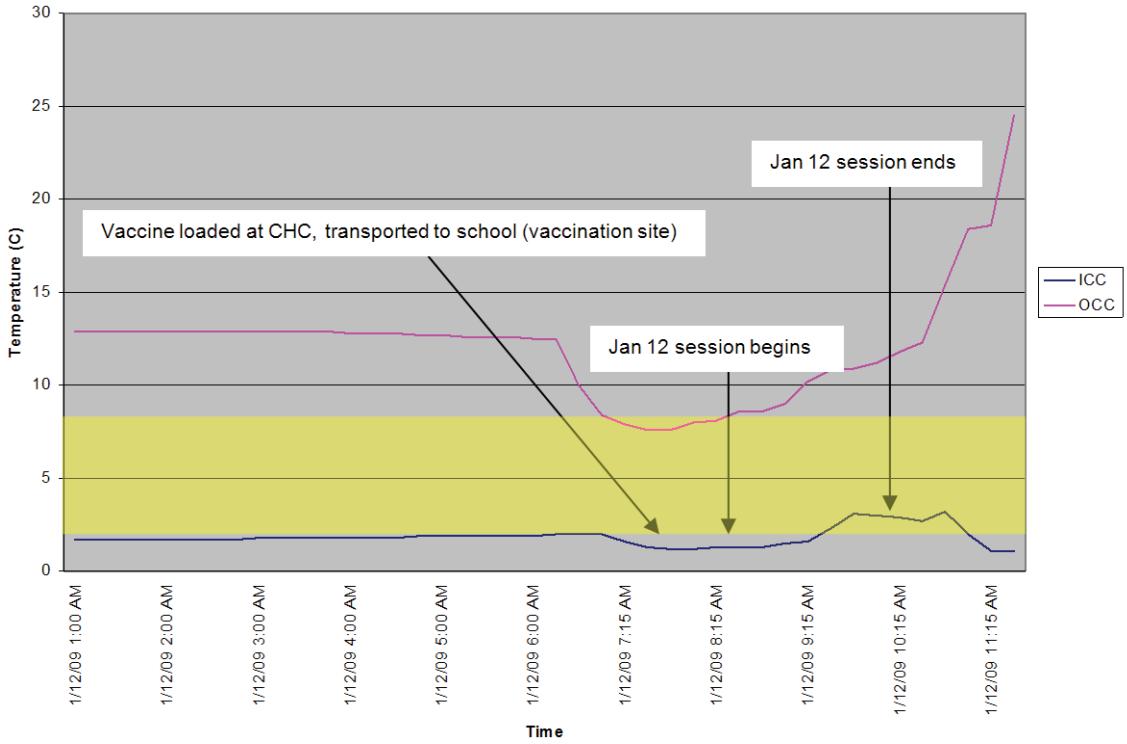
Note: Yellow shaded region represents 2° to 8°C, which is the manufacturer recommended storage temperature for HPV vaccine.

Figure 2. Data comparing ICC and OCC temperatures for HPV vaccine transport and storage during third dose vaccination sessions in Bui Huu Nghia commune (Binh Thuy district, Can Tho province).



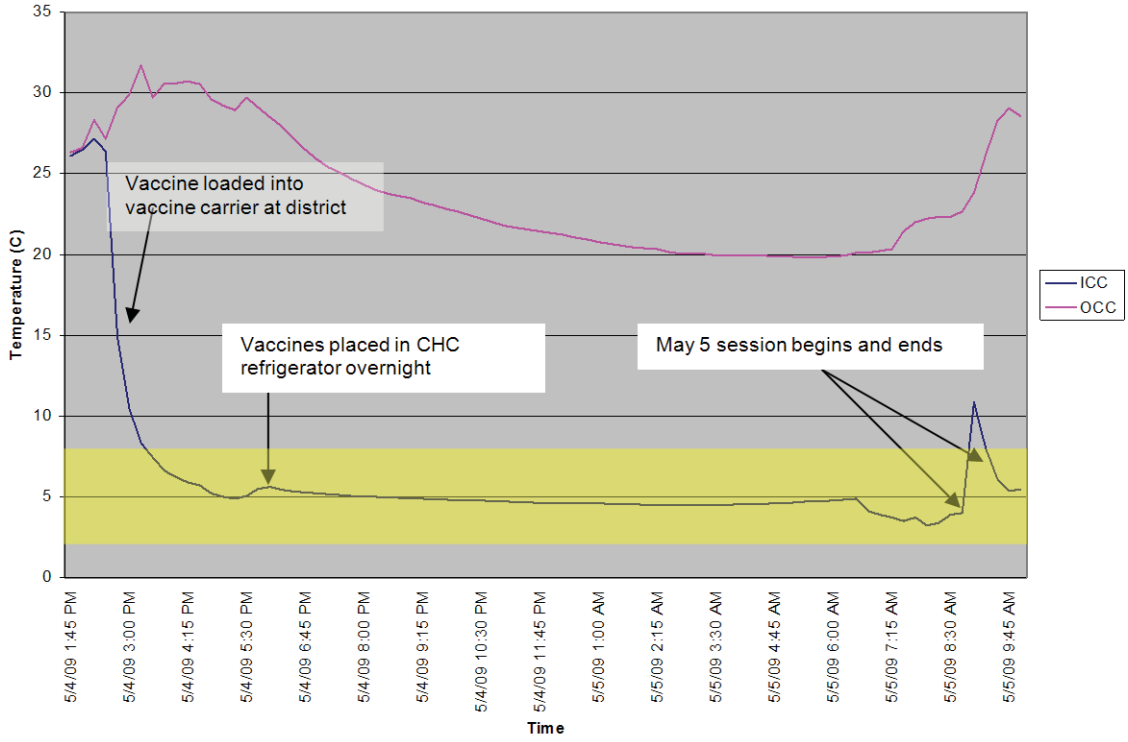
Note: Yellow shaded region represents 2° to 8°C, which is the manufacturer recommended storage temperature for HPV vaccine.

Figure 3. Data comparing ICC and OCC temperatures for HPV vaccine transport, storage, and during second dose vaccination sessions in Trung Son commune (Quan Hoa district, Thanh Hoa province).



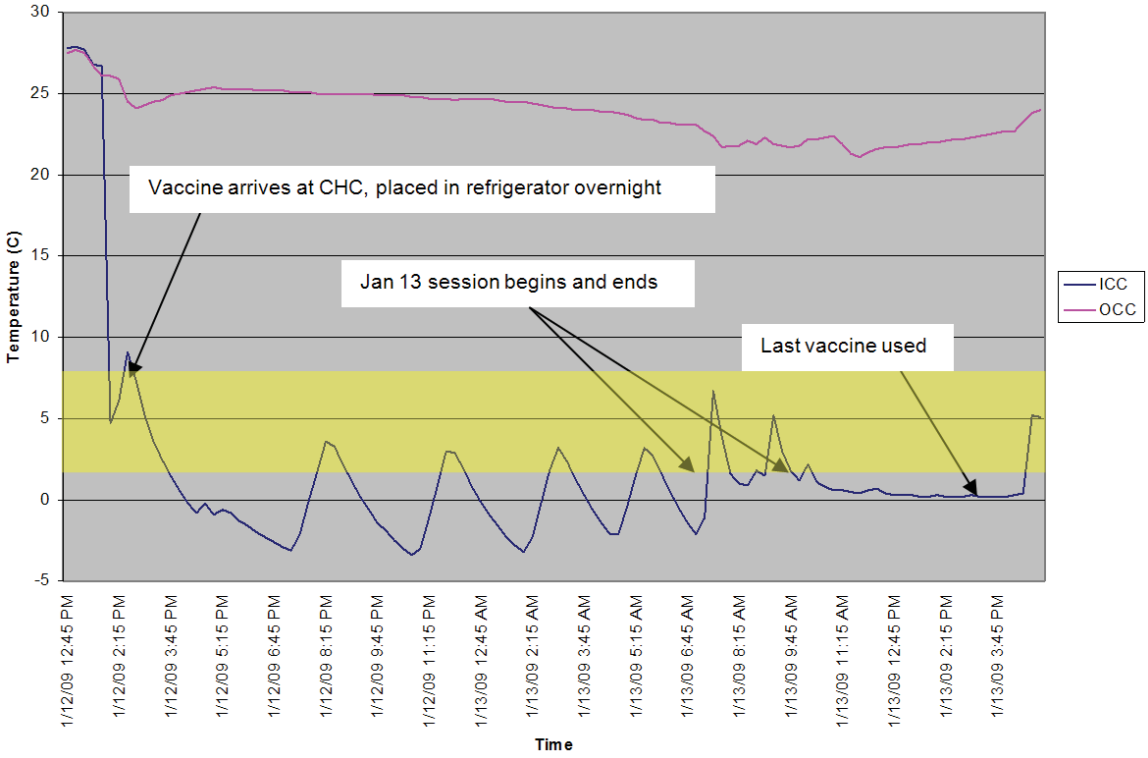
Note: Yellow shaded region represents 2° to 8°C, which is the manufacturer recommended storage temperature for HPV vaccine.

Figure 4. Data comparing ICC and OCC temperatures for HPV vaccine transport and storage during third dose vaccination sessions in Trung Son commune (Quan Hoa district, Thanh Hoa province).



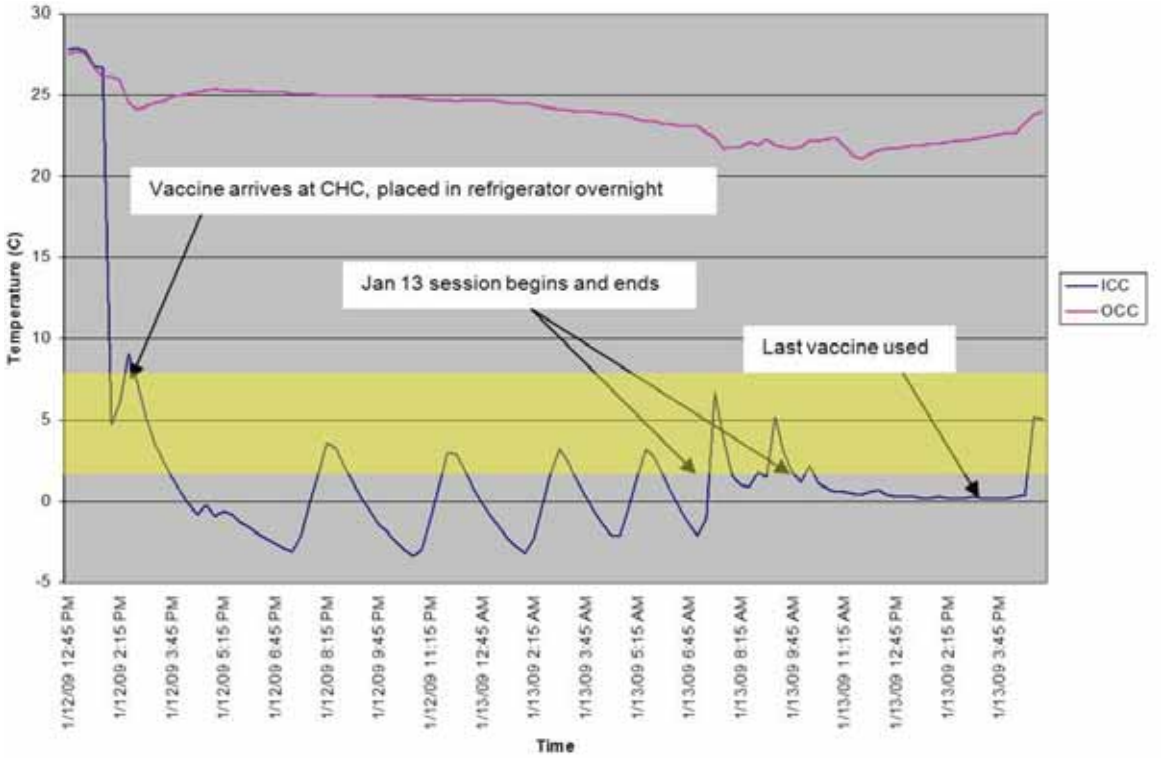
Note: Yellow shaded region represents 2° to 8°C, which is the manufacturer recommended storage temperature for HPV vaccine.

Figure 5. Data comparing ICC and OCC temperatures for HPV vaccine transport and storage during second dose vaccination sessions in Thoi An Dong commune (Binh Thuy district, Can Tho province). Note temperatures below freezing.



Note: Yellow shaded region represents 2° to 8°C, which is the manufacturer recommended storage temperature for HPV vaccine.

Figure 6. Data comparing ICC and OCC temperatures for HPV vaccine transport and storage during third-dose vaccination sessions in Thoi An Dong commune (Binh Thuy district, Can Tho province).



Note: Yellow shaded region represents 2° to 8°C, which is the manufacturer recommended storage temperature for HPV vaccine.

Discussion

There are a number of interesting findings related to this analysis. Observations to consider include the results of ambient temperature recording during storage and transport, impact of season and geography, and the apparent risk of exposure to temperatures below recommended storage temperatures.

The mean ambient temperatures by commune as measured during the immunization sessions ranged from 10.4° to 26.9°C in January and February during the second dose, and from 22.0° to 31.8°C in May and June during the third dose, so we can see a difference in the results caused by seasonality. As expected, the mean ambient temperatures were cooler in the mountainous areas both during the January/February and the May/June sessions. Looking at the recordings taken during immunization sessions, transport, and storage at the CHC, the highest reading was 31.9°C, recorded in May in Binh Thuy district. Because, as mentioned earlier, published data or recommendations for both the Merck vaccine used in this study and the GlaxoSmithKline HPV vaccine support the possibility of limited exposure to a temperature as high as 37°C; it is notable that none of the ambient temperature loggers recorded temperatures as high as that during the course of the time they were activated for this study.

Looking at the low end of the recorded temperature ranges, the HPV vaccination second-dose data in Table 2 shows that all four districts had temperatures that fell below 2ºC either during transport or in immunization sessions. During the third-dose sessions (see Table 3), half of the districts experienced temperatures below 2°C while in transport or in sessions. However, there were no examples of freezing temperatures below 0ºC during immunization sessions or transport.

For the few districts where temperature monitoring of overnight storage was conducted, during the second-dose period in January/February, the logger in one CHC recorded ICC temperatures below 0ºC, and another in a different district had a minimum temperature below 2ºC. During the May/June period, again the same logger recorded temperatures below 0ºC, and one other logger recorded a minimum temperature below 2ºC.

It is important to note that the data collected in this study only reflect the temperature that the loggers were exposed to; we cannot conclude absolutely that the vaccines were exposed to these same temperatures or that they became physically frozen. Variations in temperature in different areas of the refrigerator or carrier and variations in user compliance with study protocols could lead to differences between temperatures of the logger and the vaccine. Furthermore, concerning temperatures below 0ºC, exposure of vaccines to subzero temperatures does not necessarily mean that the vaccines were frozen and therefore damaged. Many factors play a role in the process of freezing and in the extent of freeze damage including the presence or absence of agitation, rate of temperature decline, duration of exposure, and number of freeze-thaw cycles incurred.[13]

Regardless, these data serve as a reminder that it is possible to reach temperatures in the vaccine cold chain that are too cold. It is important to practice good refrigerator management, such as using max-min thermometers, performing regular temperature

monitoring, and ordering of refrigerator maintenance if monitoring indicates refrigerator performance is not meeting the standard.

Conclusions and recommendations

Continuous monitoring of temperatures both ICC and OCC during periods of immunization activity is an interesting way to view the conditions to which vaccines may be exposed. This study was conducted in particular to help answer the question: What are some examples of ambient temperatures in which HPV vaccine sessions are being conducted? This information is being collected to contribute to answering the larger question: Would storage in a controlled temperature chain higher than the current 2º to 8ºC be feasible for vaccines?

Based on the data collected in this study, the following conclusions can be made relevant to this discussion:

- The examples gathered during this study indicate that ambient temperatures during midday vaccination sessions can range from the low- to mid-20s (Celsius) in winter, and mid-20s to lower-30s (Celsius) in summer in our study sites. These are limited examples, however, from which broad conclusions may not be drawn.
- Differences seen between the two time sessions, one conducted in winter and one in summer, indicate that if lower ambient temperatures were to be a criterion for establishing the schedule for HPV vaccination sessions, then winter would be a preferable season for their timing. While in most places it is not possible to avoid warm months over a 6-month dosing period, as is needed for HPV vaccine, the ambient temperature trends can be taken into account in session planning.
- If 37ºC were to become established as a limit for HPV vaccine exposure, as supported by some manufacturers' published stability data, then this study shows the possibility of managing vaccine sessions under ambient temperature conditions that are well within that limit.

The data collected from vaccine carriers and refrigerators during this study demonstrate that the ICC is sometimes colder than recommended. "Too cold" temperature conditions in vaccine cold chains are common in countries throughout the world and have been well documented.[14] It is important to practice good temperature management to prevent making vaccines too cold. Much work has been done by the Vietnam National Expanded Programme on Immunization in recent years to prevent freezing ICC. The fact that this study observed no temperatures below 0ºC in vaccine carriers indicates that this work is paying off. In order to maintain and further this success, the following three possible actions are suggested: 1) conduct periodic temperature monitoring of the cold chain to provide feedback on system success; 2) implement strategies to adjust the quantity of ice that is used in vaccine carriers depending on the seasonal weather conditions; 3) consider implementation of WHO's recommendation of ice pack conditioning or using chilled water packs rather than ice packs where appropriate;[15,16] 4) employ practices to prevent freezing temperatures in refrigerators such as use of max-min thermometers, performing regular temperature monitoring, and ordering maintenance if monitoring indicates refrigerator performance is not meeting the standard.

There is nothing in these findings that precludes further exploration of the use of controlled temperature chains at temperatures higher than 2º to 8ºC, and in fact this could have a positive impact given that our findings indicate that exposure to temperatures colder than recommended could be a risk in vaccine carriers and refrigerators. The following are some specific recommendations based on the results of this study:

- As mentioned earlier in this report, the labeling for the Merck HPV vaccine now allows non-refrigerated storage of the vaccine for not more than 72 hours at temperatures not to exceed 25ºC. This could be used by health workers to eliminate ice from vaccine carriers while still remaining compliant with manufacturer's storage and handling instructions. This study has shown that ambient temperatures often exceed 25ºC, but vaccine carriers with chilled water packs could provide an appropriate temperature environment for the vaccine with less risk from freezing temperatures.[16]
- Current studies are ongoing to evaluate the stability of several hepatitis B vaccine products at 37ºC. If results are positive, this study indicates that ambient temperatures in Vietnam might also be compatible for hepatitis B vaccine storage and transport over similarly short time periods.
- More testing could be done by manufacturers or research institutes to better understand the behavior of vaccines that are kept at higher temperatures or that experience fluctuating temperatures. For additional data, similar studies such as this one could be conducted in other countries with varying climate and weather. A report and data from a study carried out in Uganda also in 2009 is available from PATH.

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