Evaluation of cold chain monitoring in Kelantan, Malaysia

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An analysis was carried out on a total of 883 cold chain monitor (CCM) cards, which had been attached to batches of poliomyelitis, measles, DPT (diphtheria, pertussis, tetanus) and hepatitis B vaccines, during their transport and storage from the central store in Kuala Lumpur to Kelantan, a state in north-eastern Malaysia; 234 freeze watches attached to hepatitis B vaccines were also analysed. The monitor cards and freeze watches were observed at six levels between the central store and the periphery during distribution of the vaccines, and a colour change in any of the four windows (A, B, C, D) on the CCM cards or the freeze watches was recorded. In addition, 33 unopened vials of oral poliovirus vaccine (OPV), collected from refrigerators in 29 health facilities in Kelantan, were tested for potency using the tissue culture infective dose 50 ($TCID_{50}$) method; 14 of them (42%) did not meet the WHO criteria for potent vaccines.

The results showed that at the final destination 13.4% of all cards remained white while a colour change to blue was observed in 65% in window A, 16.6% in window B, and 4.4% in window C; none had turned blue in window D indicating that the vaccine had not been subjected to temperatures ≥34°C for 2 hours. All but 2 of the 234 freeze watches had turned purple, which indicates exposure of the hepatitis B vaccines to temperatures below 0°C. These results will assist health planners to correct the weaknesses identified in the cold chain system.

Introduction

Immunization is a powerful and very cost-effective weapon of modern medicine for the prevention of major childhood diseases. In Malaysia, immunization is routinely given against such diseases of childhood as tuberculosis, diphtheria, tetanus, pertussis, poliomyelitis, measles, rubella and hepatitis B. In 1992 the infant (under 1 year) mortality rate and toddler (1–4 years) mortality rate in Peninsular Malaysia were 11.6 and 0.8 per 1000 live births, respectively (*1*). Immunization coverage data for 1992 are shown in Table 1.

Among the Health for All goals by the year 2000, as described in WHO's Ninth General Programme of Work (1996–2001), are maintenance of a high level of immunization coverage (at least 90% of children under 1 year old), reduction of measles cases (by 90%) and deaths (by 95%), elimination of neonatal tetanus (i.e., no longer of public health significance in terms of incidence and severity), and global eradication of poliomyelitis (*2*). Although routine immunization has greatly reduced the incidence of these diseases, outbreaks have occurred from time to time. This raises questions on the effectiveness of the immunization programme, for the proper functioning of which the cold chain is vital. High coverage would have little meaning if the vaccines administered had lost their potency (*3*).

To the best of our knowledge this is the first study in south-east Asia using cold chain monitors to evaluate the effectiveness of the cold chain. It provides useful information to health planners and policy-makers for strengthening the cold chain in the national immunization programme.

Table 1: **Immunization coverage in Malaysia in 1992**

Vaccine type	Coverage (%)
BCG	98.4
OPV–I	91.2
OPV–III	90.4
Measles	79.6
DPT–I	91.7
DPT–II	91.3
HBV–I	94.8
HBV–II	90.4
HBV–III	86.7

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Site and methods

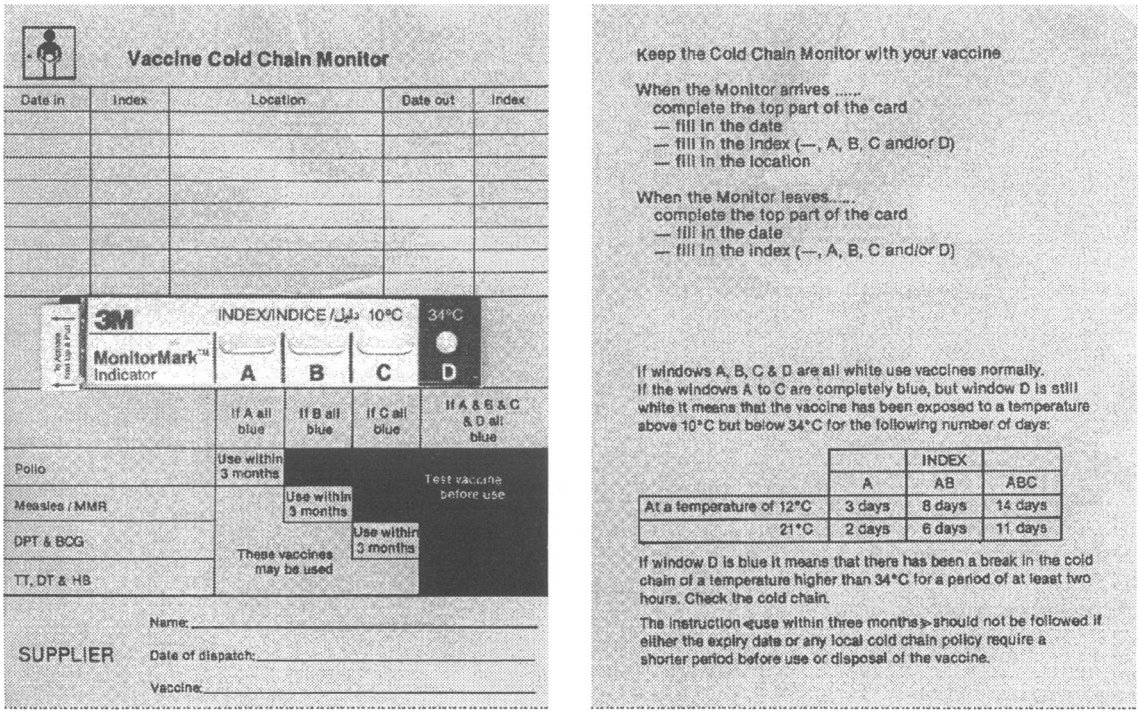
Kelantan, one of Malaysia's 13 states, is situated on the north-east coast of the peninsula and has a dry and a wet season, with little variation in temperature throughout the year (range: 22–34 °C). All ten districts in the state were included in this study; all 248 health facilities are linked by road except for a few that can only be reached by river. Vaccines from the central national store in Kuala Lumpur are always sent by air to the state-level store, but local distribution within the state is mostly by 4-wheel-drive motor vehicles. The vaccines are packed with ice and sawdust for transport and during distribution. In this study, no changes or adjustments were made in the routine vaccine supplies and flow, transportation, and usage. The staff involved in management of the cold chain had been trained in cold chain monitoring in April 1990 during a national workshop, as well as on the site by a WHO team.

Methodology

Cold chain monitor (CCM) cards (3M type) and freeze watches (FWs) (Coldmark type) are used to monitor the vaccines. Each CCM, which is effective in indicating whether the vaccines were exposed to higher than recommended temperatures, has a heat-sensitive indicator in the form of a strip with four windows (A, B, C and D in Fig. 1). The indicator operates above two different temperatures (10 °C and 34 °C). The higher the temperature above the CCM threshold, the more rapidly the colour changes to blue, which is irreversible even when exposed to lower temperatures again. The manufacturer recommends that the CCM card be refrigerated for at least 30 minutes before activation. Activation is carried out by pulling out the tab on the left-hand side of the strip. Colour changes were recorded at various transit levels along the vaccine route from level 1 (central national store) to level 6 (peripheral health facility). Levels 1 and 2 are the national store and state store, respectively, for vaccine storage purposes only. Vaccine usage for immunization starts at level 3, with maximum usage at levels 4 and 5. On the back of each CCM card are given instructions to interpret the readings (Fig. 1).

The Coldmark freeze watch is used to monitor the temperature of tetanus toxoid, triple antigen and hepatitis B vaccines, which should not be exposed to

Fig. 1. **Cold chain monitor (CCM) card: (left) front and (right) back views.**



temperatures below 0 °C. It consists of a bulb at the end of a glass tube, which remains colourless at temperatures above 0 °C but changes to purple at and below 0 °C. Vaccines are routinely dispatched by manufacturers to the central national store in Kuala Lumpur with a CCM card and FW (one CCM and/or one FW per 3000 doses). However, for the purpose of this study additional CCMs and FWs were added at the central store for vaccines that were destined for Kelantan (Fig. 2).

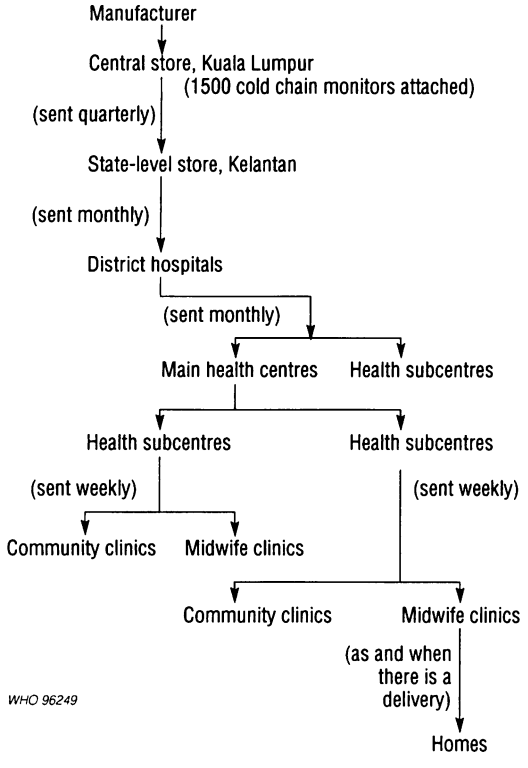
In Malaysia the frequency of dispatch to peripheral levels varies, being once in 3 months, once a month, fortnightly or weekly depending on the demand, the available storage facilities, and the distance from the health centre. Vaccines are also stored over similar periods at the periphery where, as a matter of policy, an additional 25% of the orders is held in reserve at all times.

The CCMs and FWs were attached to the various types of vaccines in their original packing, without excessive handling of the vaccines; 1500 CCMs were attached to poliovirus, measles, DPT (diphtheria–pertussis–tetanus) and hepatitis B vaccines (HBV), the last named carrying also 300 freeze watches. These were distributed following the routine schedule to the state store in Kelantan. On receipt at the various transit levels, the monitor cards were read and recorded. Once the vaccines had been completely used up, the completed cards were collected and stored at room temperature until analysis.

To test the effectiveness of the cold chain system, 33 samples of oral poliovirus vaccine (OPV) and 3 of freeze-dried measles vaccine from the peripheral transit levels were carefully packed in ice and transported in insulated flasks to the Institute for Medical Research (IMR) for potency testing using Hep-2 cells (Cincinnati line, passage number 191). Each of the poliovirus types in the OPV was titrated separately using heterologous type-specific poliovirus antisera for neutralizing the other viral types present. For each titration, a reference vaccine strain stored at −20 °C was included as standard. The poliovirus vaccine titration endpoint was calculated by the Spearman–Kärber formula and expressed as $TCID_{50}$ per dose (*4*). The origin of these 33 polio vaccine samples was as follows: state store (1), district hospitals/integrated stores (3), outpatient department (1), main health centres (6), health subcentres (13), maternal and child health centres (4), and community clinics (5).

Measles vaccine titration was performed using Vero cells and standard freeze-dried reference vaccine; the endpoint was calculated by the Spearman–Kärber formula (*4*) and expressed as $\log_{10}$ TCID per dose.

Fig. 2. **Flow-chart for cold chain monitors.**



Results

The data were analysed using WHO-EPI software.

Cold chain monitor. Of the total of 1500 CCM cards distributed, 883 (59%) were available for analysis by colour index on arrival at the various transit and final destinations (Table 2). At level 1, for example, 0.3% had turned blue in window A; no monitors were blue in windows B and C. At level 6, however, 65.6% of the CCMs had turned blue in window A, 16.6% in window B (from 0% at level 1), and 4.4% in window C (from 0% at level 1). Table 3 shows the proportions of CCM cards that turned blue during transportation and storage at each level; the percentages are not cumulative. The levels with the highest proportion of cards turning blue in window B during storage were at level 3 and level 4 (5.7% and 5.1%, resp.) (Table 3). Colour changes in windows A and B occurred more frequently during storage than during transportation.

Table 2: **Percentage of CCM cards with colour change in windows A to D on arrival at different levels of vaccine distribution**

Place	Level	Windows with colour change (%): White	A	B	C	D
Central medical store, Kuala Lumpur	L1	99.7	0.3	0	0	0
State medical store, Kelantan	L2	83.3	10.3	6.3	0.1	0
District hospital	L3	62.0	31.1	6.6	0.3	0
Health centre	L4	35.5	56.7	7.6	1.2	0
Health subcentre	L5	24.3	59.7	14.1	1.9	0
Community clinic	L6	13.4	65.6	16.6	4.4	0

Table 3: **Percentage of colour change during transport and during storage at various levels**

Place	Level	Colour change during transport (%): Route	White	A	B	C	Storage	Colour change during storage (%): White	A	B	C
Central medical store, Kuala Lumpur	L1	Supplier to L1	99.7	0.3	0	0	In L1	96.1	3.1	0.8	0
State medical store, Kelantan	L2	L1 to L2	94.8	4.5	0.7	0	In L2	88.1	11.5	0.4	0
District hospital	L3	L2 to L3	90.7	9.1	0.2	0	In L3	79.0	14.2	5.7	1.1
Health centre	L4	L3 to L4	92.8	7.0	0.2	0	In L4	78.2	16.1	5.1	0.5
Health Subcentre	L5	L4 to L5	95.7	3.3	1.0	0	In L5	81.7	16.3	1.7	0.3
Community clinic	L6	L5 to L6	92.1	7.2	0.7	0	In L6	81.4	16.7	1.9	0

Table 4 shows the percentages of CCM cards subjected to delay during transport of vaccines from the supplier to level 1 and onwards to level 6. A delay of more than 6 days for 94% of vaccine dispatches was noted between the supplier and level 1. The transport times beyond level 1 (range: 1–2 days) were within acceptable limits. Table 4 also shows the duration of storage at each transit level; 56% of the vaccines were stored for more than 2 weeks in level 1, and nearly 60% for more than a week in level 2. From level 3 to level 6 between 31% and 21% of vaccines were stored for less than a week.

Table 4: **Percentage of delays (days) during transport between levels, and of delays (weeks) during storage at various levels**

	Days: <1	1 to <2	2 to <3	3 to <4	4 to <5	5 to <6	>6
Route:							
Supplier to L1	0	0	0	0.2	5.5	0.3	94.0
L1 to L2	8.2	42.8	46.6	0.8	0	0.2	1.4
L2 to L3	89.0	5.1	2.2	0	0	0.3	3.4
L3 to L4	95.5	1.1	0	0	1.1	0.3	2.0
L4 to L5	90.7	0.7	0	2.2	0.7	0	5.7
L5 to L6	91.4	0	1	1.9	0	1.9	3.8
	Weeks: <1	1 to <2	2 to <3	3 to <4	4 to <5	5 to >6	>6
Storage in:							
L1	3.1	6.0	56.1	13.6	2.0	1.5	17.3
L2	40.5	13.1	15.5	9.5	3.3	2.1	16.0
L3	31.4	13.9	8.5	7.7	8.5	6.9	23.1
L4	27.3	16.4	9.7	8.2	10.3	2.9	25.2
L5	23.5	15.6	8.6	10.4	7.3	6.4	28.2
L6	21.8	10.9	13.5	7.1	11.5	6.4	28.8

Table 5: **Potency titres of 33 batches of poliovirus vaccines type 1 (P1), type 2 (P2) and type 3 (P3), compared with indications on the CCM cards**

CCM No.	Batch No.	Expiry date (month/year)	Log_{10} TCID per 0.1 ml			Potency	State of CCM[b]
			Type P1[a]	Type P2[a]	Type P3[a]		
001	S 1448A4B	3.92	**5.4**	4.6	5.0	Low	No card
002	S 1386A4A	9.91	**5.4**	4.6	5.1	Low	No card
003	S 1431A4A	2.92	5.6	4.6	**4.8**	Low	No card
004	S 1492A4C	12.92	5.6	4.9	5.0	Pass	No card
005	S 1492A4B	11.92	5.8	4.9	5.0	Pass	A, B
006	S 1492A4B	11.92	5.8	4.7	5.0	Pass	A, B
007	S 1448A4B	3.92	5.6	4.9	5.1	Pass	A, B
008	S 1448A4B	3.92	5.7	5.1	5.4	Pass	No card
009	S 1431A4A	2.92	5.9	4.9	5.4	Pass	No card
010	S 1431A4A	2.92	5.6	4.8	5.1	Pass	No card
011	S 1448A4B	3.92	6.0	4.8	5.4	Pass	No card
012	S 1492A4B	11.92	6.1	4.7	5.2	Pass	No card
013	S 1386A4A	9.91	**5.2**	**4.3**	**4.4**	Low	A
014	S 1492A4B	11.92	5.9	4.8	**4.8**	Low	A, B
015	S 1492A4C	12.92	5.8	4.7	5.1	Pass	No card
016	S 1492A4C	12.92	6.1	4.5	5.1	Pass	No card
017	S 1431A4A	2.92	5.6	4.6	**4.8**	Low	No card
018	S 1492A4C	12.92	5.7	4.7	5.1	Pass	A
019	S 1492A4C	12.92	5.9	4.7	5.0	Pass	A, B
020	S 1492A4C	12.92	5.5	4.5	**4.6**	Low	A
021	S 1448A4B	3.92	5.7	4.5	**4.7**	Low	A
022	S 1492A4C	12.92	5.9	4.7	**4.8**	Low	A
023	S 1492A4B	11.92	6.1	4.5	**4.7**	Low	A, B
024	S 1492A4C	12.92	5.7	4.6	**4.6**	Low	A, B
025	S 1492A4C	1.93	**5.1**	4.5	5.0	Low	A, B, C
026	S 1448A4B	3.92	5.5	4.5	5.0	Pass	A, B
027	S 1492A4C	12.92	5.8	4.4	**4.9**	Low	White
028	S 1492A4C	12.92	5.8	4.5	5.3	Pass	A
029	S 1492A4C	12.92	5.8	4.6	5.4	Pass	White
030	S 1492A4C	12.92	6.0	4.5	5.0	Pass	A
031	S 1448A4B	3.92	5.8	4.6	5.4	Pass	No card
032	S 1448A4B	3.92	5.9	4.8	5.1	Pass	No card
033	S 1492A4B	11.92	5.6	**4.1**	**4.7**	Low	A, B, C

[a] Minimum titre for a single human dose should not be less than 10^6, 10^5 and $10^{5.5}$ for poliovirus types 1, 2 and 3, respectively. According to the WHO criteria, the assay should not differ by more than $10^{0.5}$; titres below this point are indicated in **bold**.
[b] A, B and C indicate the windows in the CCM cards that had turned blue. See text for possible explanation of discrepancies.

Of the total of 300 freeze watches that accompanied the HBV vaccines, 234 were available for analysis. Except for two, all (99%) had turned purple at the state-level store.

Potency. The potency of 33 vials of poliovirus vaccine selected from various health centres was tested in the IMR using the $TCID_{50}$ method. Fourteen vials (42%) showed low potency according to the WHO criteria of potency testing (Table 5), according to which the minimum titre for a single human dose of Sabin trivalent vaccine should not be less than 10^6 infectious units for type 1 poliovirus, 10^5 infectious units for type 2 poliovirus, and $10^{5.5}$ infectious units for type 3 poliovirus (*5*).

At the 95% confidence interval the assay should not differ by more than $10^{0.5}$. Of the 14 vials of polio vaccine showing low potency, only three had tested low on more than one poliovirus type.

All three vials of measles vaccine tested had titres above the WHO-recommended values. Measles vaccine is also more heat stable than polio vaccine because it is distributed in freeze-dried form and is reconstituted just before use.

Discussion

Some weaknesses were identified through this study. Window A, for example, in 65.6% of CCM cards had turned to blue by the time the vaccines had reached the peripheral health centre (level 6); another 16.6% had turned blue at window B and 4.4% at window C by the time they reached level 6. This is an indication that the cold chain in Malaysia needs strengthening. Appropriate storage and transportation of vaccines are of utmost importance for maintaining their potency. Our study showed that the risk of

allowing HBV to freeze was greatest at the state-level store.

Inactivated vaccines cannot be identified except by potency tests, which are not widely available in Malaysia. Only large volumes of vaccines, when suspected, are sent for potency testing which is very expensive and laborious to carry out; it is usually cheaper to discard small stocks of suspected vaccine. A defective vaccine may only become apparent when a vaccinated person acquires the disease the vaccine was supposed to prevent (*6*). There is currently no convenient method for monitoring vaccines, except by using cold chain monitor cards and freeze watches. Most sensitive to high temperatures are the live viral vaccines (e.g., poliovirus and measles vaccines); killed vaccines and toxoids are generally more tolerant of higher temperatures with no refrigeration but can be destroyed by extreme temperatures, particularly freezing. A higher proportion of cards turned blue in window B at transit levels 3 and 4 which represent the district-level stores and the main health centres, respectively. Some district stores are a long distance away from the state-level store so that transport of vaccines by road can take 6–8 hours in temperatures of 30–32 °C. Similar findings were reported in a European country, but in that study the vaccines were distributed by post (*7*).

Vaccines transported from the manufacturer to level 1 remained satisfactory although 94% of them took 6 days or more to arrive. Their storage at level 1 was also satisfactory, with only 3.3% of cards changing to blue at window A and 0.8% of cards changing to blue at window B. In a study in India (*8*) it was reported that most of the cards turned blue at level 1. Most of the vaccines were stored for more than two weeks in level 1. At level 2 the storage time was much less; about 40% were stored for a week or less, the vaccines being passed on to levels 3 and 4. The current guideline is that there should be 20–25% reserve of vaccines at every level at all times for use in cases of emergency and vaccine delay. In a study in Egypt (*9*), it was reported that many areas had no vaccines in stock, which means that a number of children must have been turned away because there was no vaccine. This reduces immunization coverage and prevents the realization of our objective to immunize >90% of the susceptible population.

Poliovirus vaccine is the most heat sensitive of all the vaccines; the trivalent vaccine contains poliovirus types 1, 2 and 3 which must meet the minimum viral titres recommended by WHO for each viral type. Even if only one viral type falls below the recommended titre, the vaccine is considered to be not potent. Using these stringent criteria, 42% of the 33 vials of vaccines did not pass the potency test (Table 5). To explain discrepancies between this result and the colour change in windows A, B and C on the CCM card it is possible that the vaccine and the CCM card had been separated at some point during transit or that an older vial was attached to the CCM card and sent for potency testing. In a study carried out in India in 1992, poliovirus vaccines were tested at various temperatures and were found to be potent despite the change in windows A and B (V.B. Mandke et al., 1991, unpublished).[a]

Although 1500 CCM cards had been sent out, only 883 were received; thus, about 41% were lost or misplaced, or thrown away, perhaps because they had turned blue. This was the first time some people at the peripheral level had seen these cards, which they may not have filled in properly; or they may have been afraid to be interviewed since training to fill these cards had been conducted earlier. A similar situation was not reported in studies carried out in England (*6*), Hungary (*7*), and India (*8*).

All the 300 freeze watches which accompanied the hepatitis-B vaccines into the refrigerator in the state-level store showed temperature variations within the refrigerator with a colour change in those placed at the back of the refrigerator. As the maximum–minimum thermometer did not show freezing temperatures, it is difficult to say what went wrong. Subsequently, only a few of the freeze watches followed the hepatitis B vaccine to the peripheral level.

This study has brought to light many weaknesses in the cold chain, such as absence of contingency plans during power cuts, or inadequate training of health staff, pharmacists, storekeepers and attendants in cold chain maintenance procedures. Sometimes there were problems when vaccines were not available, or because of old refrigerators, or when there was no cold room in the state-level store, or inadequate equipment to store a large quantity of vaccines. Some thermometers were not in working order, or vehicles for transporting vaccines were not air-conditioned; some centres did not keep temperature records or had expired vaccines in stock, and potency tests were not carried out regularly. The results of this study should assist managers and health planners in the rectification of these conditions which will definitely improve the cold chain.

[a] *Editorial comment.* WHO/EPI does not recommend the use of cold chain monitors to provide an indication of the vaccines' potency. As their name implies, the CCMs are used to monitor the cold chain and warn of failure at any point. The potency of the vaccine cannot be determined by the status of the cold chain monitor.

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Résumé

Evaluation de la surveillance de la chaîne du froid dans l'Etat de Kelantan, Malaisie

La Malaisie ayant un climat chaud et humide toute l'année, avec des températures comprises entre 22°C et 34°C, il a été procédé en 1991–1992 à une évaluation du système de surveillance de la chaîne du froid et au contrôle de l'activité des vaccins utilisés dans le cadre du Programme élargi de vaccination. Au total, 883 cartes de contrôle de la chaîne du froid (CCM) jointes à 4 types de vaccins (poliomyélite, rougeole, DTC (diphtérie, tétanos, coqueluche) et hépatite B) transportés du dépôt central de Kuala Lumpur à l'Etat de Kerantan, ont été analysées; 234 indicateurs de congélation joints au vaccin antihépatite B ont également été analysés. Les cartes de contrôle de la chaîne du froid ont été observées à diverses étapes du transport, tout changement de couleur dans l'une des fenêtres (A, B, C, D) étant noté. Tout changement de couleur de l'ampoule de l'indicateur de congélation a également été noté.

L'activité de 33 flacons non ouverts de vaccin antipoliomyélitique pris dans les réfrigérateurs de 29 établissements de santé de l'Etat a été déterminée à l'Institut de recherche médicale de Kuala Lumpur par la méthode des $DICT_{50}$; 14 d'entre eux (42%) ne répondaient pas aux normes OMS d'activité des vaccins. L'observation des cartes de contrôle au point de livraison des vaccins a montré que 13,4% des cartes étaient restées blanches tandis que 65% avaient viré au bleu dans la fenêtre A, 16,6% dans la fenêtre B, 4,4% dans la fenêtre C, et aucune dans la fenêtre D. Tous les indicateurs de congélation sauf 2 avaient viré au violet, ce qui indique que les vaccins antihépatite B ont été exposés à des températures égales ou inférieures à 0°C.

Les points faibles repérés au niveau de la chaîne du froid étaient l'absence de plan de secours en cas de coupure d'électricité et l'insuffisance de la formation du personnel concernant l'intégrité de la chaîne du froid. Les problèmes constatés au niveau du transport et du stockage étaient dus au matérial trop vétuste pour assurer le maintien des températures optimales, à l'absence de chambre froide dans le dépôt central de l'Etat, au non-fonctionnement des thermomètres, à l'absence d'enregistrement quotidien des températures et parfois, dans certains centres, à la présence de vaccins périmés. Ces insuffisances devront être corrigées dans les meilleurs délais.

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