Are childhood immunization programmes in Australia at risk? Investigation of the cold chain in the Northern Territory

N.C. Miller[1] & M.F. Harris[2]

Since vaccines may lose their potency if transported or stored outside the recommended temperature range (2–8 °C), we carried out a study in the Darwin area of the Northern Territory of Australia to determine the links in the cold chain, including the extent of vaccine monitoring, and whether the vaccines were being exposed to unsafe temperatures. Sabin oral poliomyelitis vaccine (OPV) and recombinant hepatitis-B (HB) vaccine were selected for special monitoring.

A total of 127 vials of OPV and 144 vials of HB vaccine were dispatched during October, November and December 1990 to the government, independent health services and general practitioner surgeries which routinely administer these vaccines. We distributed the two vaccines with MonitorMark™ time/temperature and Coldside indicator tags attached to cards for recording the date, location and temperature exposures each time the vaccines were moved or used. A total of 65% of the OPV and 41% of the HB vaccine monitor cards were returned for analysis.

The vaccines were transported and stored at one to four locations prior to being administered. Some 23% of tagged OPV was exposed for 48 hours or more to a temperature >10 °C; 47.5% of tagged HB vaccines were exposed to −3 °C or less, the majority of them during storage in health facilities or clinics. Exposures were independent of distance from the distribution centre, mode of transport, or type of facility. Our results show that the vaccines were often exposed to temperatures outside the recommended range during transport and storage, putting them at risk of loss of potency. Freeze-sensitive vaccines were exposed to sub-zero temperatures even in tropical climates, particularly during storage in standard domestic refrigerators.

Introduction

In the Northern Territory of Australia, 85% of all childhood vaccinations are administered through government health facilities, and the remainder by general practitioners.[a] The cold chain is the system of transporting and storing vaccines within the recommended temperature range (2–8 °C) from the place of manufacture up to the time they are administered. Since vaccines may quickly lose their potency if transported or stored outside these temperatures, it is essential to maintain an uninterrupted cold chain (*1*).

No studies have been published on the Australian cold chain but several seroconversion studies have been conducted. A recent study in New South Wales indicated that 46% of children with a documented history of measles vaccination were seronegative (*2*). A measles seroconversion study conducted in a central region of the Northern Territory indicated that 42% of the children failed to seroconvert six weeks after vaccination (*3*). Following on from this, a potency study of the measles vaccine remaining from the same batches indicated subpotency (*4*). Hepatitis-B seroconversion studies of fully vaccinated infants in the Northern Territory have shown that between 54% and 95% had protective antibodies (*5*, *6*). All these results suggest deficiencies in the cold chain.

We therefore conducted a cold chain monitor study in the tropical north of the 'Top End' of the Northern Territory during October, November and December 1990. This was an exploratory study to determine the links in the cold chain, what vaccine monitoring had been done, and whether the vaccines had been exposed to temperatures that could put them at risk of losing their potency.

Materials and methods

The Northern Territory (NT) in the central north of Australia covers an area of 1 364 200 square kilo-

[1] Senior Project Officer, Disease Control, Communicable Diseases Centre, P.O. Box 40596, Casuarina NT 0810, Australia. Requests for reprints should be sent to this author.

[2] Associate Professor, School of Community Medicine, University of New South Wales, Kensington NSW, Australia.

[a] **Royal Darwin Hospital Pharmacy.** *Vaccine inventory records 1989–90.* Darwin, 1990.

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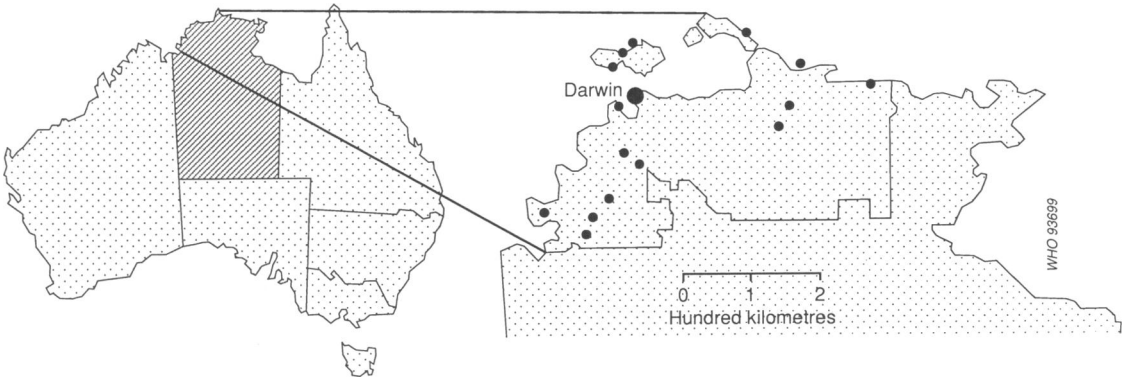
Fig. 1. **Map of the Northern Territory of Australia, with locations of the 15 rural health centres at the Top End.**



metres, with a population of 158 560 living in five urban communities and numerous rural or remote settlements. During the months of the study (October to December) the tropical north of the 'Top End' experiences the beginning of summer. Temperatures range from 25 °C at night to 33 °C during the day in and around the capital city of Darwin, and 23 °C to 36 °C in the westerly islands and the rural areas to the south and north-east.

Our study was conducted in the Darwin area in the 'Top End' where 56% (92 000) of the NT population resides, with 76% (70 000) living in the city of Darwin; there are six urban health centres and numerous general practitioner (GP) surgeries, all within 40 km of the Royal Darwin Hospital (RDH) Pharmacy, which is responsible for the distribution of vaccines to all area health facilities. Fifteen rural health centres provide health care to the remaining 24% (22 000) of the population. The rural health centres are located in settlements with populations ranging from 150 to 1800 (Fig. 1). Some of these health facilities serve remote camps or outstations; owing to distance and limited road access, many rural communities can only be reached by air.

We could not verify the temperature exposures of vaccines from the overseas manufacturer to the Australian distributor or from the distributor to the RDH pharmacy. Although the distributor indicated that vaccines were monitored from the manufacturer, the records of temperature exposure in transit were not included with shipments to the RDH pharmacy.[b] Since monitors did not accompany the vaccines from the distributor, the temperature exposure in transit could not be determined.

Study population. We selected Sabin oral poliomyelitis vaccine (OPV) and recombinant hepatitis-B (HB) vaccine for special monitoring because of the consistently larger numbers administered and their sensitivity to changes from the recommended temperature range (2–8 °C) for all vaccines. OPV has poor heat stability with loss of satisfactory titre between one hour and one day at normal ambient temperatures (>37 °C) in tropical climates (*7*). HB vaccine is unstable when frozen but has a higher resistance to thermal degradation than OPV.[c]

Monitored vaccines were sent to all government and independent health services, eight GP surgeries that regularly administer vaccines, and one private distributor. The private distributor was responsible for the distribution of only HB vaccine to the GP surgeries. The health services were stratified into urban health centres (within the greater Darwin area), large rural health centres (population >500), small rural health centres (population <500), and GP surgeries/private distributor.

Sampling. Anectodal evidence suggested that cold chain monitors were regularly separated from vaccines on arrival at health facilities and simply stored randomly in the refrigerator. Since monitors cannot be representative of vaccine exposures when handled in this manner, the monitors and vaccines were packaged in sealable plastic bags to prevent separation.

[b] **Miller N.** *Cold chain investigation in the Northern Territory.* Master of Public Health thesis, University of New South Wales, 1992: 85–87.

[c] Smith, Kline Biologicals, Rixensart, Belgium. Engerix-B® product information, 1989.

The number of vaccines tagged for the study was based on the quantities ordered during October, November and December of the previous year (447 OPV and 445 HB vaccine). Krejcie and Morgan's formula for determining sample size was used to estimate the sample size required to be representative of the population of OPV and HB vaccine used (*8*). As the health facilities varied greatly in the number of vaccines administered, we aimed for a systematic sample of vaccines sent (representing vaccinations given) and not batches of vaccines. We wanted to be able to relate exposures to populations at risk of being given non-immunogenic vaccines. The sampling was done as follows.

— Hepatitis B vaccine (single-dose vial) — one out of every 5 vials dispatched or a minimum of one if the order was for less than five vials; the expected numbers were rural 45, urban 50, and GP surgeries 51.

— Oral polio vaccines (ten-dose vial) — one out of every three vials dispatched or a minimum of one if the order was less than three vials; the expected numbers were all rural 53, urban 96, and GP surgeries 20.

Vaccine monitoring. Two time/temperature monitors have been used in the study area since 1987 and one freeze indicator was introduced in 1989:

• MonitorMark™ time/temperature tags by 3M:[d]

— 10-I tag, 12 °C over two days: introduced to monitor the cold chain in the Darwin area in 1987, paired with a 25 °C two-day tag.

— 31-L tag, 33 °C over one week: replaced the 25 °C tag early in 1990.

• MonitorMark™ (3-A) Coldside indicator tag by 3M (HB vaccine only):[d]

— 3-A tag, 26 °F (–3 °C).

The 10-I and 31-L monitors are label-like devices that contain a heat-sensitive, migrating chemical. The chemical is stored in a blotting-paper reservoir pad separated from a paper wick or track by a plastic sheet. Migration of the chemical only begins when the plastic sheet is removed by way of a tab and the reservoir comes into contact with one end of the paper track. A bright blue, irreversible colour change along the track indicates the total time exposure at a pre-set critical temperature or higher. Monitors were stored in the refrigerator until required. Fig. 2 shows the monitors and the cumulative amount of exposure indicated by each of the five track windows (indices).

The Coldside freeze indicator contains a chemical and dye that undergo an irreversible colour change after 15 to 30 minutes of exposure to –3 °C (±1 °C). These are stored at room temperature (25 °C) to prevent accidental exposure to –3 °C as they are always active.

Paired 10-I/31-L monitor tags were attached to a cold chain monitor card for recording the temperature index, date, and location at each level of the cold chain from the RDH pharmacy until the vaccine was used or discarded. A Coldside indicator was also attached to the card for HB vaccine.

Pilot study. We conducted a pilot study with 21 monitored vaccines in September. The pilot study revealed several problems:

— preparation of the monitor card was too labour intensive for a busy pharmacist;

— recording of monitor indices was inconvenient and time-consuming for staff in health facilities;

— staff were not familiar with reading, recording and interpreting monitors.

We prepared the cards in advance and monitor cards were attached to the outside of the plastic bag for ease of recording.

We accepted the reported staff familiarity with the monitors. The lack of familiarity, indicated by the pilot study, was therefore unexpected. Time constraints, limited resources and the desire not to bias the study influenced our decision not to conduct training sessions for participants. We distributed study parameters and pictorial instructions on reading the monitors. These also addressed potential ethical problems (i.e., administration of a potentially impotent vaccine).

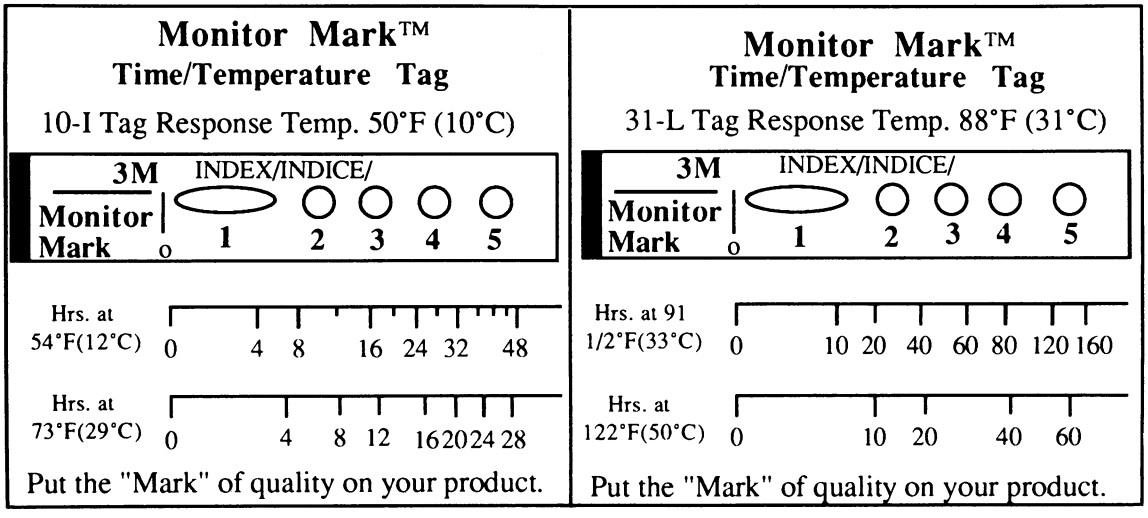
Data analysis. EPIC Version 4 data-processing software, developed by WHO, was used for analysing the cold chain monitor data.[e] The ten indices of the study monitors were combined into four groups for entry on EPIC-4. All interpretations were made on the amount of exposure indicated by the study monitors, not on the exposure represented by the indices accepted by the EPIC-4 software.

We used Fisher's exact probability test to determine if exposures recorded during transport from the RDH pharmacy to the health facilities were independent of distance and the method of transport.

[d] From Packaging Systems Division/3M, 3M Center, St-Paul, Minnesota, USA.

[e] *EPI Cold chain bibliography, 1990.* Unpublished WHO document, WHO/EPI/LHIS/09.3, 1990: 14.

Fig. 2. **Cold chain monitors (MonitorMark 10-I tag and 31-L tag) for indicating the cumulative amount of exposure by each of the five windows.**



Results

We accepted the distributor's assurance that the vaccines had not been exposed to temperatures outside the optimum during the journey from the overseas manufacturer. We felt confident that exposures in transit from the Australian distributor were minimal. Vaccines were transported by air for same-day delivery. They arrived in insulated containers with ice blocks still partially or completely frozen.

A total of 127 vials of OPV and 144 vials of HB vaccine were dispatched with individual cold chain monitors from the RDH pharmacy during the study period (69% of OPV and 44.5% of HB vaccine cold chain monitors were returned; 8 were excluded because of errors with the monitors or recording of indices). Reasons for non-return were elicited from the health facilities and included: lack of knowledge and/or understanding of the cold chain monitors or the protocol; vaccine was not used; or monitor card was discarded. There was a low return rate of HB vaccine monitors from the GP surgeries (6%).

Oral poliomyelitis vaccine

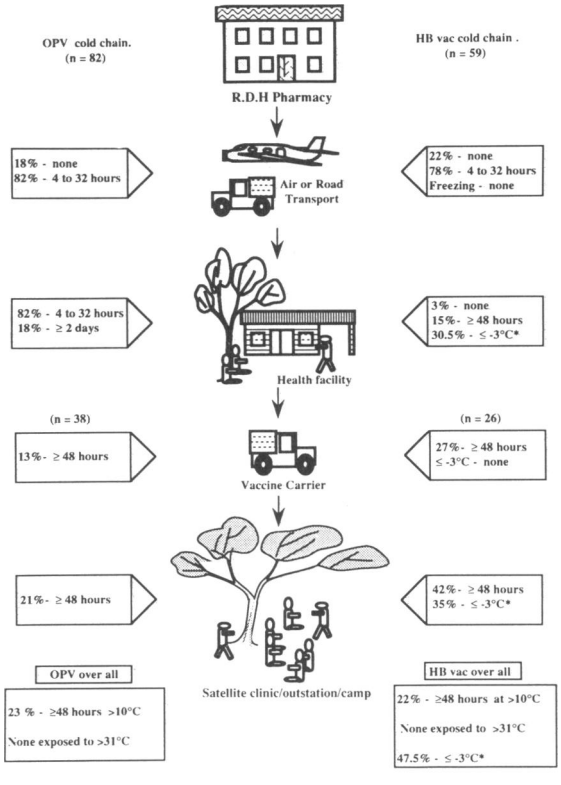
OPV monitors to all health facilities. Fig. 3 indicates exposures to >10 °C during transport to and storage at two levels of the cold chain as a percentage of vaccines to each level. Due to the sensitivity and limitations of the 10-I monitor, only significant amounts of exposure are shown. Sixty-seven (82%) of the 82 returned OPV vaccine monitors indicated exposure to temperatures >10 °C during transport between the RDH pharmacy and health facilities; some 77% of these 67 had been exposed for between one and thirteen hours and 5% for between 24 and 32 hours. During storage at the health facilities, all of the previously unexposed vaccines were exposed to temperatures >10 °C. In all, 42% (34) received further exposure at this level leaving 20% exposed for between 14 and 32 hours and 18% for 48 hours or more. The average storage time in the health facilities was 22 days (range, 0–71 days).

Thirty-eight OPV vials were transported to satellite clinics, camps or outstations. Only one received further exposure during this transport. Overall, 23% of the OPV monitors indicated exposures that put OPV at risk of loss of potency with additional exposure. Since the maximum exposure time for the 10-I monitor was only 48 hours, the level of risk could not be determined.

OPV monitors to urban and large rural health facilities. GP surgeries/private distributor and small rural health centres were excluded from analysis because of poor returns. The return rate was 86% from the six urban health centres and 48% from the five large rural health centres. Table 1 shows the exposures recorded for OPV during transit to and storage at these facilities.

Forty-five out of the 60 OPV were exposed to >10 °C for one to 13 hours during transport to urban health centres. All 12 of the OPV sent to the large rural health centres were exposed from one to 32 hours. During storage at urban health centres all of the remaining OPV were exposed to >10 °C, with 13

Fig. 3. **The cold chain between the Royal Darwin Hospital pharmacy and the distribution facilities, with percentage of exposures of OPV and HB vaccines.**



Overall – Amount of exposure (%) for all OPV and HB vac monitors at the end of the cold chain when the vaccines were used or discarded.
* – Exposure to –3 °C or below, vaccine considered impotent.

having a cumulative exposure of 48 hours or more. Although three OPV stored in the large rural health centres received additional exposure, none had a cumulative exposure of 48 hours or more, which would put them at risk of loss of potency due to the additional exposure.

Of the 36 OPV sent to satellite clinics from urban health centres, none received additional exposure during transport. One had additional exposure to >10 °C during storage in the satellite clinic and three after return to storage at the health centre, bringing to 27% the total number of OPV to urban health centres with a cumulative exposure of 48 hours or more at >10 °C.

The one OPV that was sent from a large rural health centre to a camp or outstation received additional exposure during transport. None of the OPV to large rural health centres developed a cumulative exposure of 48 hours or more at >10 °C. This was

Table 1: **Number and duration of OPV exposures to temperatures >10 °C during transit from the RDH pharmacy to the urban and large rural health facilities and during storage in the latter**

Hours	Urban	Large rural	Total
During transit:			
0	15	0	15 (21)[a]
1 to 13	45	9	54 (75)
14 to 32	0	3	3 (4)
≥48	0	0	0 (0)
Total	60	12	72 (100)
During storage:			
0	0	0	0 (0)
1 to 13	38	6	44 (61)
14 to 32	9	6	15 (21)
≥48	13	0	13 (18)
Total	60	12	72 (100)

[a] Figures in parentheses are percentages.

fewer than for urban health centres (P = 0.04; 95% CI for the difference in proportions, 1%–52%).

Hepatitis-B vaccine

Hepatitis-B monitors to all health facilities. Fig. 3 shows the percentage of HB vaccine exposed to >10 °C for 48 hours or more and –3 °C during transport to and storage at two levels of the cold chain. Since HB vaccine has a high resistance to thermal degradation (37 °C for up to seven days) (*9*), but cannot remain potent when frozen, the recorded temperatures >10 °C did not put it at risk. This was not true with the exposure ≤–3 °C. Forty-six (78%) of the 59 HB vaccines sent to all health facilities were exposed to >10 °C and none was exposed to –3 °C or less during transport from the RDH pharmacy. During storage in the health facilities, 32% (19) received exposure to temperatures >10 °C and 31% (18) to –3 °C or less.

Twenty-six HB vaccines were sent to satellite clinics or camps; two (8%) received further exposure to >10 °C but none to –3 °C or less during transport. During storage at this level, two (8%) received further exposure to >10 °C and nine (35%) to –3 °C or less.

HB vaccine monitors to urban and large rural health facilities. GP surgeries/private distributor and small rural health centres were excluded from analysis owing to the small numbers returned. The return rate was 94% for urban and 55% for large rural health centres. Table 2 shows the –3 °C exposures of HB vaccine monitors sent to and stored at urban and large rural health centres. Transport to and storage at satellite clinics/outstations/camps is not included; none of the vaccine went to this level from large rural facilities.

None of the vaccines was exposed to –3 °C or less during transport to the centres. However, during storage 13 (29%) of those sent to urban and 5 of those sent to large rural health centres received exposure to –3 °C or less. None of the 22 vaccines transported to satellite clinics or outstations/camps from the urban centres received exposure to –3 °C or less in transit, but nine received this level of exposure during storage bringing to 42% the HB vaccine to urban health centres so exposed. There was no significant difference between the proportion exposed to –3 °C or less, sent to urban or large rural health centres.

OPV and HB vaccine

Distance, type of transport and heat exposure to urban and large rural health centres. In all, 55% of the oral poliomyelitis and hepatitis B vaccines took less than one day to reach urban and large rural health centres. The remainder experienced delays of between one to more than six days. Some 85% were transported by road vehicles to urban health centres, 10% and 5% were transported by air or road, respectively, to the large rural health centres. There was no significant association between exposure to temperatures >10 °C and the distance to the health centre from the RDH pharmacy (P=0.05) or mode of transport (P=0.17).

Discussion

Despite the availability of reliable sources of power, modern refrigeration equipment with ready access to parts/repairs, and reliable transportation, the present study in the tropical north of the Northern Territory of Australia shows that vaccines can be easily exposed to temperatures outside the recommended range (2 °C to 8 °C) during transport and storage at health facilities, whether rural or urban.

Table 2: **Number of hepatitis B vaccine exposures to –3 °C during transit from the RDH pharmacy to the urban and large rural health facilities and during storage in the latter**

Exposure	Urban	Large rural	Total
During transit:			
No	45	7	52 (100)[a]
Yes	0	0	0
Total	45	7	52
During storage:			
No	32	2	34 (65)
Yes	13	5	18 (35)
Total	45	7	52 (100)

[a] Figures in parentheses are percentages.

Cold chain monitors attached to OPV and HB vaccine were exposed to temperatures >10 °C for two days or more at all levels of the Northern Territory cold chain. Additional exposures above 10 °C could cause loss of potency for OPV, the most heat labile vaccine. OPV was stored in health facilities in excess of six weeks increasing the risk of additional exposure above 10 °C. Lugosi & Battersby's cold chain monitor study in Hungary indicated that, although only 8% of measles vaccine had critical exposure above 10 °C during transport and storage, an additional 21% were at risk of deterioration owing to extended storage (i.e., from overstocking) (*10*). Increased risk from extended storage was also indicated in a cold chain evaluation in Nepal (*11*). Considering that vaccines usually reached the health facilities in one day or less, storage of vaccines for more than one month is unnecessary.

Freeze indicators attached to HB vaccine were exposed to temperatures less than –3 °C (48%) during storage in health facilities and satellite clinics or camps/outstations. Freezing causes loss of potency in HB vaccine. In the Hungarian study, 35.8% of diphtheria–pertussis–tetanus (DPT) vaccine exposures to this level occurred during storage at two levels of their cold chain and 1.8% during transport. It should be noted that the winter ambient temperature in Hungary can be as low as –12 °C (*10*). In the tropics, we do not experience ambient temperatures of less than 20 °C, even in the cooler dry season. This level of exposure to freezing was unexpected and of great concern. This alone could account for the poor response to hepatitis B vaccine in Northern Territory children. Since all vaccines travel in the same cold chain, other freeze-sensitive vaccines (i.e., DPT, adult diphtheria–tetanus, child diphtheria–tetanus, and tetanus toxoid) could lose their potency. Further investigation of the refrigerators used for vaccine storage in Australia is a matter of urgency if we are to administer an immunogenic vaccine to Australian children.

Vaccines may be at even greater risk of adverse temperature exposure during storage in GP surgeries. In general practices in England, Hunter found that 92% (33/36) of the practices did not observe guidelines for storing (*12*). Since vaccination is only a small part of a general practice, there is the added risk from: overstocking with extended storage; multiple-dose vials kept for more than one session after opening; and giving clients vaccine to store at home (e.g., HB vaccine). Hunter's study indicated that one half of the general practices sent vaccines home with the patient (*12*). There is a need for further studies of the cold chain in GP surgeries.

The 10-I/31-L cold chain monitor duo is not appropriate to monitor the temperature exposures

indicated during the study. The 10-I monitor cannot indicate cumulative exposures >10 °C beyond two days, when the more heat-labile vaccines would be at greatest risk. There were no exposures >31 °C, making the 31-L unnecessary. Since vaccines differ in their sensitivity to both temperature and amount of exposure, the single 10-N/34-AA time/temperature (used by the WHO Expanded Programme for Immunization), which can indicate exposure above 10 °C over one to two weeks, would enable staff to make informed decisions about individual vaccines. The single monitor would simplify interpretation and the cost would be reduced by one-third. The latter would help to offset the cost of monitoring to facilities previously omitted.

The cold chain monitors identified areas of weakness that were previously unobserved, stimulated interest and increased staff awareness. This alone may have improved the standard of vaccine handling during our study. The monitors can also be a useful tool for evaluating the cold chain and directing supervisory efforts. However, a cold chain evaluation in Tunisia concluded. that the strongest benefit of the monitors is not for central data collection and evaluation but for mid-level personnel to carry out self-evaluation to improve the standards of vaccine care on the spot (*13*).

The cold chain is not just a problem in the tropical north of the Northern Territory, but can be a problem for urban Australia. Barrand's study in New South Wales indicated that 46% of 204 children with reported immunization against measles were seronegative (*2*). An ineffective cold chain is suspected. This investigation has indicated that vaccines can easily be exposed to temperatures above and below the recommended range during transport and storage. It is not enough to have high levels of immunization coverage if the vaccine being administered is not potent owing to an inadequate cold chain. The National Health and Medical Research Council of Australia states; "It is imperative that all concerned with immunization adhere to the manufacturer's [storage] recommendations before use" (*14*). We have seen that the greatest exposures occurred during storage. What then are the resource implications in order to investigate, assess and strengthen the cold chain in Australia?

Although the costs of investigative studies and implementation of cold chain monitoring, staff training, and new or modified transport and storage equipment can be considerable initially, they will not be sustained costs except for the monitors. Staff training can be incorporated into existing orientation and in-service programmes and equipment can be placed on a routine replacement schedule. It has been estimated that the eradication of poliomyelitis would save the USA some $114 million a year in vaccines alone (*15*). Australia too can benefit from the successful control of immunization-preventable childhood diseases.

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Résumé

Les programmes australiens de vaccination infantile en danger? Enquête sur la chaîne du froid dans le Territoire du Nord

Le succès des programmes de vaccination infantile dépend de l'administration de vaccins de bonne qualité. Etant donné que ceux-ci peuvent perdre de leur activité si les températures recommandées (2 à 8 °C) ne sont pas respectées lors du transport ou de l'entreposage, nous avons mené une étude dans la région de Darwin, dans le Territoire du Nord de l'Australie, pour vérifier l'intégrité de la chaîne du froid. Nous avons notamment vérifié dans quelle mesure les vaccins étaient surveillés et s'ils étaient exposés à des températures dangereuses.

Les produits choisis pour cette étude ont été le vaccin antipoliomyélitique oral (VPO) Sabin et un vaccin antihépatite B (HB) obtenu par génie génétique. Au total, 127 flacons de VPO et 144 flacons d'HB ont été expédiés au cours des mois d'octobre, novembre et décembre 1990 aux services de santé publics et privés et aux cabinets de généralistes qui administrent régulièrement ces vaccins. Tous les envois de vaccins étaient accompagnés d'un indicateur de température et de durée d'exposition MonitorMark™. En outre, les vaccins HB portaient un indicateur de gel Coldside. A chaque indicateur était attachée une fiche permettant de noter la date, le lieu et les températures subies par le vaccin chaque fois qu'il était transporté ou utilisé. Au total, 65% et 41% des cartes jointes respectivement aux vaccins VPO et HB ont été retournées pour analyse. Pour le vaccin HB, le taux de réponse des centres de santé a été de 74% et celui des cabinets de généralistes de 6%.

Les vaccins ont été envoyés dans quatre localités où ils ont été entreposés avant d'être administrés. Environ 23% des échantillons de VPO ont été exposés pendant 48 heures ou plus à une température supérieure à 10 °C; 47,5% des vaccins HB ont été exposés à une température inférieure ou égale à –3 °C, le plus souvent lors de l'entreposage dans les centres de santé ou les dispensaires. Le degré d'exposition était indépendant de l'éloignement du point de distribution, du mode de transport ou du type de centre de santé en cause. Les résultats de cette étude montrent que les vaccins sont souvent exposés à des températures inférieures ou supérieures aux limites recommandées lors du transport et de l'entreposage, d'où un risque de perte d'activité. Les vaccins sensibles au gel peuvent être exposés à des températures inférieures à 0 °C, même sous les tropiques, notamment lorsqu'ils sont conservés dans des réfrigérateurs domestiques.

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