

Canada Communicable Disease Report



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NATIONAL GUIDELINES FOR VACCINE STORAGE AND TRANSPORTATION

Preamble

Maintaining vaccines at the appropriate temperature from the time they leave the manufacturer to the time of administration, i.e., maintenance of the cold chain, is a very important aspect of proper immunization delivery programs. Lack of adherence to the cold chain may result both in lack of vaccine effectiveness, undue vaccine failures, and an increased rate of local reactions after vaccine administration. Damage can be done by exposure to heat or freezing of the vaccine depending on the nature of the product. Recent studies have highlighted major deficiencies in Canada with respect to the cold chain. The Childhood Immunization Division, Bureau of Communicable Disease Epidemiology, Laboratory Centre for Disease Control has, therefore, undertaken the initiative to develop national guidelines for vaccine storage and transportation, in collaboration with those persons listed in Appendix I. The documents listed at the end of this appendix were also used in formulating these guidelines. A workshop on the practical aspects of the cold chain was part of the National Immunization Conference "Immunization in the 90's: Challenges and Solutions", held in Quebec City, 5-7 October, 1994. The participants at the workshop, over 60 in attendance, were encouraged to comment on the national guidelines.

This document is provided as a general guide for consideration. It is aimed at all health care providers, the manufacturers, the provincial and territorial health authorities, as well as health units and pharmacies. Because of the wide audience, readers may find it lacking in specific recommendations for their particular jurisdiction. Such specific instructions could be developed in the various jurisdictions, especially depending on the nature of the product used. Operational questions should be resolved by the jurisdictions in consultation with the manufacturer(s). The Childhood Immunization Division has committed itself to strengthening its support to the provinces and territories with respect to the cold chain and will be hiring a technical officer as

part of its action plan on vaccine-preventable diseases of infants and children. Information about technical issues, training, and educational material related to the cold chain can be obtained by writing to the Childhood Immunization Division, Bureau of Communicable Disease Epidemiology, Laboratory Centre for Disease Control, Tunney's Pasture, Ottawa, Ontario, K1A 0L2, or calling 1-613-957-1340 or 1-800-363-6456.

General recommendations

1. Practices relating to the cold chain should be reviewed periodically at all levels (i.e., every 6 months to 1 year). Where excessive cold chain failures occur, reviews should be more frequent.
2. Vaccines exposed to temperatures outside those stated in the manufacturer's insert or labelling should be stored in a separate, marked container in a well-functioning monitored refrigerator until clear instructions have been received on what to do with them. Because the potency of different vaccines varies depending on the type of temperature exposure, each incident must be evaluated individually.
3. Records should be kept of doses received, including lot numbers for each vaccine shipment, and of wastage after vaccine expiry dates have passed.

Recommendations about storage

1. Vaccines should never be removed from the refrigerator except for the following reasons: withdrawing a dose(s); shipping to clients; or transporting to immunization clinics. The refrigerator door should not be opened too frequently. (The World Health Organization recommends that the door should not be opened more than four times a day).
2. Vaccines should be stored in the refrigerator as soon as they are received.
3. All persons responsible for handling vaccines should know the correct storage temperatures for the various vaccines.³³

4. A refrigerator dedicated only to vaccine storage should be identified and used only for this purpose. Vaccine refrigerators should not be used to store staff lunches or specimens.
5. If there is an accumulation of more than 1 cm (or 1/4 inch) of ice in the freezer compartment of a refrigerator, defrosting is required. Vaccines should be transferred to a vaccine carrier box or another refrigerator while this is being done. The temperature should be monitored during this contingency period.
6. One person should be identified as responsible for vaccine management. Another individual should also be trained for when the first person is absent.
7. All vaccine storage refrigerators should have a maximum-minimum thermometer or, if large quantities of vaccines are stored, a continuous temperature recording device. All monitoring devices should be certified or calibrated routinely.
8. All refrigerators containing large quantities of vaccine (e.g., central vaccine distributing areas) should also be connected to a temperature alarm monitoring system.
9. Two daily temperature readings for the vaccine refrigerator should be taken and recorded — one in the morning when arriving and one at the end of the day — to ensure temperatures remain between 2° C and 8° C. A chart-recording thermometer should also be checked for temperature fluctuations, which may occur between readings. The designated staff person should record and sign off readings in a log book daily. The designated staff person should ensure that all staff handling vaccines know how to read and interpret maximum-minimum thermometers.
10. All staff handling vaccines should have training about the importance of good vaccine storage and transportation techniques.
11. Vaccines should never be stored on refrigerator door shelves because temperatures are warmer there than on the shelves of the refrigerator.
12. Space should be left between the products in the refrigerator to allow air to circulate. For freeze-dried products, for which diluent is provided in separate packages, the diluent should be stored at room temperature to conserve refrigerator space (unless the vaccine direction insert specifies that the diluent must be refrigerated).
13. Keep all adsorbed vaccines that should not be frozen away from the freezing element and away from direct contact with ice.
14. Store water bottles at the bottom, the top, and in the door spaces of the vaccine refrigerator, and keep ice packs in the freezer compartment to maintain a more constant temperature if there is a power failure.
15. Keep a sign near the electric plug outlet for the vaccine refrigerator and the power-breaker box indicating that the power cannot be turned off. Refrigerator plugs should be in a protected area where they cannot be knocked out accidentally. Vaccine refrigerators should have a designated plug outlet that is not required for other appliances.
16. Make sure that the refrigerator door is closed when not in use.
17. Vaccine inventory security must be considered when choosing a refrigerator location. If possible, the vaccine refrigerator should be placed in a room with a lockable door to prevent unauthorized handling or refrigerator entry after office hours. If this is not possible, a low traffic area should be considered. Refrigerators with lockable doors should be secured after hours.
18. Procedures in the event of vaccine refrigerator failure should be posted on or near all such refrigerators.
19. If a power outage occurs, the person responsible for vaccine storage or the delegate should put all vaccines into a thermal cold box or a container with ice packs and a thermometer until the vaccines can be transferred to another refrigerator. Large inventory storage units should be equipped with an alarming device for quick response to minimize vaccine loss. If a short power outage is anticipated (less than 1 hour), the storage unit should not be opened. If a longer power outage is anticipated, then plans for transfer are warranted.
20. Educational material on the cold chain should be available in all centres storing vaccines.
21. If a product(s) is(are) known to have been exposed to temperatures outside of the recommended range, the exposed product(s) should be put in a box marked "DO NOT USE" and placed in a functioning refrigerator. The types of products exposed should be recorded, as well as the duration and temperature of exposure, and advice on whether these products may be used or returned should be sought immediately.
22. Regular maintenance of refrigerators (cleaning coils, replacing door seals, etc.) should be performed and records kept.

Recommendations about transportation

1. Manufacturers and central pharmacies in Canada should place both heat and cold monitors in their shipments of vaccines. Ideally, and if justified by the amount of vaccine shipped, monitoring devices that record shipping conditions should be used.
2. Central pharmacies and manufacturers who make long distance shipments should periodically use electronic monitors to detect possible problems and their location.
3. Shipping boxes for most vaccines should be clearly labelled as containing perishable goods that have to be stored between 2° C and 8° C and must not be frozen.
4. All transport companies carrying vaccines should be advised that the product is perishable and should be refrigerated immediately on receipt. Guarantee should be obtained that vaccines are kept in a refrigerated container from receipt to delivery.
5. Manufacturers should obtain written documentation from transport companies concerning the handling of perishable products (transportation, warehouse storage conditions, length of time between pick up and delivery, etc.). Refrigerated vehicles should be equipped with temperature monitoring devices.
6. If a vaccine shipment has been refused by the person who ordered it, the carrier must know that the shipment requires refrigeration pending resolution of the problem. The manufacturer or point of origin must be notified immediately for disposition of shipment.
7. All vaccines should be transported in an insulated container with an appropriate number of ice packs (except when shipped under refrigerated transit). Insulated containers should have firmly-fitting lids and be constructed from an insulated material. To avoid freezing, vaccines should not be placed directly on the ice pack.
8. Anybody responsible for the shipment of vaccine must ensure that the vaccine arrives at its point of delivery at the proper temperature.
9. Because ice packs removed from the freezer may be very cold, before they are used they should be left at room temperature for a few minutes (1 to 5 depending on the size of the ice pack and the initial temperature) until water or sweat appears on the surface to avoid freezing the vaccines.

10. If evidence of freezing is present when vaccines sensitive to freezing are received (e.g., results of temperature measurements), the vaccine must not be used.
11. Oral polio vaccine should preferably arrive with some dry ice still present. If this vaccine arrives with no ice remaining but with the product still cold, it may still be used; however, if the vaccine is warm, it should not be used.
12. Insulated carrier boxes should have documented ability (must be validated) to maintain the appropriate temperature for the

anticipated maximum length of time required for the transportation.

13. When vaccines sensitive to freezing are to be shipped in outside temperatures of less than 2° C, they should be shipped in a vehicle in which the temperature should be kept higher than 2° C. If this is not possible and vaccines will be exposed to outside freezing temperatures, one should use ice packs with water at room temperature when packing the vaccine.

Appendix I List of collaborators

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Dr. Walter Yarosh, Health Viral Products Division, Bureau of Biologics, Drugs Directorate, Ottawa, Ontario

List of documents

Compendium of Pharmaceuticals and Specialties. 29th ed. Ottawa, Ontario: Canadian Pharmaceutical Association, 1994.

Product Information Sheets, 1993/94. 10th ed. WHO/UNICEF Technical Series, May 1993.

World Health Organization cold chain information: publications, instructional slide sets, and training courses.

Vaccine Distribution, Storage and Handling Guidelines. Mandatory Health Programs and Services, Public Health Branch, Ontario Ministry of Health. Draft copy, September 1994.

PROTECTING VACCINES FROM FREEZING IN EXTREMELY COLD ENVIRONMENTS*

Introduction

The World Health Organization/Pan American Health Organization (WHO/PAHO) has recommended that when vaccines are used for an outreach session they should be stored at 0° C to 8° C (32° to 46° F) in order to assure their maximum potency. In an extremely severe cold environment (up to -25° C (-13° F)) there is an increased risk certain vaccines such as diphtheria, pertussis and tetanus (DPT), diphtheria toxoid (Dt), tetanus and diphtheria toxoid (Td), and tetanus toxoid (TT) will freeze. If these vaccines reach -5° C (23° F), they will be totally and irreversibly damaged.

Vaccine carriers or cold boxes are insulated containers with water-filled packs (ice packs) surrounding the vaccine. When these containers are used during the shipment of vaccines in cold climates, freezing of the vaccines can occur very quickly and must be avoided. If the vaccines freeze, the vaccination program not

only suffers a monetary loss but there may be missed opportunities to vaccinate clients because there is no vaccine.

Therefore, health care workers must take alternative actions or use other technologies to keep these vaccines from freezing. WHO/PAHO and the Cold Chain Focal Point at the University of Valle in Cali, Colombia, undertook a study composed of a series of tests to assist health care workers in this effort. Using the same equipment that is used for shipping and/or storing vaccines, the study attempted to determine how best to prolong the "**warm life**" of vaccine carriers or cold boxes so that vaccines are not frozen during their shipment. "**Warm life**" is defined as the **number of hours that a vaccine carrier or cold box can maintain vaccine temperatures above -5° C or before ice packs are frozen.**

* Presented at "Immunization in the 90's: Challenges and Solutions". Conference organized by the Laboratory Centre for Disease Control, Health Canada, October 5-7, 1994, Quebec City, Quebec.

The purpose of this paper is to present results of tests conducted to determine the "warm life" of a well known vaccine carrier, with and without simple modifications.

The information presented in this paper can be used by health care workers to protect their vaccines from freezing during shipment.

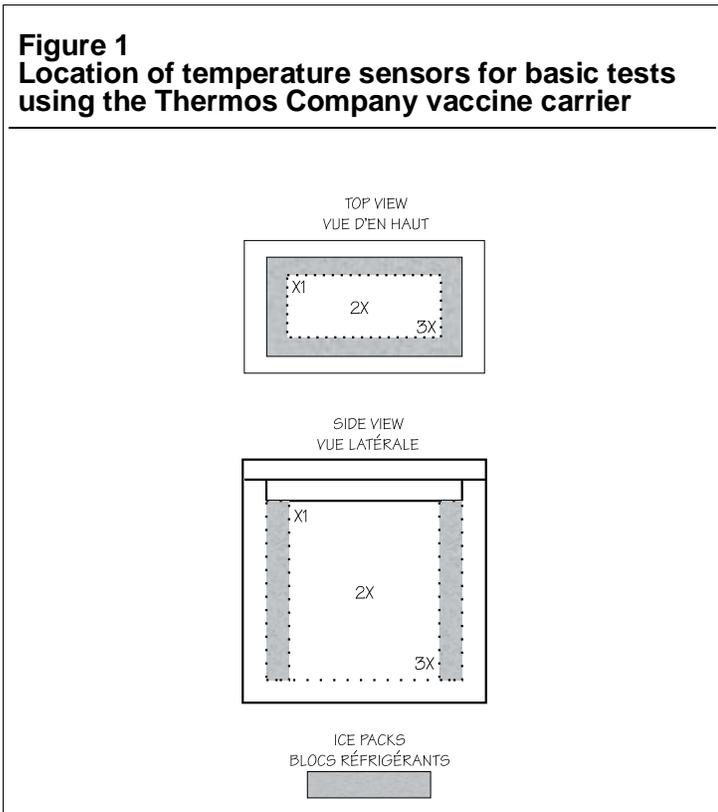
Description of the Tests

To achieve a cold environment, a horizontal freezer with enough internal volume to allow free air circulation around the vaccine carrier was used. A small fan was installed to guarantee temperature homogeneity and turbulence. The vaccine carriers were suspended to obtain complete circulation of the air. The temperature was uniformly maintained at -25° C.

The selected vaccine carrier, with 1.8 litres of capacity, was manufactured by the Thermos Company (code PIS E4/18).

Three K type thermocouples connected to a computerized data acquisition system measured the temperatures. Scanning of temperatures occurred every 5 minutes in each channel. Figure 1 shows the location of the three thermocouples along the main diagonal of the vaccine load and also the position of the ice packs. An extra thermocouple, placed inside an ice pack, was added to the carrier. Before the carrier was introduced into the freezer, **the carrier and the ice packs were stabilized at 24° C**, while the **vaccine was stabilized at 6° C**. The readings from all the thermocouples in each test were averaged.

Three tests were carried out, two using the carrier without modifications (basic test) and one with modifications. In the first basic test the ice packs, stabilized at a room temperature of 24° C, and a vaccine load of 1.8 litres were placed in the carrier.



Immediately after loading the vaccine carrier, it was placed inside the freezer (cold environment).

The second basic test was carried out using ice packs stabilized at 10° C and the same vaccine load as in the first test. No additional insulation was added.

For improving the "warm life" of the carrier, the third test was carried out by modifying the carrier using newspapers for additional insulation. The vaccine load was the same as in the previous two tests. Fifty layers of newspapers, equivalent to seven mm in paper thickness, were used to wrap all sides of the carrier. Two additional small ice packs (each equivalent to 0.4 kg of water) were added, one above and one below the vaccine load. All ice packs were stabilized at 24° C.

Results and Analysis

Table 1 summarizes the results of the three tests. The best result was obtained with the modified carrier.

EQUIPMENT	TEST	DURATION
Thermos carrier	Basic Test, Ice Packs at 24° C	60 h
	Basic Test, Ice Packs at 10° C	54 h
	Insulated + 2 Additional Ice Packs at 24° C, 1 Above and 1 Below Vaccines	72 h

Figure 2 depicts graphically the results of the first basic test. It indicates that a vaccine quickly reaches the temperature of the ice packs and that this water temperature determines the "warm life" performance for the carrier. Three temperature zones can be distinguished in Figure 2: the cooling zone at a constant rate (0 to 15 hours); the solidification zone (stable temperature due to latent heat transfer in the phase change, 15 to 60 hours — this is also known as the sub-cooling solid zone, where despite the fact that the vaccine temperature is below zero the ice packs are not completely frozen at 60 hours); and the third zone where the ice packs are completely frozen, as well as the vaccine, after 60 hours.

Figure 3 shows the results of the second basic test. The graph is similar to that obtained in Figure 2; however, the "warm life" is only 54 hours because the initial temperature of the ice packs is lower.

Discussion

These tests were carried out to provide health care workers with a set of guidelines to protect vaccines from freezing in extremely cold environments.

The test results confirm that health care workers can use the same vaccine carriers or cold boxes currently found in use, including ice packs that are above 10° C and below 24° C, to safely transport vaccines in extremely cold environments without freezing them.

However, caution should be taken because not all vaccine carriers or cold boxes will have a good "warm life" due to poor

construction and low quality material. Using containers constructed with polyurethane insulation will provide the best protection for transporting vaccines and will guard them from freezing or from reaching internal temperatures above 10° C for a longer period of time.

The "warm life" performance for whatever type of insulated container is selected for the transportation of vaccines can be determined by simply following this procedure: use empty vaccine vials and load the container with non-frozen ice packs designed for it and place it outside in the cold air and monitor the amount of time required to completely freeze the packs. These data will provide all workers with a parameter for monitoring shipments in extremely cold environments. Ice packs can be stored either in a refrigerator or on a shelf in the same room where the vaccine load will be taken from the refrigerator and put into a container. The temperature of the room where the ice packs are stored should be below 24° C. The staff (including drivers) involved in the handling and transportation of vaccines in extremely cold environments must be alerted to change frozen ice packs with non-frozen ones.

In very cold environments, ice packs stabilized at an ambient temperature of ≤ 24° C can be used for the transportation of these vaccines for a period not exceeding 8 hours. The vaccines are very heat stable and the short time (< 8 hours) that they are subjected to temperatures between 10° to 24° C will not harm them.

Figure 2
"Warm Life" Test No. 1: Thermos Company Vaccine Carrier with Ice Packs at 24° C

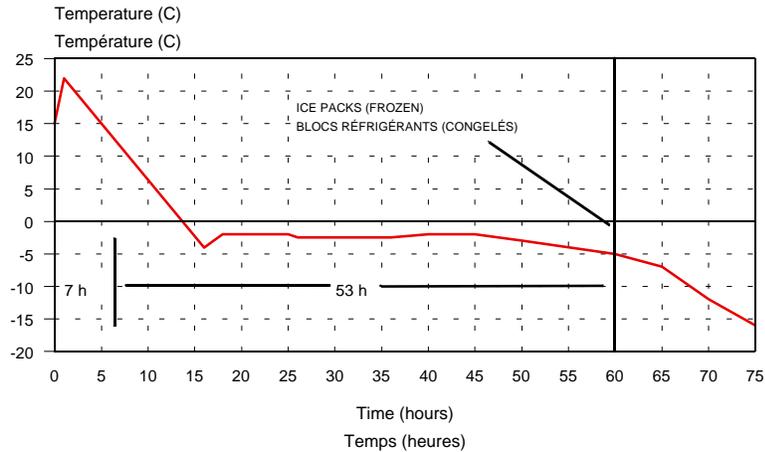
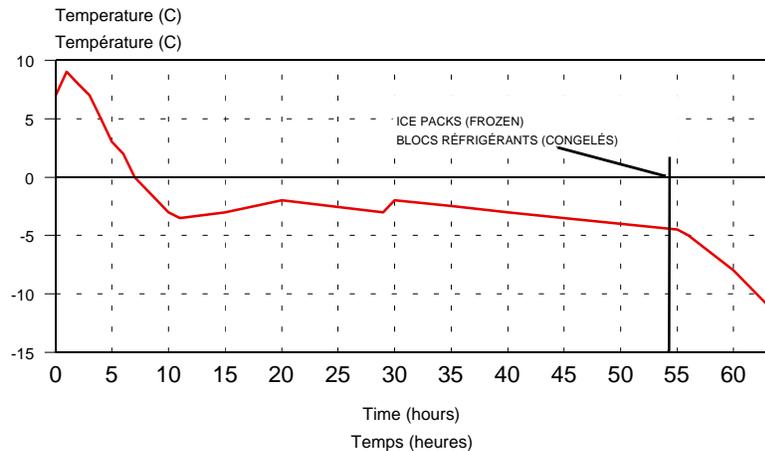


Figure 3
"Warm Life" Test No. 2: Thermos Company Vaccine Carrier with Ice Packs at 10° C



Source: P Carrasco, PAHO/WHO, Washington, DC; C Herrera, D Rancruel, M Rosillo, Universidad del Valle, Cali, Colombia.

EFFECTS OF FREEZING ON DPT AND DPT-IPV VACCINES, ADSORBED

Recent articles have emphasized the importance of properly refrigerating vaccines during their transportation and storage^(1,4). The British Columbia Ministry of Health coined the promotional phrase "Healthy vaccines (for) healthy children"⁽⁵⁾ to emphasize the importance of intact vaccine quality on the success of immunization programs. To retain their potency, most vaccines require storage at 2° C to 8° C. Alum-adsorbed vaccines, such as diphtheria, pertussis, tetanus (DPT), should not be frozen as this irreversibly alters the preparation and markedly reduces immunogenicity. Freezing is most likely to occur, but not only, during wintertime transportation of vaccines, and might go unrecognized if concurrent temperature monitoring is not performed.

The "shake test" is mentioned^(6,7) as a visual clue to identify previously frozen DPT or DPT-inactivated poliovirus (IPV) vaccines. A positive test is the presence of coarse clumps or particles in the vaccine liquid after it has been thoroughly shaken to resuspend any settled matter. Normally the resuspended liquid is milky white and opaque, without any granularity. A report from the World Health Organization⁽⁷⁾ cautions that some adsorbed DPT products are visibly altered after freezing and thawing (giving a positive "shake test") but others are altered minimally or not at all, despite potency loss. We wondered if the DPT and DPT-IPV products of Connaught Laboratories Ltd. were visibly altered after freezing or not. The company was unable to tell us what to expect. This study was designed to obtain the answer.

Methods

The vaccines used were DPT Adsorbed (Lot number 4050-31) and DPT-Polio Adsorbed (lot number 24015-11), produced by Connaught Laboratories Ltd., North York, Ontario. They were obtained from the central pharmacy of the B.C. Ministry of Health. Neither vaccine had passed the labelled expiry date. Forty single dose vials of each vaccine were used in parallel experiments, as follows:

1. Five of the 40 vials were used as controls and stored at 2° C to 8° C. At the start of the experiment two of the five vials were shaken and three were left sedimented (the normal state when vaccine is undisturbed for several hours).
2. Twenty of the 40 vials were placed in a freezer set at -10° C. Ten were shaken beforehand and 10 were left sedimented, in case the effects of freezing might differ with the degree of dispersion of the vaccine⁽⁷⁾.
3. Fifteen of the 40 vials were placed in a freezer at -70° C. Five vials were shaken beforehand and 10 were left sedimented.
4. Control vials were shaken vigorously and inspected visually 24 and 72 hours later. Similarly, about half of the vials frozen at -10° C were thawed after 24 or 72 hours, shaken and inspected. Vials frozen at -70° C were thawed and tested after 24 hours. Any samples thawed after 24 hours that had no visible alterations were returned to the freezers for another 24-hour freeze-thaw cycle, as above. Vaccine vials were inspected without magnification but with backlighting. Vials were inverted to take advantage of the label-free extended tops of the glass ampules.

Results

Control vials of both vaccines remained unchanged during the experiment, the suspended vaccine appearing milky-white and non-particulate. None of the frozen vials produced a positive "shake test", even with repeated freeze-thaw cycles or with exposure to extreme cold. Initial inspection of previously frozen vaccine revealed a milky solution very much like the control vaccine. Closer inspection revealed subtle granularity identifiable only with side-by-side comparison to a control vial. Evidence that freezing had damaged the vaccines was more obvious when sedimentation rates of thawed and control vaccines were compared after visual inspection (details not presented): thawed samples sedimented completely within 45 minutes, by which time control samples showed only the beginnings of sedimentation (the full process taking several hours). Accelerated sedimentation was evident in all frozen vials, even those exposed to -10° C for only 24 hours.

Discussion

These observations suggest that Connaught's DPT Adsorbed and DPT-Polio Adsorbed vaccines are usually not visibly altered after freezing. None of the 80 vials that we tested under various conditions, including repeated freezing of sedimented vaccine⁽⁷⁾, produced a positive "shake test". With scrupulous comparison to control vaccine, fine granularity was evident in thawed samples but this was too subtle to be useful in the field. The freeze-damaged vaccines sedimented rapidly but this too is an impractical field test because it takes 45 minutes and requires an unequivocally intact set of vials for comparison.

We emphasize that the manufacturer cautions against freezing adsorbed DPT or DPT-Polio vaccines and considers inadvertently frozen vaccine to be unfit for use. Our findings are not at odds with this: we have simply demonstrated that the damage done by freezing is not obvious on simple visual inspection. With these two Connaught products the "shake test" is not a satisfactory means to detect freezing-induced damage. The only reliable means to determine if vaccines have been inadvertently frozen and thawed is to place temperature monitoring devices beside them during transport⁽⁴⁾. This is the first recommendation regarding transportation made in the National Guidelines for Vaccine Storage and Transportation (see first article in this issue). These can consist of thermometers with minimum-maximum readings, continuous temperature recording devices (for large shipments) or simple dye-containing capsules⁽²⁾ which rupture on freezing (for small shipments).

In summary, we live in a climate where vaccines can easily be frozen during transport in winter⁽⁴⁾. It is important for vaccinators to know that commonly used adsorbed DPT and DPT-Polio vaccines are not visibly altered after freezing. The only reliable proof against freezing-induced loss of potency is to monitor the temperature of every shipment at risk, whether it is across the country or across town.

References

1. Casto DT, Brunell PA. *Safe handling of vaccines*. Pediatrics 1991;87:108-12.
2. Daniels S, Naus M. *Surveys of vaccine storage and handling in Ontario*. PHERO 1994;5:2-8.

