PROTOCOL FOR EVALUATING FREEZING IN THE VACCINE COLD CHAIN

Program for Appropriate Technology in Health
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Overview

Improperly maintained or outdated refrigeration equipment, poor compliance with cold chain procedures, inadequate monitoring and poor understanding of the dangers of vaccine freezing contribute to the weakness of the existing cold chain. Emphasis has long been placed on keeping vaccines cold, with less attention devoted to prevention of vaccine damage from freezing. Published reports and field evidence demonstrate that freezing of vaccines in the cold chain is commonplace, potentially resulting in the widespread delivery of vaccines whose potency has been compromised by the disassociation of antigen from the adjuvant. In response to this danger, WHO and manufacturer guidelines clearly state that adjuvant vaccines must not be exposed to freezing temperatures.

This protocol is designed to:

1. **Document the level of freezing in the cold chain and**
2. **Identify specific problem areas where corrective actions are warranted.**

In this protocol, temperatures are monitored continuously as vaccine shipments travel through the cold chain, from the national stores, to the provincial stores, to the district, to health centers, and finally to the outreach delivery site. This protocol can be tailored to an individual program's resources: a simple, low-cost study can be done without sophisticated monitoring tools, or a more comprehensive approach can be taken to provide more details.

The outcome of this study should help programs determine the most appropriate interventions. If evidence demonstrates, for example, that freezing occurs most commonly during vaccine transport, new procedures for conditioning of ice packs, or ice-free transport can be implemented. If there is a correlation between specific types of refrigerators and freezing, equipment replacement may be required or, alternatively, more attention given to the training of cold chain supervisors.

As with any study, this protocol requires strong central coordination and the cooperation of many individuals along the vaccine distribution cold chain. Guidelines for individual responsibilities, budgetary considerations, and equipment requirements are provided.

Background

Freezing of diphtheria, tetanus, pertussis, hepatitis B vaccines, and combination vaccines, can compromise their immunological potency. WHO and manufacturer vaccine labels state that hepatitis B, DPT, DT, and TT vaccines should be stored at temperatures between 2° and 8°C and should not be used if thought to have been frozen. Yet recent studies in Great Britain, the United States, Canada, Pakistan, Malaysia, Hungary, Mongolia, and other countries have found widespread freezing at many levels of the vaccine distribution system. Emphasis is

frequently placed on preventing vaccine heat exposure, with many immunization providers unaware that monitoring and preventing vaccine freezing is also essential.

Using this protocol, a study in Indonesia found that 75% of hepatitis B vaccine shipments were exposed to freezing temperatures, potentially damaging a significant portion of this expensive vaccine. The study identified the segments of the cold chain primarily responsible for freezing, allowing Indonesia to focus corrective actions on specific equipment and procedures.

Equipment Requirements

This protocol uses electronic temperature loggers to monitor temperatures. Freeze indicators and vaccine vial monitors (VVMs) can supply additional information, but should be considered optional. Monitoring and data recording procedures will be similar regardless of the combination of monitoring devices used.

Data Logger (required)

Several continuous temperature monitoring devices are available. This protocol describes the Gemini TinyTalk logger (WHO PIS E6/43) to provide continuous temperature data, but other loggers could be used. Recording accuracy is generally +/- 1°C. A computer is required to program and download temperature information so that it can be analyzed and printed. In most cases, a technical advisor will provide data loggers, software, and instructions.

Vaccine Vial Monitor (optional)

VVM heat exposure indicators are vaccine specific visual tools that indicate whether individual vaccine vials have received a damaging amount of heat exposure. Although VVMs are not required during the cold chain study, subsequent interventions that might remove vaccines from portions of the cold chain to prevent freezing would require VVMs on vaccines.

FreezeWatch Indicators (optional)

Freeze indicators (PIS WHO E6/45) identify when temperatures have dropped below 0ºC for more than one hour. WHO recommends that freeze indicators be included in all vaccine shipments and in all vaccine refrigerators. The planning and training for this study may provide a convenient opportunity to introduce freeze indicators.

Study Design

Study Overview

Small data loggers will be packed within inner vaccine boxes (Attachment 1) and accompany vaccine shipments to 8 different health centers (Attachment 2). Since the goal is to monitor the temperatures of the typical cold chain, the shipments should be packed, handled and stored normally, without any changes to routine procedures. Cold chain staff at each point in the cold chain will direct these monitored shipments toward the target health centers. At each point they will record the date of arrival and the date of departure on the Monitoring Form (Attachment 3) enclosed in each inner vaccine box as illustrated in Attachment 1. A study coordinator will oversee the planning and training. PATH or another outside technical

assistance agency will provide materials and train the coordinator in the programming of the data loggers and analysis of the data.

Study Planning and Preparation (technical advisor or study coordinator responsibility)

It is important to prepare for this study. A study coordinator must be identified capable of design and oversight of this cold chain study as discussed in the Personnel and Responsibilities section below. Planning discussions should include input from Ministry of Health officials, those responsible in-country for national immunization services, and available cold chain experts. Agreements with these officials may need to be formalized. A budget must be prepared (see Attachment 4) and this protocol modified to reflect the specific characteristics of the country. A realistic study schedule should be established (see Attachment 5)

Study Sites Selection (technical advisor or study coordinator responsibility)

Study provinces, districts, and health center sites should be representative of broad areas of the country. While it is inadvisable to select the most poorly managed cold chain sites with the fewest resources if this is atypical, it is important to chose study sites in which identifying vaccine freezing is most valuable. Use discussions with EPI personnel to select areas that are average to below average in terms of performance, accessibility, and temperature extremes, and staffed with responsible personnel able to fulfill study requirements.

Two provinces should be selected as the study provinces. Within each province, two districts should be selected. Within each district, two health centers should be selected, representing two different immunization scenarios (for example, one rural and remote, one urban). In summary, there should be a total of eight health centers selected as study destinations. Attachment 2 demonstrates the distribution of data loggers through the cold chain, from the central stores to the health center destination. The actual names of the provinces, districts, health centers and outreach posts should be written on this diagram or on a separate sheet, which can then be used for study planning and as a supervisory tool.

Selecting a Study Vaccine (technical advisor or study coordinator responsibility)

One type of vaccine should be selected as the vaccine to be monitored during distribution. It should be one of the freeze-sensitive vaccines (HB, DPT, TT, DT) that is distributed widely. Although many types of vaccines may be shipped in a single cold box or stored in a single refrigerator, selection of one type of vaccine will assist in identifying monitored shipments. Data loggers will be packed and shipped with the vaccine. This protocol refers to vaccines shipped with a data logger as “study vaccines.” The location of the data logger within the vaccine box is demonstrated in Attachment 1.

Activating the Data Logger (technical advisor or study coordinator responsibility)

Typically, staff from a technical assistance agency will be present to program the data loggers or to teach the study coordinator how to do it. Using a computer connection, the data logger will be activated and programmed to read at two-hour intervals, thus allowing temperature recording for five months. Each data logger will be given the name of its target health center. To direct the shipment this name will be clearly market on the vaccine inner box, the vaccine shipping carton and recorded on the Monitoring Form (Attachment 3).

Shipment Preparation (study coordinator responsibility)

At the central vaccine stores, data loggers and Monitoring Forms will be placed in eight inner boxes (typically containing 10 to 20 vials) clearly marked with the name of the target health center (see Attachment 1). These study vaccines will be packed along with vaccines being routinely delivered to the two study provinces in standard vaccine shipping cartons, four vaccine boxes per each of the two shipping cartons (see Attachment 2). Normal loading and handling procedures should be followed so the data loggers will experience typical cold chain conditions.

Ambient Temperature Monitoring (study coordinator and health staff responsibility)

To measure ambient temperatures along the distribution route, one data logger should be shipped with the vaccines to one of the study health centers, but at ambient, rather than cold chain, temperatures (see Attachment 2). A data logger should be put into a small box, labeled with destination, and shipped with the vaccines. It should be shipped and stored in the same room or vehicle as the vaccines and according to the same schedule as the vaccines, but out of direct sunlight and away from heat sources. The temperature logger recording ambient temperature should not be put in the cold boxes or refrigerators used for the vaccines. A monitoring form must be included in the box and used to record the date and time of its arrival and departure from each cold chain point.

Distribution and Monitoring (health staff responsibility)

Transport to Province—At central stores, two study vaccine cartons should be prepared. One carton should be shipped to each of the two study provinces using normal shipping procedures (see Attachment 2). Each carton should contain four data loggers, with each data logger enclosed in a separate box of monitored vaccines. These four boxes must be labeled with the destination health center and shipped with a routine vaccine shipment to the appropriate province. The Monitoring Form for each vaccine box with a data logger must be completed with the date and time of departure.

Storage at Province—Upon delivery of the vaccine shipment to the provincial vaccine stores, cold chain personnel will accept the study vaccine carton, open it and the four inner vaccine boxes containing the data loggers and Monitoring Forms. They will record the time and date of arrival on the Monitoring Form, then store the inner box containing vaccines, data logger, and Monitoring Form in the cold room or refrigerator along with other vaccines following standard practice. Study vaccine boxes should remain at the provincial store for a minimum of 1 month to adequately measure storage temperatures.

Transport to District—In each of the two study provinces, the provincial cold chain manager will follow the normal vaccine supply schedule for each the two study districts in their province. However, with the next scheduled shipment to each of the two study districts in this province, they will include the two study vaccine boxes labeled with the name of the two health centers located within each district. Before sending this shipment, the provincial cold chain manger will record the time and date on each Monitoring Form and will then pack the vaccines for shipment according to standard practice. The study vaccine boxes should be shipped in the same carton as the other vaccines being delivered and according to typical loading and transport procedures.

Storage at District— Upon delivery of the vaccine shipment from the province to each of the four study districts, district cold chain personnel will open the two study vaccine boxes labeled for the health center destinations in their district. They will record the time and dates of arrival on the enclosed Monitoring Form. They will store the inner box containing vaccines, data logger, and Monitoring Form in the cold room or refrigerator along with other vaccines, following standard practice. Study vaccine boxes should remain at district vaccine stores for a minimum of 2 weeks to adequately measure storage temperatures.

Transport to Health Center— Following the normal vaccine distribution schedule, the district cold chain manger will prepare vaccine shipments to study health centers. Upon preparation for shipment to each health center, the district cold chain manger will record the time and date on each Monitoring Form (Attachment 3), then pack the vaccines for shipment according to standard practice. One study vaccine box, labeled with the destination health center, and containing a data logger will be sent to each study health center (see Attachment 2). The study vaccines should be shipped in the same vaccine carriers with other vaccines according to typical loading and transport procedures.

Storage at Health Center— Upon arrival of the vaccine shipment from the district, cold chain personnel at each study health center will open the enclosed study vaccine box containing data loggers and Monitoring Forms (Attachment 3). They will record the time and date of arrival on the Monitoring Form and handle and store the study vaccines according to standard procedures. Study vaccines should remain at the health center for a minimum of 2 weeks to adequately measure storage temperatures.

Outreach Immunization—After at least two weeks of storage at the health center, the health center staff should prepare to monitor the next outreach session by including the study vaccine box. When preparing for an outreach session, the health center cold chain manager will record the time and date on the Monitoring Form then load the data logger into a vaccine carrier along with other vaccines according to standard procedures. At the end of the outreach session, the vaccinator will record the time and date on the Monitoring Form. This is the end of the study. Once the study has ended, data loggers can be stored at room temperature.

Data Collection and Analysis (health staff, technical advisor, study coordinator responsibility)

Use of the Monitoring Form—(Attachment 3) One person at each point should be trained in using the Monitoring Form and be responsible for completing it upon receipt and reshipment of each study vaccine shipment. This form should be modified to indicate each of the cold chain points and the study vaccine.

The technical advisor will retrieve the temperature data from the data loggers or instruct the study coordinator in how to do so. The data from the monitoring forms and data loggers should be combined to create temperature profiles of each shipment. The demarcations between parts of the cold chain should be clearly indicated. An example is given in Attachment 6. From these profiles, the level of freezing and number of freezing incidences at each point in the cold chain can be determined. A sample summary sheet is shown in Attachment 7.

Interviews (study coordinator responsibility)

To collect additional information about health worker attitudes and practices toward vaccine freezing, the study coordinator should interview several cold chain staff participating in the cold chain study. Sample interview questions are given in Attachment 8.

Evaluation and Reporting

Data from the data loggers and interviews should be combined into a report characterizing the incidence of freezing and the likely causes. Interview information can provide recommendations for ways to reduce freezing.

Personnel and Responsibilities

Technical Advisor and/or Study Coordinator

A technical advisor, such as PATH, will support the cold chain study. The technical advisor may provide direct assistance during the study or may provide additional training to the study coordinator to oversee these responsibilities:

- Design and planning (e.g. customizing this protocol, providing data loggers)
- Site selection
- Agreements with other partners (e.g. MOH agreement for use of field staff)
- Programming of data loggers
- Oversight of shipment preparation
- Data analysis
- Report preparation

Study Coordinator

A study coordinator will oversee implementation of the cold chain study. The coordinator's responsibilities include:

- Training of cold chain managers
- Supervision and troubleshooting
- Collection of data loggers at end of study
- Interviewing cold chain managers

Health Staff

The appropriate person responsible for cold chain management at each point of the cold chain in all study areas must be identified and trained. Their responsibilities include:

- Receiving study shipments
- Filling out the Monitoring Forms for each study vaccine shipment
- Directing shipments to study sites
- Transporting data logger with study vaccine for outreach (vaccinators)
- Sending data logger back to study coordinator at end of study (vaccinators)

Training and Information

The study coordinator must identify and train cold chain managers and vaccinators at each point through which study vaccines will pass. Key training topics include:

- Purpose and methodology of the study
- Importance of treating the study vaccine according to normal practices and schedules
- Identification of study vaccines
- Receiving and shipping study vaccines
- Completion of the study Monitoring Form

In addition, the coordinator will inform counterparts, such as immunization coordinators, health center doctors and/or local officials, who should be aware of the study. MOH personnel at the target province, district, and health centers will be briefed on the study procedures and instructed to handle the monitored box using standard procedures.

Using the Study Findings

The outcomes from this study should provide clarity on the severity and causes of vaccine freezing in the cold chain. This is the first step in preventing vaccine freezing. Recommended next steps include:

- Presentation of findings to immunization partners like MOH, WHO, UNICEF.
- Establishment of an expert group to review findings and make recommendations for improvements.
- Field test and validate solutions. Possible solutions might include revised training programs, new equipment, revised operating procedures, new ice-pack conditioning procedures, limited no-cold-chain transport or storage.
- Implementation and monitoring of solutions.

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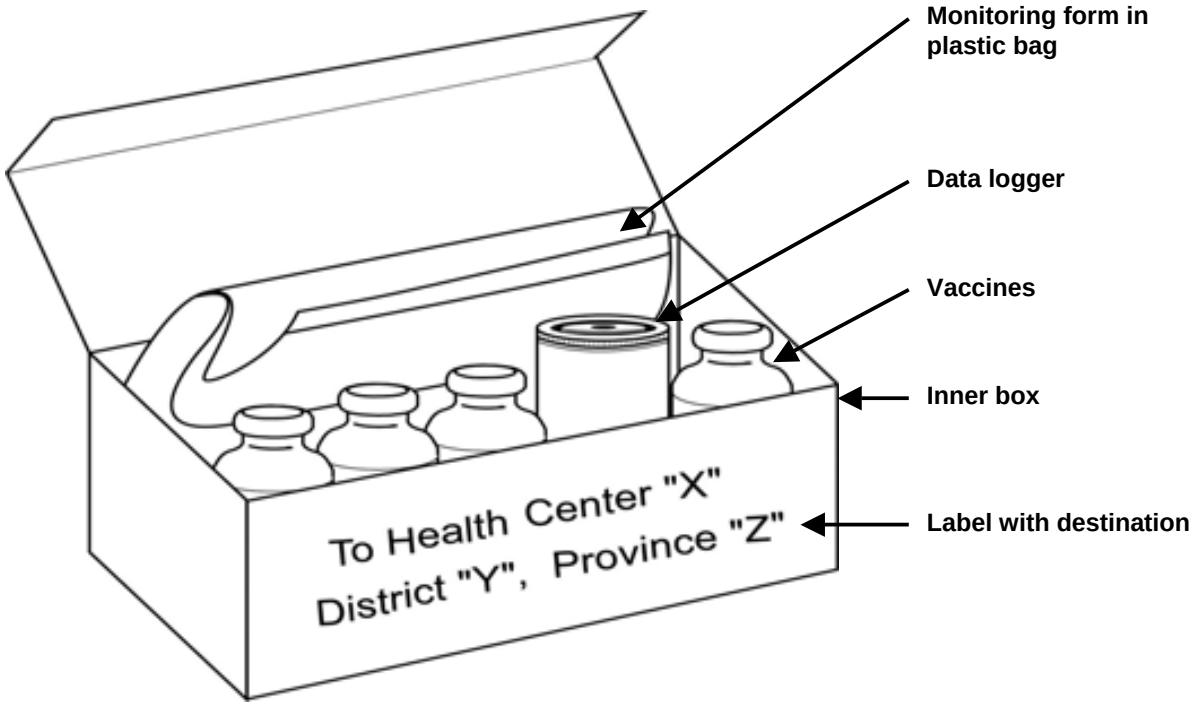
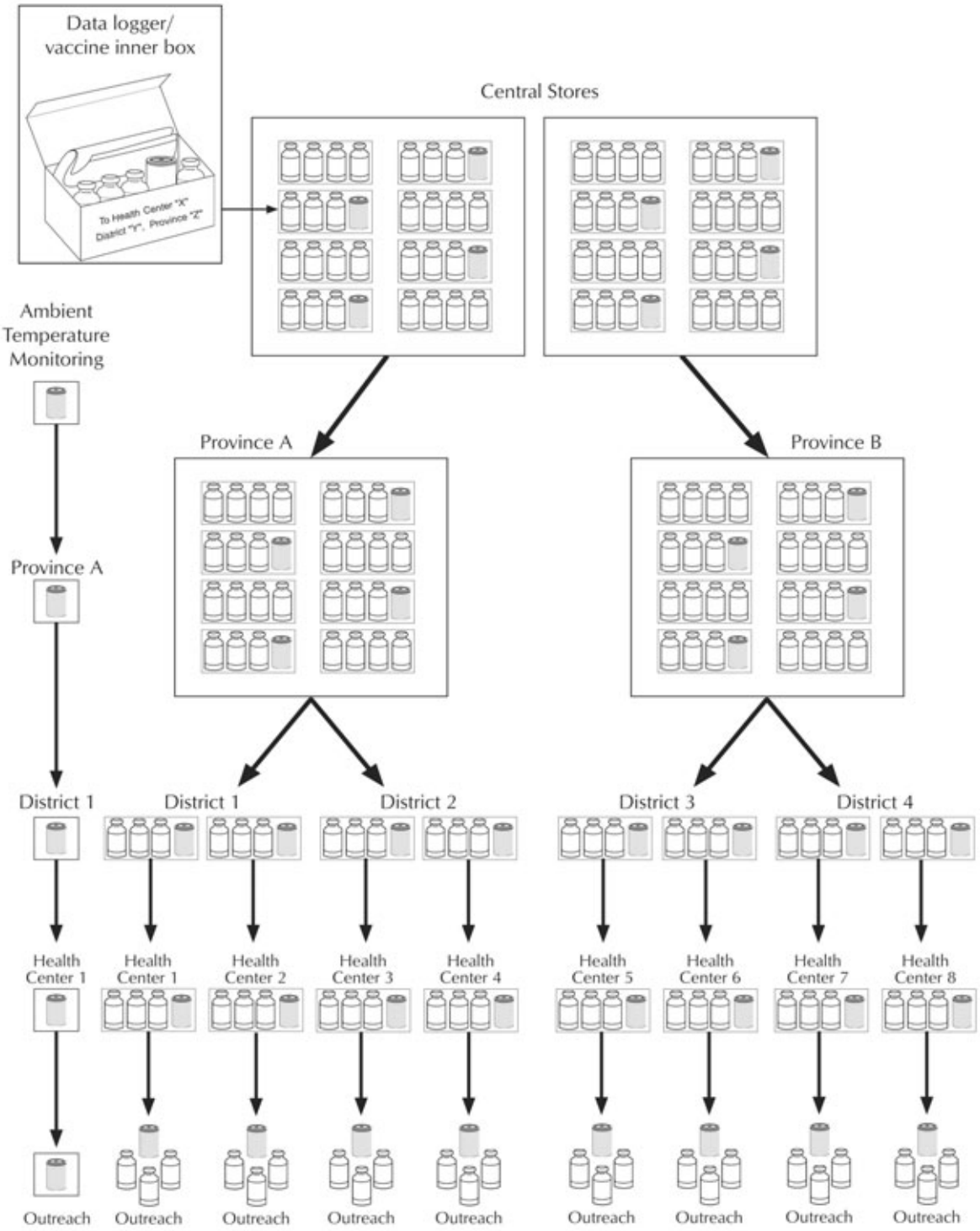
Attachment 1

Data Logger Packed in Inner Box



Attachment 2

Cold Chain Temperature Monitoring



Attachment 3

Monitoring Form

(Only for marked study vaccines)

Health center destination:_____

Data Logger ID# _____

Location	
Central Stores	**C**
Province	**P**
District	**D**
Health Center	**H**
Ambient	**A**

Facility Name	**Location**	**IN**	**IN**	**OUT**	**OUT**
		Date Received	Time Received	Date Received	Time Received

CNVP15645.xls

Attachment 4

Preliminary Budget Worksheet - Evaluating Freezing in the Vaccine Cold Chain

ACTIVITY	COST
1. PREPARATIONS	
a. Meeting with MOH and field staff	
- Perdiem	
- Local transport	
2. TRAINING	
a. Study Coordinator	
- Transport	
- Perdiem	
b. Province Participants	
- Local transport	
- Perdiem	
c. District Participants.	
- Transport	
- Perdiem	
d. Health Center Participants.	
- Transport	
- Perdiem	
3. IMPLEMENTATION	
a. Shipment arrangement	
- Transport return	
- Perdiem	
b. Data logger collection	
- Transport	
- Perdiem	
4. SUPERVISION	
- Transport (monthly visits to districts and health centers)	
- Perdiem	
TOTAL	

Attachment 5

Study Time Schedule

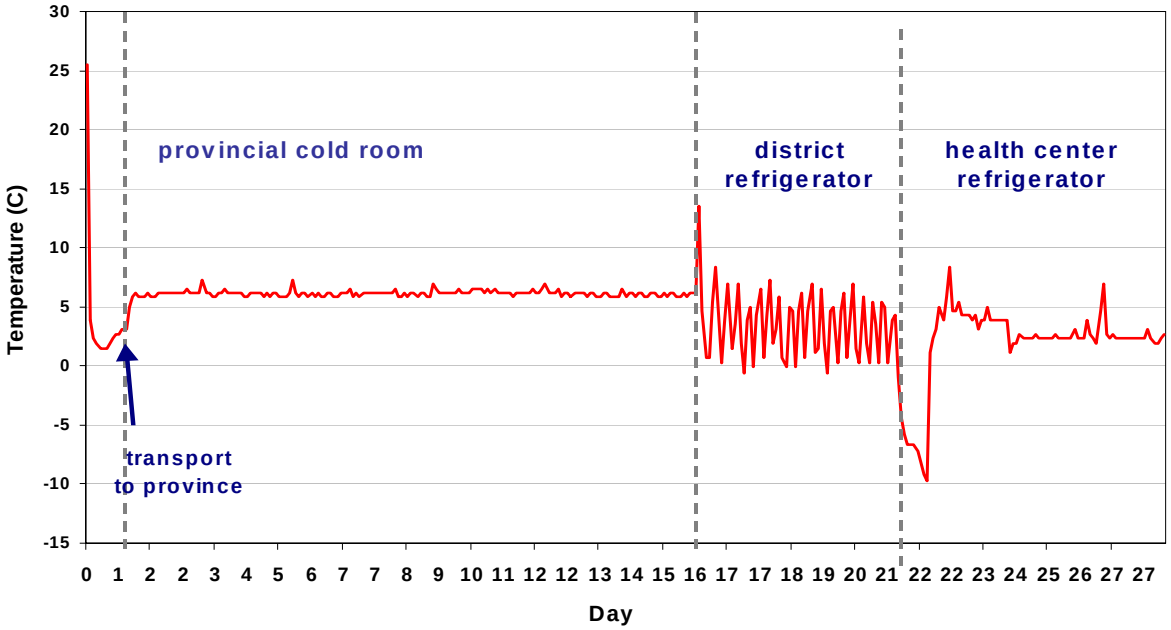
EXAMPLE

ACTIVITY	TIME																			
	Month 1				Month 2				Month 3				Month 4				Month 5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1. Preparations																				
a. Protocol Development	■																			
b. Communications with MOH, local staff	■	■	■																	
c. PATH visit				■	■															
d. Planning meetings with EPI staff				■																
e. Training				■																
2. Implementation																				
a. Shipment arrangement					■															
b. Vaccine distribution					■	■	■	■	■	■	■	■	■	■	■	■				
c. Data logger collection																	■			
3. Supervision					■				■				■				■			
4. Data entry and analysis																			■	■
5. Report																				■

Attachment 6

EXAMPLE: Indonesia Cold Chain Study

Phase 2: Ambient Transport



Attachment 7

EXAMPLE: Temperature Monitoring Summary

Min and Max Temperatures of 8 Vaccine Shipments. Two shipments per health center.

			Transport from Bio Farma to Province	Storage at Province	Transport from Province to District	Storage at District	Transport from District to Health Center	Storage at Health Center	Midwife Storage and Delivery	FINAL STATUS
Temperature Condition			Cold Chain	Cold Chain	Cold Chain	Cold Chain	Cold Chain	Cold Chain	Ambient	
Lingsar	1	Min	1.5°C	5.8°C	-	-0.6°C (8 hrs)	-	-9.7°C (20 hrs)	-	**FROZEN**
		Max	3.9°C	7.3°C	13.5°C	8.4°C	3.9°C	8.4°C	30.3°C	
	2	Min	2.3°C	2.3°C	-	-0.1°C (6 hrs)	-	-1.0°C (14 hrs)	-	**FROZEN**
		Max	6.5°C	14.9°C	5.8°C	20.2°C	3.5°C	26.6°C	30.3°C	
Bayan	1	Min	1.9°C	3.1°C	-	-2.7°C (40 hrs)	-	10.2°C	-	**FROZEN**
		Max	3.5°C	7.9°C	13.5°C	3.9°C	10.2°C	26.3°C	32.2°C	
	2	Min	5.0°C	3.1°C	-	-2.2°C (32 hrs)	-	-6.7°C (28 hrs)	-	**FROZEN**
		Max	7.7°C	18.1°C	5.4°C	20.6°C	20.2°C	13.5°C	discontinued	
Rasanae Timur	1	Min	6.5°C	5.8°C	-1.0°C (20 hrs)	-	0.7°C	1.1°C	-	**FROZEN**
		Max	6.9°C	7.3°C	-0.6°C	-	1.1°C	17.7°C	29.9°C	
	2	Min	3.1°C	3.1°C	0.7°C	1.9°C	-	6.9°C	-	**OK**
		Max	16.3°C	6.5°C	20.6°C	5.4°C	20.9°C	9.9°C	13.5°C	
Wera Timur	1	Min	3.5°C	4.3°C	-1.8°C (12 hrs)	0.7°C	21.6°C	3.1°C	-	**FROZEN**
		Max	7.3°C	7.3°C	0.3°C	8.4°C	24.1°C	16.7°C	31.4°C	
	2	Min	5.4°C	3.9°C	3.1°C	1.9°C	-	7.7°C	-	**OK**
		Max	16.0°C	7.3°C	16.3°C	4.6°C	18.8°C	13.1°C	33.7°C	
Kraton	1	Min	0.7°C	4.6°C	-1.8°C (2 hrs)	0.3°C	-	-	-	**FROZEN**
		Max	4.3°C	8.4°C	20.2°C	7.3°C	23.7°C	-	31.4°C	
	2	Min	1.1°C	4.0°C	-	-4.0°C (38 hrs)	-	1.9°C	-	**FROZEN**
		Max	3.1°C	10.2°C	8.0°C	8.4°C	14.2°C	20.9°C	discontinued	
Purwodadi	1	Min	1.1°C	4.6°C	-0.6°C (2 hrs)	-1.8°C (10 hrs)	-1.4°C (2 hrs)	9.9°C	-	**FROZEN**
		Max	3.9°C	8.4°C	11.0°C			13.8°C	33.3°C	
	2	Min	2.7°C	3.1°C	-4.0°C (4 hrs)	-1.0°C (20 hrs)	-	6.5°C	-	**FROZEN**
		Max	6.2°C	12.0°C	-	8.4°C	14.2°C	11.7°C	discontinued	
Pandian	1	Min	4.6°C	3.1°C	-0.1°C (2 hrs)	0.7°C	-	26.6°C	-	**FROZEN**
		Max	9.1°C	34.4°C	0.3°C	8.0°C	-	28.1°C	43.3°C	
	2	Min	2.3°C	3.1°C	6.2°C	3.9°C	-	1.9°C	-	**OK**
		Max	11.0°C	13.1°C	9.9°C	16.3°C	7.7°C	8.8°C	34.1°C	
Arjasa	1	Min	5.0°C	3.5°C	-1.8°C (20 hrs)	5.0°C	-0.6°C	3.5°C	-	**FROZEN**
		Max	7.7°C	35.3°C	-0.1°C	11.7°C	4.6°C	16.7°C	28.1°C	
	2	Min	2.3°C	3.5°C	-	3.5°C	0.7°C	6.2°C	-	**OK**
		Max	10.6°C	12.8°C	11.7°C	16.7°C	22.7°C	20.6°C	34.9°C	
Freezing Events / Total			**0/16**	**0/16**	**8/16**	**7/16**	**1/16**	**3/16**	**0/13**	**12/16**

Attachment 8

Interview Guidelines

Cold chain personnel can be interviewed individually or in groups. The following questions and topics are designed to help determine their knowledge and attitudes toward freezing in the cold chain.

- Does freezing harm vaccines? Which vaccines?
- How can you tell if a vaccine has been frozen?
- What do you do if you know a vaccine has been frozen?
- Do you think freezing occurs at this point in the cold chain?
- What causes freezing to occur at this point in the cold chain?
- What equipment changes or training could be done to reduce freezing?
- What else could be done to reduce cold chain freezing?
- Do you have clear guidelines explaining how to reduce freezing and what to do if vaccines are frozen?
- Did you receive training on these topics?