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RESEARCH ARTICLE

Investigating Cold-Chain System and Efficacy of Vaccines Reaching the End User in Turkey and Related Regulations

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Summary

Immunization programs are implemented according to the Expended Program of Immunization (EPI) in the WHO member countries. The cold-chain component of the program is just as important as the immunization coverage. Vaccines are produced and released as safe and efficient. But, how safe and efficient are they by the time they're administered in situ?

The aim of our study is to monitor and to evaluate the cold-chain for vaccines used in Turkey between the Primary Vaccine Store and the health service on the field. Furthermore, we collected batches designated vaccines used in this study to Primary Vaccine Store in cold chain conditions and retested tested them for their potency and virus content. The Hepatitis B Vaccine and Oral Polio Vaccine (OPV) were monitored due to their high sensitivities against freezing and high temperatures,, respectively.

We sent the products to 7 geographical regions in Turkey using small continuous temperature recorders that record temperature data for long periods of time. The health workers were not informed that they would receive vaccines with these spying thermometers. A small note was put in the small boxes of vaccines informing health workers what they had to do after receiving them.

Evaluating the thermometers collected from the field, we found that the cold chains in warehousing and transportation were reliable. And the potency tests performed by the National Control Authority were found to be satisfactory according to the references.

The results obtained showed that the vaccines designated the 7 geographical regions were transported to the targets (health services) safely and efficiently, by maintaining the cold chain conditions.

Key Words: *Vaccines, Freezing effect to vaccines, cold-chain, public health strategy, storage and transportation of vaccines.*

Türkiye'de Son Kullanıcıya Ulaşan Aşılarda Soğuk Zincir Sisteminin ve Etkinliğin İncelenmesi

Özet

Üye ülkelerde aşılama programları, WHO'nun Genişletilmiş Aşılama Programı (GAP)'na göre yürütülmektedir. Programda aşılamanın kapsamı kadar soğuk-zincir konusu da büyük önem taşımaktadır. Aşılar, güvenilir ve etkin şekilde üretilir ve dağıtılırlar. Ancak, uygulandıkları ana kadar güvenirlik ve etkinliklerini korurlar mı?

Bu çalışmanın amacı, Türkiye'de kullanılan aşıların ilk saklandıkları Primer Aşı Deposundan, sahada sağlık merkezlerinde kullanıldıkları ana kadar soğuk zinciri izleyip değerlendirmektir. Ayrıca, bu çalışmada belirli aşılar, saklandıkları Primer Soğuk Hava Deposundan kullanıldıkları yere yollanıp tekrar geri dönüşlerinde test edilerek potensleri ölçülmüştür. Çalışmada Hepatit B aşısı donmaya ve Oral Polio Aşısı (OPA) sıcaklığa en hassas aşılar olmaları nedeniyle seçilmişlerdir.

Türkiye'de 7 coğrafi bölge olduğundan seçilen aşılar bu bölgelerin her birine, uzun süre sıcaklığı takip etme olanağı veren kayıt edicilerle beraber yollanmışlardır. Sağlık çalışanları kutulardaki casus termometrelerden haberdar edilmemişlerdir. Aşı ve casus termometre bulunan kutulara, bunun ulaştığı sağlık çalışanlarının ne yapacağını açıklayan birer not konmuştur.

Kutulardaki casus termometrelerin kayıtlarının değerlendirilmesinden, depolama ve transfer sırasında soğuk zincirin korunduğu ve aşıların güvenilir olduğu anlaşılmıştır. Refik Saydam Merkez Hıfzıssıha Enstitüsü Halk Sağlığı Laboratuvarlarında yapılan potens ve virulans testlerinde aşılar yeterli bulunmuştur.

Sonuç olarak aşıların transferlerinin Türkiye'de her coğrafi bölgeyi temsilen gönderildikleri şekillerde soğuk zincir içinde korundukları, güvenilir ve etkili oldukları bilgisine varılmıştır.

Anahtar Kelimeler: *Aşılar, Donmanın aşılara etkisi, soğuk zincir, halk sağlığı stratejisi, aşıların saklanma ve taşınması.*

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INTRODUCTION

Active immunization is obtaining a response similar to an immune response after a natural infection. The whole microorganism or a processed part of it (like toxic, purified antigen or antigen tailored by genetically engineered methods) is administered to the humans without a significant immune reaction. With this immune response, two types of immunity can be obtained:

a. Humoral immunity
b. Cellular immunity

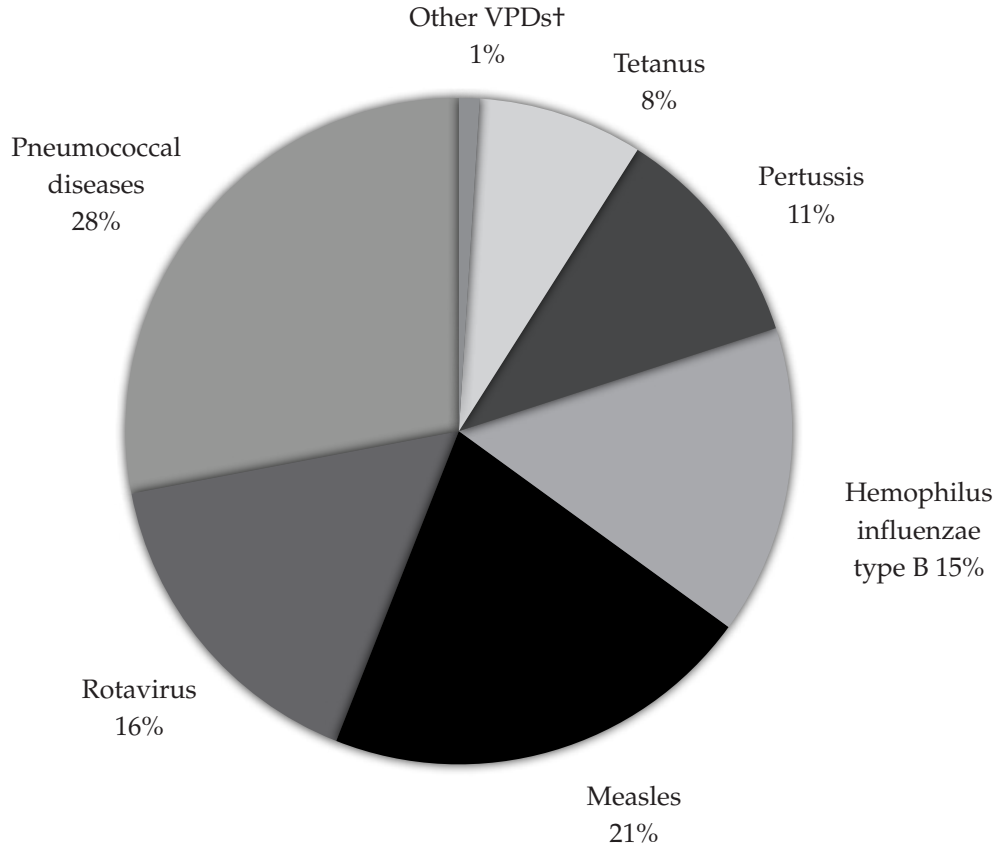
The decreases in death rates after addition of new vaccines to the immunization programs are shown in Figure 1.

RATIONALE

Vaccines are biological products which are very sensitive to freezing. The storage and transportation of the vaccines without losing its efficacy and safety from production to the end-user is called the **cold-chain** (Table 1), (2).

Table 1. Sensitivity of Vaccines to Freezing **(3)**.

Rate	Vaccine
Very Sensitive	Hep B
	Hib (Liq)
	DTP, DTP-Hep B, DTP-Hib, DTP-Hep B+Hib
Less Sensitive	DT
	Td
	TT, Hib Lyoph, Pnomococcal Conj.



* An estimated 2.5 million deaths worldwide (of a total of 10.5 million for this age group) are caused by diseases for which vaccines are currently available.
† Diphtheria, hepatitis B, Japaese encephalitis, meningococcal disease, poliomyelitis, and yellow fever. (In older age groups, approximately 600,000 hepatitus B deaths are preventable by routine immunization.)

Figure 1. The percentages of deaths from vaccine –preventable diseases (VPDs)* among children aged <5 years, by disease-worldwide, 2002 (1).

Cold-chain storage is necessary to prevent damage to vaccines caused by exposure to high temperatures. However, keeping the vaccines too cold can be just as harmful as keeping them too warm, because many vaccines can cause loss of potency which can never be restored. So, vaccine's efficacy can diminish and the risk of adverse events following immunization may increase.

Special conditions for cold-chain were not identified when the vaccination management issues started. Yet health workers and cold-chain managers are often unaware of how vaccine freezing occurs and the significances of its consequences. Therefore, the maintenance of temperature control of the vaccines during transportation and storage is the main responsibility of the health professionals. The cold-chain covers the whole national or international steps of produced vaccines from producers to the airports, main ware-houses, regional ware-houses, provincial cold ware-houses, public health centers and to the end-user/public, as well as international and national conditions during storage and transportation. The cold-chain system has three elements:

i. The health staff providing health services and using instruments,
ii. The equipment required for the safe transportation and storage of the vaccines.
iii. The procedure required for the distribution and the use of vaccines; and the program management (4). In time, all these staff got accustomed to keep the vaccines at temperatures as low as possible. So, gradually cold-chain storage/transportation became "very cold-chain storage/transportation".

Studies conducted in several countries:

i. in hot climates
ii. in cold climates
iii. in developed countries
iv. in less-developed countries

show frequent occurrences of sub-zero temperatures in the cold chain (3).

The Effects of "Very Cold-Chain"

- If the temperature reaches temperatures as low as -20°C, problems arise due to this: (Figure 2a, 2b) (3).
- Freeze-sensitive vaccines have Al as adjuvant. On freezing, these vaccines loose their potency and this change is irreversible,
- Cold rooms or refrigerator thermostats that are adjusted improperly or too frequently,
- Vaccines that are incorrectly positioned in cold rooms or refrigerators,
- Inadequate temperature monitoring of cold-chain equipment.

Therefore, in recent years, "freezing" became the most important problem of the cold-chain and the WHO started implementing several strategies-to prevent vaccines from freezing:

- Reducing the risk of freeze damage to vaccines,
- Preparing programs following the best practices in the aide-memoire,
- Increasing awareness about the issue,
- Implementing clear operational guidelines,
- Assessing the extent of the vaccine-freezing problem in their cold-chain systems,

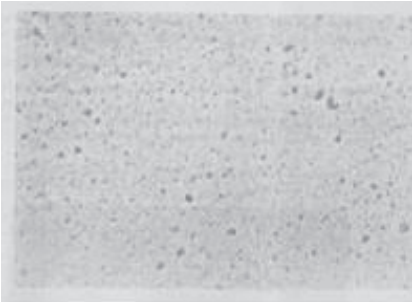


Figure 2a. Fine-grain structure of Al gel stored at the optimal temperature (3).

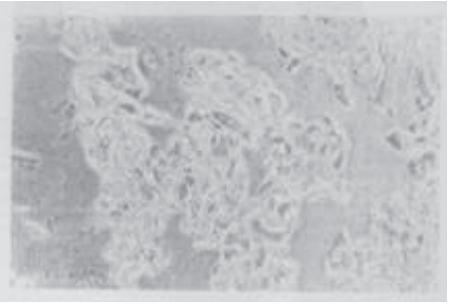


Figure 2b. DTPA vaccine affacted by freezing (at –18°C) showing large conglomarates of massed precipitates with crystalline structure (phase contrast microscope) (3).

– Implementing the corrective measures, if necessary.

Additionally, transportation of vaccines excluding cold-chain is another strategy. But, this route is not validated yet.

Cold-Chain Applications

In the beginning, it was unknown that the vaccines had to be stored in cold-chain. Then, it was determined that the vaccines could become inactive due to the temperature. Exposure to high temperatures (30–35°C) causes degradation of vaccines. Likewise, repeated exposure to the high temperatures (even if they are under 30°C) might cause the same result. Therefore, continuation of the cold-chain necessitates maintenance (5). The vaccines like OPV, MMR, measles and BCG are sensitive to heat; whereas, inactive vaccines are sensitive to cold.

On the other hand, all other vaccines should not be frozen and should be stored at temperatures between +2°C and +8°C, at all levels of the cold-chain. Liquid formulations of vaccines containing hepatitis B, pertussis, tetanus and diphtheria and their combinations should not be frozen (6). But, this time all vaccines were exposed to cold-chain without paying attention to the types of the vaccines (7, 8). In the 21st century, it was determined that freezing damaged the physical stability and the potency of the vaccines. The WHO has started a "global training program" covering all member countries in the world. These courses are organized in 9 different themes at 16 different centers. The course entitled "Pharmaceutical Cold-Chain Management on Wheels" was organized by Turkey in June-2010 (9).

The number of vaccine producers is very limited in the world. The countries (that can't produce vaccines) can provide vaccines by the help of the WHO bodies like UNICEF, GAVI, PAHO.

Temperatures are controlled in the cold-chain by different methods (13-28) (Figure 3):

Instrument	Int. Transport	Main Ware -house	National Transport	Regional Ware-house	Regional Transport	Public Health Centre
LCD monitored transport indicator						
Vaccine Monitoring Card						
Vial Temp. Monitor						
Freezing Indicator						
Computed Temp. Recording Inst.						
Thermometer						
Mini-max Thermometer						
Electronic Temp. Monitor						

Figure 3. Are the temperatures controlled sufficiently in the cold-chain **(10)**?

i. Refrigerators

Vaccines, vaccine diluents and ice-packs can only be put in dedicated refrigerators; but are not put in the refrigerator door. Refrigerators should not be filled too much. In order to maintain the cool temperature when the electricity cuts occur, a few bottles containing salt water should be put in the bottom part of the refrigerator. It should be checked using thermometers that he temperature is kept between 0 and 8°C. VVM (Vaccine Vial Monitoring) containing vaccines should be checked by monitors.

ii. Cold Boxes for Vaccine Transportation

There are ice packs in these cold boxes and they are used for the storage of vaccines for 2-5 days from the main health center to the designated region, or when the refrigerator is out of order (Figure. 4).

Figure 4. Cold boxes for vaccine transportation **(11)**.

iii. Boxes with Holders for Vaccine Transportation

They look like cold boxes. The differences to cold boxes are the smaller size and a handle. Generally, mobile vaccination teams use these for transportation purposes and vaccines can be stored for 24hrs (Figure 5).

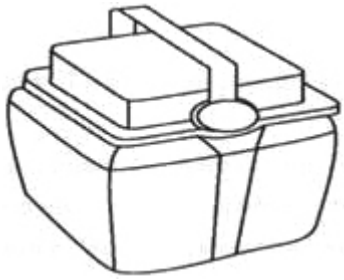


Figure 5. Cold box with a handle for vaccine transportation **(11)**.

iv. Ice Packs

They are used in cold boxes for vaccine transportation. Their numbers and the sizes are dependent on the needs. It contains tap water. The most important point is "not to have the vaccines in direct contact with the ice packs".

v. Thermometers

There are different types of thermometers like the dial type, alcoholic types, electronic types, min-max types, and none of these thermometers are with a temperature monitoring ability (Figure 6). On the contrary, some digital thermometers have temperature monitoring features.

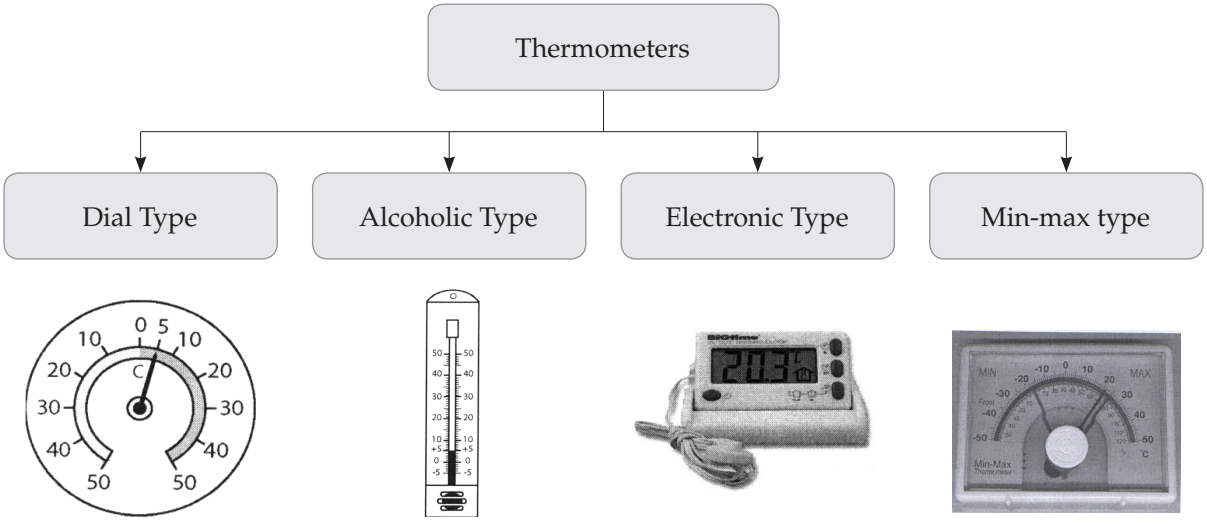


Figure 6. Different types of thermometers **(12)**.

vi. Cold-Chain Monitoring Cards

These cards can record and contain strip monitors (Figure 7). There are 4 areas (A-D) on these cards. The areas on the card become bluish with the high temperatures one by one. For the purposes of monitoring, the exposure times to high temperatures can be seen. They do not inform on the instant temperature increases. They are used for the transportation of vaccines of high sensitivities.

Figure 7. Cold-Chain Monitoring Card (4).

vii. Freezing Indicators

These indicators irreversibly show exposure of vaccines to low temperatures. There are two types of freezing indicators; dye type and digital type.

Dye indicators are of two varieties (Figure 8):

a. 9800 FW: is activated at (-)4°C and dyes the background red,

b. 9805 FW: is activated at 0°C and dyes the background black,

Digital indicators are also of two varieties (Figure 9):

a. The ones that contain electronic temperature measuring unit,

b. The ones with their (√) sign denoting usability turning to alarm (X) sign, if the vaccine is exposed to high temperatures for 1 h.

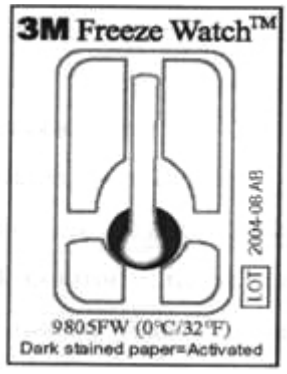


Figure 8a. Non-frozen (No problem in vaccine) (12).

Figure 8b. Frozen (Problematic vaccine) (12).

(a) **(b)**

Figure 9a. Digital Type Freezing Indicators (OK Display), 9b. Digital Type Freezing Indicators (Alarm) (12).

viii. Vaccine Vial Monitors (VVM)

VVM is a fixed label adhered on the vaccine vial (Figure 10). It changes color after a long period of exposure to excessive temperatures. Depending on its color, it can be either used or discarded. This color gives an opinion on the cold-chain break.

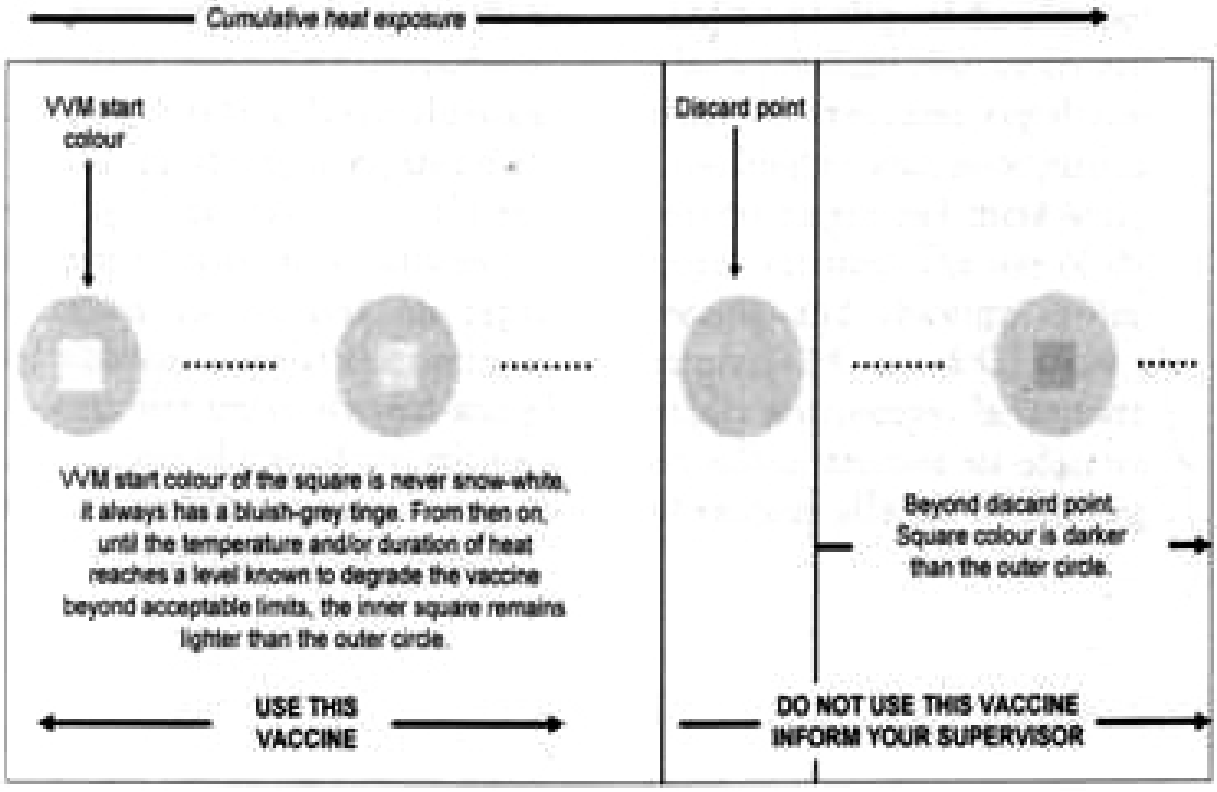


Figure 10. Vaccine Vial Monitor **(12)**.

ix. Digital Thermometers Recording for a Long Periods of Time

They were invented by the WHO for the temperature monitoring purposes (Figure 11) and were launched to be used regularly for the first time in Turkey. Refrigerators used for all kinds of vaccine storages (in Expanded Program for Immunization=EPI) should have these digital thermometers. They have 30 days record memory capacity. When the cold-chain breaks, alarm sign appears. They give information on the periods of exposure to high and normal temperatures.

Figure 11. Digital refrigerator thermometer **(12)**.

AIM

The main problem in the EPI program is the "freezing". There are 4 seasons governing in Turkey. Therefore, freezing and cold-chain problems are also valid for Turkey. OPV and Hep B vaccines were evaluated from the freezing and cold-chain viewpoint. National cold-chain was evaluated for the storage and domestic transportation.

Applications in Turkey

Ministry of Health provides all vaccines free of charge. EPI has been applied since 1985 (4, 29, 30). 10 different vaccines, 5 different antiserums and PPD solutions are stored/transported for long periods in Turkey.

MATERIALS and METHODS

Vaccines: Hep B was chosen as the most sensitive vaccine to freezing (Serial No: 202088, Indonesia). Oral Polio Vaccine (OPV) was studied as the most sensitive vaccine to high temperatures (Serial No: 0803, S. Korea).

How Cold-Chain Works in Turkey?

Ministry of Health-Central Cold Warehouse/Store

2 Main Warehouses in Ankara
Cold rooms are equipped with electronic type thermometers
4 shipping terms
Max storage period of vaccines is 6-9 months
Shipping by frigorificvehicles

Province Health Directorate-Cold Warehouse/Store

81 provinces/81 Colt Warehouses
Cold rooms are equippe with electronic type thermometers
Max storage period of vaccines is 3 months
Shipping by frigorific vehicles within "the working day"

Public Health Centers-Refrigerators

Since 2006
Record keping with digital thermometers (30 days along)
Public/Immunization

Transportation Vehicles Equipped with Cooling and Heating Facilities

These vehicles are used for distribution of vaccines in the peripheric regions.
They transport vaccines to 7 geographical regions

In-Provincal Vaccine Transportation

Cold boxed
Cold boxes with holders
Ice packs
Water packs
Equipped with digital thermometers
VVM
(all heat indicators proposed by WHO)

Figure 12. Flow chart (4)

Conditions: 10 vials of Hep B (or OPV) containing "spy thermometers" were transported from the Min. of Health's Central Cold Warehouse to all regional end-points. Spy thermometers were programmed to keep records for 4 months.

Spy Thermometers: Tinytag Talk 2 Temperature Loggers were used as spy thermometers, having 16000 records capacity and recording every 11 min. At the end of 123rd day, recordings were stopped automatically. Hep B and OPV vaccines were transported to the 7 geographical regions of Turkey with spy thermometers, with warning messages to the end-users in the packages (Figure 12 and 13). After opening the packages at the end-user health facility, the staff were asked to return the spy thermometers to the Min. of Health's Main Center.

Figure 13. HepB+Spying Thermometer.

Figure 14. OPV+Spying Thermometer.

Tests on the Returned Vaccines: Eliza tests were performed on the returned-Hep B vaccines for potency, and the virus contents were determined on the returned OPV vaccine for the efficacy by National Institute of Public Health Control Labs operating under European Pharmacopeia (31). Briefly;

Cell Culture and Virus

Primary monkey kidney cell cultures (PMK) were used for production, cultivation and titration of Polio virus types 1-3 (Sabin).

The vaccine strain was obtained from the culture collection of the National Inst. of Public Health Labs. When neurovirulence effect was found proper, supernatant medium and cells were harvested and were frozen at -60°C.

Virus Titration Assay

Separate vials of the vaccine were titrated for infectious virus. One vial of an appropriate virus reference preparation was used for validation of each assay. For a three valent vaccine, the estimated mean virus titrates must be: not less than $1x10^{6.0}$ infectious virus units ($CCID_{50}$) per single human dose for type 1; not less than $1x10^{6.0}$ infectious virus units ($CCID_{50}$) for type 2; and not less than $1x10^{5.5}$ infectious virus units ($CCID_{50}$) for type 3.

For the monovalent and divalent vaccines, the minimum virus titrates are decided by the competent authority.

Method: Groups of 8 to 12 flat-bottomed wells in a microtitrate plate were inoculated with 0.1ml of each of the selected dilutions of virus followed by a suitable cell suspension of the Hep-2 (Cincinnati) line. The plates were incubated at a suitable temperature. The cultures were examined on days 7-9.

The assay is not valid if:

- The confidence interval (P=0.95) of the log of the virus concentration of the reference preparation is greater than ± 0.3,
- The virus concentration of the reference preparation differs by more than 0.5 log $CCID_{50}$ from the assigned value,
- The range of the virus concentrations found for the replicates for any sample is greater than 0.8 Log $CCID_{50}$.

RESULTS

Potency Test Results of Hep B Vaccine

Potencies were found as 0.5, 0.99 and 1.08 $mg.mL^{-1}$ for the reference vaccine, at the embarkation point (Min. Health's cold warehouse) and on return (with spying thermometer), respectively.

As a result, Hep B vaccine was found keeping its potency when administered to the patient. No cold-chain break was observed.

Virus Content Test Results of OPV Vaccine

The findings are given in Table 2.

Table 2. Virus Content Test Results of OPV.

OPA Virus Type	Test Results for the Content of First Virus*	Test Results for the Content of Last Virus**	Reference Results
OPA, Type 1	6,28 CCID50/ dose LOG 10	6,39 CCID50/ dose LOG 10	6,0 CCID50/ dose LOG10 (min.)
OPA, Type 2	5,0 CCID50/ dose LOG 10	5,14 CCID50/ dose LOG 10	5,0 CCID50/ dose LOG 10 (min.)
OPA, Type 3	5,74 CCID50/ dose LOG 10	5,86 CCID50/ dose LOG 10	6,28 CCID50/ dose LOG10 (min.)

As a result, OPV Vaccine was found keeping its virulance when administered to the patient.

Evaluation of Cold-Chain Results

The cold-chain results obtained from different regions are as follows:

Niğde/Hep B Vaccine:

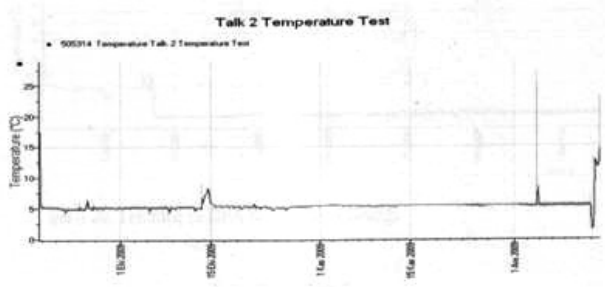


Figure 15. Hep B Vaccine/Cold-Chain Thermal Record.

Hep B Vaccine was stored between +4 and +8°C throughout the period.

Samsun/OPV Vaccine:

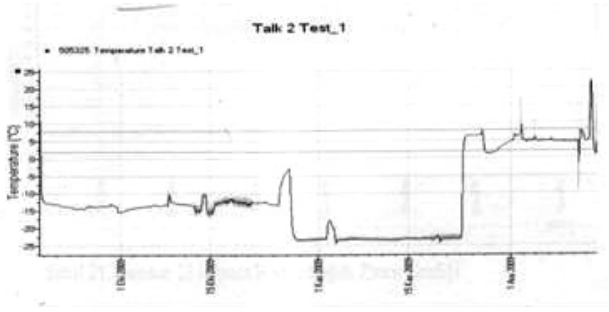


Figure 16. OPV Vaccine/Cold-Chain Thermal Record.

OPV Vaccine was stored and transported between -24 and -4°C (1 month); and between +1 and +11°C (1.5 month).

Van/OPV Vaccine:

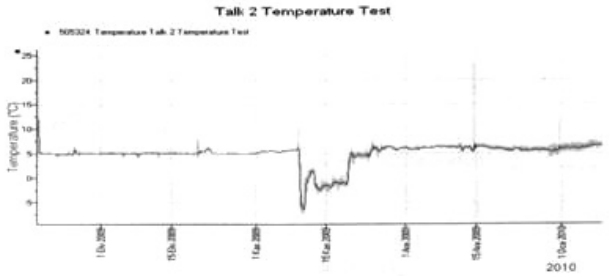


Figure 17. OPV Vaccine/Cold-Chain Thermal Record.

OPV Vaccine was stored and transported between +4 and +8°C (1 month) and between -7 and +5°C (1 month).

Tekirdağ/OPV Vaccine:

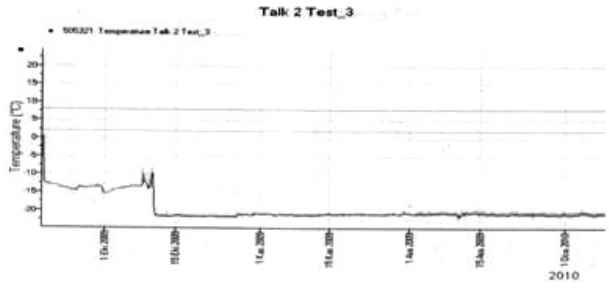


Figure 18. OPV Vaccine/Cold-Chain Thermal Record.

OPV Vaccine was stored at minus temperatures all the time.

Samsun/Hep B Vaccine:

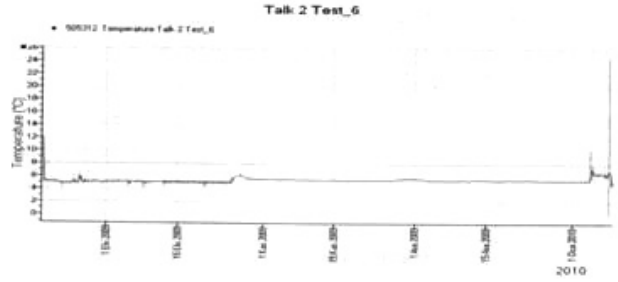


Figure 19. Hep B Vacc/Cold-Chain Thermal Records.

Hep B Vaccine was stored and transported between +4 and +8°C all the time, except for an instantaneous 10°C on administration.

Diyarbakır/OPV Vaccine:

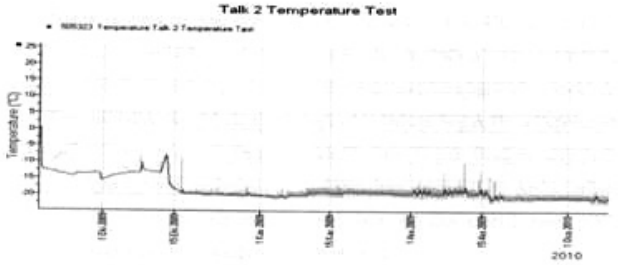


Figure 20. OPV Vaccine/Cold-Chain Thermal Records.

OPV Vaccine was stored and transported between -8 and -22°C.

Manisa/OPV Vaccine:

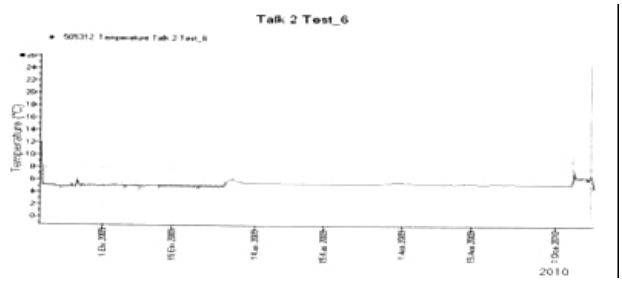


Figure 21. OPV Vaccine/Cold-Chain Thermal Records.

OPV Vaccine was stored and transported between -21 and +4°C.

Overall Results: All VVMs present on the vials and thermal records showed that all vaccines reached the endpoint user safely keeping the cold-chain.

CONCLUSION

The success of a disease-prevention goal in public health depends not only on the number of vaccinated people, but also on the number of the stable and refrained cold-chains, for high potency vaccines.

Additionally, the cost associated with wasting vaccines damaged due to freezing has to be reduced. It was understood that the vaccines can maintain its efficacy and safety when they are stored/transported in cold-chain without any break.

The use of all temperature control equipment recommended by the WHO is very important. In this study, no cold-chain break was observed for Hep B and OPV vaccines.

The investigated vaccine OPV stability depends on the storage and transportation temperature of -20°C. At the health facility, the temperatures may be between 2 to 8°C.

The other lyophilized vaccines (other than OPV) like BCG, measles, MMR (mumps, measles and rubella), yellow fever, hib, rabies, may also be kept frozen at -20°C if the cold-chain space permits. However, this is neither essential nor recommended. These vaccines should be stored between 2 to 8°C.

Liquid formulations of vaccines containing diphtheria, pertussis, tetanus, Hep B, Hemophilia Influenza type B, IPV and their combinations must not be frozen.

The national strategy of Turkey sets a model system for cold-chain storage/transportation of vaccines to the other member states of the WHO.

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(*) Part of our research results have been issued on the web-site of Ministry of Health, Directorate of Fundamental Health Services, Vaccines Task Group by the following web-addresses:

– http://asicalismagrubu.org/soguk_zincir2.asp
– http://asicalismagrubu.org/soguk_zincir5.asp
– http://asicalismagrubu.org/soguk_zincir6.asp
– http://asicalismagrubu.org/soguk_zincir7.asp
– http://asicalismagrubu.org/soguk_zincir8.asp