Vaccine 38 (2020) 5202–5211

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A vaccine cold chain temperature monitoring study in the United Mexican States

Verónica Carrión Falcón [a], Yara Verónica Villalobos Porras [b], César Misael Gómez Altamirano [c], Umit Kartoglu [d,*]

[a] Francisco Zarco 2947, Colonia Melchor Ocampo, Ciudad Juarez, Chihuahua CP32380, Mexico
[b] Area of Personal Property and Specialized Equipment, OPD Jalisco Health Services, Amsterdam #1486 int 15, Arcos Vallarta, C.P 44130 Guadalajara, Jal, Mexico
[c] Agreements and Committments, National Health Council, Lieja 7 Alcaldía Cuauhtémoc, Colonia Juárez, Ciudad de Mexico C.P. 06600, Mexico
[d] Extensio et Progressio, 1a chemin du Pre-d'Orsat, 1245 Collonge-Bellerive, Switzerland

ARTICLE INFO

Article history:
Received 9 February 2020
Received in revised form 1 June 2020
Accepted 5 June 2020
Available online 22 June 2020

Keywords:
Vaccines
Cold chain
Temperature monitoring
Vaccine vial monitor
VVM

ABSTRACT

Vacine cold chain assessments conducted in various parts of the world indicate that maintaining equipment at the temperature range recommended by the World Health Organization (WHO) is not always observed. It has been also the case that staff rather prioritize protecting vaccine from heat damage, thus often exposing vaccines to freezing temperatures. As a result, inadvertent freezing of vaccines is a largely overlooked problem all over the world. In a recent systematic review, comparison of the occurrence of freezing temperatures during storage and transport were found to be a global problem occurring both in the resource-rich as well as the resource-limited settings. A vaccine cold chain temperature monitoring study was conducted using standard WHO study protocol with the objective to document potential problems and to identify appropriate control measures. Multiple temperature monitoring devices were used in the study to evaluate user friendliness of these devices and staff attitudes towards them. In general, majority of the time, temperatures were kept between recommended temperature range of 2–8 °C. Temperature variation got wider when products moved from 3PL Laboratory to service points. The wider variation is found at the service points. High temperature excursions were observed or short periods of time while exposures to freezing temperatures were more both higher in number and duration, however, shake test with these vaccines indicated no freeze damage. 91% of staff believed that they did not have the necessary tools to detect if a vaccine had been damaged by a temperature excursion outside the 2–8 °C range, and all staff believed that inclusion of such devices (e.g. vaccine vial monitor) in the system would improve cold chain operations as they have became aware of problematic areas through this study.

1. Introduction

All vaccines are time and temperature sensitive products: all are sensitive to heat, some to freezing and some to light, and they must be stored and transported at controlled temperatures [1]. The increasing portfolio of vaccines require more effective and efficient operation of complex supply chains. Personnel handling the vaccines should have the necessary education, training and experience to perform their jobs effectively.

Assessments conducted in various countries on effective vaccine management (EVM) indicate that maintaining equipment at the temperature range recommended by the WHO is not always observed [2]. Moreover, in case of such temperature breaches, no proper follow-up actions are taken. Many countries still lack appropriate temperature monitoring tools for vaccine stores and refrigerators. Among the studies documenting temperature breaches there are some that indicate that these breaches may affect the vaccines [3–7]. It has been also observed that cold chain practices tend to rather prioritize protecting vaccine from heat damage, thus often creating the risk of exposure to freezing temperatures. As a result, inadvertent freezing of vaccines is a largely overlooked problem all over the world. In a recent systematic review, comparison of the occurrence of freezing temperatures during storage and transport were found to be a global problem occurring both in the resource-rich as well as the resource-limited settings [8]. To-date there were no EVM assessment or temperature monitoring in the vaccine cold chain study organized in United Mexican States. From the program quality perspective, it is critical to have such evaluations to identify problems and intro-

* Corresponding author.
E-mail address: umit@kartoglu.ch (U. Kartoglu).

https://doi.org/10.1016/j.vaccine.2020.06.014
0264-410X/

duce preventive, detective, and mitigation measures to improve program delivery.

This vaccine cold chain temperature monitoring study documented potential problems in a vaccine cold chain and identified appropriate control measures.

2. Objectives

The purpose of the study was to document full temperature history in selected vaccine distribution routes including storage facilities and service points along the vaccine cold chain, and to identify specific problem areas where corrective actions and control measures might be warranted.

Specific objectives of the study can be summarized as follows:

- Document the temperature history of selected distribution routes including storage and transport.
- Identify the exposure of vaccines to temperatures outside the recommended range of 2 °C to 8 °C.
- Identify specific problem areas and suggest corrective actions and control measures.
- Assess user friendliness and performance of temperature monitoring devices included in the study (data logger, threshold indicators and vaccine vial monitor (VVM)).

3. Material and methods

World Health Organization (WHO) recommended temperature monitoring in the vaccine cold chain study protocol was used in the study [9]. As recommended by the WHO protocol, two study sites (Chihuahua and Puebla states) were selected taking into consideration distance, as well as the climatic situation. In each state, two municipalities were randomly selected. Further down, two villages were randomly selected from each municipality.

In addition to data loggers, threshold indicators and VVMs were included in the study packages. Table 1 illustrates all temperature monitoring devices included in the study.

EDGE™ M-300 is a lithium battery operated wireless, Bluetooth® enabled temperature sensor. Three LED status lights provide visual confirmation of connection and notification of alarms. The sensor responds to temperatures between −40 °C to +85 °C with ±0.3 °C accuracy, and IP67 protection against ingress dust and water immersion. Setting was done to record with 20 min intervals. The sensors placed inside the study package was set to 2 °C low and 8 °C high alarms, while sensors placed outside the study package had no alarms set. Temperature readings that are stored on EDGE devices are viewed within wireless range with the help of EDGEVue mobile application (or with web application for Windows) [10].

LIMITmarker® F-M is a single use, irreversible, chemical high temperature threshold indicator for 25 °C for 2 h (accuracy ±1.0 °C). LIMITmarker® F-A threshold temperature is 9 °C. When temperature limit is exceeded, the round window starts turning pink/red [11].

FREEZEmarker® L is a single use, irreversible, chemical freeze threshold indicator for 0 °C for 30 min (accuracy ± 1.0 °C). Once the device is exposed to such temperature for at least 30 min, the clear liquid in the bubble turns opaque, preventing the tick mark to be seen [12].

VVM is a WHO Performance, Quality and Safety (PQS) prequalified cumulative time and temperature integrator [13]. VVM has an active surface (square in the middle) and a printed outer reference circle. It gives clear visual signal to health workers whether vaccines were exposed to a cumulative temperature over time that vaccines could possibly be affected. The vaccines remain usable as long as the square color is lighter than the outer reference ring. At the discard point (endpoint), the color of the square matches the color of the outer reference circle. WHO and UNICEF recommends inclusion of VVMs on all vaccines [14]. VVMs come in six

Table 1
Temperature monitoring devices included in the study packages.

EDGE™ M-300	LIMITmarker® F-M and F-A	FREEZEmarker® L	HEATmarker® Vaccine vial monitor
Electronic data logger with internal sensor. Read with the EDGEVue application. Accuracy ±0.3 °C.	F-M 25 °C (2 h), F-A 9 °C (2 h) threshold indicator with ±1.0 °C accuracy	−0°C (30 min) freeze indicator with ±1.0 °C accuracy	WHO prequalified time and temperature integrators - vaccine vial monitor (VVM14 and VVM30 are included in the study)
	Before reaching endpoint 	Before freezing exposure 	Start point 
			End point 
EDGEVue application 	After reaching endpoint  	After freezing exposure 	Beyond the end point 

different types for various stability groups of vaccines. In this study only VVM14 and VVM30 types were used. VVM14 means that the VVM would reach its discard point in 14 days if kept at constant 37 °C.

All four devices included in the study are products of Temptime Corporation.

3.1. Study packages

Mono-dose Hepatitis B (HepB) and measles-mumps-rubella (MMR) vaccines, both manufactured by Serum Institute of India were selected as the study vaccines. VVM selection of types 14 and 30 was done to match with the vaccines: VVM14 (MMR) and VVM30 (HepB). Dot VVM14 and VVM30 were received from Temptime (USA), and were applied onto flip off caps of the study vaccine vials manually during the preparation of study packages. Each study package included 25 vials of HepB vaccine and 18 MMR vaccine. Each vial is numbered from 1 to 43 with a permanent marker. In order to facilitate conducting shake test at the final point in case of negative temperature exposure along the cold chain, in addition to these vaccines, one more vial of HepB vaccine that was purposely frozen as negative control was included in the package. The negative control vial was marked as "frozen" with a permanent marker. Other two chemical threshold indicators (FREEZEmarker® L and LIMITmarker® F-M and F-A) were affixed onto the monitoring form. One EDGE™ M-300 with low and high alarm settings (2 °C and 8 °C) was included in the study package. Another EDGE™ M−300 was prepared with no alarms and marked with the name of the destination. Both devices had 40 min delay start for conditioning purposes.

Study packages were prepared at the central warehouse (from now on central warehouse is referred as "laboratory" where vaccines are being stored after being imported) prior to the start of the study. Before closure of the study packages, monitoring forms were filled in with the necessary information and status of all temperature monitoring devices were noted. Individual study packs were placed inside cartons which were then labelled with the name of the four municipalities participating in the study. Each carton contained two individual study packs for service points. The second dataloggers for ambient temperature monitoring were put together in an outer package, attached to each carton. When the cartons were broken down for further distribution, corresponding second datalogger was attached to the outside of the pack.

3.2. Monitoring form

In addition to the VVMs that were on the cap of all vaccines, all temperature monitoring devices were affixed to the monitoring form that went into each study package (Fig. 1). Health staff handling the study packages both for dispatch and receipt filled in necessary information on dispatch and receipt.

3.3. Study flow

Representatives from all levels were brought together for a one-day orientation on study methodology and roles and responsibilities in handling the study packages.

Products were kept for one month at the laboratory, state warehouse, and municipality warehouse, and 15 days at the service points. No special arrangements were made for storage of the product; all facilities followed their routine practice. Dispatch of products from laboratory to state and municipality warehouses and to service points were done by temperature-controlled truck.

All temperature monitoring devices were read by staff on dispatch and arrival to each facility. The study flow is shown in Fig. 2.

All staff involved in handling study packages at all levels were given an 11-question survey on the cold chain and the user friendliness and performance of the temperature monitoring devices included in the study.

4. Results

The study was initiated on 23 July 2018 with the storage of all study packages in 3PL Laboratory. The dispatches from the warehouses to different lower levels were done on different dates, this resulted in some of the storage periods longer than planned. The very first completion was with 107 days and 20 h and 54 min at Chignaahuapan health centre, and the longest completion was at Anapra with 143 days and 7 h and 35 min. The temperature profile inside the study packs ranged from −7.94 °C (San Francisco Teotihuacan health centre) to +14.42 (Tierra Nueva health centre). The temperature profile by location measured inside the study packages is given in Table 2. Temperatures measured outside the study packs varied between −8.27 and 14.77 just slightly above and/or below the temperature measured inside the study packs.

Fig. 3 shows the minimum and maximum temperature recordings inside the study packages along the vaccine cold chain throughout the study.

Ninety two percent of the time, temperatures were kept between recommended temperature range of 2–8 °C. Temperature variation got wider when products moved from 3PL Laboratory to service points. The wider variation is found at the service points. The biggest range was found in Tierra Nueva (13.82 °C) followed by San Francisco Teotihuacan (13.67 °C). However, it should be noted that the negative temperatures in Tierra Nueva were recorded between 26 October 2018 at 02:07 am and 09:27 am for 7 h and 20 min. Same day manual recording of the temperature indicated as 2.5 °C.

Despite this, it should be noted that temperatures below 0 °C and above 8 °C are found to be short exposures by time (less than one hour). In Chihuahua state store, half of the time, temperatures were below 2 °C but did not exceed 0 °C. Vaccines were kept at temperatures between 1.99 °C and 0.0 °C 91% of their storage time. In Anapra service point, a similar pattern was observed, but much shorter (16% of the storage time). Regarding the temperatures above the 8 °C, the longest exposure was observed in Galeana (5% of the storage time).

Fig. 4 gives full details of temperature recordings by a selected destination (San Francisco Teotihuacan).

The negative temperature excursion in San Francisco Teotihuacan was due to malfunction of the refrigerator over the night which was noticed in the morning.

The color change observed in LIMITmarker® F-A (9 °C for 2 h) was as expected in Tierra Nueva facility. FREEZEmarker® L was also found to be triggered in San Francisco Teotimihuacan service point. Remaining devices were marked as satisfactory (OK status, no alarm) in all other routes. No significant changes were observed in VVMs.

4.1. Cold chain personnel feedback

A total of 19 cold chain personnel involved in handling study packages were given an 11-question survey. Nine of these staff were nurse, while one was medical doctor, and six were engineers. Staff were asked whether they can determine if vaccines were damaged by heat if there was a power outage, and the refrigeration unit registered temperature excursions outside of the required 2–8 °C range. All 19 respondents indicated that there is no way to determine such a heat damage in vaccines unless a VVM is used. All staff highly rated (out of 5 as the highest score) the usefulness

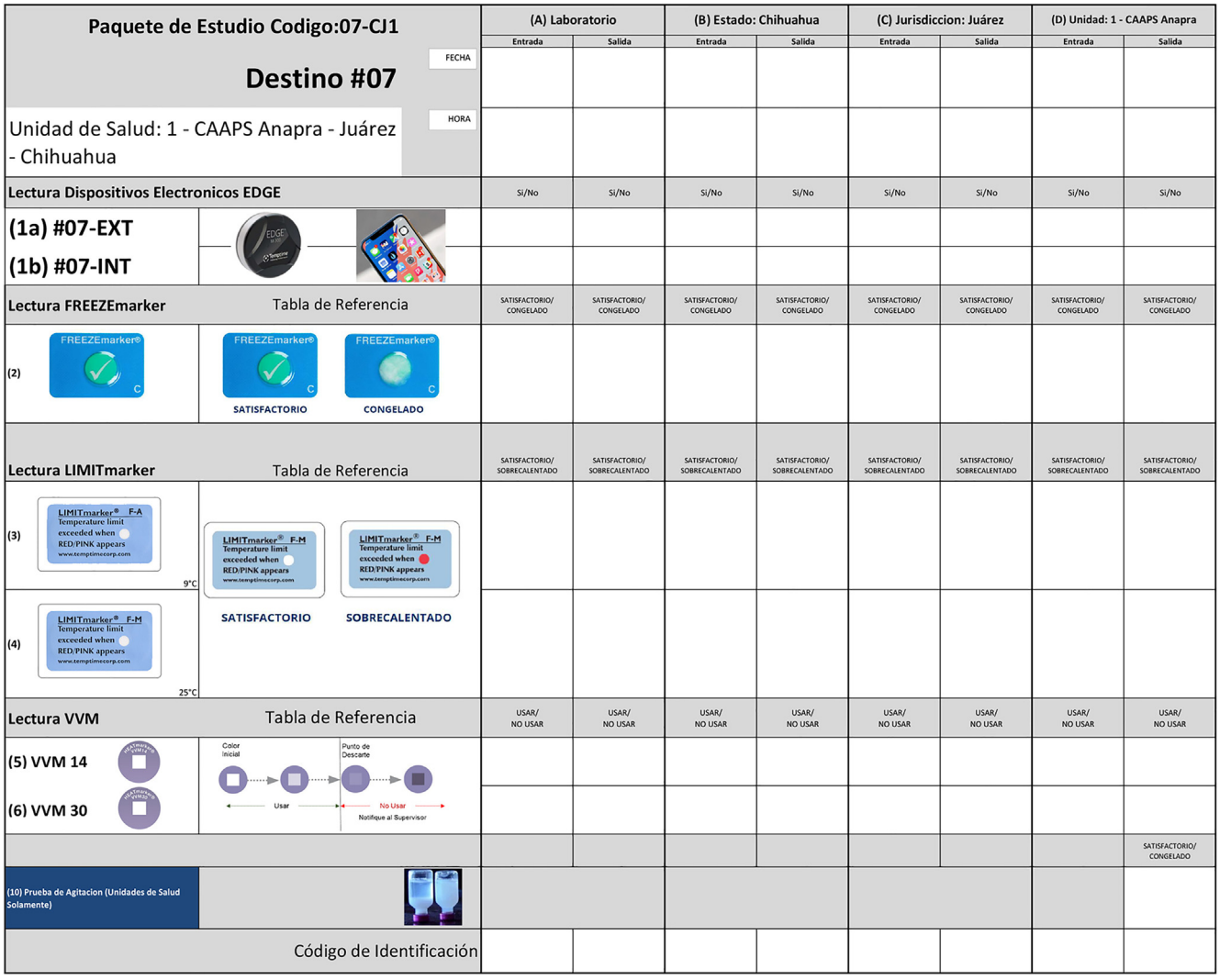

Fig. 1. Monitoring form (blank).

of LIMITmarker® F-M and F-A (4.8), FREEZEmarker® L (4.9), as well as VVMs (4.9). All staff found interpretation of LIMITmarker® F-M and F-A, FREEZEmarker® L, as well as VVMs easy (5.0). Interpretation of EDGE™ M-300 was also rated as 4.4. All 19 staff members answering the questionnaire, responded that VVM is very reliable indicator, very easy to read, and helps them to make informed decisions.

The opinions expressed by vaccine personnel obtained through the survey are summarized as follows:

- 91% (17 staff) believe that they do not have the necessary tools to detect if a vaccine has been damaged by a temperature excursion outside the 2–8 °C range.
- 6% (1 staff) think that the shake test is sufficient to detect a freezing event.
- 100% (19 staff) believe the VVM would help them determine whether a heat excursion has occurred somewhere along the cold chain and damaged the vaccines.
- 61% (12 staff) believe that excursions **do** occur at their respective points/storage facilities, while 39% (7 staff) believe that excursions **do not** occur at their points of control/storage facilities in the vaccine cold chain.

A few typical comments from the questionnaire are reported below:

"It has been a very rewarding experience for all of us in the vaccine program, given the major impactof allowing us to evaluate our cold chain, where we have been really unaware of our temperature excursions."

"These devices are of great utility and would greatly improve the cold-chain, and as such, we would not only be able to vaccinate people – but ALL of the population."

"The use of said devices strengthens the cold chain in our State and it assures that we are using quality biologics – which generates confidence in our operational personnel and in parents of families/children."

"I much prefer the VVM since we would then be able to determine of a vaccine had been over heated during transport to our health unit – or to another unit."

"A very good activity which interested me very much – since you can know if you are working with a biologic that is in good condition; I hope this is implemented here; we could work with much more confidence/security, knowing that we are administering vaccines that work."

5. Discussion

At the Laboratory's 3PL central warehouse the vaccines were kept at recommended temperature range. At state level, except

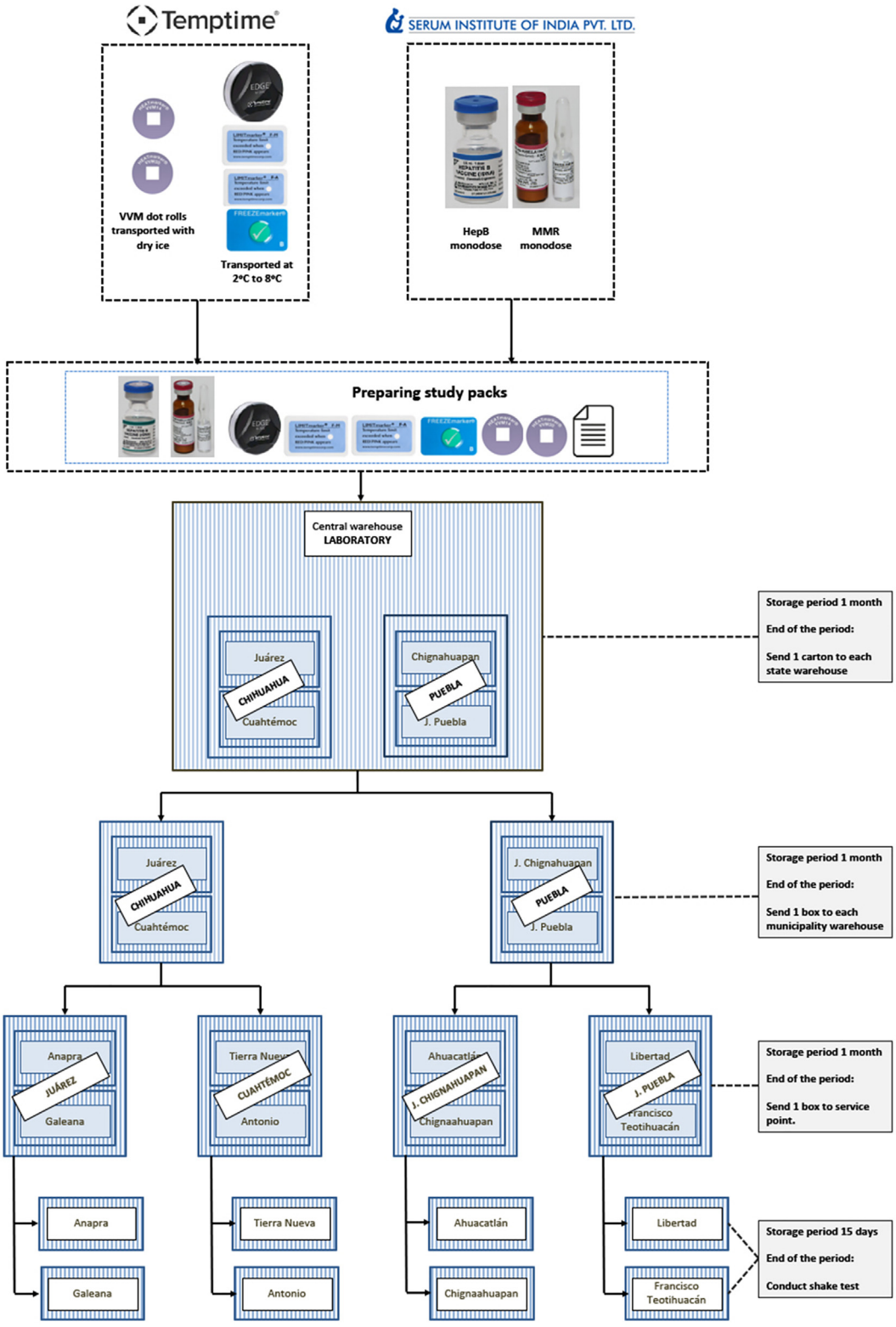

Fig. 2. Study flow.

for a couple of short exposures to temperatures above 8 °C in Puebla and again short exposures to temperatures below 2 °C both in Chihuahua and Puebla, the vaccines were at the 2–8 °C temperature range during their storage. Storage at the regional levels were generally found to be within the recommended temperature range with the exception of a few high and low temperature excursions.

5.1. Temperature excursions below 2 °C

The most serious negative temperature exposure was observed at San Francisco Teotihuacan service point refrigerator. The lowest temperature recorded during the storage was −7.94 °C. This negative temperature exposure started after midnight and was in total 7 h and 20 min (see Fig. 5).

Table 2
Temperature profiles along the vaccine cold chain from 3PL Laboratory to service points.

	Region	Service point	Temp °C	Central store 3PL Laboratory	Transport to state	State store	Transport to region	Regional store	Transport to SP	Service point refrigerator
CHIHUAHUA	Juárez	Anapra	Min	5.02	4.48	1.50	0.12	0.10	5.51	−1.01
			Max	6.42	6.77	5.13	5.02	6.34	5.67	8.06
		Galeana	Min	5.02	4.33	1.48	0.04	0.04	5.21	0.66
			Max	6.24	6.45	4.75	4.5	6.25	5.63	12.6
	Cuahtémoc	Tierra Nueva	Min	4.92	4.41	1.67	2.66	2.43	3.21	0.60
			Max	6.16	6.48	4.87	3.78	4.59	3.46	14.42
		San Antonio	Min	4.99	4.44	1.45	2.80	2.68	3.26	3.17
			Max	7.00	6.42	4.06	3.60	4.30	3.49	5.84
PUEBLA	J. Chignahuapan	Ahuacatlán	Min	5.08	5.39	1.51	4.64	4.36	2.45	2.73
			Max	6.38	6.80	6.84	6.02	6.05	6.84	7.98
		Chignaahuapan	Min	5.10	5.48	1.50	1.91	4.38	4.78	4.09
			Max	6.21	8.19	8.52	5.67	5.80	5.64	6.02
	J.Puebla	Libertad	Min	5.01	5.32	1.42	4.39	2.95	3.42	3.88
			Max	6.25	7.77	7.63	4.44	5.87	4.12	13.73
		San Francisco Teotihuacan	Min	5.05	5.45	1.41	4.35	3.16	3.35	−7.94
			Max	6.59	6.68	6.48	4.70	5.99	4.32	5.73

Note: Temperature data from each study pack differs slightly for study packs that are kept together in the storage facilities and/or dispatched. This is mainly because of thermodynamics affected on the positioning of the study packs and the cold air flow. However, these differences are not significant.

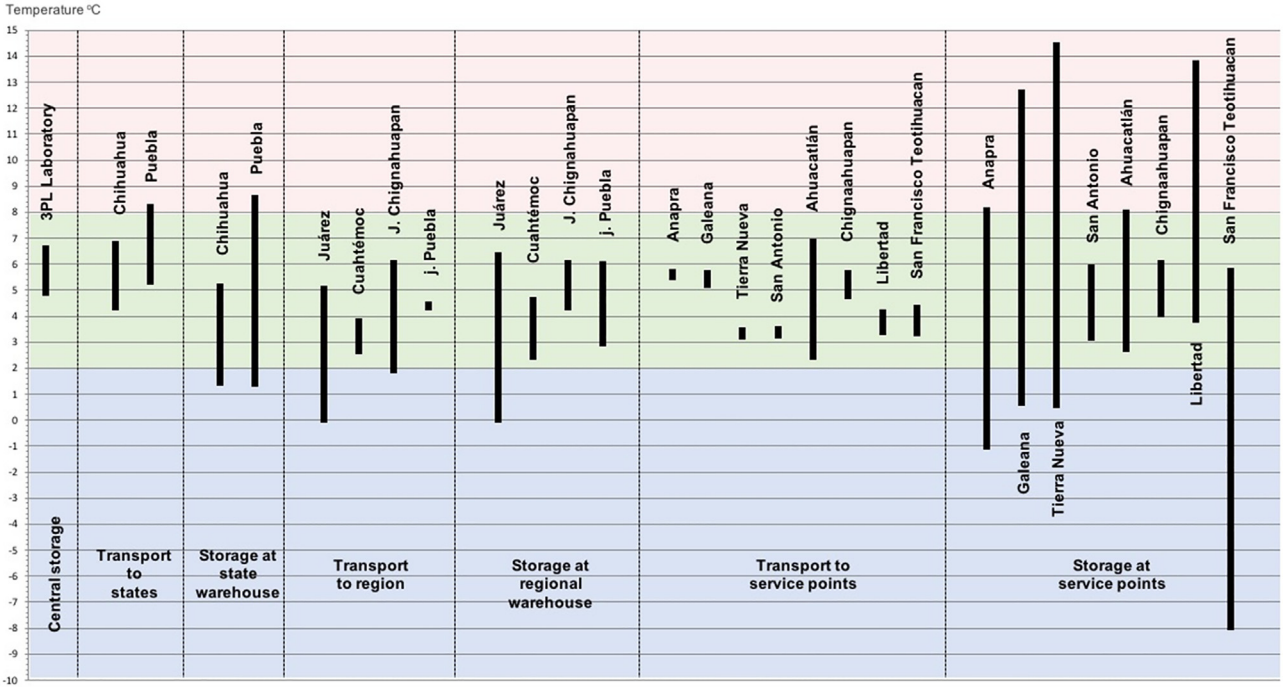

Fig. 3. Minimum and maximum temperature recordings along the vaccine cold chain throughout the study (July-December 2018).

This exposure resulted in FREEZEmarker® L to trigger. Despite 7 h and 20 min exposure to temperatures below 0 °C, no physical difference was observed in HepB vaccines in the morning. The shake test resulted in a pass result, meaning that vaccines were not affected by freezing. Although scientific freezing point for HepB is at −0.5 °C, freezing is a very complex process and requires more than negative temperature exposure below the particular freezing point of the product. In the validation of the shake test study, freeze sensitive vaccines, including HepB were exposed to −2°C for 24 h and none of the vaccines were found to be affected at this exposure [15]. Besides average temperature being set close to 2 °C, there is no other explanation what could have triggered this one-time event on that particular night.

The temperature returned to normal the following morning, therefore without continuous temperature logging or freeze indicators, overnight excursions such as the one experienced would have gone unnoticed.

The lowest temperature recorded in Juárez comes right after receiving the shipment of study package from Chihuahua. Once the study package is moved in to Juárez storage facility, in 45 min the temperature of the package reached 2.5 °C, and continued to 5 °C. Fig. 6 shows the details of this dispatch, transport and arrival period.

A temperature-controlled truck is used for transport. Common practice is to use conditioned icepacks inside the expanded polystyrene (EPS) insulated boxes where the products are loaded. In theory, the additional 0 °C conditioned icepacks create quite a strong cold thermal mass inside the container forcing heat to be removed from the vaccines, and potentially risking vaccines to be exposed to freezing temperatures especially in the case of inadequate conditioning. In theory, when a temperature-controlled truck is used, additional thermal mass is not required in packages.

Another detail analysis of the negative temperature exposure during the storage at Anapra service point indicates that the aver-

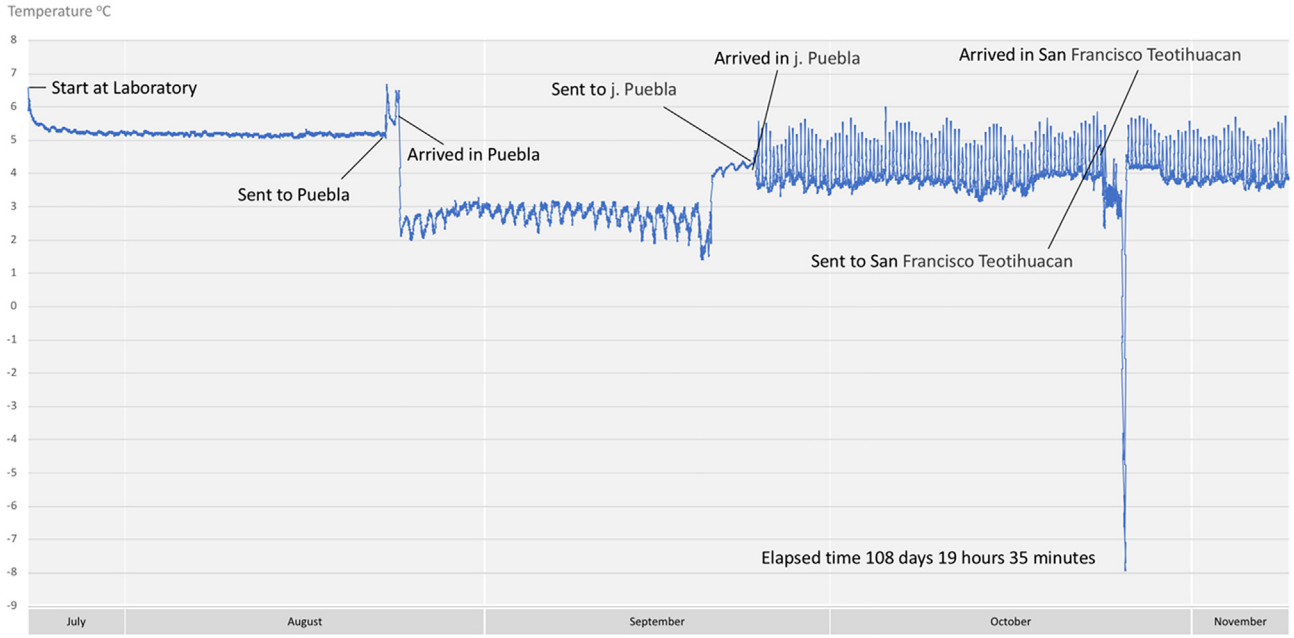

Fig. 4. Temperature profile throughout the study, destination San Francisco Teotihuacan.

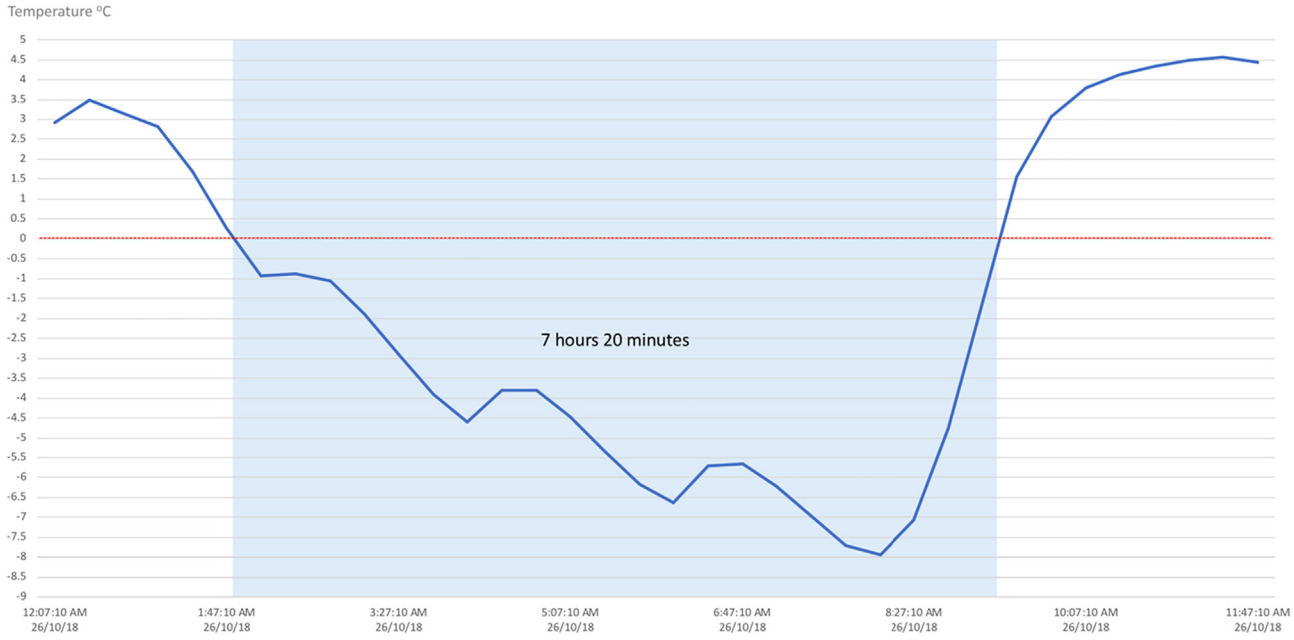

Fig. 5. Negative temperature exposure at San Francisco Teotihuacan service point refrigerator.

age temperature in the refrigerator is set too low (around 2 °C), and as a result, the cycling temperatures always go to 0 °C and sometimes below. Fig. 7 shows a two-day period from this service point to illustrate the problem.

A similar phenomenon is found in Chihuahua state cold room. 91% of their storage time vaccines were exposed to temperatures below 2.0 °C. However, the temperatures never reached 0.0 °C. Full storage time and temperatures in Chihuahua state cold room are displayed in Fig. 8.

5.2. Temperature excursions above 8 °C

The high temperature exposures were observed in Galeana and Tierra Nueva service points refrigerators, however, both exposures are quite short in duration (1 h and 20 min in Galeana and 2 h in Tierra Nueva). These exposures in nature did not have any visible impact on the VVM14 and VVM30. However, in both occasions LIMITmarker® F-A was triggered, but not the LIMITmarker® F-M. Most likely, long opening time of the refrigerator door or not properly closed door might have caused this exposure.

5.3. Staff survey

All staff indicated that there is no way to determine heat damage with vaccines unless a VVM is attached. It is also critical that all staff believed that inclusion of such devices in the system would improve cold chain operations as they have become aware of problematic areas through this study. The cold chain personnel exhib-

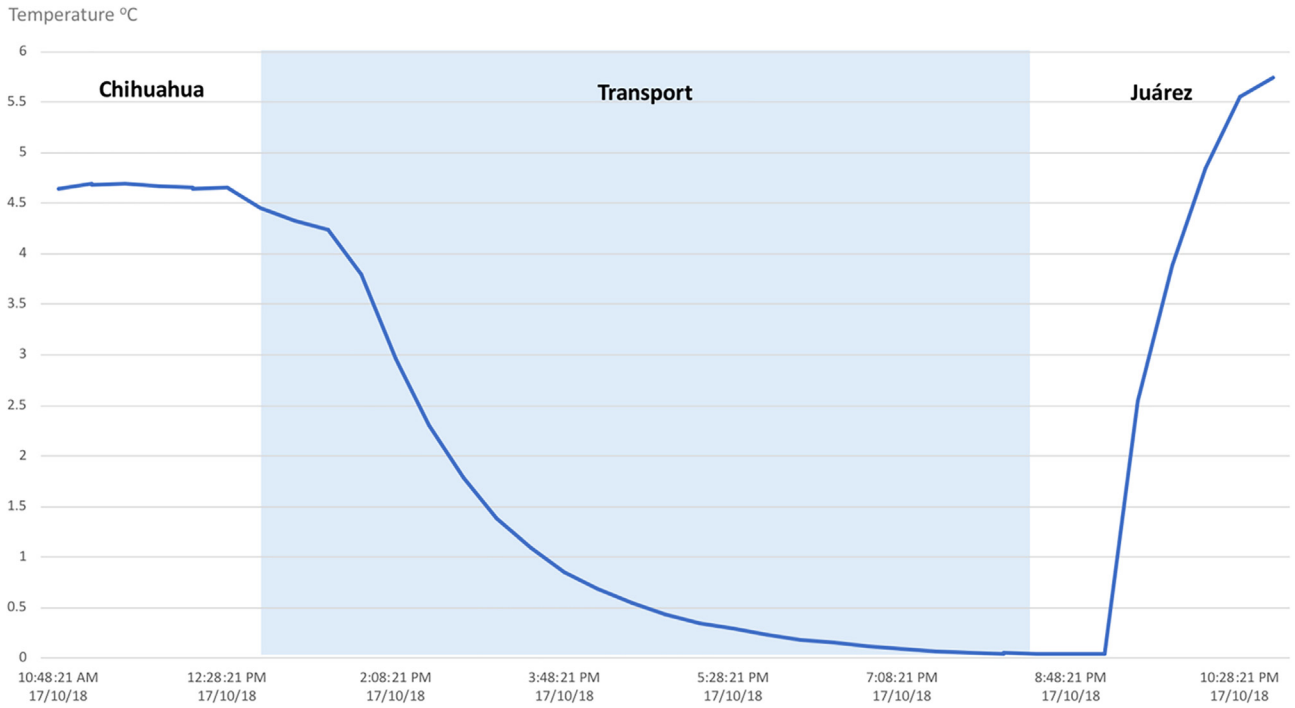

Fig. 6. Temperature details of dispatch, transport and arrival of study package between Chihuahua and Juárez.

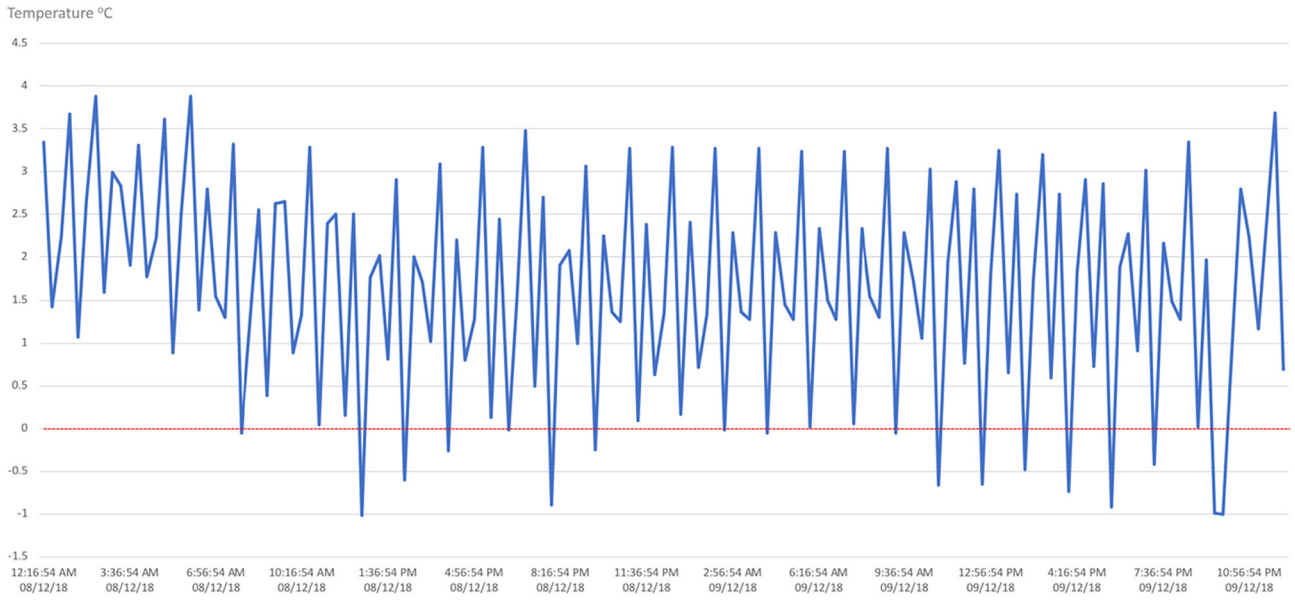

Fig. 7. Cyclic details of temperature in Anapra service point refrigerator.

ited a high level of understanding on cold chain risks and material handling procedures. However, not observing serious high and low temperature exposures during the study does not validate the Mexican cold chain free from such exposures.

6. Observations

Although, 92% of the time, temperatures during the storage and transport remained within the recommended temperature range of 2 °C to 8 °C, there were occasions where vaccines were exposed to temperatures below 2 °C and above 8 °C. Current practices for temperature monitoring at storage and distribution consist of situations where likelihood of exposures might increase. For example, almost in all cold chain equipment, the average temperature is found to be set below optimum 5 °C, and in many cases around 2 °C. In addition, temperature monitoring of the equipment currently is not found to be optimal. For example, the state and municipality level cold rooms have chart recorders but not in use. They monitor temperatures via temperature sensor/display manually, three times a day. Although discrepancies were found between manually recorded temperature data and the study data-logger recordings, since it was not part of the study protocol, it will be addressed in a separate paper. Vaccines are distributed via temperature-controlled truck which has an electronic sensor in the main cabin, however, temperatures are not logged automatically, and requires manual operation to check and record. No tem-

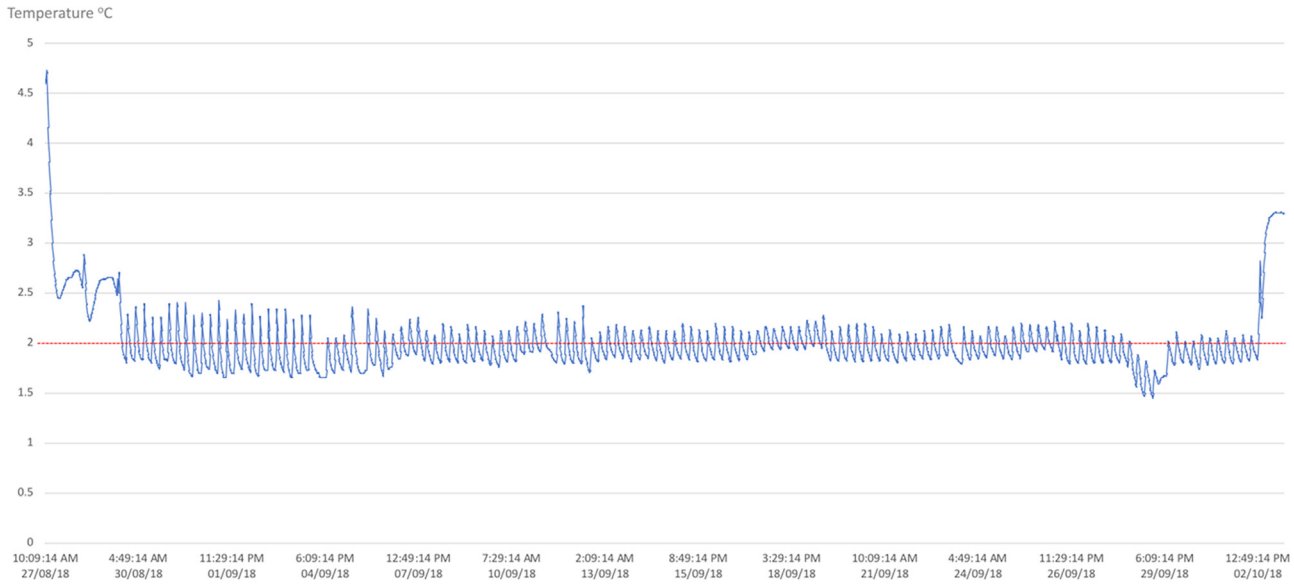

Fig. 8. Chihuahua state cold room temperatures during the storage of study packs.

perature monitoring device is used when vaccines are transported in EPS boxes with regular trucks. Service level refrigerators have chart recorders, again not used. As a result, temperature monitoring is done through electronic thermometer with no memory function.

7. Conclusion and recommendations

As indicated by all staff involved in the study as well as research team's observation, tools to detect temperature excursions are not optimum. Therefore, an expanded monitoring program is recommended, ideally through unit-level or package-level freeze and heat indicators. These indicators would provide a visual, easy to interpret signal of whether a temperature excursion has occurred at any point along the cold chain from the point of manufacturing. These tools would empower health workers at the frontline and hardest to reach areas by giving them the ability to make informed decisions that will avoid the use of temperature damaged vaccines and/or avoid the discarding of good vaccines that are only suspected of damage. Thus, reducing wastage and increasing the effectiveness of vaccination programs.

As a continuous improvement step, it is recommended that trainings be carried out with all personnel and to clarify the circumstances under which detection of temperature excursions are possible and the procedures to follow upon a detection, especially following introduction of new tools and related procedures.

Because of having the average temperature close to 2 °C almost in all cold chain equipment, it is critical that the cold rooms and service point refrigerators be temperature mapped and the set-points calibrated and raised to 5 °C.

Since service point refrigerators do not have WHO recommended temperature monitoring devices which makes it not possible to monitor temperatures during weekends and holidays, service point refrigerators should all be equipped with WHO recommended 30-day electronic refrigerator temperature logger [16]. In the cases of EPS insulated boxes are used with regular trucks, all boxes should have WHO recommended freeze indicators [17]. For easy reference, LIMITmarker® type threshold indicators would help health personnel especially in monitoring temperatures during the transit.

Such temperature monitoring studies (as this one) give a snapshot picture of the performance, unless special observation is carried out, these studies do not identify potential problems of the system which may manifest certain weaknesses align together. In this sense, the above given examples and in general all cold chain processes from accepting international shipments, storage and distribution practices should be evaluated in detail with conducting risk assessment to identify the risk scores and to recommend appropriate control measures. Without such a risk assessment, the cold chain operations in Mexico would remain prone to hazards with uncertain likelihoods.

In general, as recommended by the WHO, the system would benefit from inclusion of VVMs on all vaccine purchases. Although, the general belief that adding VVM would increase the vaccine prices may not be applicable to Mexico. First of all, Mexico is a self-procuring country and goes to international tenders itself not being part of the PAHO Revolving Fund. Using UNICEF as a procurement agency, despite additional service fees to be paid to UNICEF, vaccine prices with VVM may still be lower than the vaccine prices Mexico is paying today through its own procurement system. This is naturally coming from the negotiating power UNICEF is holding due to the amount of vaccine it procures.

Lastly, it is recommended that whole-life unit-level monitoring is implemented with easy to read indicators. As observed along the cold-chain, small excursion occurred at various points in time resulting in deviations from the 2–8 °C range. According to the Mexican regulations (NOM-059-SSA1-2015 (10.5.9.6)) – "All temperature excursions must be investigated and a CAPA (Continuous Action Preventive Action) must be established". Given the complexities associated with such investigations, and the fact that temperature data and thermal history of the product is often not available, investigations are difficult, time consuming and often inconclusive. In some cases a potency assay can be used to determine whether heat damage had occurred; not only does this pose the reverse logistical challenges of getting the samples to the testing lab, but the tests take time, and during the testing period, the entire vaccines in question must be maintain in quarantine which creates a secondary logistical challenge. If the potency test is not pursued, vaccines that had gone through a temperature excursion, but are not thermally damaged could be wrongfully discarded leading to unnecessary wastage of good vaccines. For this reason,

it is recommended to implement the use of indicators that can be read and interpreted by the health workers at the point of use. This would empower the workers to make meaningful and timely decisions, streamlining the process and reducing wastage.

Funding

The temperature monitoring devices used in the study were donated by Temptime Corporation USA. Standard WHO study protocol was used. Temptime Corporation was not involved in the design, data collection, analysis, interpretation or writing of this report, nor the decision to submit the article for publication.

CRediT authorship contribution statement

Verónica Carrión Falcón: Conceptualization, Project adminsitartion, Supervision, Writing - review & editing. **Yara Verónica Villalobos Porras:** Conceptualization, Formal analysis, Writing - review & editing. **César Misael Gómez Altamirano:** Conceptualization, Writing - review & editing. **Umit Kartoglu:** Writing - original draft, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Authors thank Karla Sofia Amador Saavedra and Mario Aguilar of TPT Suppliers, Franco Rubén Vargas of NTA Logistics for facilitating the logistics in the field. Authors also acknowledge supervisors of the states and municiplaities for their support during the study.

References

[1] WHO. Temperature sensitivity of vaccines. WHO/IVB/06.10. Geneva: World Health Organization; 2006. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/69387/WHO_IVB_06.10_eng.pdf?sequence%20=1&isAllowed=y.

[2] Kartoglu U, Mistien J. Tools and approaches to ensure quality of vaccines throughout the cold chain. Expert Rev Vaccines 2015;13(7):843–54. https://doi.org/10.1586/14760584.2014.923761.

[3] Wirkas T, Toiklik S, Miller N. A vaccine cold chain freezing study in PNG highlights technology needs for hot climate countries ISSN. 0264–410X. Vaccine 2007;25(4):691–7. https://doi.org/10.1016/j.vaccine.2006.08.028.

[4] Sow C, Schlumberger M, Mireux F, Ouedraogo SM, Betsem E, et al. Challenges of cold chain quality for routine EPI in south-west Burkina-Faso: An assessment using automated temperature recording devices. Vaccine 2018;36(26):3747–55. https://doi.org/10.1016/j.vaccine.2018.05.062.

[5] Murhekar MV, Dutta S, Kapoor AN, Bitragunta S, Dodum R, et al. Frequent exposure to suboptimal temperatures in vaccine cold chain system in India: results of temperature monitoring in 10 states. Bull World Health Organ 2013;91(12):906–13. https://doi.org/10.2471/BLT.13.119974.

[6] Techathawat S, Varinsathien P, Rasdjarmrearnsook A, Tharmaphornpilas P. Exposure to heat and freezing in the vaccine cold chain in Thiland. Vaccine 2007;25(7):1328–33. https://doi.org/10.1016/j.vaccine.2006.09.092.

[7] Yauba S, Joelle S, Jude N, Tracy BO, Marie K, et al. Temperature monitoring in the vaccine cold chain in Cameroon. J Vaccines Vaccin 2018;9(1):384. https://doi.org/10.4172/2157-7560.1000384.

[8] Hanson CM, George AM, Sawadogo A, Schreiber B. Is freezing in the vaccine cold chain an ongoing issue? A literature review. *Vaccine* 2017;35(17):2127–33.

[9] WHO. Study protocol for temperature monitoring in the vaccine cold chain. WHO/IVB/05.01. Rev.1. Geneva; World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/70752/WHO_IVB_05.01_REV.1_eng.pdf?sequence=1&isAllowed=y.

[10] Temptime Corporation. Wireless temperature sensors. http://temptimecorp.com/temperature-indicators-sensors/edge-electronic-sensors/ [accessed on 23 November 2019].

[11] Temptime Corporation. LIMITmarker. http://temptimecorp.com/temperature-indicators-sensors/heat-indicators/limitmarker-heat-indicator/ [accessed on 23 November 2019].

[12] Temptime Corporation. FREEZEmarker. http://temptimecorp.com/temperature-indicators-sensors/freeze-indicator/ [accessed on 23 November 2019].

[13] WHO. PQS performance specification: Vaccine vial monitor. WHO/PQS/E006/IN05.3, 15 May 2018. Geneva; World Health Organization. http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/catdocumentation.aspx?id_cat=35 [accessed on 4 December 2019].

[14] WHO. WHO-UNICEF policy statement on the implementation of vaccine vial monitors: The role of vaccine vial monitors in improving access to immunization. WHO/IVB/07.04. Geneva: World Health Organization; 2007. https://apps.who.int/iris/bitstream/handle/10665/69713/WHO_IVB_07.04_eng.pdf?sequence=1&isAllowed=y [accessed on 11 December 2019].

[15] Kartoglu Ümit, Özgüler Nejat Kenan, Wolfson Lara J, Kurzatkowski Wiesław. Validation of the shake test for detecting freeze damage to adsorbed vaccines. Bull World Health Organ 2010;88(8):624–31. , http://www.who.int/bulletin/volumes/88/8/08-056879.pdf. https://doi.org/10.2471/BLT.08.056879.

[16] WHO. PQS performance specification: 30-day electronic refrigerator temperature logger. WHO/PQS/E006/TR06.3, 8 September 2010. Geneva: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/69713/WHO_IVB_07.04_eng.pdf?sequence=1&isAllowed=y [accessed on 11 December 2019].

[17] WHO. PQS performance specification: Irreversible freeze indicator. WHO/PQS/E006/IN03.1, 30 November 2006, Geneva: World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/69713/WHO_IVB_07.04_eng.pdf?sequence=1&isAllowed=y [accessed on 11 December 2019].