Methods for Accurate Cold-Chain Temperature Monitoring Using Digital Data-Logger Thermometers

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Abstract. Complete and accurate records of vaccine temperature history are vital to preserving drug potency and patient safety. However, previously published vaccine storage and handling guidelines have failed to indicate a need for continuous temperature monitoring in vaccine storage refrigerators. We evaluated the performance of seven digital data logger models as candidates for continuous temperature monitoring of refrigerated vaccines, based on the following criteria: out-of-box performance and compliance with manufacturer accuracy specifications over the range of use; measurement stability over extended, continuous use; proper setup in a vaccine storage refrigerator so that measurements reflect liquid vaccine temperatures; and practical methods for end-user validation and establishing metrological traceability. Data loggers were tested using ice melting point checks and by comparison to calibrated thermocouples to characterize performance over 0 °C to 10 °C. We also monitored logger performance in a study designed to replicate the range of vaccine storage and environmental conditions encountered at provider offices. Based on the results of this study, the Centers for Disease Control released new guidelines on proper methods for storage, handling, and temperature monitoring of vaccines for participants in its federally-funded, Vaccines for Children program. Improved temperature monitoring practices will ultimately decrease waste from damaged vaccines, improve consumer confidence, and increase effective inoculation rates.

Keywords: Digital Data-Logger Thermometers; Vaccine Storage and Handling; Thermometer Validation Methods; Metrological Traceability

INTRODUCTION

Vaccines require strict temperature-controlled storage and accurate temperature monitoring. The majority of vaccines administered in the United States are stored in refrigerators, which must be maintained between 2 °C and 8 °C. Improperly-stored vaccines lose their effectiveness, putting patients at risk. In particular, if refrigerated vaccine is frozen accidentally, it suffers an irreversible loss of potency. Patients who unknowingly receive a previously-frozen vaccine will not be protected against disease. This creates as public health threat, as the potential for outbreaks of vaccine-preventable diseases rises. A 2007 meta-analysis published in the journal *Vaccine*, which included results from studies published in over 20 countries, estimated that 14% to 35% of delivered vaccines were subjected to freezing temperatures [1].

In 2009, the Centers for Disease Control (CDC) approached NIST to investigate vaccine storage and temperature monitoring problems within the Vaccines for Children (VFC) Program, a program that distributes approximately $4 billion worth of vaccines annually to low-income families via more than 44,000 VFC providers. NIST evaluated VFC cold-chain management practices in a series of studies designed to replicate everyday conditions in vaccine provider offices [2,3]. Effective vaccine storage and handling practices hinge on the use of suitable temperature-controlled storage cabinets, along with an accurate temperature monitoring setup capable of tracking vaccine temperature history.

Prior to the NIST-CDC studies, VFC providers relied on twice-per-day, visual inspection of analog thermometers kept inside refrigerators in order to assess vaccine storage conditions and identify possible temperature excursions. This paper will focus on the methods and results of a study aimed at improving the temperature monitoring practices of VFC providers. Inexpensive digital data-logger thermometers were identified as a possible solution to the widespread absence of continuous temperature monitoring systems in vaccine storage units.

MEASUREMENT OBJECTIVES

We evaluated the performance of multiple digital data-logger thermometers for temperature monitoring of refrigerated vaccines, based on the following test criteria:

1. Out-of-box performance and manufacturer-specified accuracy over the temperature range of 0 °C to 10 °C, where accuracy is defined as the difference between the measured value and the true value.
2. Long term stability and measurement drift
3. Proper use so that measurements reflect stored vaccine temperatures.

METHOD AND RESULTS

We utilized two thermometer validation methods to quantify the performance of seven digital data-logger models over 0 °C to 10 °C, the temperature range applicable to refrigerated vaccine storage. The loggers tested included stand-alone units with self-contained air temperature sensors (labeled LA, LB, and LC) as well units with detachable temperature probes (LE1 and LE2, LF). Two units featured both a self-contained temperature sensor (LD ext, LG ext) and a detachable probe (LD probe, LG probe). Each probe or readout unit featured one of the following types of sensing elements: thermistor, RTD, or type-K thermocouple.

Ice Melting Point Testing

To capture logger performance at 0 °C, we designed an ice melting point test setup large enough to measure the seven test loggers and three type-T thermocouple reference thermometers (TC1, TC2, TC20) simultaneously. The standard realization uncertainty (k=2) of the ice melting point, constructed using the method given in Reference 1, is ± 0.002 °C[4]. For this study, a large Styrofoam box was lined in plastic and packed with a mixture of distilled water and shaved distilled water ice. The loggers and thermocouples were buried in the ice melting point mixture and set to collect data overnight.

We repeated these measurements three times over the course of our vaccine storage study to track logger stability over time and identify any possible measurement drift. Table 1 shows the ice melting point measurements recorded by the data loggers and reference thermocouples for each of the three trials. Each value represents the average temperature taken over a 2 h period, following equilibration. The manufacturer's accuracy specification for each device is also given. Missing data points, shown as dashes, reflect the fact that additional data loggers were acquired for study after the first ice point trial.

TABLE 1. Ice melting point temperature readings of digital data loggers and reference thermocouples (°C).

Sensor Name	Mfg. Accuracy Spec	Trial 1 (08-Dec-09)	Trial 2 (15-Mar-11)	Trial 3 (06-Jul-11)
TC1	0.1	0.0	0.0	0.0
TC2	0.1	-	0.0	0.0
TC20	0.1	-	0.0	0.0
LA	0.5	-0.1	-0.1	-0.1
LB	0.5	-	0.0	0.0
LC	0.3	0.5	0.5	0.5
LD internal	0.5	-	-0.2	-0.2
LD probe	0.5	-0.2	-0.2	-0.2
LE1 probe	0.5	-0.1	-0.1	-0.1
LE2 probe	0.5	-0.1	-0.1	-0.1
LF	0.3	-	0.0	0.0
LG probe	0.4	-	-0.1	-
LG internal	0.4	-	0.4	-

Performance Validation at 0 °C

Because the ice melting point occurs at exactly 0.00 °C, we expect each data logger placed in the ice and water mixture to record a temperature within the range of 0 °C ± the manufacturer-stated accuracy, which is the maximum permissible error for use. Logger temperature readings outside this range indicate that the device should be removed from service and recalibrated or replaced. In this study, all of the tested digital data loggers and thermocouples performed within manufacturer specifications at the ice point, with the exception of logger LC. The manufacturer-stated accuracy for logger LC is ± 0.3 °C, but in all three ice point trials, this logger recorded an average temperature of 0.5 °C. In a provider office setting, these results would indicate that logger LC is unsuitable for vaccine temperature monitoring in its present condition, and should be returned to the manufacturer for

recalibration/adjustment or replaced with a new device. Before putting any newly-calibrated or replacement logger into service, the end-user should always perform another ice point check on the device to verify that it is within specifications.

Results obtained from ice melting point validation testing may be used to apply a linear correction to future measurement results. We have employed this technique in the analysis of our calibrated reference thermocouple comparison tests.

Long-term Stability and Drift

Regular ice point testing is useful for assessing device stability and measurement drift over time. We simultaneously measured each available test data logger and reference thermocouple in the same ice point setup on three different occasions, spaced out over a period of 19 months. The ice point temperature data produced by each device was consistent between separate trials (Table 1). Of the five digital data loggers available for Trial 1, all five successfully reproduced the same temperature data a full 19 months later. Throughout the study, we detected no measurement drift in any of the data loggers, despite nearly constant use over a period of 1 to 2 years.

These types of digital data loggers appear sufficiently stable for long-term use in vaccine temperature monitoring. However, users should never assume that any temperature monitoring device remains stable for long periods of time. A regular validation schedule, such as annual measurement at the ice point, is necessary to maintain traceability and confidence in measurement accuracy. If a structured validation protocol is followed, digital data loggers may be used to stably monitor temperature for many months or years.

Comparison to Calibrated Reference Thermocouple

The seven digital data-logger models were also tested over the range of 2 °C to 10 °C by comparison to a calibrated reference thermocouple. All of the stand-alone logger units were placed in one plastic tray, and each of the logger probes were inserted into a single large bottle containing 500 mL of ethylene glycol. Both the tray and the glycol-filled bottle were positioned next to each other on a center shelf of a purpose-built, pharmaceutical refrigerator, chosen for its ability to stably maintain temperature within a narrow band of the easily-adjusted set point. Three NIST-calibrated, type-T thermocouples (TC1, TC2, TC20) were included as reference thermometers. TC1 was kept inside the glycol-filled bottle along with the data logger probes, TC2 was positioned inside the plastic tray with the stand-alone logger units, and TC20 was attached to the outside of a vaccine vial placed in the same plastic tray. The data logger and thermocouple setup is shown in Fig. 1.

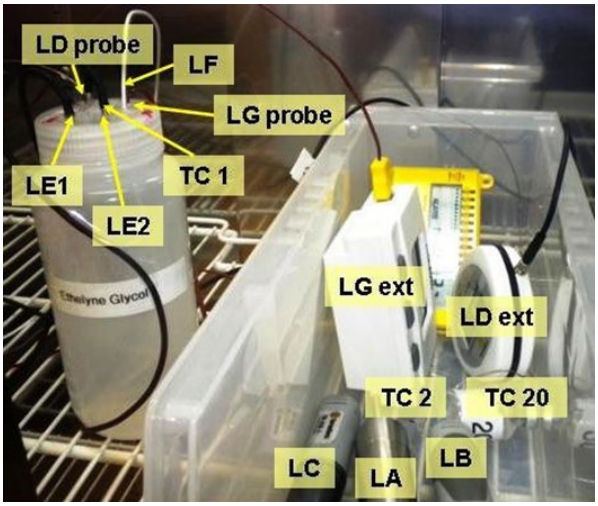

FIGURE 1. Thermocouple and data logger setup during comparison testing over 2 °C to 10 °C.

To capture the logger performance over the temperature range of interest, we recorded measurements at each of the following refrigerator temperature set points: 2 °C, 4 °C, 6 °C, 8 °C, and 10 °C. In each trial, we adjusted the refrigerator set point to the appropriate temperature value and allowed the cabinet to fully equilibrate over a period of at least 6 hours. Following equilibration, we set the data loggers and thermocouples to record temperature data overnight. All logger sample intervals were set to 1 reading / min, with the exception of LG, which was factory-set to 1 reading / 5 min. The thermocouple measurement system recorded temperatures every 10 s.

A sample of the data collected for a refrigerator set point trial is shown in Fig. 2. A linear offset correction, taken from the ice melting point measurements described in the previous section, was applied to the data collected by each device. Thermocouple measurements are shown as line graphs, and data logger readings as point measurements. Data points from probe-type sensors, kept in glycol, are distinguished by round markers; readings from air temperature sensors are denoted by triangles.

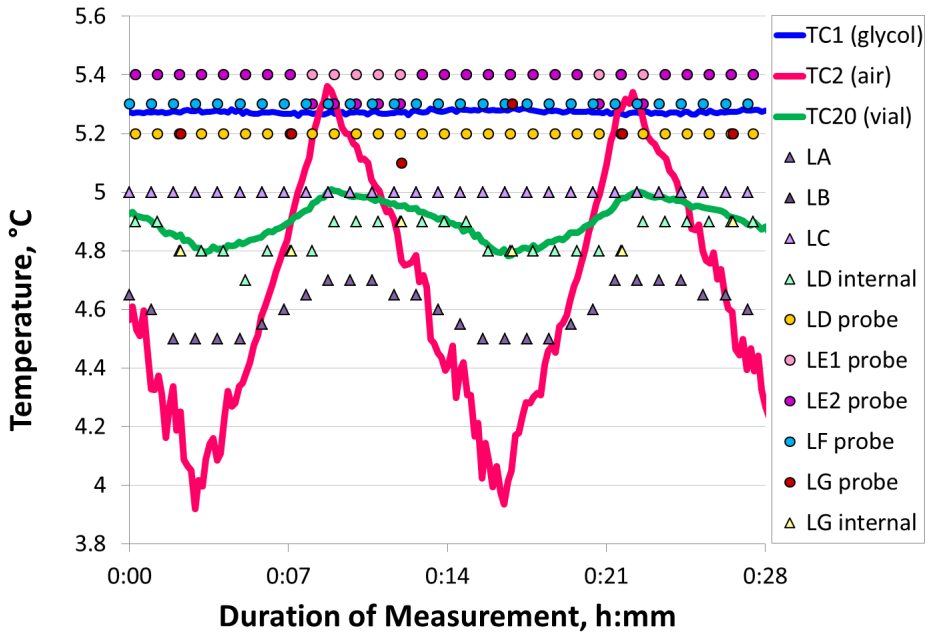

FIGURE 2. Selection of temperature data from a thermocouple comparison test with refrigerator set to 4 °C.

The temperature waveform recorded by TC2 (pink) is characteristic of the pharmaceutical refrigerator's air temperature control, with oscillations centered approximately about 4.7 °C. The 0.7 °C offset from the specified set point (4 °C), highlights the importance of a properly-validated temperature monitoring device in any vaccine storage system, even in the case of an expensive, purpose-built pharmaceutical refrigerator. While refrigerator air is subject to temperature oscillations and gradients, the larger thermal mass of items stored inside a unit causes these effects to be significantly dampened. Selecting a temperature monitoring device and setup that closely approximates the properties and conditions of actual stored vaccines is critical to obtaining meaningful temperature data.

Glycol or other buffer liquid inside a bottle provides a good approximation for the thermal properties of liquid vaccine. The temperatures recorded by TC1 (blue) are most similar to the conditions inside of a vaccine vial. TC20 was attached to the outside glass of a vaccine vial, and therefore is indicative of the glass/air interface temperature, rather than the contained vaccine liquid temperature. Because of this, we chose TC1 as the reference thermometer for this study.

We quantified data logger performance and suitability for temperature monitoring of refrigerated vaccines by comparing the temperature data recorded by each logger to the values recorded by TC1.

For each temperature set point trial, we collected data for 12 h or more to ensure full equilibration and to capture steady-state temperature readings at each set point. A linear offset correction, taken from the ice melting point test results, was applied to data collected by each device. We then calculated the average thermocouple and logger temperature readings over a 2 h sample of data extracted from each trial. Using the thermocouple (TC1, in glycol) average as the reference temperature, we determined each logger's difference from the expected value. This comparison is summarized in Fig. 3a and Fig. 3b.

In these graphs, the blue line at 0 °C represents the reference temperature, normalized across all trials. The data points correspond to the average difference from the reference temperature recorded by each logger. Each temperature set point trial is denoted by a different colored symbol, as indicated in the graph legends. For example, during the 2 °C set point trial, logger LC recorded temperatures on average 0.1 °C lower than those recorded by the reference thermocouple. During the 10 °C set point trial, this same logger showed an average offset of about −0.6 °C from the reference thermocouple readings.

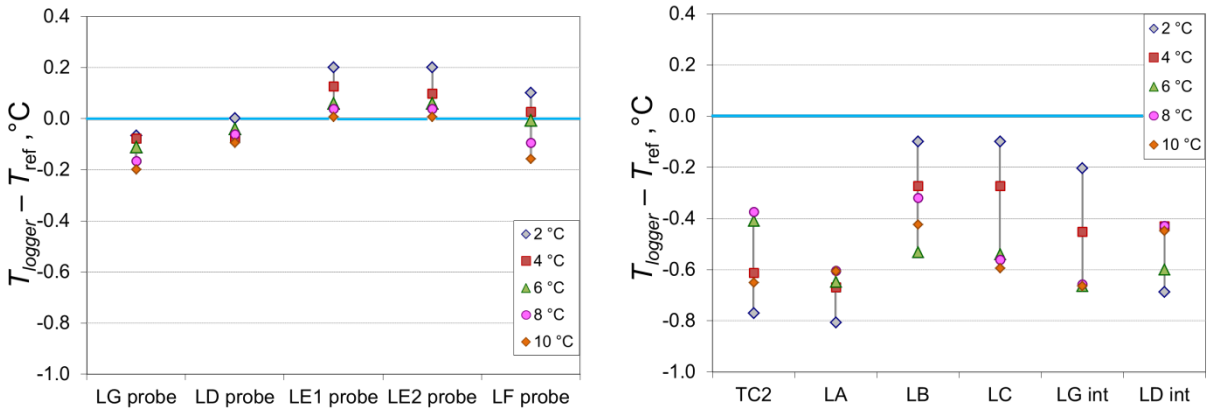

FIGURE 3A, 3B. Data logger temperature offset from reference thermocouple at different refrigerator temperature settings.
Fig. 3a. (Left) Loggers featuring external sensor probes kept in a glycol-filled bottle.
Fig. 3b. (Right) Stand-alone units with self-contained air temperature sensors.

The differences in temperature measurements recorded by loggers with probes in glycol (Fig. 3a, left) and loggers with air temperature sensors (Fig. 3b, right) are significant. The 2012 vaccine storage and handling guidelines released by Centers for Disease Control for their Vaccines for Children providers recommend the use of a temperature monitoring device with an uncertainty within ± 0.5 °C. In the case of the air temperature sensors shown above, deviations as large as −0.8 °C are a serious concern. Providers relying on data from these types of units risk wasting vaccines deemed spoiled by "false positive" temperature alarms, or potentially administering ineffective vaccines by failing to detect true temperature excursions. By contrast, probes kept in a buffer medium, such as glycol, provide a clearer indication of temperatures of stored liquid vaccine.

Evaluation Based on Manufacturer Accuracy Specifications

In this section, we will evaluate the results from both the ice melting point and reference thermocouple comparison tests with respect to manufacturer accuracy specifications. These results and specifications are summarized below in tables 2a and 2b. The ice point data reflects the absolute difference of the average value measured by each logger from the expected temperature, 0.0 °C. The Ref. TC Comparison Maximum Error column contains numerical values from graphs Fig. 3a and 3b. In tables 2a and 2b, the largest difference calculated for each logger out of the five temperature set point trials is shown.

TABLE 2A. Comparison of manufacturer accuracy specifications and logger test results. Loggers featuring an external probe in glycol are shown. (± °C)

Sensor Name	Mfg. Accuracy Specification	Ice Point Measured Error (T = 0 °C)	Ref. TC Comparison Maximum Error (2 °C to 10 °C)
LD probe	0.5	0.2	0.1
LE1 probe	0.5	0.1	0.2
LE2 probe	0.3	0.1	0.2
LF probe	0.4	0.0	0.2
LG probe	0.5	0.1	0.2

TABLE 2B. Comparison of manufacturer accuracy specifications and logger test results. Loggers featuring an air temperature sensor are shown. (± °C)

Sensor Name	Mfg. Accuracy Specification	Ice Point Measured Error (T = 0 °C)	Ref. TC Comparison Maximum Error (2 °C to 10 °C)
LA	0.5	0.1	0.8
LB	0.5	0.0	0.5
LC	0.3	0.5	0.6
LD internal	0.5	0.2	0.7
LG internal	0.4	0.4	0.7

For a data logger in a chosen setup to be a viable vaccine temperature monitor, both error values should fall within the manufacturer-specified accuracy. In our testing, all five data loggers utilizing the external probe in glycol setup performed to within or better than manufacturer accuracy specifications over the full 0 °C to 10 °C range. ILAC G24:2007 suggests utilizing a window of 80% of the maximum permissible error to determine recalibration intervals [5]. All five probe-type data loggers also met this stricter condition, achieving error readings within 80% of the manufacturer's tolerance band in both the IMP and comparison tests.

By contrast, while four out of five stand-alone, air temperature sensing devices performed within or better than manufacturer specifications at the ice melting point, only one device, LB, met the same specification during comparison testing. Stand-alone data loggers may be perfectly acceptable for applications requiring continuous room temperature measurements, but a logger setup featuring an external probe in a glycol-filled bottle is superior to an air-temperature sensing device for the purpose of refrigerated vaccine temperature monitoring.

The purpose of vaccine temperature monitoring is to ensure that liquid vaccines are stored at the temperatures required to preserve their efficacy. Vaccine storage units withstand thermal gradients and fluctuations in response to a variety of mechanical and use factors. However, as long as the liquid vaccines are maintained within the proper temperature range, the details of refrigerator air temperature variations are insignificant. Thermal mass added by vaccine vials and packaging slows heat transfer between refrigerator air and the contained vaccine liquid. As a result, the vaccines experience smaller and less frequent temperature fluctuations than in the surrounding air. Gradual changes and trends are coupled with a time-lag effect. The disparity between the temperature behavior of air and stored vaccines makes it difficult, if not impossible, to effectively predict vaccine temperatures using only air temperature data.

For this application, a data logger with an air-temperature sensor is measuring the wrong parameter. To successfully replicate the kinetic temperature of stored vaccine, it is important to choose a thermometer setup that mimics the conditions and physical properties of the vaccines. A data logger probe in glycol setup is a simple, inexpensive, and effective way to accomplish this end.

Our results also indicate that a basic ice point check may be used to validate the performance of these logger types for use in temperature monitoring of refrigerated vaccines, because of the linear error propagation that occurs over the small range of use. A logger that meets manufacturer accuracy specifications at the ice point will also meet these specifications for temperatures in the 0 °C to 10 °C range, provided that it is used correctly (e.g., with an external probe in buffer medium).

SUMMARY

A digital data-logger thermometer featuring an external probe kept in a glycol-filled bottle provides effective, continuous temperature monitoring of stored vaccines. Provided that a structured validation protocol is followed, digital data loggers of this type can be used to stably monitor vaccine temperature for many months or years. By contrast, loggers featuring sensors designed to record air temperature are insufficient for vaccine temperature monitoring applications.

A regular validation schedule, such as annual ice point testing, is required to maintain traceability and confidence in measurement accuracy. For most users, annual ice melting point checks represent the simplest and most economical method for maintaining data logger validation and traceability.

In November 2012, the Centers for Disease Control released an updated Vaccine Storage and Handling Toolkit[6], with many changes based on the work in this and other NIST vaccine-related studies.

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