


Cold chain logistics: the pathways of vaccines and thermolabile medicines to patients in municipal primary care

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ABSTRACT. For the quality assurance of thermolabile medicines and vaccines, it is imperative that all stages of the cold chain are satisfied. The aim of this study was to analyze the temperature of boxes containing medications and vaccines on routes between the Regional Health Facility of Apucarana, Paraná State, to the cities it serves, using the parameters of the Cold Network Manual. The temperature within the boxes remained within the recommended range (2 to 8°C) for 44.44% of the routes that were tracked, of which 30.55% had boxes assembled with medications and 13.88% had boxes containing vaccines. Therefore, for most of the routes (55.55%), the internal temperature of the boxes was outside the recommended range, i.e., below 2°C or above 8°C. It was concluded that the transport of thermolabile drugs and vaccines between the Regional and Municipal levels do not meet the technical specifications provided for in the Cold Network Manual. As the temperature within the boxes exceeded the recommended temperature range for more than half of the routes followed, it can be inferred that the processes related to the transport of these products are not being followed with the necessary rigor. Municipal managers should be aware of these needs including the modernization of measurement instruments and equipment and the investments in continued education for the team that operates the cold chain network.

Keywords: medicine transport; vaccine transport; thermolabile drugs; cold network; pharmaceutical logistics.

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Introduction

Specialized medicines can be accessed by patients through pharmacies; however, these medicines may require special attention in terms of storage, particularly those that are thermolabile (Rodrigues Oriqui, 2012). Insulin is no longer the only refrigerated medicine found in community pharmacies.

While nurses have been working with cold network regulations for many years for the appropriate transport and storage of vaccines, pharmacists in Brazil are just learning how to manage it effectively. In 1979, Brazil launched the first edition of the Manual of the Cold Network of the National Immunization Program, and a great effort was allocated to the training of technicians to ensure the quality and safety of vaccines and serums offered to the population (Brazil, 2017). Since then, four editions of the manual have been published and the continued education of the immunization program personnel has been maintained, considering those involved throughout the entire vaccine chain, from industry to the vaccination room (Brazil, 2017).

Temperature is one of the factors that contributes the most to the instability of a substance. To minimize this instability, drugs are maintained at controlled temperature, usually between 2 and 8°C for the entire storage time (Brazil, 2017). Depending on how it was stored, the same drug may perform differently (Rodrigues Oriqui, 2012). Administering a drug that was stored incorrectly can have several consequences for the patient; although some drugs may undergo a loss of efficacy of little relevance, others may become toxic (Silva et al., 2012). When it comes to vaccines, any loss of potency is permanent and irreversible (Yakum, Athedjies, Walter, & Watcho, 2015).

The maintenance of medicines at a constant temperature requires equipment such as refrigerated chambers operating in the range between + 2°C and + 8°C and instruments for temperature measurement (Brazil, 2017). The standard temperature measuring instrument is the thermometer, which, like the

refrigerated chambers, are calibrated from the relationship between the values indicated by a standard measuring instrument and the corresponding known values of the magnitude to be measured (ANVISA/MS, 2015). The thermometer was first invented in the late 16th century by Galileo Galilei. In 1714, Daniel Gabriel Fahrenheit invented the mercury thermometer, then in 1780, the maximum and minimum thermometer was developed by the English physicist James Six. At the end of the 20th century, the evolution to digital recording thermometers occurred, also known as data loggers (Chojnacky, Strouse, Miller, & Stevenson, 2011).

The temperature measurement procedures are just as important as the instruments. The operations of temperature management are described in standardized documents (ANVISA/MS, 2015). Quality assurance of thermolabile drugs requires continuous monitoring of the entire storage cycle, from manufacturing to use. In this cycle, the stages of transportation, where the drug is taken from one point to another, are considered the most vulnerable to temperature fluctuations (ANVISA/MS, 2015). The transport stages involve moving products to/from different storage locations, distinct types of transportation, delays owing to traffic, and exposure to different environmental conditions. For a drug that requires specific temperature conditions, these factors have a major influence on its quality. Hence, cold chain transport systems should be evaluated to ensure that these services achieve their purposes satisfactorily (ANVISA/MS, 2015).

In 2017, the regulatory body for services and products that may affect the health of the Brazilian population, ANVISA, published the document 'Guidance for the Qualification of Transportation of Biological Products' in its second version. This guide is a reference for compliance with current legislation and addresses only matters related to transportation. According to this guide, "All persons and companies involved in transport activities have the responsibility to ensure that the appropriate transport conditions are maintained, from the departure of the manufacturer company to delivery to the final customer". The manufacturer considers its first buyer as the final customer; however, to reach the patient, drugs and vaccines still must go through several hands (Brazil, 2017).

The legal requirements for the handling and distribution of thermolabile drugs are known as Good Storage and Distribution Practices, and these state that personnel working with these products should be trained to act effectively. This reinforces the idea that people are the most critical element in cold chain processes (Freitas, 2013; Kartoğlu, Vesper, Teraäs, & Reeves, 2017).

Temperatures should be recorded at appropriate times and cold chain failures should be reported and corrected accordingly. In the transportation of loads under the responsibility of the manufacturing company, these procedures are carefully adhered to; however, the same has not been observed in the final transport stages, which involve the transportation of small loads between the smaller levels, such as the municipalities (Costa et al., 2017). Guidance for the Qualification of Transport of Biological Products recommends only the monitoring of temperature during the transport of biological products in the national territory (ANVISA/MS, 2015).

In Brazil, the transportation of medications after the end of the manufacturer's monitoring, in terms of temperature, has not been fully evaluated. This study aimed to assess the transportation conditions of thermolabile drugs and vaccines between a Regional Health Facility and the municipalities it serves, where transportation is not conducted by professional logistics companies but by municipal employees themselves. The objective of this work was to determine whether this transportation conditions met the technical specifications provided in the Manual of the Cold Network.

Material and methods

This case study was conducted from April to August 2018, and the standards described in 'Guidance for the Qualification of Transportation of Biological Products' (ANVISA/MS, 2015) and the Manual of the Cold Network of the National Immunization Program (Brazil, 2017) were followed.

The transport routes of vaccines and biological drugs between the Regional Health Facility and the 16 municipalities under its jurisdiction were monitored. This study followed the routes of vaccines, insulin, and other medications. With this distribution, there were some municipalities that did not have three routes mapped, because they did not receive thermolabile drugs, and one that did not receive insulins. In the end, 36 routes were followed.

2.1. Temperature monitoring instruments – For temperature-monitoring purposes, a datalogger and a digital thermometer (maximum and minimum) were used.

A calibrated TagTemp-Stick data logger (Novus Automation) was used. A computer is required for reading the data of the datalogger using a company-specific program. Dataloggers were activated and configured for

temperature collection every 2 minutes. The datalogger would automatically stop collecting data when the memory was full; however, this did not occur on any route followed in this study. Thus, temperatures were recorded not only during the transport time, but also the time after the box was opened. For the purposes of this study, the times between the assembly and the opening of the box were considered and analyzed.

A calibrated digital maximum and minimum thermometer with internal and external sensors was used (Incoterm). The features of this thermometer included: liquid crystal display (LCD); internal temperature range of - 10.0°C and + 60.0°C; external temperature range of - 50.0°C and + 70.0°C; resolution int/ext, 1°C/°F; precision int/ext, $\pm 1^\circ\text{C}/^\circ\text{F}$; accuracy, $\pm 5\%$ RH.

Positioning of the temperature recorders – A datalogger was placed inside a medicine or vaccine box of each route in a central position to minimize the movement of the data register. A maximum and minimum thermometer accompanied the box to record the ambient temperature of the transport period. The boxes used in the transport of the products had a maximum capacity of 32 L.

Means of transport – Cars of the municipality, not always for the exclusive transportation of medicines or vaccines, were used. Most of these cars had air conditioning. The average ambient temperature recorded was 27.5°C, with the coldest day being 10.0°C and the warmest 34.6°C.

Characterization of routes – All routes left from the Regional Health Facility, located at 435 Osório Ribas de Paula Street in the city of Apucarana, Paraná state, and transported the drugs and/or vaccines to the 16 municipalities that it serves. The routes were mapped and were between 20 and 150 km. The duration of the transport process varied according to the distance, with routes between 20 and 90 minutes.

Procedures for data collection – The driver performing the transport and the person receiving the box read the thermometer and recorded the temperature. At the time of delivery of the box to the driver, he/she was instructed to fill in a data collection sheet, which included the mileage of the vehicle at the exit of the Regional Health Facility and on arrival in the municipality. The time of assembly of the box and output were collected by the researcher. The datalogger was configured at the time of the assembly of the box, and the digital thermometer was also zeroed at this time. At the time of departure, the person responsible for receiving the box was contacted and oriented on how to fill in the reading data of the thermometer and to record the opening time of the box. The data logger, thermometer, and the completed data collection sheet were returned to us for analysis.

The quantitative data of the observed temperatures were submitted to percentage calculations in Excel® spreadsheets.

Results and discussion

Dataloggers recorded a total of 21:30 hours of temperature readings for the 36 routes (Figure 1). Temperature data recorded while the test boxes were in transit represented > 99% of this total time.

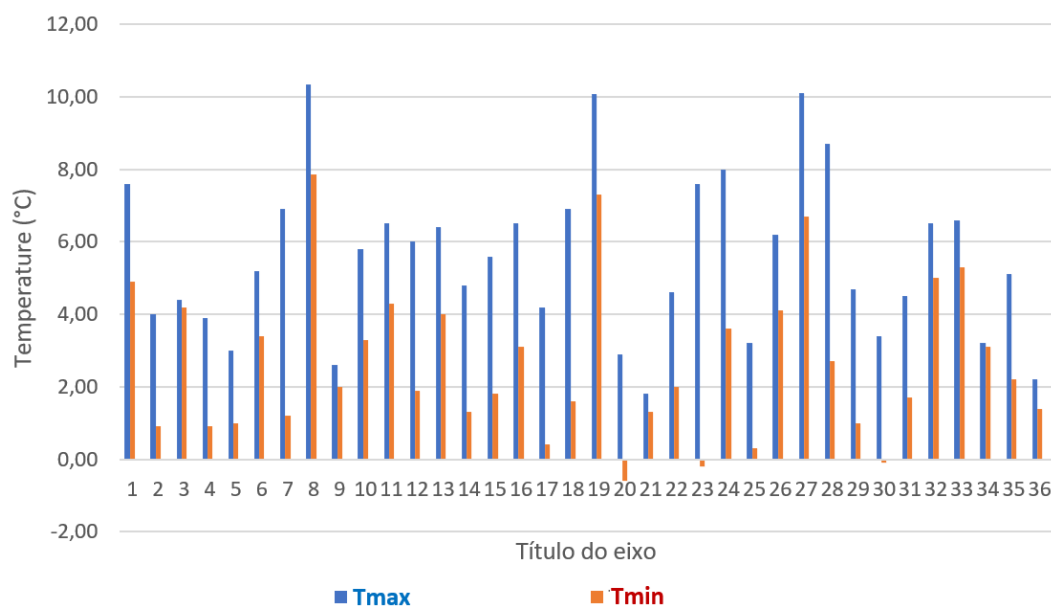


Figure 1. Maximum (Tmax) and minimum (Tmin) temperatures (°C) within the test boxes on the 36 tracked routes.

It was observed that the internal temperature of 55.55% of the boxes on the tracked routes were outside the recommended range; 8.33% had exposure to temperatures below 0°C, and 13.89% to temperatures above 8°C (Table 1).

Table 1. Number and frequency of routes within and outside the recommended temperature range (2–8°C).

| Number of routes | Total | Frequency (%) |
|----------------------------------|-------|---------------|
| Monitored | 36 | |
| Temperature within the range | 16 | 44.44% |
| Temperature outside of the range | 20 | 55.56% |
| Below 2°C | 17 | 47.22% |
| Below 0°C | 3 | 8.33% |
| Above 8°C | 5 | 13.89% |

Exposing drugs and vaccines to negative temperatures is a problem that has been cited by several authors (Oliveira, Gallardo, Arceêncio, Gontijo, & Pinto, 2014; Rao Ricote-Lobera et al., 2014; Schreiber, & Lee, 2017; Brown, Prosser, & Zwinkels, 2017; Lennon et al., 2017), and the Cold Network Manual (Brazil, 2017), which widely discusses how to minimize this problem. In this study, 8.33% of the tracked routes had a probable freezing temperature (Table 1). The reading of the data loggers was very different from the those of the maximum and minimum thermometer, and no professional was able to observe the temperature excursions that occurred. Despite this, there was no alert on the part of the professionals, there was no monitoring of the transport temperature and nonmandatory recording of these temperatures in the record maps.

During storage, temperature control of cold chambers and refrigerators is routine. Owing to power outages, warming is reported more often than freezing and substantial amounts of vaccines or medications are lost in these situations. Freezing goes unnoticed because professionals do not know how to visually recognize freezing, and it generally affects products that are closest to the refrigerated coils (Kristensen, Lorenson, Bartholomew, & Villadiego, 2016). Therefore, the probability of unnoticed freezes is high (Kristensen et al., 2016). One literature review found 15 articles exploring the transport segment of vaccines in several countries - no Brazilian - in 2007. Of these studies, 12 were from low-income countries, with a mean prevalence of temperatures below the recommended range of 19.8%, while this prevalence was 38% in high-income countries (Hanson, George, Sawadogo, & Schreiber, 2017).

A study was conducted in 6 countries, including Brazil, where a semi-structured questionnaire was carried out with stakeholders at various levels of vaccine supply in relation to the need for vaccines with greater temperature stability (Kristensen et al., 2016). For Brazil, regarding the perception of vaccine freezing and heating, 73% of the participants (14/19) believed that exposure to heat was a major concern. When asked if exposure of vaccines to freezing temperatures was a problem, in Brazil, 37% of participants (7/19) said 'yes', while 58% (11/19) answered 'no'.

The monitoring of temperature during the transportation of vaccines and medicines is commonly performed with maximum and minimum digital thermometers, with a sensor positioned at the end of an extender cable, which goes inside the box. It is very difficult for a professional to observe a temperature excursion with this type of thermometer, unless this temperature continues during the day and is observed at the defined check time (Kartoğlu & Milstien, 2014). The temperature is displayed on a screen and required subsequent annotation in record sheets, and thus, human error can occur in this process. If there is a disruption in the cold chain, that is, if the temperature fluctuates above or below the recommended range, these thermometers do not offer a record of the elapsed time, which complicates the decision-making process. Despite meeting ANVISA's requirements and being simple and easy to use, this type of temperature monitoring does not guarantee reliable temperature traceability (Brazil, 2017). The datalogger shows how the temperature varied throughout the monitoring time, allowing an assessment of whether or not there were unacceptable temperature excursions, and thus, accurate decisions can be made to correct, measure, reduce, or eliminate the cold chain problems (World Health Organization, 2011).

Another aspect to be taken into account is that, in addition to measuring instruments and refrigeration equipment, it is the people who perform the procedures, investigate problems and correct them, who must have the necessary knowledge and skills to operate the cold chain network (Kartoğlu et al., 2017). This makes people the most critical element of the cold chain network. The continuous improvement of professionals is a basic requirement for those who work with vaccines or medicines that require controlled temperature conditions (Kartoğlu & Milstien, 2014).

The routes accompanied in this study transported vaccines and medicines that require special temperature conditions. Vaccines are sent to municipal vaccination rooms, and nurses and nursing technicians are those who work with them. Vaccines have been a part of nursing for a long time, but for pharmacists, working with refrigerated drugs is not common practice; some municipal pharmacies do not even have a refrigerator or refrigerated chamber, and in some municipalities, even insulin administration is left to nursing professionals. Ensuring the delivery of medicines and vaccines to the population further from large centers requires planning, coordination, and resources (Kartoğlu, 2016; Amaral, 2013; Kartoğlu, Nelaj, & Maire, 2010).

In the routes followed, negative temperatures were observed only in the boxes carrying medications (14.28%; Table 2).

Table 2. Frequency of negative temperatures on the monitored routes by type of product transported.

| Negative temperature per loaded product - amount and frequency | | | |
|--|----------------------|-------------|-------|
| Transported product | Negative temperature | | Total |
| | Yes | No | |
| Drugs | 3 (14.28%) | 18 (85.72%) | 21 |
| Vaccines | 0 | 15 (100%) | 15 |
| Total | 3 (8.33%) | 33 (91.7%) | 36 |

Accidental freezes still occur in 33% of high-income countries to 35% in low-income countries, cold chain equipment fails and is underutilized by 20 to 50%, respectively, as assessed in the 55 countries funded by the Global Alliance for Vaccines and Immunization (GAVI) (Rao et al., 2017; Ricote-Lobera et al., 2014; Murhekar et al., 2013). Ricote-Lobera et al. (2014) showed that in 64% of the receipts of thermolabile drugs without temperature monitors, in the hospital of their study, the pharmacist could not guarantee that there was no temperature excursion, creating potential incidents that shorten the life of the drug.

The temperature remained within the recommended range 44.44% of the time. Overall, 30.55% of the boxes that were within the range had medications, and 13.88% contained vaccines. Most of the boxes (55.55%), therefore, traveled with temperatures outside the recommended range, that is, below 2°C or above 8°C (Table 3).

Table 3. Frequency of monitored routes that remained within the recommended range (2–8°C) by type of transported product.

| Transported product | No | Yes | Total |
|---------------------|-------------|-------------|-------|
| Drugs | 10 (27.77%) | 11 (30.55%) | 21 |
| Vaccines | 10 (27.77%) | 5 (13.88%) | 15 |
| Total | 20 (55.55%) | 16 (44.44%) | 36 |

Conclusion

The thermolabile drugs and vaccines transportation conditions assessed in this study did not meet the technical specifications provided in the Cold Network Manual. When temperatures were beyond the recommended range, no communication or notification was made. Municipal managers should be made aware of the modernization of measurement instruments/ equipment and invest in the continuing education for the team that operates the cold network. Professionals responsible for storage and distribution have the commitment to ensure the quality of medicines and vaccines delivered to the population by adhering to the Cold Network Manual specification, until technological innovations are implemented to improve this safety.

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