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Review

Is freezing in the vaccine cold chain an ongoing issue? A literature review ☆

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ABSTRACT

Vaccine exposure to temperatures below recommended ranges in the cold chain may decrease vaccine potency of freeze-sensitive vaccines leading to a loss of vaccine investments and potentially places children at risk of contracting vaccine preventable illnesses.

This literature review is an update to one previously published in 2007 (Matthias et al., 2007), analyzing the prevalence of vaccine exposure to temperatures below recommendations throughout various segments of the cold chain. Overall, 45 studies included in this review assess temperature monitoring, of which 29 specifically assess 'too cold' temperatures. The storage segments alone were evaluated in 41 articles, 15 articles examined the transport segment and 4 studied outreach sessions. The sample size of the studies varied, ranging from one to 103 shipments and from three to 440 storage units. Among reviewed articles, the percentage of vaccine exposure to temperatures below recommended ranges during storage was 33% in wealthier countries and 37.1% in lower income countries. Vaccine exposure to temperatures below recommended ranges occurred during shipments in 38% of studies from higher income countries and 19.3% in lower income countries.

This review highlights continuing issues of vaccine exposure to temperatures below recommended ranges during various segments of the cold chain. Studies monitoring the number of events vaccines are exposed to 'too cold' temperatures as well as the duration of these events are needed. Many reviewed studies emphasize the lack of knowledge of health workers regarding freeze damage of vaccines and how this has an effect on temperature monitoring. It is important to address this issue by educating vaccinators and cold chain staff to improve temperature maintenance and supply chain management, which will facilitate the distribution of potent vaccines to children.

Contents

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1. Introduction

Immunizations are hailed as one of the most important public health interventions known saving millions of lives every year. Vaccines are responsible for the eradication of smallpox and the global community is currently working towards the eradication of polio. To reach current disease elimination and eradication targets, high immunization coverage rates are required. A well-functioning cold chain is at the center of ensuring potent vaccines reach their intended population in an equitable and timely manner [2,3].

Vaccines are biological products that slowly become inactive over time and must be kept within narrow temperature ranges from manufacturers to those receiving them [3]. When exposed to temperatures outside of this narrow range, the loss of potency may be accelerated [4]. Before 2007, attention had been focused on examining the effects of vaccine exposure to heat. However, exposure to freezing temperatures are equally damaging to the quality of many vaccines as the process renders them inactive [4]. When exposed to freezing temperatures, the adjuvants contained in some vaccines clump together adversely affecting the immunological properties of these vaccines [4]. Thus, the World Health Organization (WHO) recommends the following vaccines be stored and transported at 0–10 °C: Diptheria-tetanus containing vaccines, tetanus toxoid (TT), hepatitis A and B, human papillomavirus (HPV), meningitis C, pneumococcal (PCV), cholera, influenza, haemophilus influenza b (Hib), typhoid and inactivated poliovirus (IPV) [4]. In 2015, approximately 59% of vaccines procured from the United Nations Children's Fund (UNICEF) Supply Division's (SD) catalogue are freeze-sensitive [5]. Furthermore, the number of freeze-sensitive vaccines recommended by the WHO has increased by 50% over the last ten years [4,6].

In 2007, a review of studies examining temperatures in the vaccine cold chain from 1985 to 2006 reported that in all segments of distribution, vaccines in 75–100% of monitored vaccine shipments had been exposed to freezing temperatures [1]. This 2007 review seems to have raised awareness about the risks of vaccine exposure to freezing temperatures in both developed and developing countries of varying climates.

The objective of this updated review is to examine the results of more recent monitoring studies regarding freezing temperatures within the immunization supply chain.

2. Methods

2.1. Identification of temperature monitoring studies

For this review, seven search terms were used alone and in combination to search gray and peer reviewed literature in PubMed, Popline, Embase, Biosis, and Google Scholar. In addition, the WHO and TechNet21 websites were searched for gray literature. The search terms were (i) vaccine, (ii) temperature, (iii) thermostability, (iv) storage, (v) transport, (vi) freeze, and/or (vii) cold chain. All searches were limited to studies published between July 2006 to August 2015, and did not include studies from Matthias et al. [1]. In addition, unpublished studies that evaluated the temperature of the storage of vaccines either in facilities, during transportation or at outreach sessions in any country were included in this review.

2.2. Data extraction

The following information was extracted from each of the studies that met the inclusion criteria:

1. Year the study was published.
2. Year the study was conducted.
3. The country in which the study was conducted.
4. Type of temperature measuring equipment used.
5. Freeze threshold temperature or the temperature that was considered "too cold".
6. Duration vaccines were at or below the freeze threshold (the time threshold after which was considered as "too cold").
7. The duration of temperature monitoring.
8. The frequency of temperature monitoring.
9. Unit of analysis (refrigerators, transport in vaccine carriers, transport in refrigerated trucks, etc.).
10. Study sample size (number of refrigerators or shipments).
11. Number of samples that registered freezing temperatures.
12. Percentage of samples that registered freezing temperatures or temperatures out of the recommended range of 2–8 °C.
13. Minimum temperatures observed.

2.3. Analysis

Data were analyzed from studies that reported temperature monitoring results. Different segments of the cold chain were analyzed separately to account for differences in endpoints across studies. Analysis of data from published studies includes means and standard deviations (SD) of study sample sizes and years of studies as well as the weighted means and SDs of the percent of samples found below recommended temperatures. Some studies provide temperature data for more than one administrative level and for more than one cold chain segment; therefore, an individual study may have multiple data points. In addition, each country was categorized by region and World Bank income status [7]. Wealthier countries are defined as those with upper-middle to high income status and lower income countries are defined as those in low to lower-middle income status.

Rigorous monitoring was defined as studies in which both the frequency and duration of exposure to temperatures below recommended temperatures were reported. For duration of monitoring, anything more than 1 week was assigned a 1 and less was assigned a 0. For frequency of monitoring, any study with continuous monitoring was given a 1, while spot checks or one time point only measurements were given a 0. Rigor was calculated by then multiplying the two to determine a single indication (0 or 1). Rigorous studies were identified by a 1.

Data was entered, stored and tabulated in Excel™ (Microsoft, Redmond, WA).

3. Results

The literature and web search was completed on March 21, 2016 and yielded 1070 articles. Screening of these articles led to the removal of 889 citations based on relevance of abstracts and titles. The remaining 181 full text citations were screened according to the study inclusion criteria. The secondary and final screen yielded 45 articles for final inclusion in the review (Tables 1 and 2).

Of the 45 articles, 33 are from peer-reviewed journals and 12 are from gray or unpublished literature. Thirteen articles describe temperature monitoring data from the African region, 12 from the Western Pacific region, nine from the South East Asian region, three from the Americas, four from the Eastern Mediterranean and four from Europe.

Studies from all income levels are represented. Seven studies are from high-income countries (HIC), 13 are from upper-middle income countries (UMIC), 15 are from lower-middle income countries (LMIC) and eight are from low-income countries (LIC). Two