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The effect of cool water pack preparation on vaccine vial temperatures in refrigerators

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ABSTRACT

Cool water packs are a useful alternative to ice packs for preventing unintentional freezing of vaccines during outreach in some situations. Current guidelines recommend the use of a separate refrigerator for cooling water packs from ambient temperatures to prevent possible heat degradation of adjacent vaccine vials. To investigate whether this additional equipment is necessary, we measured the temperatures that vaccine vials were exposed to when warm water packs were placed next to vials in a refrigerator. We then calculated the effect of repeated vial exposure to those temperatures on vaccine vial monitor status to estimate the impact to the vaccine. Vials were tested in a variety of configurations, varying the number and locations of vials and water packs in the refrigerator. The calculated average percentage life lost during a month of repeated warming ranged from 20.0% to 30.3% for a category 2 (least stable) vaccine vial monitor and from 3.8% to 6.0% for a category 7 (moderate stability) vaccine vial monitor, compared to 17.0% for category 2 vaccine vial monitors and 3.1% for category 7 vaccine vial monitors at a constant 5 °C. The number of vials, number of water packs, and locations of each impacted vial warming and therefore percentage life lost, but the vaccine vial monitor category had a higher impact on the average percentage life lost than any of the other parameters. The results suggest that damage to vaccines from repeated warming over the course of a month is not certain and that cooling water packs in a refrigerator where vaccines are being stored may be a useful practice if safe procedures are established.

1. Introduction

Loss of vaccine due to damage from freezing is an ongoing problem. Studies from 2006 to 2015 reported that 19% of vaccine shipments in lower-income countries and 38% in higher-income countries were exposed to temperatures below recommended values [1]. Freeze damage carries two risks: that a freeze-damaged vial will be detected and therefore must be discarded, and that a freeze-damaged vial will not be detected and therefore might be administered, offering lower protection than expected. Freeze damage to a single vial can be detected using a simple shake test for aluminum-adjuvanted vaccines [2]. Wastage from freeze damage can be expensive; in 2015, freeze-sensitive vaccines worth US $1.2 billion were procured through UNICEF [1]. With the increasing use of freeze-sensitive vaccines that do not contain adjuvants and do not respond to the shake test, such as inactivated polio vaccine [3], there is increasing risk of freeze damage going unnoticed. Studies have associated vaccine exposure to freezing temperatures during transport with lower immune response [4–6]. Inadvertent freezing can occur when vaccine vials are transported in insulated carriers with ice packs to protect them from high ambient temperatures; unless the packs are partially melted first (conditioned), they can freeze adjacent vials. To combat this problem, should the commensurate reduction in cool life be acceptable, WHO recommends using water packs cooled to 2–8 °C as an alternative to conditioned ice packs for transporting freeze-sensitive vaccines. However, WHO also states that these water packs should never be cooled in a refrigerator that contains vaccines to avoid raising temperatures and compromising vaccine potency [7]. Complying with this requires a second refrigerator in clinics and health posts—an additional cost not easily absorbed in low-resource settings. While this recommendation assumes that placing warm water packs into a refrigerator is likely to damage vaccines, the thermal impact of such a practice has not been investigated.

Abbreviations: DTP, diphtheria, tetanus, pertussis; hep B, hepatitis B; HPV, human papillomavirus; IPV, inactivated polio vaccine; MMR, measles, mumps, and rubella; OD, optical density; OPV, oral polio vaccine; PQS, Performance, Quality and Safety; WHO, World Health Organization.

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Evidence about the effect of recooling water packs alongside vaccines could enable better decisions about the need for using a separate refrigerator.

The impact of heat exposure on potency is unique to each vaccine and manufacturer. A tool that can be used to generalize this impact is the vaccine vial monitor (VVM), a heat-sensitive label required on WHO prequalified vaccines. Similar methods have been used in previous studies [8,9] but have not been documented in detail. Each prequalified vaccine is assigned to one of four categories of VVM based on its heat stability; these are designated VVM2, VVM7, VVM14, and VVM30 (Table 1), with VVM2 vaccines being the least heat stable [10].

VVMs consist of a reference circle with a color-changing indicator dot inside. The lifetime can be defined as the time it takes for the optical density (OD) of the indicator dot to match the OD of the reference circle (referred to as the endpoint by WHO). This lifetime is temperature dependent, and there is a known relationship between temperature and lifetime for each VVM category based on the Arrhenius equation, $k = A * \exp(-E_a/RT)$. In this equation, k is the rate constant, E_a is the activation energy, R is the gas constant, A is a constant, and T is the temperature in kelvin [11]. The rate constant k is the bridge from lifetime versus temperature to lifetime remaining versus time: for a linear reaction, the equation for lifetime remaining versus time is $y = -kt + b$, where k is the rate constant from the Arrhenius equation, b is the starting lifetime, and y is the remaining lifetime. WHO specifies the lifetime at two constant temperatures for each category of VVM (Table 1). Each WHO PQS-specified lifetime-temperature point includes an implied reaction rate: 100% of the lifetime remains at 0 days; 0% of the lifetime remains at the endpoint. Because only two points are given to define the reaction rate, the reaction is assumed to be linear for currently available VVMs [12].

The goal of our study was to understand the impact on vaccine life of cooling warm water packs in a refrigerator used to store vaccines by using VVM life as a proxy for vaccine life and the Arrhenius equation for calculation of VVM life. This would give us information on the value of having a dedicated refrigerator for cooling water packs.

2. Materials and methods

The overall design of testing was to place water packs at 43 °C into a refrigerator with vaccine vials at 2–8 °C and measure the temperatures of the vials over time to generate warming curves. These curves were subsequently analyzed using calculated time-temperature curves for each category of VVM to estimate the impact of cyclic warming on vaccine life.

To prepare for testing, 10-mL vials were filled with water and some were instrumented with thermocouples (OMEGA Engineering, Inc., 5SRTC-TT-T-36, Stamford, CT, USA). Before the start of each test, the selected number of vials was arranged in a PQS-prequalified refrigerator (SunDanzer, model BFRV15, Tucson, AZ, USA) to cool. PQS-prequalified water packs (Blowkings, model BK 6, Mumbai, India) instrumented with thermocouples were conditioned to 43 °C, the "hot zone" temperature for prequalifying cold chain equipment [13], and placed inside the refrigerator. Several arrangements (Fig. 1) of varying numbers of vials and water packs were tested in duplicate or triplicate. Each test contained up to 18 instrumented vials; locations of these vials in each arrangement are available in Appendix 1.

Temperature collection at a rate of two samples/minute (NI cDAQ-9172 chassis, 9211 thermocouple input module, NI SignalExpress software, National Instruments Corporation, Austin, TX, USA) began immediately following placement of the water packs in the refrigerator and continued until the vials and water packs reached at least 5 °C. Warming curves were plotted and then trimmed to include only the values from the first measurement to the last one where the vial temperature exceeded 5 °C. In this way, excursion curves were generated so that a low refrigerator set point or a long test would not artificially deflate the impact of warming. A threshold of 5 °C was chosen as it is the middle of the cold chain temperature range and is a standard testing point for VVMs [14].

Once warming curves were trimmed, an intermediate step was necessary to use VVMs to generalize the thermal impact of warming to vaccines in each category of VVM. To apply the time-temperature curves for VVMs to the measured data, it was necessary to calculate those curves from the published lifetime-temperature points. In the Arrhenius equation, $k = A * \exp(E_a/RT)$, k is the slope of the linear reaction at any given temperature (Fig. 2). Since the reaction is linear, k is equal to 100%/lifetime in days and the equation becomes $1/L = A * \exp(E_a/RT)$, where L is the lifetime. Two lifetime-temperature points are specified, leaving only two unknowns in the Arrhenius equation. Using the Arrhenius equation for each category of VVM, the reaction rate and percentage life lost during a time period at any temperature can be calculated. The Arrhenius equation for each category of VVM is shown in Table 1.

The known Arrhenius equation for each VVM must then be applied to the warming curves to estimate the impact of warming. To do this, the percentage life lost for each data point is calculated by finding the daily life lost at that temperature from the Arrhenius equation and then calculating the life lost in 30 s at that temperature. The total life lost due to warming is the sum of the values for life lost at each 30-s data point. This process is demonstrated in Fig. 2.

It is likely that vaccines would be exposed to excursions from 5 °C more than once from placement of warm water packs, but only at the last stage before use. This would be at the final health

Table 1
Vaccine vial monitor (VVM) lifetime/temperature points taken from the World Health Organization (WHO) Performance, Quality and Safety (PQS) specification for VVMs. The specification requires that 90% of VVMs reach endpoint in the specified time within each specified temperature range. Examples of vaccines in each category from the WHO prequalified vaccines database and Arrhenius equations with constants calculated from the midpoint of the 90% tolerance range of WHO-supplied lifetime/temperature points are listed [10].

VVM category (vaccine examples*)	No. days to endpoint at +25 °C to +37 °C	No. days to endpoint at +22 °C to +25 °C	Time to endpoint at +2 °C to +5 °C	Arrhenius equation at midpoint of 90% tolerance range of temperatures
VVM2: least stable (OPV; some influenza)	2	NA†	225 days	$\frac{100\%}{L} = 1.4422 * 10^{17} e^{\frac{-12,429}{T}}$
VVM7: moderate stability (IPV; MMR)	7	45	>2 years	$\frac{100\%}{L} = 2.1532 * 10^{18} e^{\frac{-13,652}{T}}$
VVM14: medium stability (DTP; pentavalent)	14	90	>3 years	$\frac{100\%}{L} = 1.0766 * 10^{18} e^{\frac{-13,652}{T}}$
VVM30: high stability (Hep B; HPV)	30	193	>4 years	$\frac{100\%}{L} = 5.1131 * 10^{17} e^{\frac{-13,657}{T}}$

* Oral polio vaccine (OPV); inactivated polio vaccine (IPV); measles, mumps, and rubella (MMR); diphtheria, tetanus, pertussis (DTP); hepatitis B (hep B); human papillomavirus (HPV).
† VVM (Arrhenius) reaction rates are determined at two temperature points. WHO supplies a general range at a third point for VVM7, VVM14, and VVM30.