Thermal Analysis of Refrigeration Systems Used for Vaccine Storage

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CDC Contact: Tony Richardson, Public Health Advisor
Current Problem

CDC administers ~ $3 billion of vaccine through Vaccines for Children (VFC) program each year.

Storage temperature control is vital to maintaining vaccine potency
- Storage outside 2 °C to 8 °C range can render vaccines ineffective
- A meta-analysis estimates 14 to 35% of delivered vaccines are subjected to inappropriate storage temperatures

Social and economic costs of improperly stored vaccines
- Cost of manufacturing and delivering vaccine wasted
- Vaccine delivery delayed
- Reported vaccination rates are erroneously high
- Recipients are not protected

$3 B/yr program X 30% loss due to known thermal excursions = $900 M/yr loss
Background and Purpose

Challenges in ensuring VFC providers follow good vaccine storage and temperature maintenance practices

- 45,000+ providers, many different storage and temperature monitoring methods
- Suitability of commercial refrigerators for vaccine storage not well documented
- Impact of refrigerator loading pattern, normal refrigerator use, environmental temperature fluctuations, …unknown!
- Inadequate temperature monitoring: improper thermometer placement, possible device inaccuracies, and absence of continuous temperature data collection

Need for research that matches everyday conditions experienced by vaccine providers

- Improve storage and handling guidelines and practice
Experimental Method: Measurement System

- 19 thermocouples and 3 to 6 electronic data loggers arranged throughout refrigerators
  - Calibrated at ice point (0 °C)
  - Sensors attached to vaccine vials, walls, inside glycol-filled bottles, and hanging in air
  - Recorded data continuously during trials lasting 15 hours to several days

<table>
<thead>
<tr>
<th>Device name</th>
<th>U(k=2), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermocouple measurement system</td>
<td>0.12</td>
</tr>
<tr>
<td>Data logger A</td>
<td>0.58</td>
</tr>
<tr>
<td>Data logger B</td>
<td>1.41</td>
</tr>
<tr>
<td>Data logger C</td>
<td>0.67</td>
</tr>
<tr>
<td>Data logger D</td>
<td>0.59</td>
</tr>
<tr>
<td>Data logger E</td>
<td>0.59</td>
</tr>
</tbody>
</table>

- Rate of data collection
  - Thermocouples = 10 s
  - Data loggers = 30 s to 1 min

- 100,000 – 500,000 data points collected during each trial
  - Complete picture of temperature behavior over time
  - Condense into representative samples and averages to find correlations between tested criteria and temperature trends
Experimental Method: Tested Criteria

4 refrigerator styles
- Freezerless, Dormitory-style, Dual Zone Fridge/Freezer, Pharmaceutical grade

Varied refrigerator loading patterns
- Low, medium, and high density loads
- Plastic trays, cardboard boxes, and combined trays/boxes storage configurations
- With and without water bottles (3 - 5% total capacity) in refrigerator door

Normal use simulation - open / close refrigerator door
Door left ajar
Increased room temperature
Power outage and recovery
### Experimental Method: Measurement Matrix

<table>
<thead>
<tr>
<th>Trial</th>
<th>Load Density</th>
<th>Packing Style</th>
<th>Water Bottles</th>
<th>Measurement Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>Trays</td>
</tr>
<tr>
<td>1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>4</td>
<td>x</td>
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<td>5</td>
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<td>6</td>
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<td>x</td>
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<tr>
<td>7</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
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<tr>
<td>8</td>
<td>x</td>
<td></td>
<td>x</td>
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<tr>
<td>9</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
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<tr>
<td>10</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
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<tr>
<td>13</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
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<tr>
<td>15</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
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<tr>
<td>16</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

- Cross cutting matrix captures range of normal usage conditions
  - Normalize measurements across different refrigeration systems
- Refrigerator temperature set points left unchanged throughout study
  - “Out of box” midpoint temperature dial settings ~ 4 – 6 °C
Results: temperature stability of refrigerators

Freezerless Refrigerator

Dual Zone Refrigerator

data collected over 26 day period

Pharmaceutical Refrigerator

Dorm-style Refrigerator

51 days

45 days

31 days

top wall

near cooling unit

back of tray, near wall

severe set point drift after 2 weeks
Comparison of Refrigerator Performance in Response to Tested Criteria

I. Loading density

<table>
<thead>
<tr>
<th>Little or No Impact</th>
<th>Negative Impact on Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREEZERLESS</strong></td>
<td><strong>DUAL ZONE</strong></td>
</tr>
<tr>
<td>• No significant impact on performance</td>
<td>• Possible minor increase in location-specific temperature variation for high density loads</td>
</tr>
<tr>
<td><strong>PHARMACEUTICAL</strong></td>
<td><strong>DORM-STYLE</strong></td>
</tr>
<tr>
<td>• No significant impact on performance</td>
<td>• Noticeable impact on performance due to lack of air circulation</td>
</tr>
<tr>
<td></td>
<td>• High-density loading patterns increased location-specific temperature variation</td>
</tr>
</tbody>
</table>

Density variation pattern in dorm-style fridge

Low Density Pack  | Medium Density Pack  | High Density Pack
### II. Packing style (Trays, Boxes, or Mixed)

<table>
<thead>
<tr>
<th>FREEZERLESS, PHARMACEUTICAL &amp; DUAL ZONE</th>
<th>DORM-STYLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No noticeable impact on performance</td>
<td>• Indeterminable due to overall poor refrigerator stability</td>
</tr>
</tbody>
</table>

Packing style variation in freezerless refrigerator

- Plastic Trays
- Cardboard Boxes
- Mixed Trays and Boxes
III. Opening/ closing refrigerator door

<table>
<thead>
<tr>
<th>Little or No Impact</th>
<th>Negative Impact on Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHARMACEUTICAL</strong></td>
<td><strong>DORM-STYLE</strong></td>
</tr>
<tr>
<td>• Vial temperatures not significantly affected</td>
<td>• Most sensors record brief temp increases, overall decrease</td>
</tr>
<tr>
<td></td>
<td>• Exacerbates already poor temperature control</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DUAL ZONE</strong></td>
<td></td>
</tr>
<tr>
<td>• Small increases in vial temps, but remained within 2 °C to 8 °C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FREEZERLESS</strong></td>
<td></td>
</tr>
<tr>
<td>• Small increases in vial temps, but remained within 2 °C to 8 °C</td>
<td></td>
</tr>
<tr>
<td>• Water bottles in door reduced temperature change. Without bottles, temp increased up to 1.2 °C higher</td>
<td></td>
</tr>
</tbody>
</table>
III. Door opening continued

False Alarm Alert: Temperature Monitor Placement Matters!

Sensors in air, attached to walls, or near cooling vents show temperature spikes > 8 °C in all refrigerator types

TC #19 (magenta) shows temperature < 2 °C

- Inside glycol-filled bottle, directly on glass shelf under cooling vent
- Repeated door opening results in driving temp down
- Monitor placed in this location NOT a good indicator of stored vaccine temperature!
IV. Door left ajar

<table>
<thead>
<tr>
<th>Refrigerator type</th>
<th>time until vial temp &gt; 8 °C</th>
<th>maximum vial temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREEZERLESS</td>
<td>1 to 49 min</td>
<td>18.6 °C</td>
</tr>
<tr>
<td>DUAL ZONE</td>
<td>3 to 60 min</td>
<td>19.5 °C</td>
</tr>
<tr>
<td>PHARMACEUTICAL</td>
<td>35 min, most did not exceed</td>
<td>8.7 °C</td>
</tr>
<tr>
<td>DORM-STYLE</td>
<td>1 to 5 min</td>
<td>23.8 °C</td>
</tr>
</tbody>
</table>

- Rate of temperature increase dependent on vial storage method and location
- Water bottle ballast reduced negative impact of open door
- Pharmaceutical type refrigerator best equipped to withstand accidents
- Some TCs (air, walls, near cooling vent) driven below 2 °C once door closed

Freezerless Refrigerator Trial
## V. Increasing room temperature

<table>
<thead>
<tr>
<th>Little or No Impact on Performance</th>
<th>Negative Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FREEZERLESS</strong></td>
<td><strong>DORM-STYLE</strong></td>
</tr>
<tr>
<td>- Room and fridge temperature directly related</td>
<td>- Room and fridge temperature directly related</td>
</tr>
<tr>
<td>- For every 1 °C increase in room temp, fridge temp rises ~0.1 °C</td>
<td>- For every 1 °C increase in room temp, fridge temp rises ~0.3 °C</td>
</tr>
<tr>
<td>- Small room temp fluctuations will not greatly impact refrigerator performance</td>
<td>- Small room temp fluctuations pose greater threat</td>
</tr>
<tr>
<td><strong>DUAL ZONE</strong></td>
<td></td>
</tr>
<tr>
<td>- 1 °C change in ambient temp → fridge temp ± 0.05 °C</td>
<td></td>
</tr>
<tr>
<td>- Moderate room temp fluctuations will not greatly impact refrigerator performance</td>
<td></td>
</tr>
<tr>
<td><strong>PHARMACEUTICAL</strong></td>
<td></td>
</tr>
<tr>
<td>- Very small impact on performance</td>
<td></td>
</tr>
<tr>
<td>- 1 °C change in ambient temp → fridge temp ± 0.02 °C</td>
<td></td>
</tr>
<tr>
<td>- Able to withstand large room temp fluctuations</td>
<td></td>
</tr>
</tbody>
</table>
## VI. Power outage

<table>
<thead>
<tr>
<th>Refrigerator type</th>
<th>Time after power off until vial temp &gt; 8 °C without water bottles</th>
<th>Time after power off until vial temp &gt; 8 °C with water bottles</th>
</tr>
</thead>
<tbody>
<tr>
<td>FREEZERLESS</td>
<td>1.5 to 4.75 hrs</td>
<td>2 to 8 hrs</td>
</tr>
<tr>
<td>DUAL ZONE</td>
<td>1.25 to 4.75 hrs</td>
<td>1.25 to 4.75 hrs</td>
</tr>
<tr>
<td>DORM-STYLE</td>
<td>0.75 to 2.5 hrs</td>
<td>1 to 4.25 hrs</td>
</tr>
<tr>
<td>PHARMACEUTICAL</td>
<td>0.75 to 2.25 hrs</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Vials that resisted thermal excursions during an outage the longest were:
- Contained in boxes, trays, and/or original packaging
- Placed away from the top refrigerator shelf
- In a fridge with a water bottle “temperature ballast”

Pharmaceutical fridge suffered from poor insulation provided by glass doors

Allow 6 to 9 hrs for thermal re-equilibration following an outage
## VII. Defrost cycle

<table>
<thead>
<tr>
<th>FREEZERLESS</th>
<th>DORM-STYLE</th>
<th>DUAL ZONE</th>
<th>PHARMACEUTICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Defrost cycle runs every 2-3 days</td>
<td>- No defrost cycle</td>
<td>- Defrost cycle runs at ~30 h intervals</td>
<td>- Impact of defrost cycle on internal fridge temperature / performance is negligible</td>
</tr>
<tr>
<td>- Vials occasionally exceeded 8 °C for &lt;15 min</td>
<td>- Refrigerator interior quickly becomes encased in frost and ice</td>
<td>- Vial temperatures increased ~0.5 °C, did not exceed 8 °C</td>
<td></td>
</tr>
<tr>
<td>- Thermometers in air / near walls recorded dramatic temperature spike followed by a drop below 2 °C</td>
<td></td>
<td>- Some sensors in air / near walls recorded temperatures &gt; 8 °C for 10-20 min, followed by a drop below 2 °C for &lt;10 min</td>
<td></td>
</tr>
</tbody>
</table>

### Continuous Temperature Monitoring
- Vital to proper vaccine storage
- Current “manual check” system:
  - Possible false alarm if checked during defrost cycle
  - Failure to recognize existence of defrost cycle and take any necessary protective measures
- Freezerless fridge example
  - Cumulative effect of time above 8 °C during multiple defrost cycles?
  - Evaluate on case-by-case basis
- Monitor placement is very important!
Vaccine Vial Storage Methods and Locations

DUAL ZONE

- Never place vials directly on glass shelf = 2 - 5 °C colder

PHARMACEUTICAL

- No storage in vegetable crisper: thermally isolated + floor level runs cold

FREEZERLESS

- 1 – 2 °C colder than main fridge space
**Vaccine Vial Storage Methods and Locations**

**DUAL ZONE**
- Never place vials directly on glass shelf = 2 - 5 °C colder
- No storage in vegetable crisper: thermally isolated + floor level runs cold

**PHARMACEUTICAL**
- Avoid storing on top shelf – near cooling vent. First location to exceed max allowed temp during outages.
- Manufacturer recommends no floor storage, but vial TC maintained at 2 – 8 °C throughout testing

**FREEZERLESS**
- 1 – 2 °C colder than main fridge space
Vaccine Vial Storage Methods and Locations

**DUAL ZONE**

- Never place vials directly on glass shelf = 2 - 5 °C colder
- No storage in vegetable crisper: thermally isolated + floor level runs cold

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- Avoid storing on top shelf – near cooling vent. First location to exceed max allowed temp during outages.
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**FREEZERLESS**

- 1 – 2 °C colder than main fridge space

*Best storage practice – place vaccines in center fridge space, contained in original packaging, cardboard boxes, and/or plastic trays to minimize thermal excursions*
Vaccine Vial Storage Methods and Locations

**DORM-STYLE REFRIGERATOR**

- Consistently unacceptable performance, regardless of vaccine storage location
- Placement on/ near floor, cooling and freezer unit further reduces temperature stability
- No “good” storage area

The dorm-style refrigerator is NOT recommended for vaccine storage under any circumstance!
Vaccine Temperature Monitoring: Electronic Data Loggers

ADVANTAGES

- **Continuous monitoring** - ensures that all thermal excursions are captured, improving confidence in vaccine supply efficacy
- Easy to use
- Quickly analyze results, eliminating time-consuming paperwork
- Archival data stored electronically
- Alarm capabilities, some with email notification mean that problems are revealed (and can be dealt with) immediately
- Wireless models allow for real-time monitoring
- Can be calibrated by end-users at the ice point

DISADVANTAGES

- Data logger use requires computer capability and some training
Monitoring Vial Temperature Effectively

Best Location for Temperature Sensors

Sensor probe inside glycol-filled bottle, placed in the same locations as vials.
Monitoring Vial Temperature Effectively

Best Location for Temperature Sensors
- Sensor probe inside glycol-filled bottle, placed in the same locations as vials

Worst Location for Temperature Sensors
- Sensors attached to walls
Dual Zone Case Study:
Does freezer setting affect refrigerator performance?

- Sensors arranged throughout both freezer and refrigerator compartments
- Varied freezer set point dial, refrigerator temp setting left unchanged
  - 50%, 75%, and 100% (maximum cold setting)
- Change in refrigerator sensor temperatures ~10% temperature drop recorded by freezer sensors
Dual Zone Case Study: Is this refrigerator model suitable for frozen vaccine storage?

Freezer thermostat dial set to midpoint position: vaccine vial temperatures between -13 °C and -11 °C

Maximum cold setting: vial temperatures fluctuate between -19 °C and -13 °C
- Upper limit exceeded
- 5 °C fluctuation due to freezer control is large – no room for set point error

Defrost cycle temperature spike
- 2+ hr thermal excursion > -15 °C, every 24 hrs
- Possible significant impact on vaccine quality

Upper temperature limit for frozen vaccine storage = -15 °C
Summary of Results

Freezerless, dual zone, and pharmaceutical type refrigerators are suitable for refrigerated vaccine storage
- Performance unaffected by variations in packing density or type
- Able to withstand small (2 - 5 °C) environmental temperature fluctuations
- Water bottle ballast improves temperature stability under non-ideal conditions
- Store vaccine vials in boxes or trays placed in the center of the refrigerator
- Dual zone freezer control may not be adequate for maintaining vaccines < 15 °C

Dorm-style refrigerators should NOT be used for vaccine storage
- Severe temperature control drift
- Lack of air circulation = spatial thermal non-uniformity
- Susceptible to small room temperature fluctuations

Continuous temperature monitoring is an integral part of effective vaccine storage management
- Manual checks do not sufficiently capture temperature behavior over time
- Thermal excursions most likely to occur when nobody is around
- Widespread implementation of electronic temperature loggers is a simple and inexpensive way to dramatically improve vaccine storage practices
- Proper placement of temperature monitors is crucial to obtaining meaningful data
- Sensor placement should match locations/ methods in which vaccine vials are stored
Next Steps

**Guidelines for use of vaccine-storage refrigerators**
- Include measurements of small, under-the-counter pharmaceutical grade model

**Develop methods for accurate cold-chain measurements with electronic thermometers**
- In-depth testing of at least five data-logger models to evaluate
  - Manufacturer-specified accuracy
  - Stability over 6 month period
  - Proper use so that measurements reflect vaccine vial temperatures
- Validation of IR thermometers (used in VFC site visits)

**Improve guidelines for purchasing thermometers**
- “NIST certified” and “NIST traceable” claims sometimes lack official status, authentication or validation
- Appendix to NSF thermometer certification requirements in NSF ANSI 2

**Investigate technologies for cold-chain monitoring during shipment**
- Performance of chemically activated sensors and electronic data loggers

**Test new storage and handling guidelines for practicality, user friendliness**
- Evaluation by CDC, AIM, VFC program coordinators and selected VFC clinics
Thank You!

Many thanks to the Virginia and DC VFC Programs for their contributions to this study.

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