Thermal Analysis of Refrigeration Systems Used for Vaccine Storage

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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
  - <u>Recipients are not protected</u>

$3 B/yr program X 30% loss due to <u>known</u> thermal excursions = $900 M/yr loss

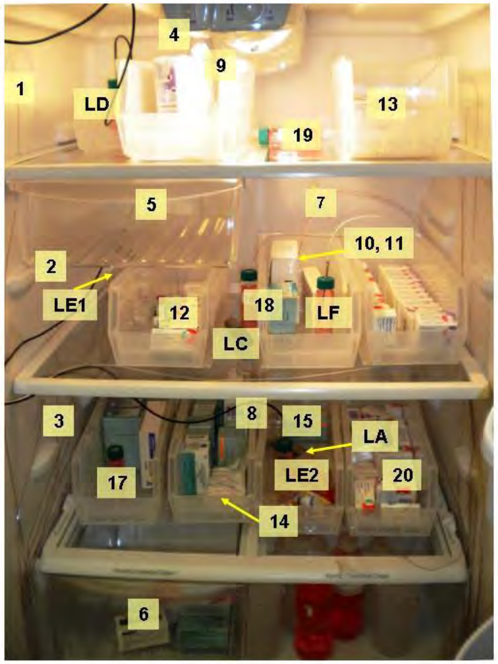
Background and Purpose

- 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

Device name:	U(k=2), C
Thermocouple measurement system	0.12
Data logger A	0.58
Data logger B	1.41
Data logger C	0.67
Data logger D	0.59
Data logger E	0.59

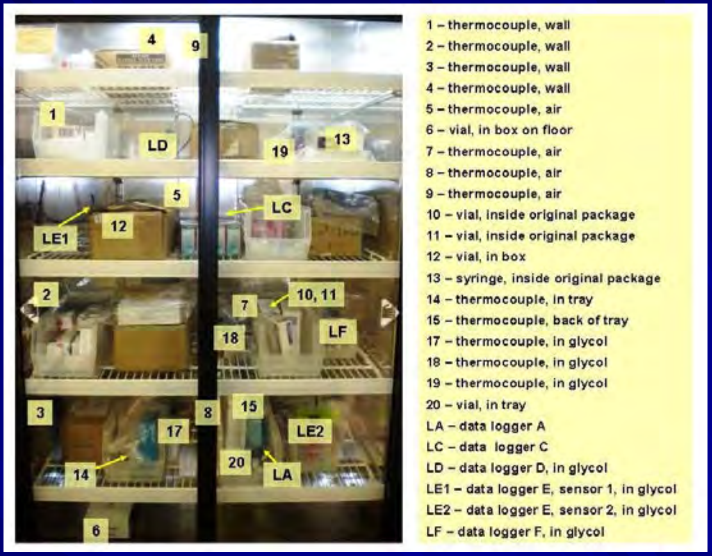


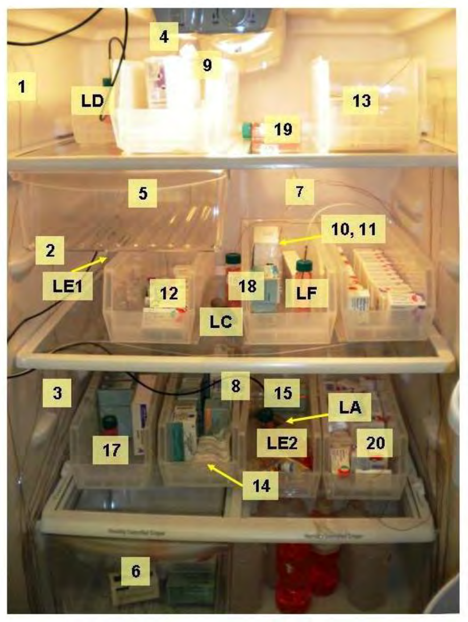
1 – thermocouple, wall
2 – thermocouple, wall
3 – thermocouple, wall
4 – thermocouple, wall
5 – thermocouple, air inside drawer
6 – vial, inside drawer
7 – thermocouple, air
8 – thermocouple, air
9 – thermocouple, air
10 – vial, inside original package
11 – vial, inside original package
12 – vial, in tray
13 – vial, in tray
14 – thermocouple, in tray
15 – thermocouple, back of tray
17 – thermocouple, in glycol
18 – thermocouple, in glycol
19 – thermocouple, in glycol
20 – vial, in tray
LA – data logger A
LC – data logger C
LD – data logger D, in glycol
LE1 – data logger E, sensor 1, in glycol
LE2 – data logger E, sensor 2, in glycol
LF – data logger F, in glycol

- **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**



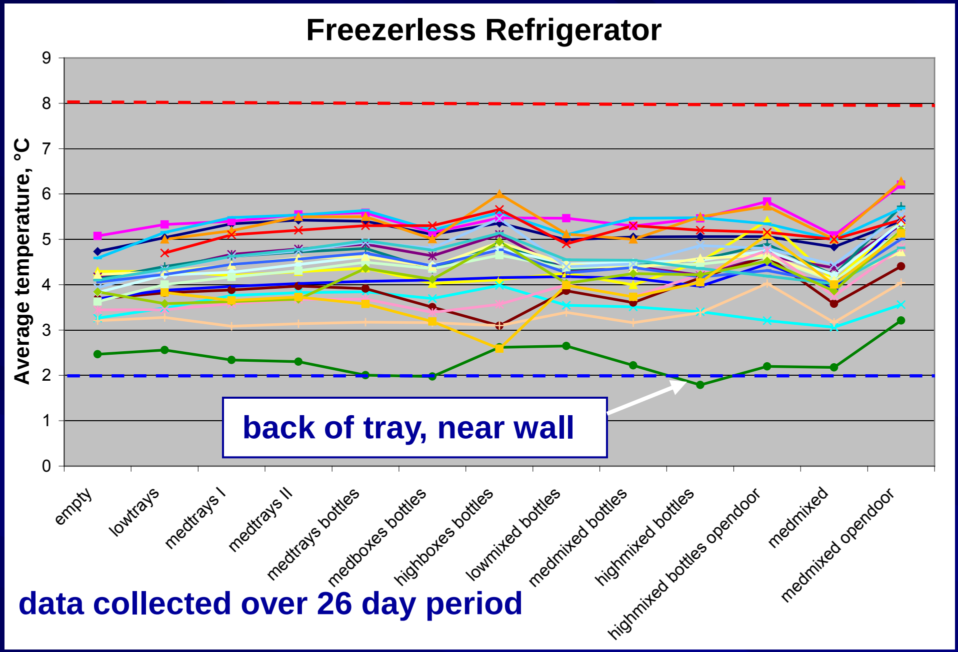


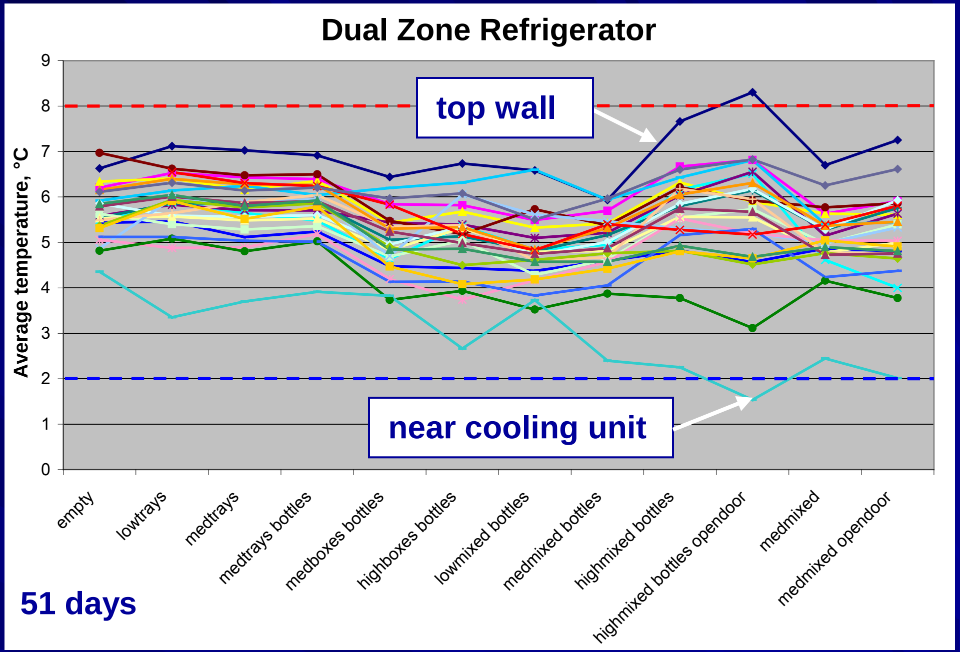
Experimental Method: Measurement Matrix

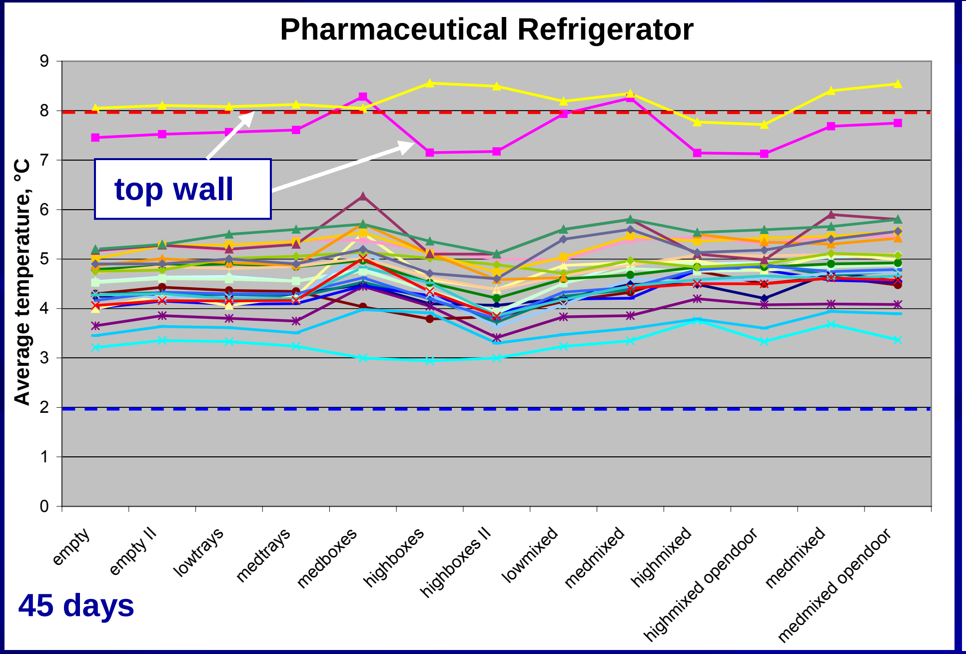
Trial	Load Density			Packing Style			Water Bottles	Measurement Parameters
	Low	Medium	High	Trays	Boxes	Mixed		
1	x			x				normal
2		x		x				normal
3		x		x			x	normal
4		x			x		x	normal
5		x		x			x	normal
6			x		x		x	normal
7	x					x	x	normal
8		x				x	x	normal
9			x			x	x	normal
10			x			x	x	increase room temp
11			x			x	x	periodic door opening
12			x			x	x	power off
13		x				x		normal
14		x				x		increase room temp
15		x				x		periodic door opening
16		x				x		power off
17	x			x				normal
18	x			x				periodic door opening

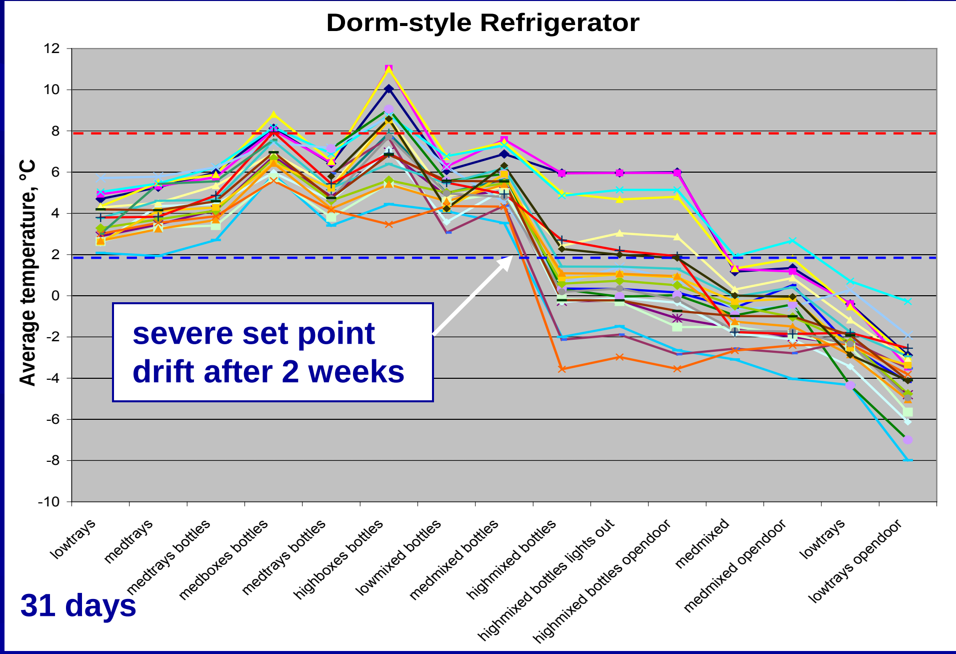
- Cross cutting matrix captures range of normal usage conditions
  - Normalize measurements across different refrigeration systems
- Refrigerator temperature set points left unchanged throughout study
  - "Out of box" midpoint temperature dial settings ~ 4 – 6 °C

Results: temperature stability of refrigerators









Comparison of Refrigerator Performance in Response to Tested Criteria

I. Loading density

Little or No Impact	Negative Impact on Performance
FREEZERLESS • No significant impact on performance	**DUAL ZONE** • Possible minor increase in location-specific temperature variation for high density loads
PHARMACEUTICAL • No significant impact on performance	**DORM-STYLE** • Noticeable impact on performance due to lack of air circulation • High-density loading patterns increased location-specific temperature variation

Low Density Pack | Medium Density Pack | High Density Pack

Density variation pattern in dorm-style fridge

II. Packing style (Trays, Boxes, or Mixed)

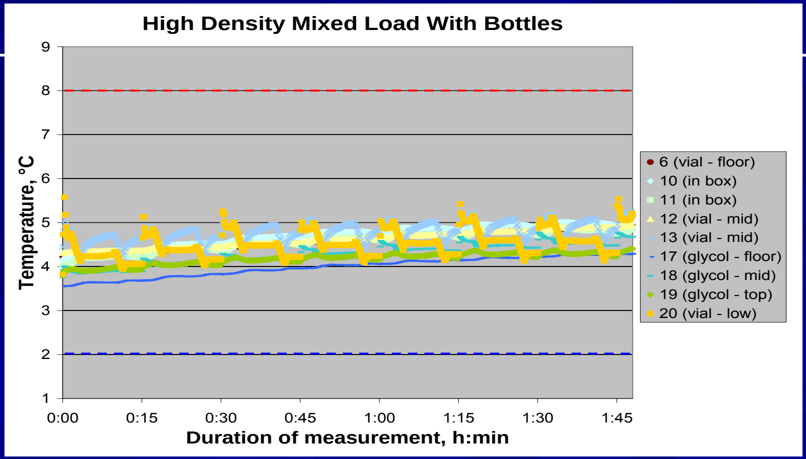
FREEZERLESS, PHARMACEUTICAL & DUAL ZONE	DORM-STYLE
• No noticeable impact on performance	• Indeterminable due to overall poor refrigerator stability

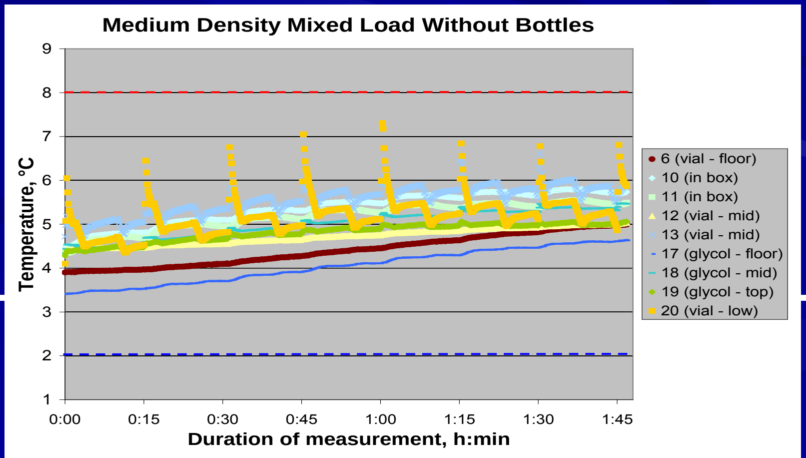
Plastic Trays Cardboard Boxes Mixed Trays and Boxes

Packing style variation in freezerless refrigerator

III. Opening/ closing refrigerator door

Little or No Impact	Negative Impact on Performance
PHARMACEUTICAL • Vial temperatures not significantly affected	**DORM-STYLE** • Most sensors record brief temp increases, overall decrease • Exacerbates already poor temperature control
DUAL ZONE • Small increases in vial temps, but remained within 2 °C to 8 °C	
FREEZERLESS • Small increases in vial temps, but remained within 2 °C to 8 °C • Water bottles in door reduced temperature change. Without bottles, temp increased up to 1.2 °C higher	

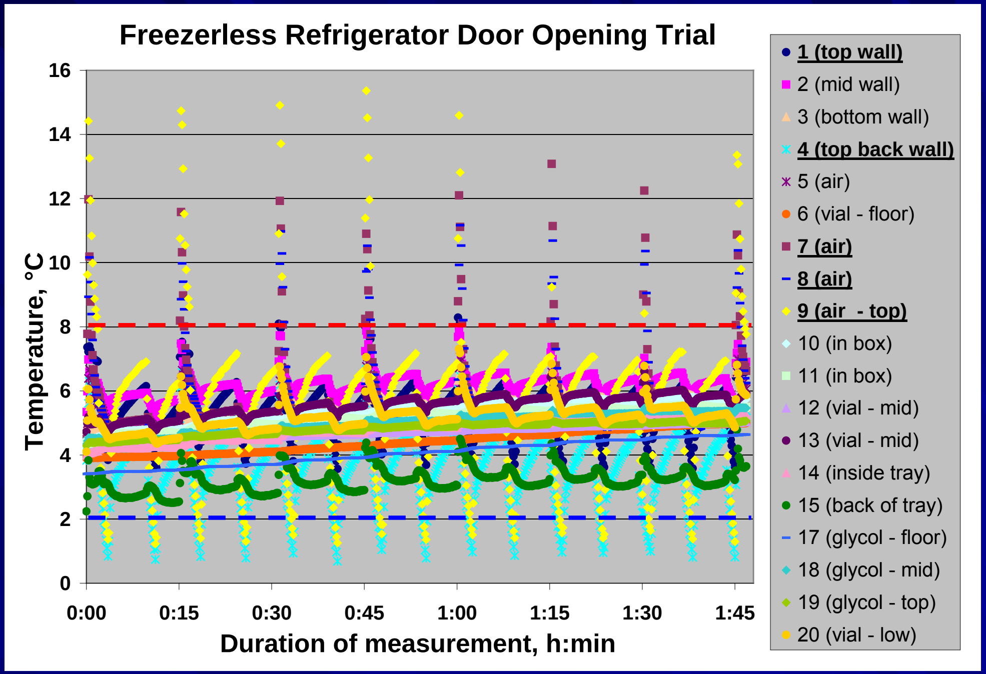




III. Door opening continued

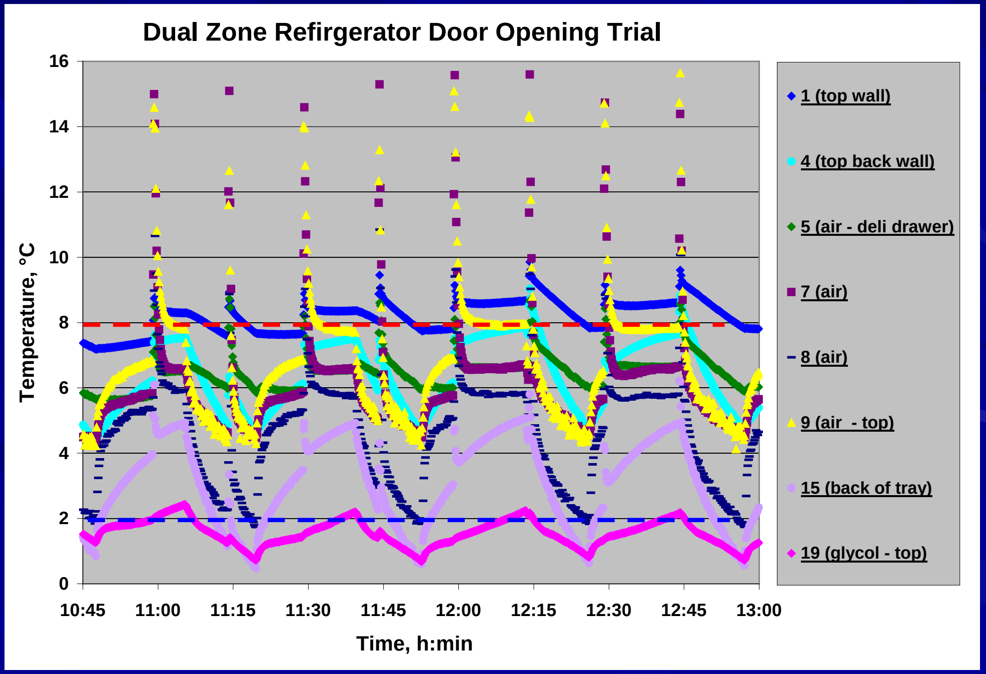
False Alarm Alert: Temperature Monitor Placement Matters!

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



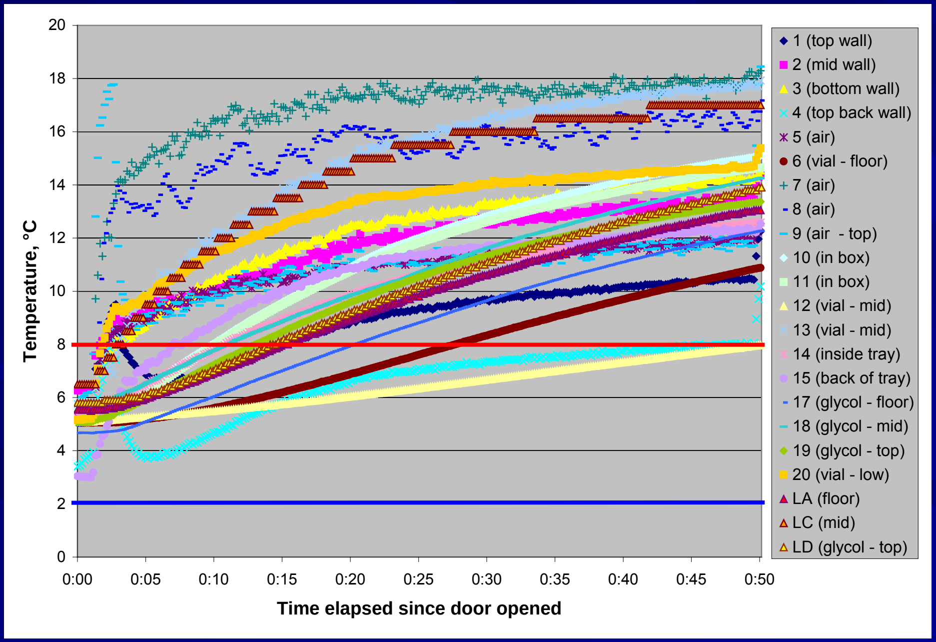
TC #19 (magenta) shows temperature < 2 °C

- 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

Refrigerator type	time until vial temp > 8 °C	maximum vial temp
FREEZERLESS	1 to 49 min	18.6 °C
DUAL ZONE	3 to 60 min	19.5 °C
PHARMACEUTICAL	35 min, most did not exceed	8.7 °C
DORM-STYLE	1 to 5 min	23.8 °C



Freezerless Refrigerator Trial

- 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

V. Increasing room temperature

Little or No Impact on Performance	Negative Impact
FREEZERLESS • Room and fridge temperature directly related • For every 1 °C increase in room temp, fridge temp rises ~0.1 C • Small room temp fluctuations will not greatly impact refrigerator performance	**DORM-STYLE** • Room and fridge temperature directly related • For every 1 °C increase in room temp, fridge temp rises ~0.3 C • Small room temp fluctuations pose greater threat
DUAL ZONE • 1 °C change in ambient temp → fridge temp ± 0.05 °C • Moderate room temp fluctuations will not greatly impact refrigerator performance	
PHARMACEUTICAL • Very small impact on performance • 1 °C change in ambient temp → fridge temp ± 0.02 °C • Able to withstand large room temp fluctuations	

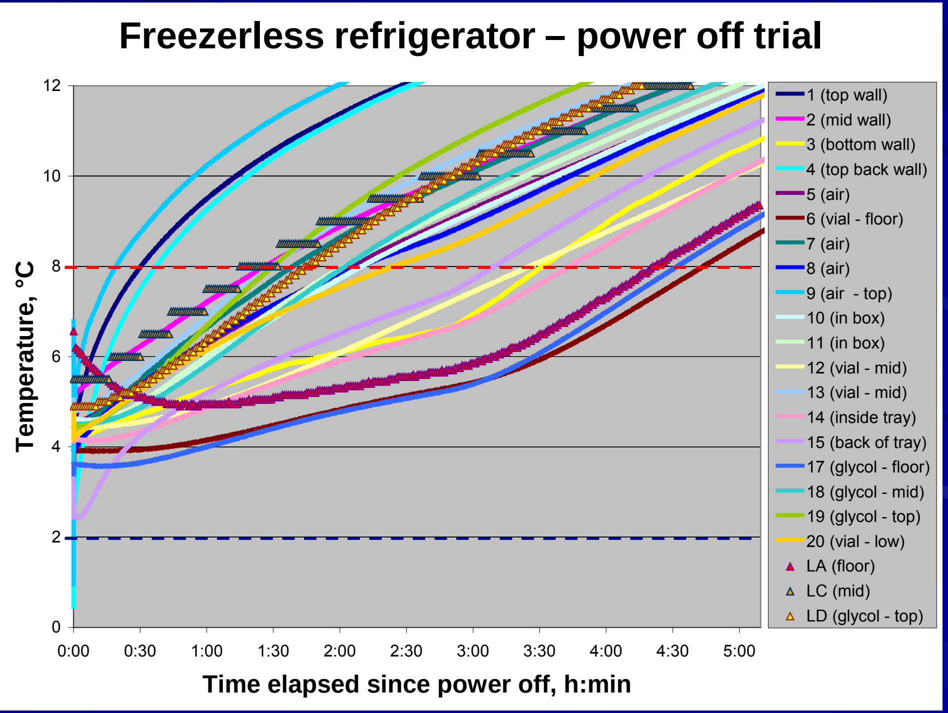
VI. Power outage

Refrigerator type	Time after power off until vial temp > 8 °C	
	without water bottles	with water bottles
FREEZERLESS	1.5 to 4.75 hrs	2 to 8 hrs
DUAL ZONE	1.25 to 4.75 hrs	1.25 to 4.75 hrs
DORM-STYLE	0.75 to 2.5 hrs	1 to 4.25 hrs
PHARMACEUTICAL	0.75 to 2.25 hrs	n/a

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"

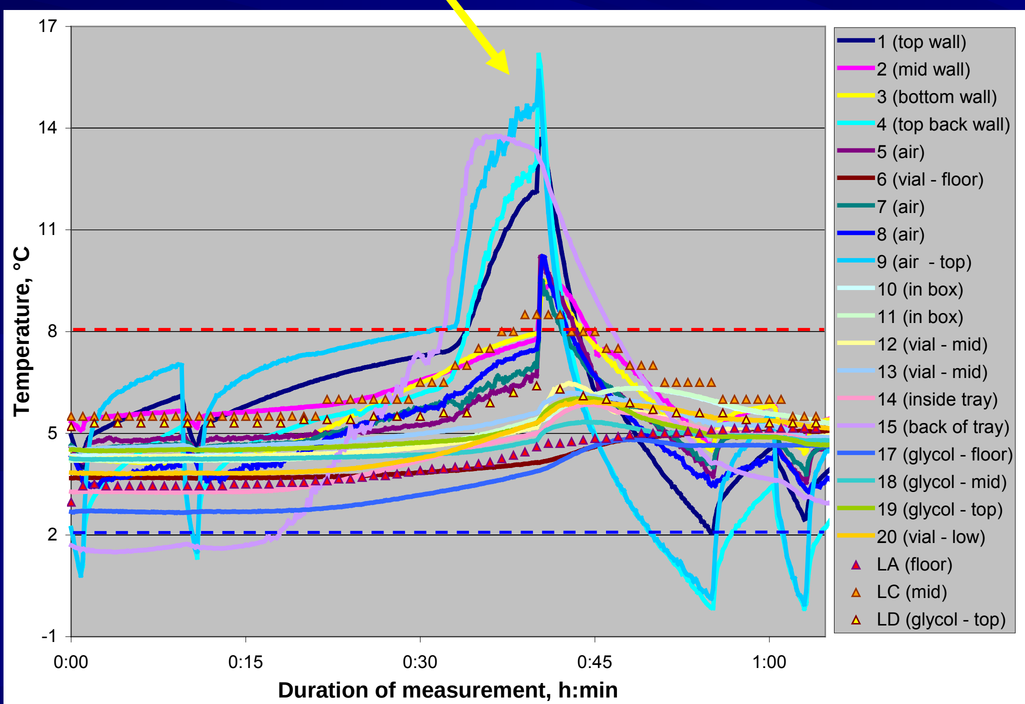
Pharmaceutical fridge suffered from poor insulation provided by glass doors



Allow 6 to 9 hrs for thermal re-equilibration following an outage

VII. Defrost cycle

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



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

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

PHARMACEUTICAL

FREEZERLESS

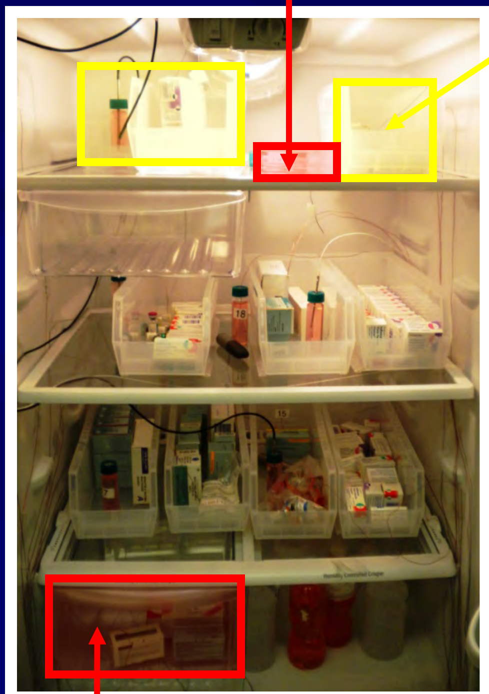
1 – 2 °C colder than main fridge space

Vaccine Vial Storage Methods and Locations

DUAL ZONE	PHARMACEUTICAL	FREEZERLESS

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

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



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

Manufacturer recommends no floor storage, but vial TC maintained at 2 – 8 °C throughout testing

1 – 2 °C colder than main fridge space

Vaccine Vial Storage Methods and Locations

DUAL ZONE | **PHARMACEUTICAL** | **FREEZERLESS**

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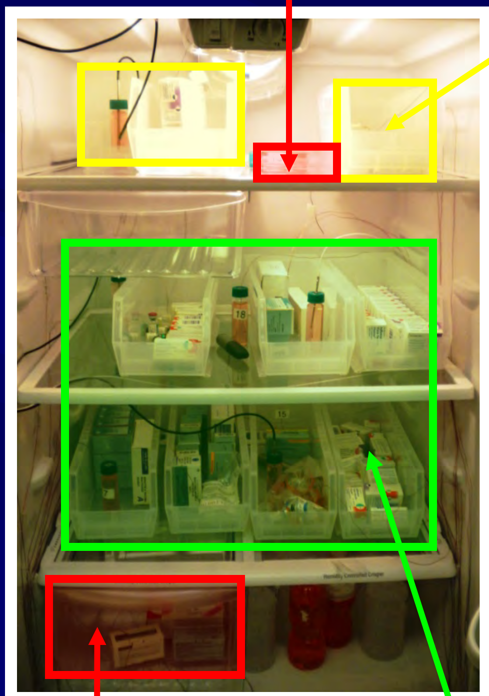


No storage in vegetable crisper: thermally isolated + floor level runs cold

Manufacturer recommends no floor storage, but vial TC maintained at 2 – 8 °C throughout testing

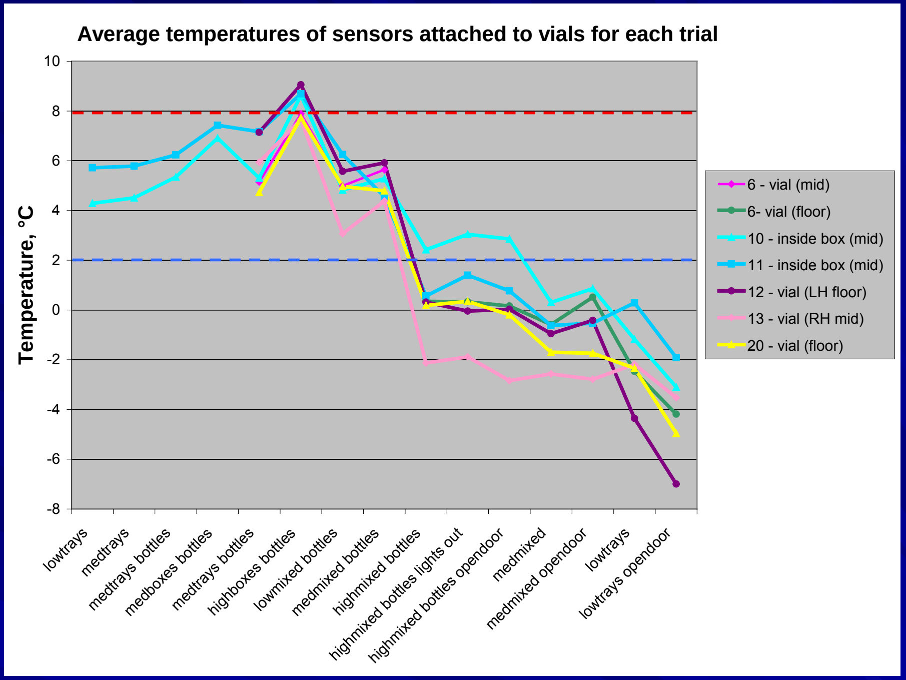
1 – 2 °C colder than main fridge space

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

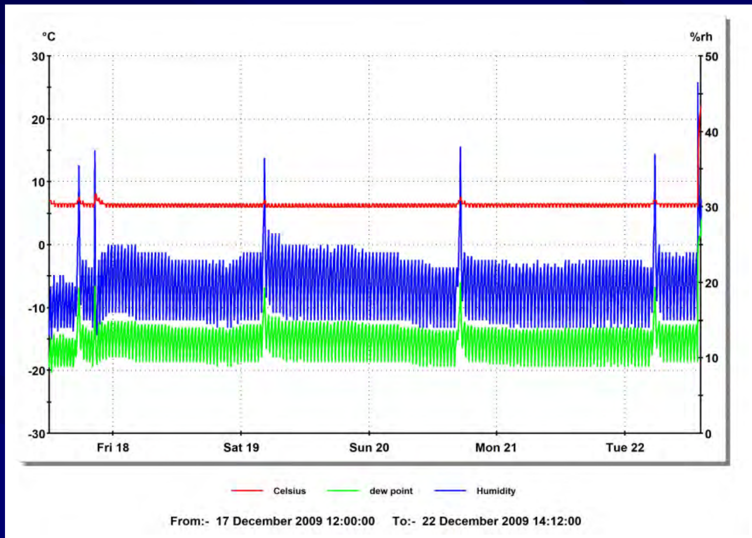
DORM-STYLE REFRIGERATOR

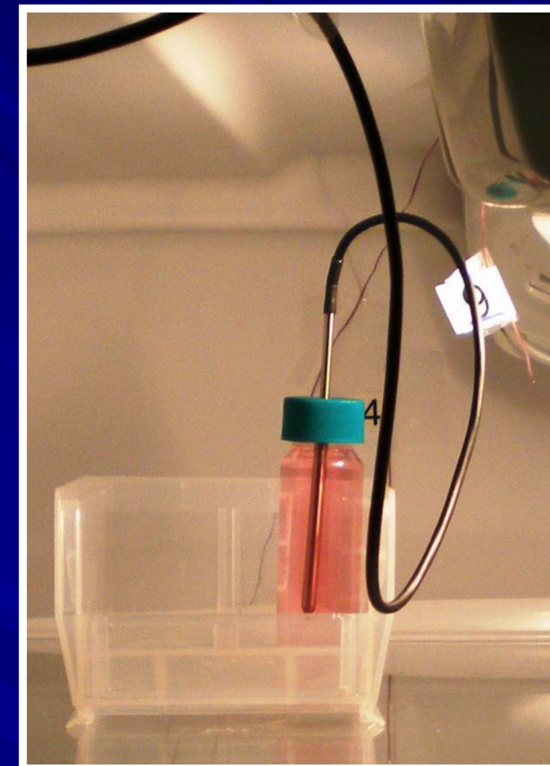
- Consistently unacceptable performance, regardless of vaccine storage location
- Placement on/ near floor, cooling and freezer unit further reduces temperature stability
- No “good” storage area



The dorm-style refrigerator is NOT recommended for vaccine storage under any circumstance!

Vaccine Temperature Monitoring: Electronic Data Loggers





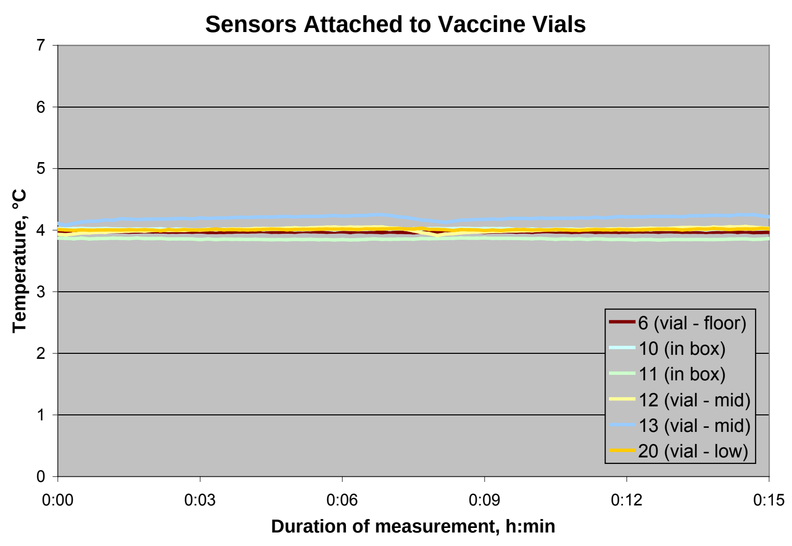
ADVANTAGES

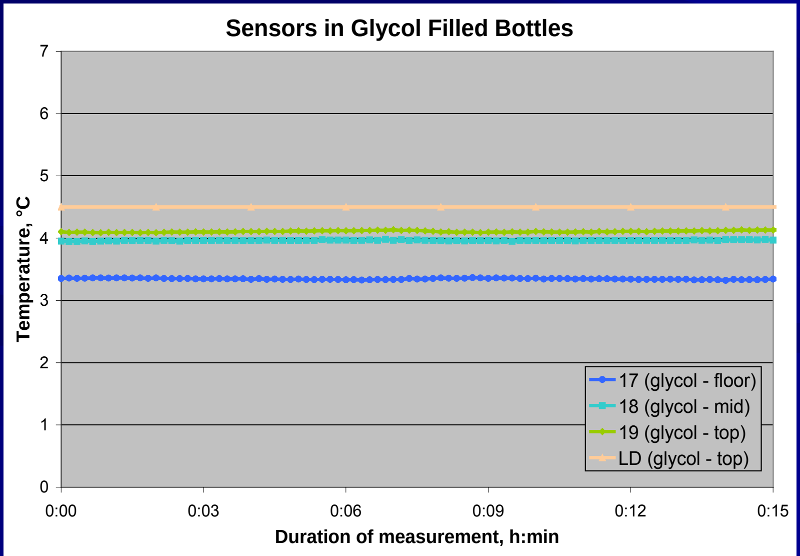
- **Continuous monitoring** - ensures that all thermal excursions are captured, improving confidence in vaccine supply efficacy
- Easy to use
- Quickly analyze results, eliminating time-consuming paperwork
- Archival data stored electronically
- Alarm capabilities, some with email notification mean that 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

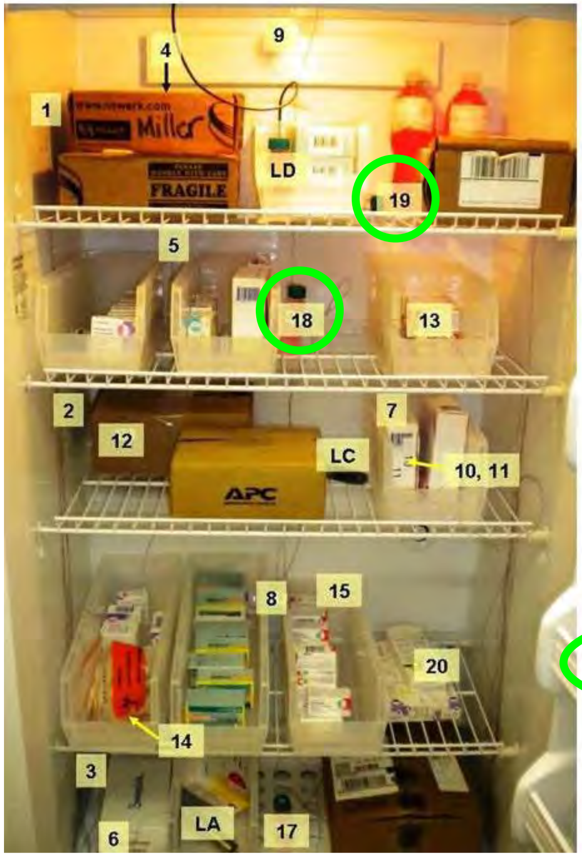
Monitoring Vial Temperature Effectively





Best Location for Temperature Sensors

sensor probe inside glycol-filled bottle, placed in the same locations as vials



1 – thermocouple, wall
2 – thermocouple, wall
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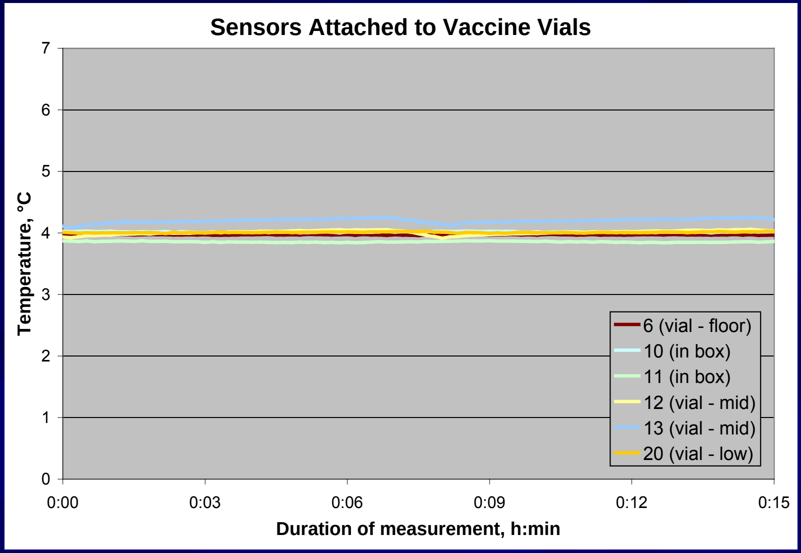
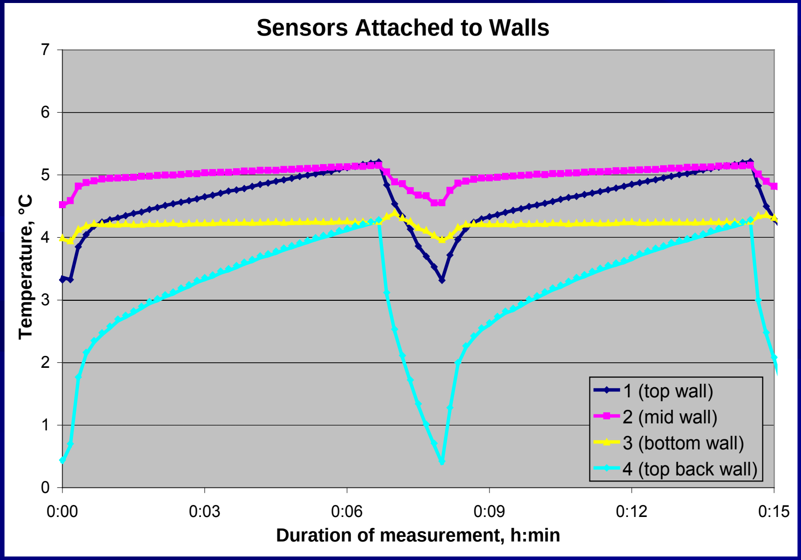
4 – thermocouple, wall
5 – thermocouple, air
6 – vial, inside box
7 – thermocouple, air
8 – thermocouple, air
9 – thermocouple, air
10 – vial, inside original package
11 – vial, inside original package
12 – vial, inside box
13 – vial, in tray
14 – thermocouple, in tray
15 – thermocouple, back of tray
17 – thermocouple, in glycol
18 – thermocouple, in glycol
19 – thermocouple, in glycol
20 – vial, on top of box
LA – data logger A
LC – data logger C
LD – data logger D, in glycol

Monitoring Vial Temperature Effectively



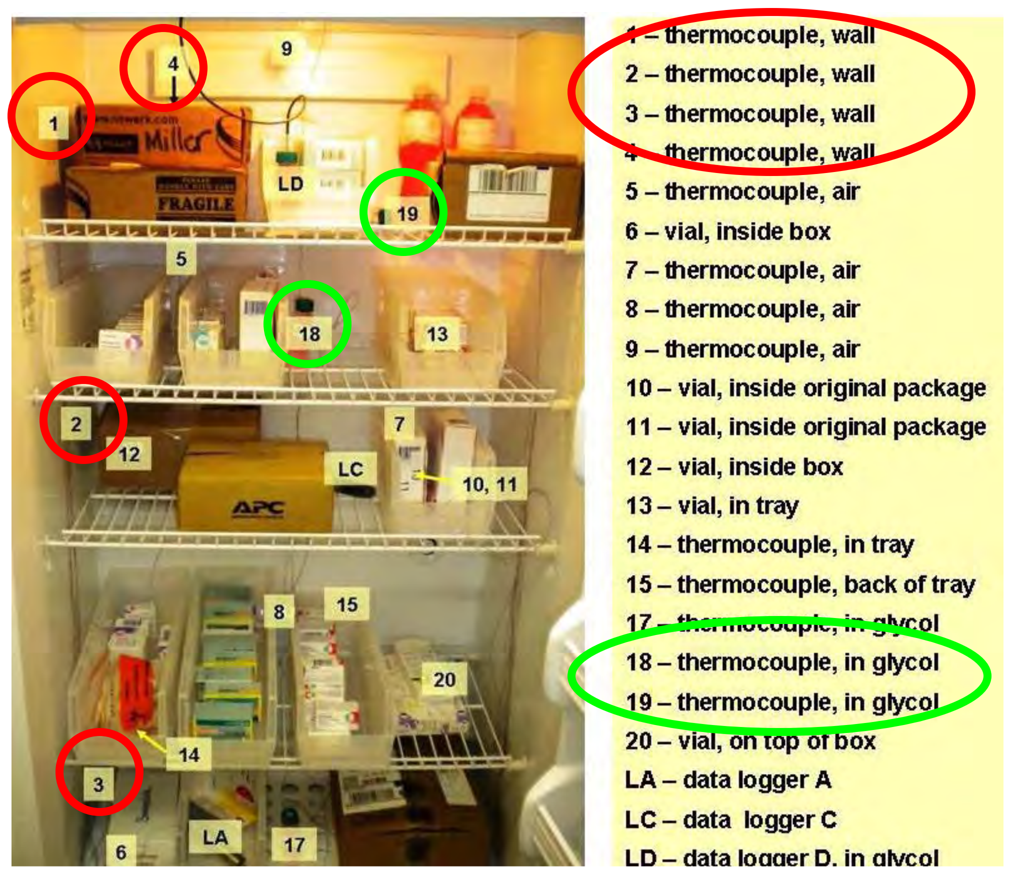


Best Location for Temperature Sensors

sensor probe inside glycol-filled bottle, placed in the same locations as vials

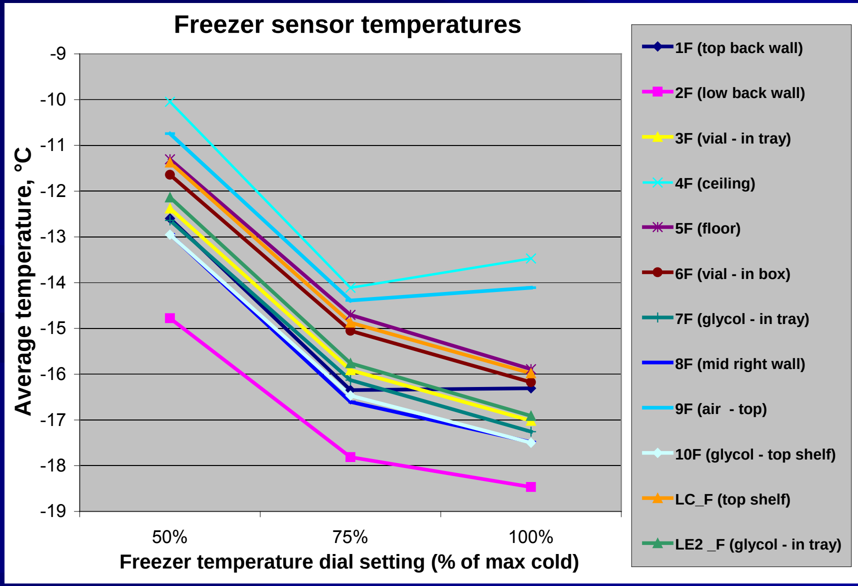
Worst Location for Temperature Sensors

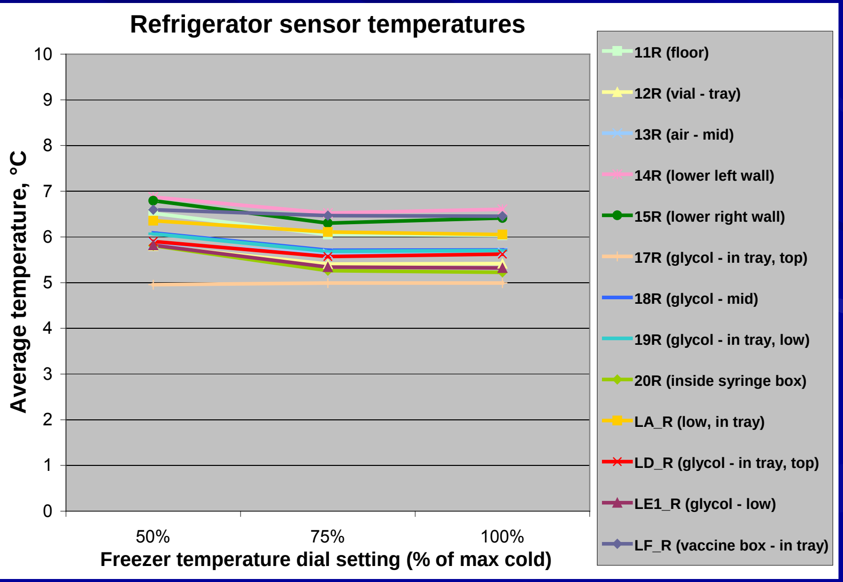
Sensors attached to walls



Dual Zone Case Study:
Does freezer setting affect refrigerator performance?

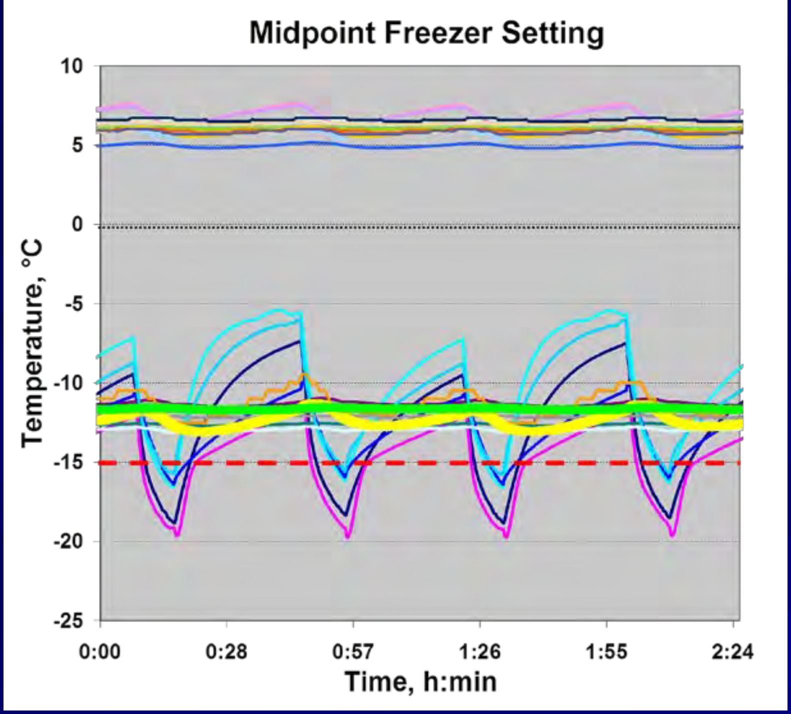
- Sensors arranged throughout both freezer and refrigerator compartments
- Varied freezer set point dial, refrigerator temp setting left unchanged
  - 50%, 75%, and 100% (maximum cold setting)
- Change in refrigerator sensor temperatures ~10% temperature drop recorded by freezer sensors

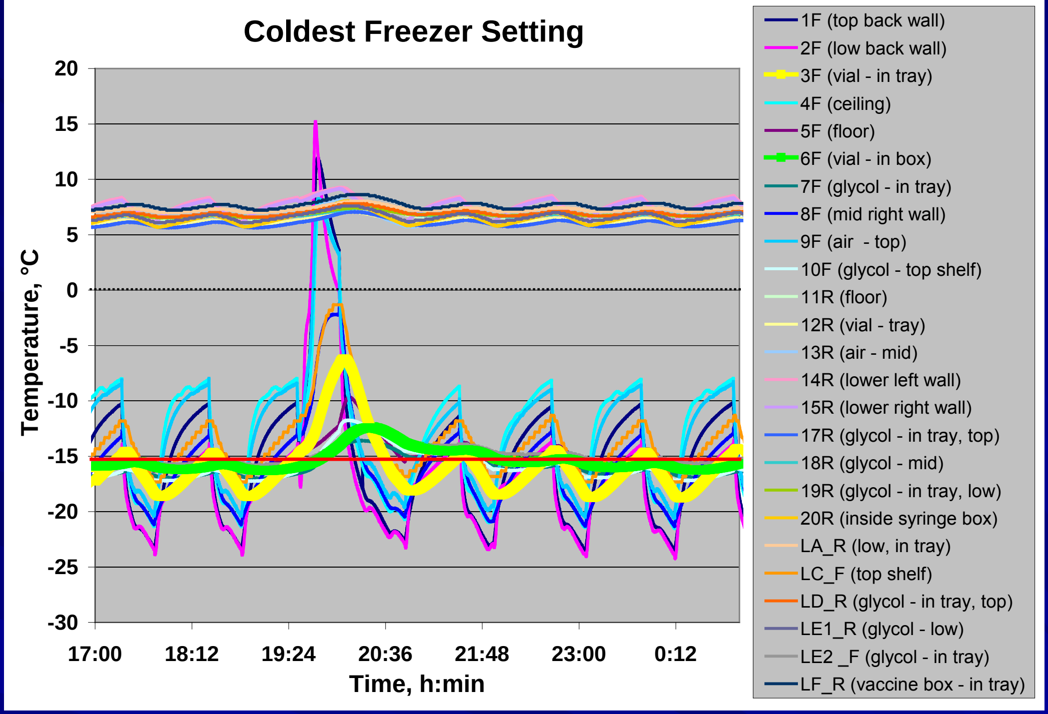




Dual Zone Case Study:

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

Upper temperature limit for frozen vaccine storage = -15 °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

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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