

Thermostability of Vaccines



Why are all vaccines sensitive to heat and some to freezing?

Why is thermostability of vaccine important?

What can be done to improve the thermostability of vaccines?

Goals of stability studies in product development

- Establish product stability characteristics:
 - Understand factors that influence stability → strategies to minimize product decay during storage
 - Generate real time and real condition stability data → support proposed shelf life for licensure
 - Establish forced degradation characteristics → support post-licensure manufacturing changes
 - Generate data at temperatures relevant to CTC

From: WHO Informal Consultation on Scientific and Regulatory Considerations on Stability of Vaccines under a Controlled Temperature Chain

Dean Smith & Tong Wu, Ph.D., Health Canada
4 June 2013, PEI, Langen, Germany

General considerations for stability studies

- Adequate testing points → rates of product decay may differ at different intervals over the shelf-life
- Potency assessment using a battery of tests → note that all tests have limitations
- Data analysis:
 - Note trends, not just compliance with specifications
 - Determine the rate of product decay using appropriate statistical methods: ***explore alternate approaches***

From: WHO Informal Consultation on Scientific and Regulatory Considerations on Stability of Vaccines under a Controlled Temperature Chain

Dean Smith & Tong Wu, Ph.D., Health Canada
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Stability-indicating parameters

- Potency: most critical for vaccines
- Safety
 - Residual toxin / reversibility of toxoid
 - Toxicity of degradation products
- Additional parameters
 - Moisture content for lyophilized vaccines:
 - pH
 - Adsorption to alum *or* other adjuvant characteristics

From: WHO Informal Consultation on Scientific and Regulatory Considerations on Stability of Vaccines under a Controlled Temperature Chain

Dean Smith & Tong Wu, Ph.D., Health Canada
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Vaccine Antigens: Complex Macromolecular Structures

Review: Kumru O et al, Biologicals 42: 237 (2014)

Live, Attenuated Virus:

Measles, Mumps, Rubella, Varicella, Yellow Fever,

Vaccinia, Rotavirus, Polio, Adenovirus

Inactivated Virus:

Hepatitis A, Polio, Influenza

Recombinant Virus-like Particles:

Human Papillomavirus, Hepatitis B

Live, Attenuated Bacteria:

BCG (tuberculosis), Typhoid Fever

Inactivated Bacteria:

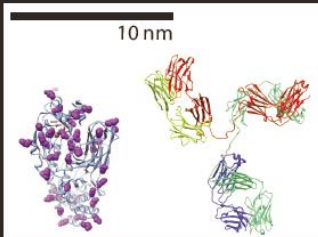
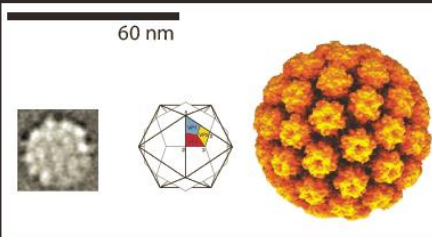
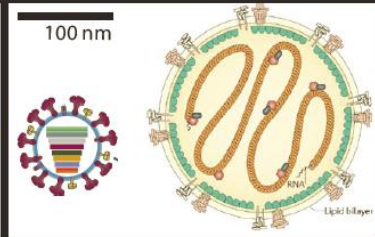
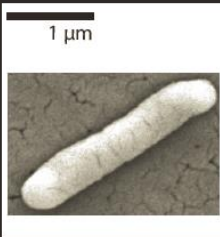
Anthrax, wPertussis

Bacterial (proteins):

aPertussis, Diphtheria, Tetanus

Bacterial (polysaccharides):

*Haemophilus B, Pneumonia, Meningitis
(often linked to protein carriers)*

							
5-10 nm	10 nm	22 nm	30 nm	60 nm	100 nm	250 nm	2-4 μm
85-110 kDa	150 kDa						
CRM-197	IgG	HBsAg VLP	Poliovirus	HPV VLP	Influenza virus	Measles virus	Salmonella typhi

Examples of Commercial Vaccine Dosage Forms

Review: Kumru O et al, Biologicals 42: 237 (2014)

	<u>Adjuvant</u>	<u>Formulation</u>	<u>Delivery</u>
<u>Recombinant or Inactivated Viral Vaccines</u> <i>HPV, Hepatitis B</i> <i>Hepatitis A, Polio, Influenza</i>	Aluminum (some with new adjuvants)	Liquid	Injection
<u>Inactivated, Purified or Conjugated Bacterial Vaccines</u> <i>wPertussis, Anthrax</i> <i>aPertussis, Diphtheria, Tetanus, Anthrax</i> <i>Haemophilus B, Pneumonia, Meningitis</i> <i>(many linked to protein carriers)</i>	Aluminum	Liquid	Injection
<u>Live, Attenuated Viral Vaccines</u> <i>Measles, Mumps, Rubella, Varicella,</i> <i>Yellow Fever, Vaccinia</i> <i>Rotavirus, Polio,</i> <i>Influenza</i> <i>Adenovirus</i>	None	Lyophilized Liquid Liquid Lyo/Tablet	Injection Oral Nasal Oral
<u>Live, Attenuated Bacterial Vaccines</u> <i>BCG (tuberculosis), Typhoid Fever</i> Oral	None	Lyophilized	Injection,

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Vaccine Distribution World-Wide: Stability Issues in the “Vaccine Cold Chain”

Review: Kumru O et al, Biologicals 42: 237 (2014)

***Freeze
Sensitive?***

***Heat
Sensitive?***

Live Viral Vaccines

- / +

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Live Bacterial Vaccines

- / +

+++

***Recombinant or Inactive
Viral Vaccines***

+++

- / +

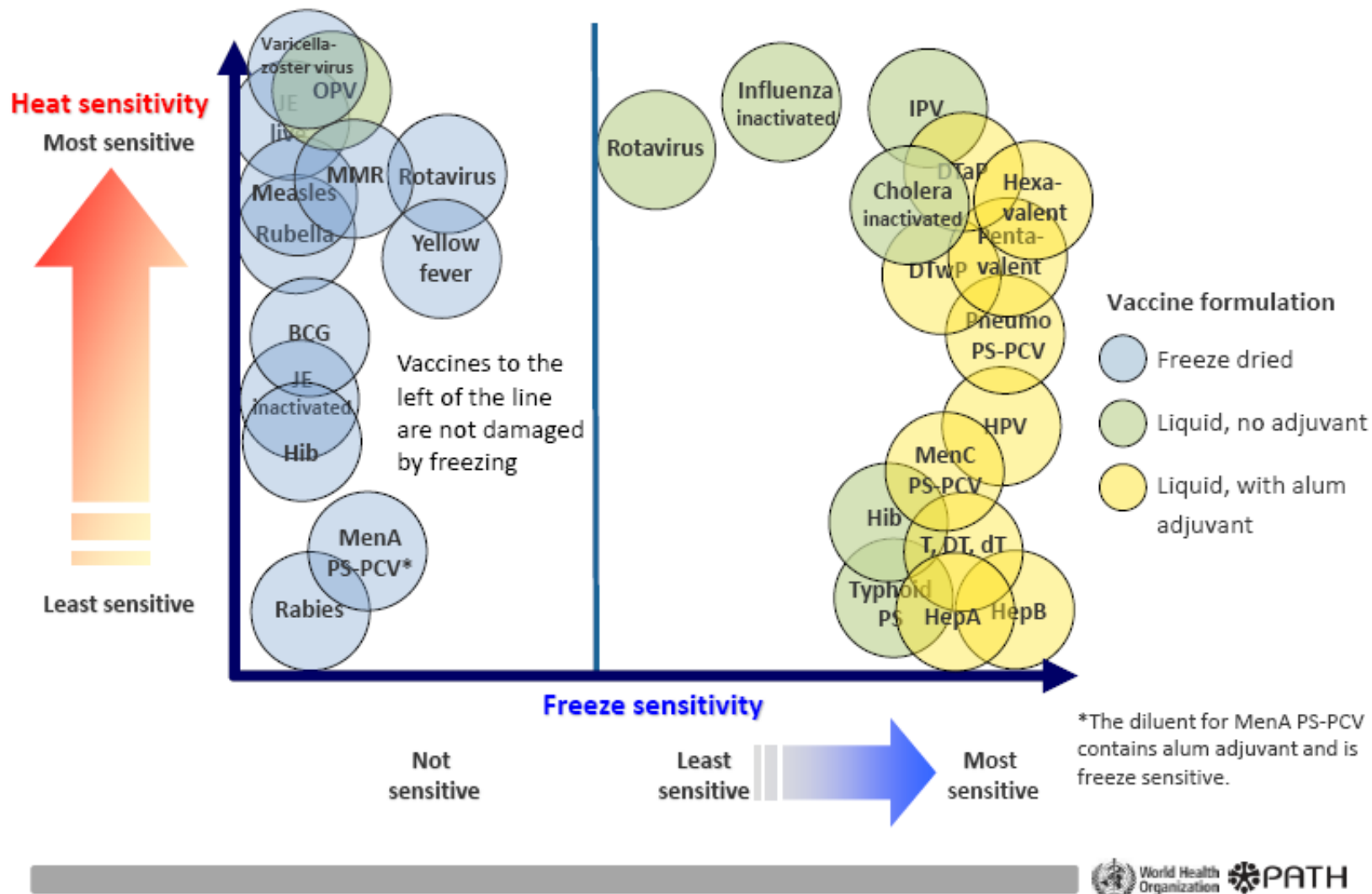
***Inactivated, Purified or Conjugate
Bacterial Vaccines***

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- / +

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Temperature sensitivity of vaccines



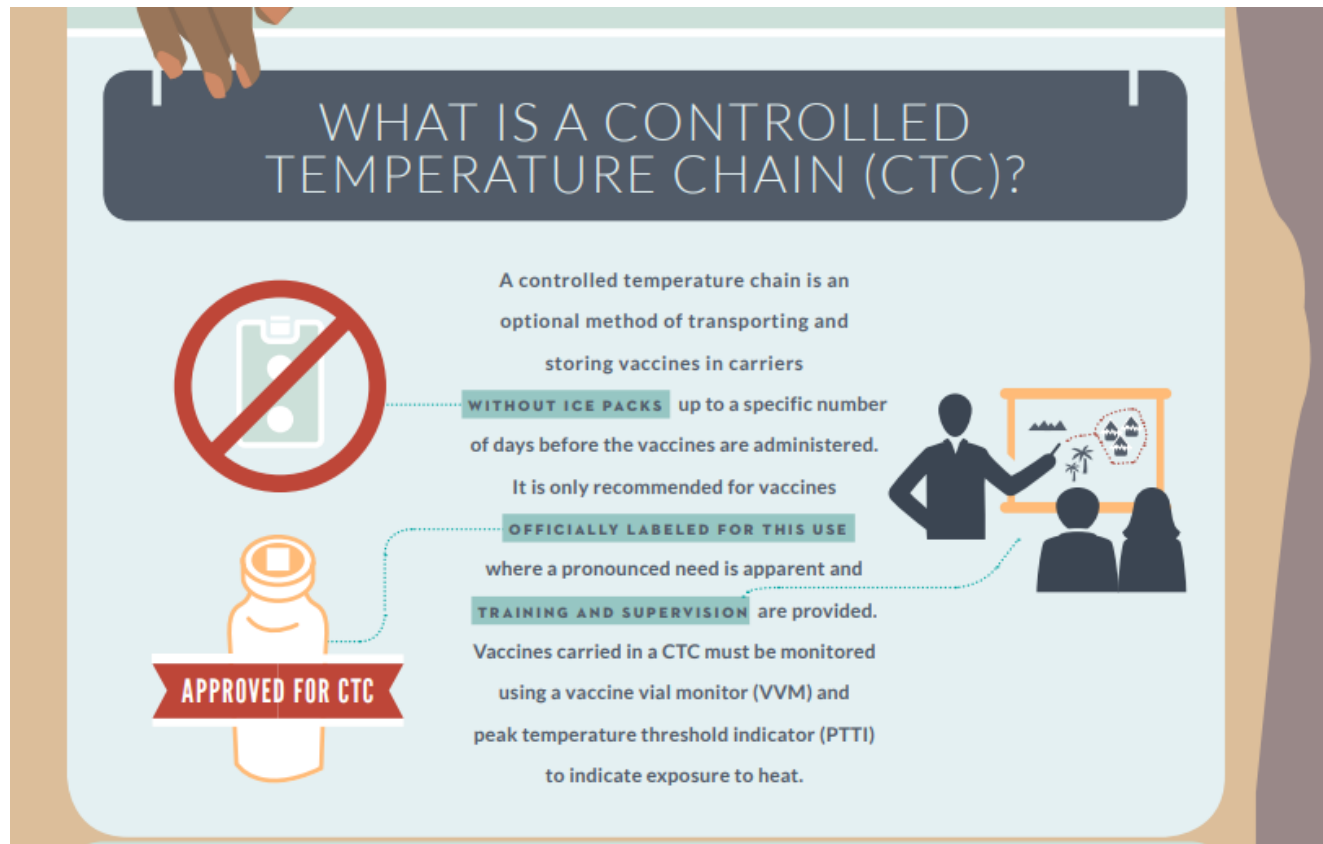
B. Schreiber & D. Chang Blanc - TechNet Bangkok 2015

**The innovation of the
Controlled
Temperature
Chain (CTC) –
where do we
go from here?**



**World Health
Organization**

Controlled Temperature Chain: No Ice packs for days



Challenge for vaccine stability, safety and efficacy

Overview of Novel Approaches to Stabilize Vaccines

Formulation Composition

- New additives
- New approaches to identify combinations of additives

Formulation Processing Technologies

- Novel drying or delivery technologies

Novel Antigens with Improved Stability

- Molecular design of current antigens
- New macromolecules: e.g., DNA/RNA vaccines

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Analysis of Some Interesting Approaches Formulation Composition

Past Examples

- Trehalose in the 1980s
- Deuterium Oxide in the 1990s
- Polyethylene glycol in the 2000s

Formulation and Rationale

Lyophilized for heat stability

Liquid for heat stability

Liquid for freeze stability of alum vaccines

Examples from Today

- | | | |
|-------------------------|--------------|---|
| • Silk protein | Vaxess | http://www.vaxess.com |
| • Buffer mixtures | Arecor | http://www.arecor.com |
| • Sucrose and raffinose | Stabilitech | http://www.stabilitech.co.uk |
| • Lipid mixtures | VBI Vaccines | http://www.vbivaccines.com |

Overall, novel additives have had a limited impact to date...

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Novel approaches to identify stabilizers

Increasing number of research papers on the use of high throughput screening technologies:

- Empirically identify unique combinations of common excipients
- Empirically focus on specific vaccine and specific stress
- Most likely will become useful tool in future, but more from point of view of resources, time, and potentially patents

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Novel drying and delivery technologies

General Examples

- Freeze-drying
- Spray-drying
- Foam-drying
- Microneedles

Formulation and Rationale

Lyophilized formulations of aluminum vaccines
Lyophilized for heat stability
Lyophilized for heat stability
Novel delivery technology

Specific Examples:

PATH	http://sites.path.org/vpfst/product-stability/heat-stability
Sologenix	http://www.soligenix.com
Aridis	http://www.aridispharma.com
Aktiv-dry	http://www.aktiv-dry.com
Nova Labs	http://www.novalabs.co.uk

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Novel Antigens with Improved Stability

- Molecular design to improve stability of antigens
 - Many research papers and programs to improve antigen stability at molecular level
 - Long term research programs...
- New classes of macromolecular antigens with potential of improved stability
 - e.g., commercial polysaccharide and protein VLP vaccines are more stable than viral vaccines
 - e.g., peptide and nucleic vaccine candidates. RNA as vaccine candidates include:
 - Curevac <http://www.curevac.com>
 - Moderna <http://modernatx.com/>
 - Novartis Vaccines (now GSK...)

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Highly Stable Rotavirus Vaccine – 540 days at 37°C



Stability of heat stable, live attenuated Rotavirus vaccine (ROTASIIL®)

Sameer P. Naik, Jagdish K. Zade*, Rajendra N. Sabale, Sambhaji S. Pisal, Ravi Menon, Subhash G. Bankar, Sunil Gairola, Rajeev M. Dhere

Serum Institute of India PVT LTD, 212/2, Hadapsar, Pune 411028, India

8 °C up to six hours as, at higher temperatures; any micro-organism introduced during the reconstitution process could multiply.

The thermo-stability of ROTASIIL®, ironically, has thrown up a new challenge in terms of vaccine vial monitors (VVM). The presently available VVM portfolio (Max VVM30: 30 days at 37 °C) does not begin to cover the extreme thermo stability of ROTASIIL which is 18 months- (540 days) at 37 °C. Efforts to develop a more appropriate VVM are on-going.

It has been already noted that there is remarkable reduction in mortality from diarrheal disease after vaccine introduction in



Requirements to Implement

*From a Published Review
from PATH...*

Chen D, Kristensen D, Expert Rev Vaccines. 2009 May;8(5):547-57. Opportunities and challenges of developing thermostable vaccines

Table 3. Challenges involved in developing thermostable vaccines.

Issue	Challenges	Consequences and solutions
Regulatory		
Addition of novel stabilizers, adjuvants or excipients	Novel components might be unproven in terms of safety, immunogenicity or quality of raw ingredients	Additional regulatory scrutiny might be applied; use excipients of proven safety whenever possible
Introduction of novel production processes or novel equipment	Production facilities need to comply with good manufacturing practices in order to produce material for clinical trials	Additional regulatory scrutiny might be applied
Healthy infants are the target population	The tolerance of serious adverse events in healthy infants is extremely low	Use excipients of proven safety if possible; new formulations might not be adopted
Convincing demonstration of safety will be required	Very rare, serious adverse events can be detected only in very large clinical trials	Postmarketing surveillance will be required
Technical		
Formulation development might be complex	There is no predictive rapid potency assay; many diseases/vaccines do not have good predictive preclinical models	Lack of preclinical models might increase amount of clinical testing needed for approval
Demonstrating clinical efficacy of reformulated product	There is still a lack of validated clinical end points and biomarkers (including assays of immune function) for many diseases	Longer, larger clinical trials with clinical end points might be needed; noninferiority trials comparing immunogenicity with existing vaccine might be possible
Reformulation of vaccines that are used in combinations	The components of combination vaccines can interact differently with each other and also with excipients	Extensive development and testing can be required, including noninferiority clinical studies
Commercial & intellectual property		
Costs associated with developing and obtaining registration for reformulated vaccines are large and are not compatible with the low prices paid for vaccines for public-sector markets	Lack of commercial incentive for manufacturers to produce improved formulations	Procurement incentives might be required to convince vaccine manufacturers to invest
It is often difficult to quantify the problem (e.g., health and economic impact of vaccine instability) and the potential benefits of the stable vaccines	Improvements such as thermostability might not lead to a sufficient price premium to cover the development costs	Economic analyses of the impact of the stability improvement upon the whole immunization system could be useful; advocacy might be needed around both the problem and solution to proceed
Vaccine producer IP	The need to protect IP means that manufacturers are often reluctant or unable to share critical information (e.g., formulations, production methods and assays) necessary to develop improvements to vaccines outside of individual vaccine-manufacturing facilities	R&D might be limited to individual manufacturers and the pace of development driven by their interests
Technology IP	The owners of stabilization technologies must be convinced of public-sector health priorities to ensure that such technologies are made broadly available and do not adversely impact the affordability of public-sector vaccines	Organizations acting on behalf of public-sector interests can create contract mechanisms to protect IP on behalf of the public sector; advocacy might be needed around both the problem and solution to proceed
IP: Intellectual property.		

Links to Pertinent Publications

ORIGINAL ARTICLE

Visual Indicators on Vaccine Boxes as Early Warning Tools to Identify Potential Freeze Damage

Ronald Argenf MD, PhD,*†, Niro Wood,† Mario C. Clerneck,‡ and Diane Tipping§

Background: The aim of this study was to determine whether the use of visual focus indicators on monitors could assist health care providers in identifying monitors that may have been exposed to potentially damaging temperatures.

Methods: Twenty-seven sites in Connecticut involved in the Vaccine for Children Program participated. In addition to standard procedures, visual focus indicators (VFCIndicator® I, Sorpline Corporation, Moon Palace, NY) were affixed to each box of vaccine that required refrigeration be-

Results: During the 24 weeks, a 3.27 times experimental trigger rate found from indicator events in 40 of the 47 trigger types. A total of 66 triggered device indicator events occurred in all 4 types of triggers used. Only 1

of the linear event was identified by a temperature monitoring device. Temperature recorded in vaccine data logs before, from vaccine event onset until the 37°F to 40°F (2°C to 10°C) range in all but 1 instance. A total of 36,054 doses of linear event vaccine were stored at the time of a third dose vaccine event. Observed since these instances

in a visual trace indicator (over-impregnated, visual trace) and no trace found on brown-containing MSW dose (14.0% of total dose). Of all doses tested, 14,373 doses (80.5%) were of light brown, sensitive variety; 1769 of those doses (12.5%) had suggested indicators on the boxes. Conclusion: Visual trace indicators are useful to the early identification

Key Words: racing, horse, indicator, exercise, storage, vaccine

(Japet De Cille Pease 201506: 64-66)

cost of \$1.6 billion.² The VCP program is administered by the US Centers for Disease Control and Prevention (CDC).

For vaccines to be effective, they must be properly stored and handled from the time of manufacture through delivery to the storage in the provider's office.⁵ Whereas exposure to any inappropriate conditions, including excessive heat or cold exposure

can affect potency of subunit vaccines, a single exposure to freezing temperatures will destroy some vaccines, such as lipid vaccines that contain an aluminum adjuvant.¹ Should loss of potency occur in patients who receive the vaccine will not be protective against vaccine-preventable diseases.

In recent years, there have been indications that storage and handling of vaccines within required temperature ranges, including shipment of vaccines from the distributor to a hospital,¹⁰ were an ongoing problem in the United States. A survey conducted in

2004 by the Association of Communication Managers (ACM) demonstrated considerable variability among city and state communication programs in the United States.² A field survey conducted by the California Department of Public Health found that 4 hospitals in Santa Jose, Calif., had shared vaccine resources at least 1

in Santa Ana, Calif., had died during outbreaks at lower than freezing temperatures for 7 months in 2000. As a result, 164 newborns were given potentially defective hepatitis B vaccine. In 2003, another investigation found a significant 79% correlation between a 75% of vaccinee schizophrenia in Wisconsin's community

health centers that experienced prolonged freezing temperatures and that region's rate of pneumonia.¹ In 2004, the Hartford (Connecticut) HealthCare Medical Group reported that the effective rates of SMO vaccinations given to SLD patients since January 2003 were 90%, 80%, and 80% for patients with SLD, SLD with



Biologicals

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Free/Share

Vaccine instability in the cold chain: Mechanisms, analysis and formulation strategies

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FIGURE 1 | **Flowchart**

doi:10.1016/j.biologicals.2014.05.002

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Tools and approaches to ensure quality of vaccines throughout the cold chain

Expert Rev. Vaccines 12(7): 843-854 (2013)

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The Deamed Program on Immunization was designed 40 years ago for two types of vaccines. Those that are heat stable but freeze sensitive and those that are sensitive to freezing but heat labile. A cold chain was developed for transport and storage of such vaccines and established in all countries, despite limited access to resources and electricity in the poorest areas. However, cold chain problems occur in all countries. Recent changes to vaccines and vaccine handling include development and introduction of new vaccines with a wide range of stability characteristics. The need for a new cold chain system for these vaccines is becoming a free threat, development of regulatory pathways for both vaccine development and the supply chain, and emergence of new temperature monitoring devices that can pinpoint and avoid problems. With such tools, public health groups have now encouraged vaccine manufacturers to provide for use in flexible cold chains and these tools should be considered for future updates.



Thank you!!!