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
4 June 2013, PEI, Langen, Germany

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
4 June 2013, PEI, Langen, Germany

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*

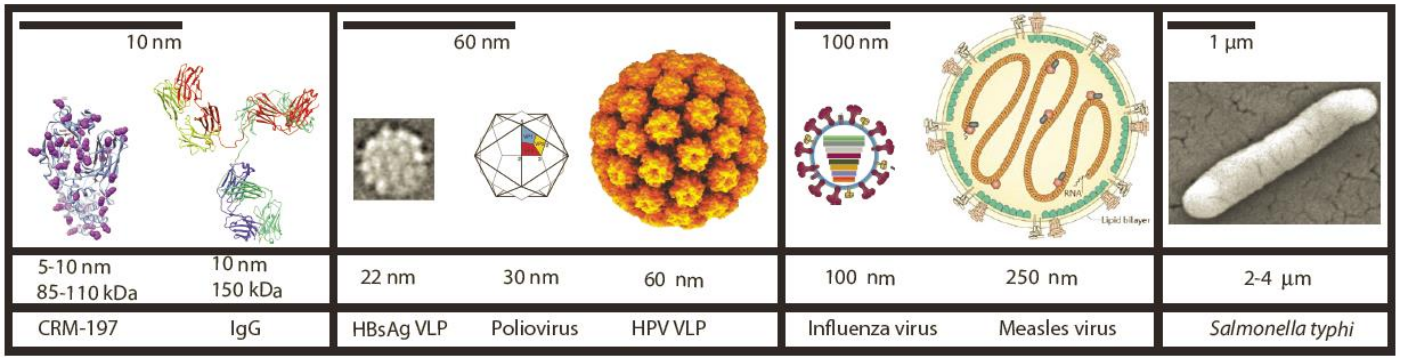
Recombinant Virus-like Particles: *Human Papillomavirus, Hepatitis B*

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)*



Examples of Commercial Vaccine Dosage Forms

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

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

Slide Courtesy of Prof. David Volkin, Univ of Kansas

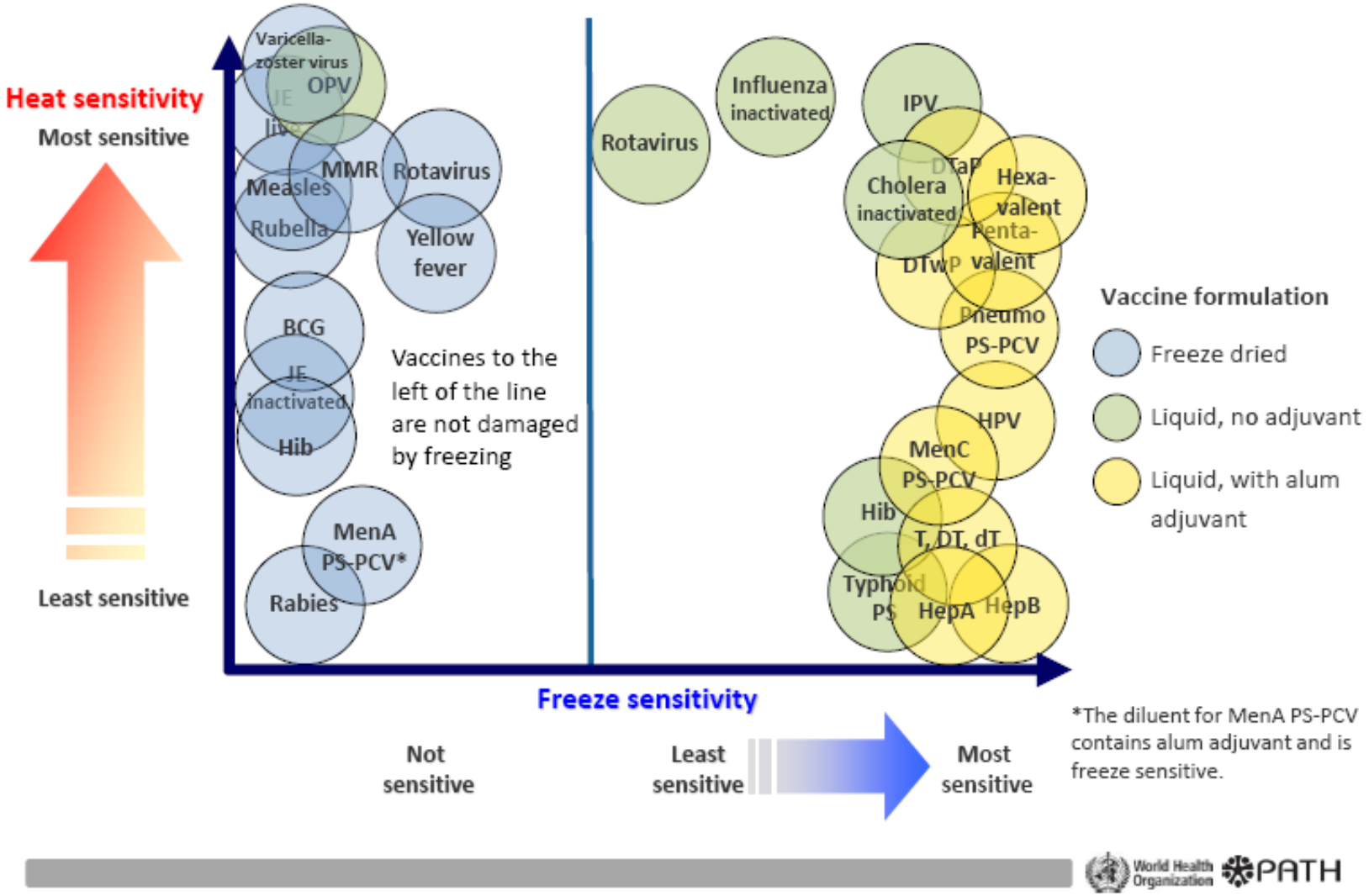
Vaccine Distribution World-Wide: Stability Issues in the "Vaccine Cold Chain"

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

	Freeze Sensitive?	***Heat Sensitive?***
Live Viral Vaccines	- / +	**+++**
Live Bacterial Vaccines	- / +	**+++**
Recombinant or Inactive Viral Vaccines	**+++**	- / +
Inactived, Purified or Conjugate Bacterial Vaccines	**+++**	- / +

Slide Courtesy of Prof. David Volkin, Univ of Kansas

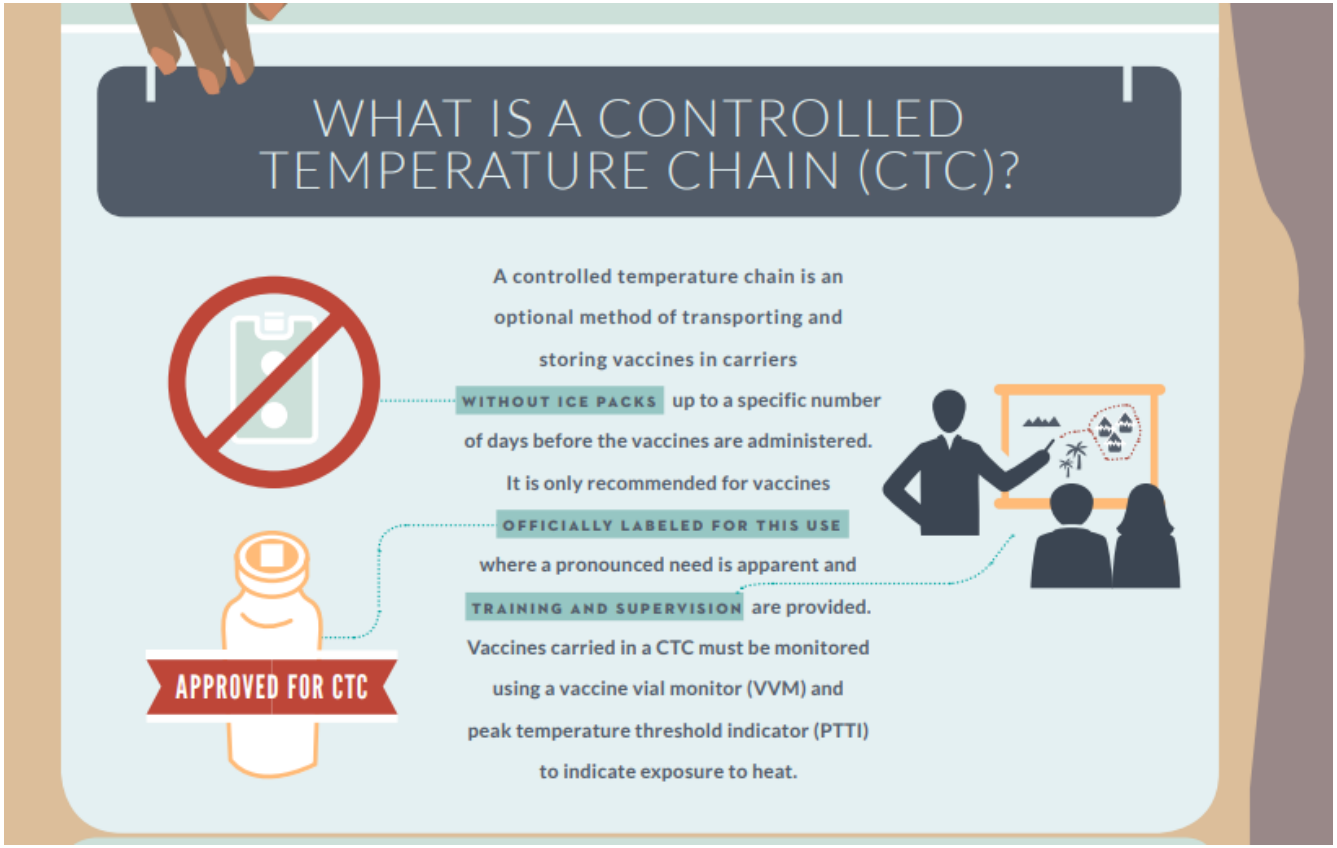
Temperature sensitivity of vaccines



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

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	**Formulation and Rationale**
• Trehalose in the 1980s	Lyophilized for heat stability
• Deuterium Oxide in the 1990s	Liquid for heat stability
• Polyethylene glycol in the 2000s	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

Slide Courtesy of Prof. David Volkin, Univ of Kansas

Novel drying and delivery technologies

General Examples	Formulation and Rationale
• Freeze-drying	Lyophilized formulations of aluminum vaccines
• Spray-drying	Lyophilized for heat stability
• Foam-drying	Lyophilized for heat stability
• Microneedles	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

Slide Courtesy of Prof. David Volkin, Univ of Kansas

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…)

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Highly Stable Rotavirus Vaccine – 540 days at 37°C

ARTICLE IN PRESS

Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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…

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.

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

Links to Pertinent Publications

ORIGINAL ARTICLE

OPEN

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

Ronald Angyal, MD, FAAP,* Allan Wood,† Marla C. Clemens,‡ and Diane Tipping§

Biologicals

Volume 42, Issue 5, September 2014, Pages 237–259

ELSEVIER

Review

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

Ozan S. Kumru[a], Sangeeta B. Joshi[a], Dawn E. Smith[b], C. Russell Middaugh[a], Ted Prusik[b], David B. Volkin[a]

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doi:10.1016/j.biologicals.2014.05.007

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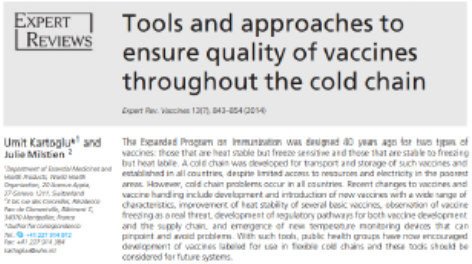

EXPERT REVIEWS

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

Expert Rev. Vaccines 12(7), 843–854 (2014)

Umit Kartoglu[1] and Julie Milstien[2]

The Expanded 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 stable 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 characteristics, improvement of heat stability of several basic vaccines, observation of vaccine freezing as a real 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 development of vaccines labeled for use in flexible cold chains and these tools should be considered for future systems.

Thank you!!!