Improving the vaccine supply chain in developing countries via increasing freeze protected cold chain equipment
When President Clinton established the Clinton Foundation in 2002, fewer than 300,000 people living with HIV/AIDS were receiving life-saving antiretroviral (ARV) medicines.

Today, more than **seven million** patients are accessing treatment in the developing world
CHAI is an independent nonprofit with in-depth operations in more than 32 countries

Who we are

- **Founded**: In 2002, as an initiative of the Clinton Foundation
- **Leadership**: President Clinton, Chairman of the Board; Ira Magaziner, CEO and Vice Chairman of the Board
- **Staff**: >1,300 staff
- **Budget**: $110 million in 2013

Where we work
CHAI plays a unique role - it is not a donor or implementer by nature, but instead focuses on management and markets.

By helping to organize commodity markets and better manage national programs, CHAI has a catalytic impact: governments and donors are able to do more with available resources.

EXAMPLE
Engaging vaccine manufacturers to supply to GAVI markets

EXAMPLE
Assisting countries to introduce Pentavalent, PCV, Rotavirus and HPV vaccines

EXAMPLE
Communicating country preferences and data to suppliers to improve products
Vaccines and immunization is one of CHAI’s strategic areas of focus at both the global and in-country levels

- **Vaccines**
  - Accelerate introduction of new vaccines, reduce prices of vaccines, and improve the efficiency and effectiveness of vaccine delivery systems

- **Value for Money**
  - Increase efficiency of spending on key health commodities and identify and pursue significant structural inefficiencies in global health spending

- **Malaria**
  - Support rapid scale-up of effective treatment and diagnosis, achievement of elimination where feasible, and sustained financing

- **Human Resources for Health**
  - Improve the production, distribution, and quality of health professionals to significantly accelerate closing the human resource gap

- **HIV/AIDS and TB**
  - Improve efficiency and effectiveness of global spending, increase long-term survival for PLWHA & accelerate scale-up of eMTCT & TasP

- **Maternal, Newborn, and Child Health**
  - Accelerate scale-up of essential child treatment with a focus on zinc/ORS and improve systems to reduce maternal/neonatal mortality in key countries

- **Applied Analytics**
  - Generate evidence needed to improve healthcare through expertise in epidemiology, economics, program measurements, and evaluation methods

- **Access to Medicines**
  - Accelerate patient access to healthcare by coordinated and intensive engagement on supply and demand side of the market
In-country CHAI teams have supported governments to introduce new vaccines and improve immunization delivery in eight focus countries:

**Nigeria**
- Supporting development of Penta, PCV and IPV introduction plans
- Supported improvement of vaccine supply chain
- Provide ongoing budgeting and financing assistance to the MOH

**Cameroon**
- Supporting planning for the introduction of rotavirus and IPV vaccines
- Improving vaccine supply chains

**Uganda**
- Supporting IPV and HPV introductions
- Supporting immunization supply chain strengthening

**Ethiopia**
- Supported MOH and GAVI to minimize delays in PCV introduction amidst global supply shortage
- Supporting MOH to improve vaccine supply chain

**Kenya**
- Provided broad management support and detailed planning for PCV introduction
- Supported development of robust proposal to GAVI for rotavirus

**Tanzania**
- Supported introduction of concurrent PCV and rotavirus introductions
- Working with MOH to improve vaccine supply chain and service delivery

**Malawi**
- Assisted the MOH to conduct cold chain expansion
- Supported the introduction of PCV vaccine

**Mozambique**
- Supporting the government to improve immunization supply chain and delivery systems
1. Background on vaccine freezing risks in the cold chain
2. Understanding the urgency for introducing freeze protection standards
3. Mitigating the risk with freeze protection standards and technology

**Need**
Freeze Protection Standards

**Urgency**
Significant CCE demand in 2014-18
1. Background on vaccine freezing risks in the cold chain
Freezing causes serious damage to many vaccines, reducing potency and thus having a negative impact on immunization outcomes and public health.

*Freezing damages the protein structure of many vaccines*

Freeze damage to vaccine proteins reduces the potency of many vaccines.

*Antibodies generated by properly stored Hep B vaccine vs frozen-thawed vaccine*

Evidence shows that vaccine freezing occurs throughout the vaccine supply chain, during both transport and storage at all types of facilities.

A CHAI study in one developing country found freezing across the vaccine supply chain.

% of vaccine shipments exposed to freezing at each level of the supply chain:

- **Central cold store**: 0%
- **Regional cold stores**: 40%
- **Zonal cold stores**: 67%
- **District cold stores**: 38%
- **Health facilities**: 50%
- **Outreach sites**: 18%
- **Transport**:
  - **Central cold store** to **Regional cold stores**: 20%
  - **Regional cold stores** to **Zonal cold stores**: 25%
  - **Zonal cold stores** to **District cold stores**: 21%
  - **District cold stores** to **Health facilities**: 18%
  - **Health facilities** to **Outreach sites**: 18%
  - **Outreach sites** to **Arrival**: 18%

Global research suggests that:

- Over 75% of vaccine shipments are exposed to freezing at some point in the supply chain.
- At least 21% of refrigerators used in developing countries for vaccine storage expose vaccines to freezing.

Therefore, preventing vaccine freezing will increase "effective immunization rates".

Sources: 2010 CHAI study conducted in country; Matthais D. et al., “Freezing temperatures in the vaccine cold chain: a systematic literature review” in *Vaccines* (2006)
Freezing of vaccines has a negative impact on public health outcomes for children in many developing countries.

25% fewer children who had been given frozen Hep B vaccine showed an adequate antibody response to the vaccine, likely due to freeze damage.

<table>
<thead>
<tr>
<th>% of children with adequate Hep B antibodies following immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non frozen vaccines</td>
</tr>
<tr>
<td>95</td>
</tr>
</tbody>
</table>

Eliminating vaccine temperature damage in 3 countries could avert over a million cases of disease and thousands cases of child mortality.

**Estimated health outcomes of future thermostable vaccines in Cambodia, Ghana, Bangladesh**

<table>
<thead>
<tr>
<th>Country</th>
<th>Disease cases averted</th>
<th>Deaths averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>98,810</td>
<td>1,140</td>
</tr>
<tr>
<td>Ghana</td>
<td>190,281</td>
<td>2,118</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>987,696</td>
<td>13,258</td>
</tr>
</tbody>
</table>

Note: In this analysis, thermostable vaccines can act as a proxy for normal vaccines with no temperature damage.


“Potency loss does occur when freeze-sensitive vaccines undergo the phase change to a frozen state. Many epidemiological studies have also pointed to vaccine freezing as a possible contributor to low immune response in vaccinated individuals and the existing literature relating freeze exposure to potency loss is compelling enough to suggest some degree of impact on immune response.” – PATH, 2006
2. Understanding the urgency for introducing freeze protection standards
The volume and value of freeze-sensitive vaccines being procured is increasing, raising the public health benefits of “freeze protection.”

Value (in millions of USD) and volume (millions of doses) of vaccines procured by UNICEF SD, 1996 to 2014

Sources: UNICEF SD vaccine procurement data available online at:
Demand for two major freeze sensitive vaccines is expected to increase, driven in part by Indian introduction of these vaccines.

Low and middle income country (including India) forecast demand for PCV and pentavalent vaccine from 2014 to 2034, in millions of doses.

India began pentavalent introduction in 2014. This introduction will be complete in all states by April 2015.

India will likely begin widespread public sector PCV introduction in 2022/23.

Sources: CHAI Analysis
Vaccine CCE procurement is expected to be steady and constant over the next few years; now is a good time to install the right technology.

Freeze protection standards are critical to implement now as significant CCE demand is expected over the next five years.

**GAVI-eligible market demand for SDDs and ILRs from 2014-2018, in units**

- **From 2014 to 2018, total demand of vaccine refrigerators is expected to reach 110,000 units from the 53 GAVI-eligible countries, as new vaccine introductions and replacement needs in-country require large CCE procurement.**
- **Implementing freeze protection standards in 2014 is critical to accelerating the uptake of freeze protected units in this high period of demand.**

Surveyed countries include Nigeria, Ethiopia, Tanzania, Mozambique, Kenya, Uganda & Malawi. Detailed extrapolation for India, Pakistan, Bangladesh, DRC, Republic of Sudan & Afghanistan. High-level extrapolation for remaining 40 GAVI-eligible countries.
3. Mitigating the risk with freeze protection standards and technology
Proposed standard to categorize freeze protection capabilities

**User Dependent Freeze Protection (DFP)**
User interventions required to mitigate freezing risk

**User Independent Freeze Protection (IFP)**
No user interventions required to mitigate freezing risk

- Proposed standard describes technologies based on the **necessary interventions required** for users to prevent freeze exposure
- **Codifies WHO PQS guidance** on operating CCE
- Nomenclature **aligns with existing messaging** from suppliers on proper use of equipment
- **Unbiased** standard with respect to technology and supplier
User-Dependent Freeze Protection (DFP) is dependent on the user to prevent freezing

**Definition:** Freeze protection is **DEPENDENT** on proper healthcare worker use and operation

- **Freezing temperatures exist** within refrigerator compartment
- **Interventions must be observed** to mitigate risks

**✓ Always store vaccines in baskets, away from sidewalls**

**✓ Regular defrosting**

**Compartment surface area where freezing temperatures can exist**

**Baskets used to store vaccines away from walls**
User-Independent Freeze Protection (IFP) technology prevents vaccine freezing independent of user operation

**Definition:** Freeze protection is **INDEPENDENT** of healthcare worker's use and operation

- Protection is intrinsic to the refrigerator design in that compartment sidewall surfaces never reach vaccine freezing temperatures.

- **Safely store vaccines anywhere** in the fridge, even in contact with walls

- **No defrosting required**

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**Phase Change Material (PCM)**

**Patented Sure Chill technology**
Answering the freezing problem through introduction of WHO PQS freeze protection standards

Market challenges:
- **No accepted standard** for categorizing freeze protection in WHO PQS
- **Lack of IFP options** in capacity and technology segments
- **Significant demand** over next 5 years

Solution:
- **Introduce WHO PQS freeze protection standardization to:**
  - Emphasize to **countries** the importance of procuring and operating FP
  - Provide market signal to **suppliers** for designing to FP standard
  - Enable **global partners** to advise appropriate FP procurement and operation
  - Allow **donors** visibility into vaccine investment protection and insistence on levels of FP in donor-funded country procurements

**ULTIMATE GOAL:** Make an affordable and proven independent freeze-protected fridge option available in every PQS capacity and technology segment of CCE.
Many stakeholders are working to develop and support the increased adoption of other technologies to prevent freezing, such as RTMDs.

**How it works:**
An remote temperature monitoring device (RTMD) is placed on a vaccine fridge, and sensors placed inside of the fridge take readings every few minutes, transmitted to cloud via cellular network.

When an unsafe temperature is detected, RTMD will transmit an alert via SMS, phone, or email to the appropriate personnel. This enables:

1. Proactive action to prevent vaccine damage due to freezing and heating
2. Awareness of cold chain system in order to better direct maintenance and repair efforts
3. Evidence-based decision-making in future procurements of cold chain equipment
# Sensitivity to freezing of various vaccines

## Freeze sensitivity

<table>
<thead>
<tr>
<th>Freeze sensitivity</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most sensitive</td>
<td>DTaP</td>
</tr>
<tr>
<td></td>
<td>DTaP-hepatitis B-Hib-IPV (hexavalent)</td>
</tr>
<tr>
<td></td>
<td>DTwP</td>
</tr>
<tr>
<td></td>
<td>DTwP-hepatitis B-Hib (pentavalent)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td></td>
<td>Meningitis C (polysaccharide-protein conjugate)</td>
</tr>
<tr>
<td></td>
<td>Pneumococcal (polysaccharide-protein conjugate)</td>
</tr>
<tr>
<td></td>
<td>T, DT, dT</td>
</tr>
<tr>
<td>Least sensitive</td>
<td>Cholera (inactivated)</td>
</tr>
<tr>
<td></td>
<td>Influenza (inactivated, split)</td>
</tr>
<tr>
<td></td>
<td>Hib (liquid)</td>
</tr>
<tr>
<td></td>
<td>Inactivated poliovirus</td>
</tr>
<tr>
<td></td>
<td>Typhoid PS</td>
</tr>
</tbody>
</table>

These vaccines are not damaged by freezing.

<table>
<thead>
<tr>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis A (polysaccharide-protein conjugate)*</td>
</tr>
<tr>
<td>Rotavirus (liquid and freeze dried)</td>
</tr>
<tr>
<td>Yellow fever</td>
</tr>
<tr>
<td>Bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>Hib (freeze dried)</td>
</tr>
<tr>
<td>Japanese encephalitis (live and inactivated)</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
</tr>
<tr>
<td>Oral poliovirus</td>
</tr>
<tr>
<td>Rabies</td>
</tr>
<tr>
<td>Rubella</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
</tr>
</tbody>
</table>

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**Caution:**

- Never expose these vaccines to zero or subzero temperatures.
- Avoid the use of ice for transport.

* The diluent for MenA PS-PCV contains alum adjuvant and is freeze-sensitive.

Note: Bolded vaccines are freeze dried.