

## Taking advantage of the true heat stability of vaccines

### Thinking outside 2°C to 8°C

For more than 30 years, health care workers have followed strict cold chain rules for vaccine storage to the best of their abilities. These rules, which stated that vaccines must be kept between 2°C and 8°C at all times, often required enormous investments of both time and resources. Keeping vaccines within this temperature range is often difficult if not impossible in settings with limited cold chain and ice pack production capacity, and influences the design and selection of immunization strategies.

Meanwhile, research has shown that many vaccines are in fact more heat stable than their current label suggests. Studies in both the laboratory and field have validated the feasibility of using vaccines out of the cold chain for limited periods of time, using [vaccine vial monitors](#) to indicate when the vaccines have been exposed to cumulative levels of heat that may negatively affect potency.

Project Optimize, a World Health Organization (WHO) and PATH collaboration, is working to enable the use of vaccines in a controlled temperature chain (CTC), which allows vaccines to be kept and administered at temperatures of up to 40°C for a single period of time immediately before administration.



*Clockwise from left: a small portion of the ice packs for which freezer space must be found during a campaign in Ghana; an overflowing national negative temperature storage cold room during a polio campaign in Mali; humidity in vaccine carriers often leads to labels becoming unreadable, resulting in vaccine wastage from a Mali polio campaign.*

### Potential to reduce costs, save time, and increase coverage

The effort to license vaccines according to true temperature stability has implications for how vaccines are developed and delivered across the globe. Maintaining cold chain conditions is always difficult but especially so in low- and middle-income countries. While most countries have functioning cold rooms at the national level, the ability to maintain 2°C to 8°C storage declines at lower levels of the chain. Many health care centers lack reliable electricity or functioning equipment. Furthermore, health care workers often conduct vaccination as part of outreach activities away from health posts, in locations where cold chains are nonexistent.

Faced with the challenges of maintaining the cold chain, some countries, such as Chad, China, India, Indonesia, Mali, Papua New Guinea, and Vietnam, have taken vaccines outside of the cold chain during the final legs of distribution in order to enable them to vaccinate their populations in a timely manner. This approach has been used successfully for both heat-stable vaccines, such as hepatitis B, and vaccines with a lower stability profile, such as oral polio. However, this is considered “off-license” use, which is not supported by manufacturers or regulators and for which no official guidelines are available. Thus, countries are using the product without guidance on best practices. By doing this, they assume the full risk and liability themselves.

## Charting a pathway for on-license vaccine use in a controlled temperature chain

Regulatory approval that allows for on-license use of vaccines in a CTC is important to ensure that vaccines remain potent and safe throughout their life cycle.

Current CTC work is focused on re-licensing existing vaccines that are either delivered in campaigns (e.g., Meningitis A and yellow fever) or through special strategies (e.g., hepatitis B birth dose and human papillomavirus). These delivery strategies show the greatest potential to benefit from the CTC approach due to the large volumes, short time frames, non-traditional sites, non-routine schedules, and extensive outreach required—all of which make it challenging to deliver vaccines in the traditional cold chain. The first vaccine going through this process is MenAfriVac, the Meningitis A vaccine developed by Serum Institute of India through the Meningitis Vaccine Project, a WHO/PATH collaboration.

### Why consider a controlled temperature chain?

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| <b>Reduce costs and system constraints</b>                    | Reduce the storage space required, maintenance, and ice pack preparation (which includes time, supplies, and energy).                              |
| <b>Reach more people</b>                                      | Provide services to those in hard-to-reach areas and marginalized populations.   |
| <b>Deliver vaccines to the right groups at the right time</b> | Deliver vaccines such as hepatitis B birth dose to infants, tetanus toxoid vaccine to women, and human papillomavirus vaccine to adolescent girls. |
| <b>Reduce and eliminate the risk of freezing</b>              | Protect heat-stable vaccines, which are often damaged by freezing.   |
| <b>Promote more integrated supply chains</b>                  | Enable the integrated distribution of heat-stable vaccines and drugs.  |

## Controlled temperature chain strategic approach

Optimize is collaborating with vaccine manufacturers, regulatory agencies, WHO, and PATH to advance work in four complementary, interlinked streams that are outlined below. This strategy and work plan have been endorsed by WHO's Immunization Practices Advisory Committee and forms the framework for addressing the complex issues in this area.

The four streams are as follows:

1. **Vaccines:** Exploring and defining regulatory pathways to license specific vaccines for higher-temperature storage in collaboration with manufacturers, regulators, and WHO's prequalification team.
2. **Countries:** Conducting country studies on CTC practices and development of operational guidelines for country-level CTC decision-making and implementation. This work is being conducted in collaboration with the WHO Regional Office for Africa and under the guidance of WHO's Immunization Practices Advisory Committee.
3. **Technologies:** Ensuring that proven technologies are available to support CTC implementation, including peak threshold indicators and storage equipment.
4. **Incentives:** Defining mechanisms to incentivize the licensing of products to reflect their true stability and ensuring that countries have access to product information as well as the ability to select products that meet their needs.

In addition, in order to provide guidance for national regulators, WHO's Quality, Safety and Standards team, through its regulatory collaborating centers initiative, is convening a small working group of regulatory experts to develop the document, *Scientific Considerations for Regulatory Review of Vaccines Used in a Controlled Temperature Chain*. This WHO publication is aimed at helping regulators who are new to the CTC approach proceed in a safe and scientifically sound manner, allowing for flexibility in vaccine management without compromising efficacy.

In the near future, project Optimize hopes to not only provide countries with flexibility in vaccine storage and use requirements, but to ensure that appropriate guidance and technologies are available, along with an evidence base documenting the benefits and limitations of the CTC approach.

## Project partners

- National regulatory authorities
- Serum Institute of India
- Vaccine manufacturers (within the Developing Countries Vaccine Manufacturers Network and the International Federation of Pharmaceutical Manufacturers & Associations)
- WHO Immunization, Vaccines and Biologicals; Quality, Safety and Standards team
- WHO Regional Office for Africa
- WHO Regional Office for the Western Pacific

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