The controlled temperature chain (CTC): frequently asked questions

last updated in October 2023

This document provides an overview on behalf of the World Health Organization's (WHO) Department of Immunization, Vaccines and Biologicals (IVB), of the "controlled temperature chain" (CTC) by answering the following questions:

1. What is a Controlled Temperature Chain (CTC)?

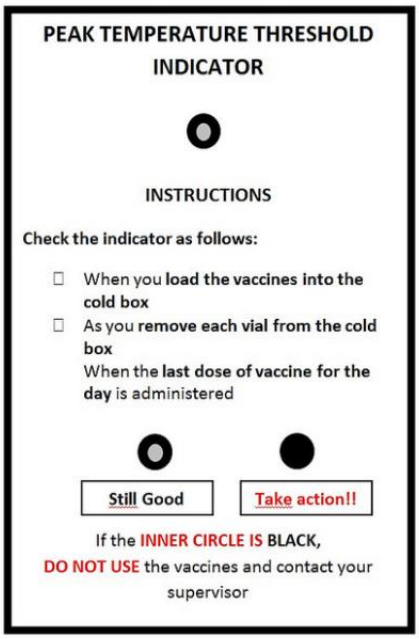
The “controlled temperature chain” (CTC) is a short-term vaccine management strategy that leverages the thermostability profile of a given vaccine product in order to facilitate delivery without the varied constraints of the cold chain. When applying CTC conditions, vaccines may be kept at temperatures outside of the standard cold chain of +2°C to +8°C for a limited period of time under monitored and controlled conditions, as appropriate to the stability of the antigen. A CTC typically involves a single excursion of the vaccine into ambient temperatures not exceeding a specified threshold temperature and for a duration of a specific number of days, just prior to administration.

The World Health Organization (WHO) has established the following programmatic criteria for a vaccine to be labelled for and used in a CTC:

1. The vaccine should be used alone or in combination only with other vaccines, which are also licensed for use in a CTC.
2. The vaccine must be able to tolerate ambient temperatures of at least +40°C for a minimum of 3 days and should be accompanied by:
    a. A vaccine vial monitor (VVM) on each vial, and
    b. A peak threshold indicator in each vaccine carrier (see Question 2).
3. The vaccine should be licensed for use in a CTC by the relevant regulatory authorities, with a label that specifies the conditions.

2. What is a peak temperature threshold indicator?

In order to be sure that CTC-qualified vaccines have not been exposed to temperatures higher than +40°C, a “peak temperature threshold indicator” must accompany the vaccines at all times when in a CTC to monitor the temperature exposure of the vaccines. This indicator is a card with a sticker which changes color from light grey to black, as soon as the temperature exposure has exceeded +40°C. If this occurs, all vaccines in that vaccine carrier have to be discarded, following an appropriate investigation and documentation of the event.



Peak temperature threshold indicators do not replace VVMs, as they measure peak exposure, while VVMs measure cumulative exposure to heat. The latter will not be sufficient to monitor short exposure to temperatures higher than accepted by CTC criteria. The two temperature monitoring tools are therefore complimentary to one another.

3. What are the origins of the CTC approach and which vaccines have already been licensed or relabelled for use in this way?

In recognition that an increasing number of vaccines are able to tolerate temperatures well above those officially stated on their labels or package inserts (+2°C to +8°C), WHO has been supporting efforts to assess and take advantage of the true heat stability of vaccines. Upstream work includes engaging in dialogue with vaccine manufacturers to ensure that new vaccine labels, where possible, reflect a maximum heat stability compatible with WHO's definition of a CTC and that existing vaccines are assessed to generate a clearer picture of their actual heat stability and the potential for re-licensure and pre-qualification for use in a CTC.

Both WHO's Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ)[1] document and the Vaccine Presentation and Packaging Advisory Group's (VPPAG) Generic Preferred Product Profile for Vaccines [2] were updated in 2015 to reflect heat stability preferences. Both now contain strong recommendations for vaccines to be tested and licensed according to CTC conditions, where feasible.

In February 2017, the following four priority vaccines were proposed by the CTC Working Group, operating as a sub-group to WHO's Immunization Practices Advisory Committee (IPAC)and accepted by IPAC for the first phase of CTC work from 2017-2020:

1. Human Papilloma Virus (HPV) vaccine
2. Oral Cholera Vaccine (OCV)
3. Tetanus toxoid (TT) containing vaccines
4. Hepatitis B birth dose

These vaccines were selected based on three criteria:

- potential in terms of adequate heat stability,
- delivery strategy that would benefit from CTC use
- technical feasibility of CTC licensure

In 2020, the Strategic Roadmap for CTC Priority Vaccines[3] was reviewed by the CTC Working Group (CTC-WG). Typhoid Conjugate Vaccine (TCV) was added as an additional priority vaccine and the CTC-WG confirmed that the commitments outlined in the Roadmap are still relevant and valid for an extended time period through 2024, in view of the many targets still not being met.

As of October 2023, there are four vaccines licensed and labelled for CTC use:

Disease	Vaccine	Storage criteria	Days
Meningitis A	MenAfriVac®	40°C	3 days
HPV	Gardasil®	40°C 42°C	4 days 3 days
	Gardasil 9	40°C	4 days
Cholera	Shanchol™	40°C	14 days
Typhoid	Typbar	40°C 55°C	7 days 3 days

[1] Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification - Revision 2014. (WHO/IVB/14.10) http://www.who.int/iris/bitstream/10665/148168/1/WHO_IVB_14.10_eng.pdf

[2] https://cdn.who.int/media/docs/default-source/immunization/product-and-delivery-research/vppag_gppprecs.pdf?sfvrsn=9ad9488c_3&download=true

[3] ttps://www.who.int/publications/i/item/WHO-IVB-17.20

Additionally, for hepatitis B birth dose, in 2017, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) updated its recommendation as follows:

"In settings where administration of a birth dose is restricted by access to cold storage, [out of cold chain (OCC)] storage of monovalent hepatitis B vaccine and exposure to ambient temperatures for limited time periods at the point of delivery could improve birth-dose coverage. If an OCC policy for a monovalent hepatitis B vaccine product is adopted, which is an off-label use of the vaccine, it is strongly recommended that the WHO recommendations for OCC and CTC use of vaccines be followed."
From WER9227.pdf (who.int)- on p.390[4]

A similar interim OCC recommendation was issued for EuBiologics's Oral Cholera Vaccine (OCV), Euvichol, in September 2023, to be considered valid until a decision is issued on the CTC prequalification of the upcoming reformulation of Euvichol (ie. Euvichol-S):

"*Based on an assessment of evidence, SAGE acknowledged the public health benefit of the use of the killed whole cell bivalent (O1, O139) OCV (EuBiologics) under controlled temperature chain (CTC) conditions of not more than 10 days at ambient temperatures not exceeding 40°C*."[5]

Efforts are underway through the Vaccine Innovation Prioritization Strategy (VIPS) to re-label other vaccines for CTC use, including vaccines against covid-19, cholera, hepatitis B, more HPV products, meningitis, rotavirus, and tetanus.

Any implementation of a CTC or OCC/CTC-like strategy for the above-mentioned eligible vaccines should be conducted with the appropriate guidance and monitoring tools. Immunization programmes are urged not to adopt a CTC approach in an ad-hoc manner, without proper planning, training, and monitoring.

4. How is CTC different from "out of the cold chain" (OCC)?

The controlled temperature chain is very specific about the conditions under which the vaccine can be used (see WHO definition above). In order for a vaccine to be labelled for CTC use, it must undergo the process of approval by the appropriate regulatory authorities and WHO prequalification. This signals that the vaccine is safe and fully validated for use in this new format. A CTC-approved product will have the conditions governing its use in a CTC detailed in the product insert.

Out of the cold chain (OCC) implies a departure from established and approved EPI policies and vaccine manufacturer product-handling recommendations and is thereby considered "off-label" vaccine use. Unlike CTC, OCC does not have a clear definition or monitoring regulations. OCC is understood as any practice involving the removal of a given vaccine from the cold chain based on indications that this vaccine is thermostable, but without the regulatory approval of storage under these conditions by national regulatory authorities and without subsequent prequalification by WHO of an on-label indication for such storage.

[4] From WER9227.pdf (who.int) - on p.390
[5] From https://cdn.who.int/media/docs/default-source/immunization/sage/2023/september/sage_sept2023_meeting_highlights.pdf?sfvrsn=5ac08c01_4

5. What role does CTC play globally?

Moving the CTC agenda forward requires stakeholders to work closely together to advocate for this new approach and to provide technical assistance in a streamlined and coherent manner. In the interest of engaging partners in a shared and realistic agenda, and to ensure that CTC maintains the appropriate attention and strategic direction, the CTC working group (CTCWG) was established under the authority of the Immunization Practices Advisory Committee (IPAC) with a view to clarifying and articulating priorities and obtaining necessary technical insights and guidance. The mission of the CTC-WG has been to convene key CTC stakeholders to define a shared vision and strategy for CTC and to increase advocacy with vaccine manufactures, as well as with potential implementing countries for this innovative approach. The working group served as a platform to engage in a constructive dialogue with countries, manufacturers and regulatory authorities to identify demand and priorities, to increase the number of CTC licensed products, and to facilitate their implementation. The following organizations were represented in the CTC-WG: WHO, UNICEF, Gavi, PATH, MSF, DCVMN and IFPMA.

As of 2021, the mission of the CTC-WG was transferred to and maintained by the VIPS-Working Group, which includes VIPS Alliance representation.

WHO's position regarding OCC and CTC was published by IPAC and validated by SAGE as the following:

> The WHO Immunization Practices Advisory Committee (IPAC) recommends that countries store, transport and distribute vaccines at temperatures above 8°C only if these products have been licensed for use in a Controlled Temperature Chain (CTC). IPAC further calls for acceleration of vaccine licensing and labelling consistent with CTC usage. The committee recognises that manufacturers, regulators, national programmes and immunization partners consider that on-label indication of temperature storage conditions will enhance communication of correct handling and maintenance of the quality of vaccines above 8°C.
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> Nevertheless, IPAC recognizes that under special circumstances such as emergency situations, countries may consider delivering certain vaccines out of the cold chain (OCC) for public health benefit especially for otherwise unreachable populations. Should a country choose to use a vaccine OCC, this should only be an interim short-term step while licensure and labelling consistent with CTC is sought for the vaccine. Further, IPAC recommends that countries observe the following five conditions:
>
> 1. Understand that any associated liability with OCC off-label use must be accepted by the country, irrespective of WHO guidance;
> 2. Apply the OCC strategy only to:
>   a. a specific vaccine product, not to a class of vaccine products, where stability data suggest thermostability appropriate to the country's climate. Due caution is necessary with live attenuated vaccines in particular and adequate provision of cold chain management of reconstituted vaccines at the vaccination sites is essential.
>   b. a vaccine product fitted with a vaccine vial monitor (VVM);
> 3. Set and monitor explicit time and temperature limitations on the use of the specific product OCC;
> 4. Ensure adequate vaccine handling training of health workers; and
> 5. Use appropriate temperature monitoring tools in addition to VVM, such as peak temperature threshold indicators.

For more information, please refer to: https://cdn.who.int/media/docs/default-source/immunization/ipac/ipac_statement_occ_ctc_october_2016.pdf?sfvrsn=fe1e7d9e_6

6. Is CTC still at an experimental stage?

CTC is not an experiment. Applying the CTC approach to a vaccine implies a fully validated strategy, involving registered use of the vaccine that is approved by the manufacturer, by the appropriate regulatory authorities, and by WHO's prequalification team. A vaccine which has a CTC label, is no different from any other vaccine on the market. It has an authorization for use in CTC, supported by scientific data that demonstrate that this vaccine remains as safe and potent under a CTC as it is when kept between +2°C to +8°C. CTC is an expansion of the label to enable more flexibility for use of the vaccine in extreme conditions that facilitate the vaccination programmes.

7. What are the advantages of CTC, what should be considered when implementing CTC?

Advantages of CTC	Considerations when implementing CTC
Infrastructure:	
Reducing cold chain needs: Removing a vaccine from the cold chain to enter a CTC reduces the space needed within the cold chain, as well as the burdens and costs associated with maintaining the cold chain.	As CTC is often a new practice for vaccinators, deviating from their standard approaches, concern has been expressed regarding the potential risk of confusion among health workers, especially with subsequent campaigns involving non-CTC eligible vaccines. However, experience so far has shown that health workers are able to distinguish between CTC and non-CTC eligible vaccines and there has been no evidence to date of operational errors committed on account of confusion created by the implementation of CTC.
No need for icepacks: No additional freezer capacity is needed to prepare ice packs and more vaccines can be carried in one vaccine carrier. Conditioning the ice packs is no longer required either.	One peak threshold indicator per vaccine carrier or equivalent will be necessary. These are a low-cost paper cards with a temperature-sensitive sticker costing well under US$ 1 each, depending on the quantities needed.

Wastage:	
Fewer problems with humidity: Unopened vaccines vials are frequently discarded when the label becomes detached or unreadable after a day in a humid vaccine carrier. A CTC eliminates this problem: since there is no need for ice or conditioned icepacks the vaccine carrier remains dry.	Higher levels of closed-vials vaccine wastage may be seen in a CTC context if the vials need to be discarded because the vaccines have been exposed to temperatures above the permitted threshold (usuall +40°C), or the time limit (number of days) has been passed. This means that careful attention is required when forecasting the amount of vials needed. Care must also be put into the management and monitoring of the vials of vaccines used in a CTC, to ensure use within the time limit to avoid unnecessary wastage. It should be noted that once taken into a CTC, vaccines must be used and cannot be returned to the cold chain. CTC cannot be paused.
Operations:	
Savings of staff time: There is specifically less need to plan and manage additional cold-chain requirements, such as ice-pack conditioning and logistics issues. The time used for planning cold-chain space, freezing and conditioning ice packs and managing the cold-chain equipment needed for transportation can be reallocated to supervisory and field activities.	Initially, additional time and resources may be required to familiarize vaccinators and supervisors with this new approach.
Increased ease of vaccine transportation: Since the vaccines can be put in the vaccine carrier without conditioned ice packs, this will reduce the volume and weight that need to be transported by health workers.	
Reduced transportation costs: Health workers no longer need to travel so frequently to the district level to pick up vaccines and/or conditioned ice packs, as a larger number of vaccines can be carried at one time and there is no need to stock up on ice packs for the next day.	
Climate Change:	
The reduced dependence on the cold chain translates into a lower carbon footprint and increased energy efficiencies, making CTC a more ecological approach to vaccine delivery.	

8. When and how should a vaccine be used in a CTC?

A vaccine that is licensed and labelled for use in a CTC can be used in a CTC provided the following conditions are met:

1. The vaccine is strictly used within the limits of time and temperature specified on the label and/or package insert.
2. The vaccine is used in a campaign or during a special vaccination outreach strategy (where it is less likely to be delivered in an integrated manner with other vaccines requiring still the cold chain) where ambient temperatures do not typically exceed +40°C.
3. It is kept in the CTC during a single time period not exceeding the maximum allowed time specified in the CTC label, immediately before its use.
4. Peak temperature threshold indicators accompany the vaccines at all times as soon as they are used in the CTC and monitored regularly.
5. Health workers are trained in advance of the campaign to understand the conditions under which the CTC can be used and to maintain standard cold chain precautions up to the point that the vaccine enters the CTC, followed by the necessary monitoring during the duration of the CTC, through to vaccine administration and vial disposal.

WHO recommends that a CTC only be adopted when there are sufficient resources and time available for proper planning, training, supervision and monitoring. CTC should only be considered for the geographic areas where the flexibility offered by this innovation will make a difference to the logistics of the vaccination activity. Examples of the latter would include cold chain constraints and challenging outreach conditions.

All conditions under which a lyophilized vaccine is licensed for CTC should be applied to the corresponding diluent. For MenAfriVac®, despite the fact that the diluent comes with an indication that it should be stored under +25°C, the use and reconstitution with the diluent has been validated at 40°C.

Note: Guidelines for decision makers and managers, as well as guidance on training and field implementation are available for all vaccines licensed for use in a CTC.

9. How is CTC compatible with supply chain investment?

A key objective of CTC is to complement supply chain investments and to help overcome burdens and constraints associated with delivering vaccines in a standard cold chain. Investment in CTC will be an important complement to supply chain investments, as the latter will not always reach all the way to the most vulnerable populations. For example, maintaining the cold chain in epidemiological outbreaks in rural areas or when delivering vaccines to mothers' and newborns' homes, would always oblige health workers to rely on conditioned ice-packs, which is burdensome, costly, and not always feasible.

10. Are countries obliged to use a CTC strategy?

The CTC license is an additional flexibility offered to countries, but they do not have to use it. If the immunization programme is strong and there are no logistical challenges for the conduct of immunization campaigns or outreach activities, leveraging the additional flexibility offered by the CTC may not be needed. Advantages and disadvantages of CTC have to be assessed in each case.

11. Should a CTC strategy be followed in the entire area of a vaccination campaign?

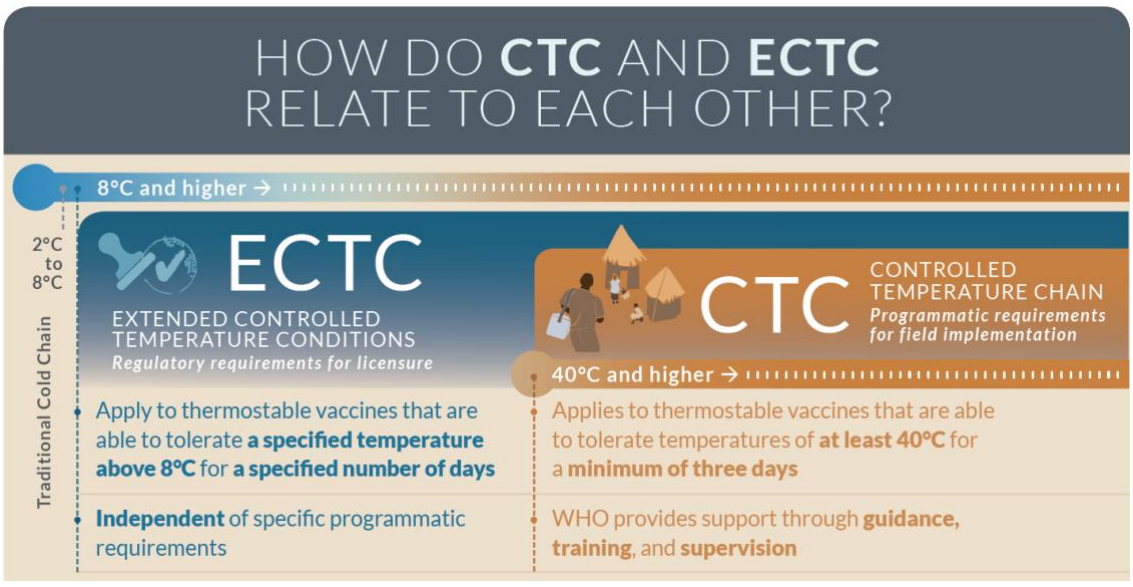
The CTC approach can be implemented nationally, or only in targeted areas. It can have the most impact in targeted areas where cold-chain capacity or performance is insufficient or suboptimal, and where ice pack freezing capacity is not reliably available, limited or expensive. It would however be best to implement the CTC throughout an entire district or administrative area, rather than within specific areas or health centres of that area, as this may not be cost-efficient and could carry the risk of confusing health personnel.

12. Why aren't more vaccines labelled for CTC use?

Generating the required data to confirm a vaccine's compatibility with CTC use can be costly and time-consuming. Manufacturers must be convinced that such an investment is worthwhile. One additional difficulty is that the regulatory pathway for approving a vaccine for use in a CTC is complex and varies from one product to another. National regulatory authorities (NRAs) are new to this approach and require guidance on how to review such licensure or relabeling requests. In the interest of clarifying the required regulatory pathways for CTC, the WHO Health products policy and standards team, responsible for vaccine regulation matters, developed guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions, commonly referred to as the ECTC Guidelines and approved by the ECBS (WHO *Expert Committee on Biological Standardization* (*ECBS*) in 2015.

13. What is the difference between CTC and ECTC?

The Extended Controlled Temperature Conditions (ECTC) refer to the regulatory requirements for a vaccine to be used outside of the standard cold chain. They do not reflect programmatic requirements or preferences and can apply to any specified temperature above 8°C for any specified number of days. CTC is a specific programmatic approach to vaccine management taking the conditions in most low-income countries into consideration. From the programmatic perspective, for vaccines delivered through WHO/UNICEF, manufacturers have been informed that for programmed delivery under CTC, a label claim for stability of at least three days tolerating at least 40°C is preferred. The infographic below illustrates how CTC and ECTC relate to each other. For more information on ECTC please see: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/extended-controlled-temperature-conditions



14. Where can I obtain more information on CTC?

You will find additional information on CTC including **WHO's 3-part film on CTC** here: https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization/supply-chain/controlled-temperature-chain-(ctc)

Videos
Part 1 – CTC: Delivering vaccines more easily
Part 2 – CTC: Implementing in the field
Part 3 – CTC: Future Development

Publications
There has been a lot of scientific literature published on CTC. A large selection is available on the WHO website through the following link:
https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization/supply-chain/controlled-temperature-chain-(ctc)/publications-and-guidance

In addition, the online forum hosted on TechNet-21.org features discussions related to CTC: http://www.technet-21.org/en/discussions/tags/17-controlled-temperature-chain

For additional information on CTC and WHO's activities in this area of work, you may also contact: **vaccines@who.int**