The controlled temperature chain (CTC): frequently asked questions

This document provides an overview of the “controlled temperature chain” (CTC) by answering the following questions:

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General Questions:

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

   The “controlled temperature chain” (CTC) is an innovative approach to vaccine management allowing vaccines to be kept at temperatures outside of the traditional 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 +40°C and for 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 in a campaign or special strategy setting. CTC is not currently recommended for immunization through routine delivery.
   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 must be licensed for use in a CTC by the relevant regulatory authorities, with a label that specifies the conditions.

2. **What is a peak threshold indicator?**

   In order to be sure that vaccines have not been exposed to temperatures higher than +40°C, a “peak 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 is the case, all vaccines in that vaccine carrier have to be discarded, following an appropriate investigation and documentation of the event.

   Peak threshold indicators do not replace vaccine vial monitors, as they measure peak exposure, while VVMs measure cumulative exposure to heat. The latter will not be sufficient to monitor short exposure to temperature higher than accepted by CTC criteria.

3. **What are the origins of the CTC approach?**

   In recognition that an increasing number of vaccines are able to tolerate temperatures well above those officially stated on their labels (+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](#)
Both now contain strong recommendations for vaccines to be tested and licensed according to CTC conditions, where feasible. Currently, the vaccine MenAfriVac™ is the only vaccine licensed and labelled for CTC use. Efforts are underway to re-label other vaccines for CTC use, including vaccines against yellow fever, hepatitis B, HPV, rotavirus, pneumococcal disease and cholera.

4. **How is CTC different from “out of the cold chain”?**

“Out of the cold chain” is not a term that corresponds to specific criteria, nor is it an official label. The term does not imply specific temperature or time limits. 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. “Out of the cold chain” does not imply official approval by the appropriate regulatory authorities, nor by WHO. A CTC approved product will have the conditions governing its use in a CTC detailed in the product insert.

5. **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 programs.

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6. **What are the advantages and disadvantages of CTC?**

<table>
<thead>
<tr>
<th>Advantages of CTC</th>
<th>Disadvantages of CTC</th>
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<tbody>
<tr>
<td><strong>Infrastructure:</strong></td>
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<tr>
<td>Reducing cold chain needs: Removing a vaccine from the cold chain to enter a CTC reduces the space needed within the cold chain.</td>
<td>As CTC is a new practice, there is a 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.</td>
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<tr>
<td>No need for icepacks: No additional freezer capacity is needed for ice packs and more vaccines can be carried in one vaccine carrier.</td>
<td>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 under US$ 1 each, depending on the quantities needed.</td>
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<tr>
<td><strong>Wastage:</strong></td>
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<td>Fewer problems with humidity: Unopened vaccine 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 icepacks the vaccine carrier remains dry.</td>
<td>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 +40°C, or the time limit (number of days) has been passed. This means that careful attention is required to manage the vials of vaccines used in a CTC to ensure use within the time limit to avoid unnecessary wastage.</td>
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<td><strong>Operations:</strong></td>
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<td>Savings of staff time: There is specifically less need to plan and manage additional cold-chain requirements, such as ice-pack freezing and logistics issues. The time used for planning cold-chain space, freezing ice packs and managing the cold-chain equipment needed for transportation can be reallocated to supervisory and field activities.</td>
<td>Initially, additional time and resources may be required to familiarize vaccinators and supervisors with this new approach.</td>
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<td>Increased ease of vaccine transportation: Since the vaccines can be put in the vaccine carrier without freezing ice packs, this will reduce the volume and weight that need to be transported by health workers.</td>
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<td>Reduced transportation costs: Health workers no longer need to travel so frequently to the district level to pick up vaccines and/or frozen 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.</td>
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7. 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 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 strategy (CTC is not currently recommended for routine immunization) 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 threshold indicators accompany the vaccines at all times as soon as they are used in the CTC.
5. Health workers are trained in advance of the campaign to understand the conditions under which the CTC can be used and to maintain traditional cold chain precautions up to the point that the vaccine enters the CTC.

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 districts 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. For MenAfriVac™, see: http://www.who.int/immunization/documents/WHO_IVB_13.04_5_6/en/

8. 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, the use of the additional flexibility offered by the CTC may not be needed. Advantages and disadvantages of CTC have to be assessed in each case.

9. 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 available, limited or expensive. It would however be best to implement the CTC throughout an entire district rather than within specific areas or health centres of that district, as this may not be cost-efficient and could carry the risk of confusing health personnel.
10. 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. This is why raising awareness about this option and ensuring that countries’ need for CTC licensed vaccines is made known has become a high priority for WHO. On 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 requests. WHO is facilitating the development of guidelines to support such regulatory assessment. These guidelines are expected to be available during the course of 2015.

11. What has been published on CTC?

The following publications relating to CTC can be consulted for further information:

- Zipursky et al. *Benefits of using vaccines out of the cold chain: Delivering Meningitis A vaccine in a controlled temperature chain during the mass immunization campaign in Benin*
- Lydon et al. *Economic benefits of keeping vaccines at ambient temperature during mass vaccination: the case of meningitis A vaccine in Chad*

In addition, the online forum hosted on TechNet-21.org features discussions related to CTC: [http://www.technet-21.org/forum/controlled-temperature-chain](http://www.technet-21.org/forum/controlled-temperature-chain)
Meningitis A and CTC:

Currently, the vaccine MenAfriVac™ is the only vaccine licensed and labelled for CTC use. MenAfriVac™ has been shown to remain effective at temperatures of up to 40°C for a single period of up to four days just prior to its administration. Safety and efficacy have been key considerations throughout the process of re-labelling MenAfriVac to allow for its use in a CTC. Specific guidelines on using CTC during a MenAfriVac™ campaign can be found here:

http://www.who.int/immunization/documents/WHO_IVB_13.04_5_6

1. Is financial support available for countries interested in using a CTC strategy?

Gavi, the vaccine alliance, offers to provide extra support for countries adopting a CTC approach. Countries should however submit an application, with a plan and budget to support their request. The application should describe how, where and when the country will use the CTC approach and compliance with the WHO implementation guidelines will be ensured.

Delivery of MenAfriVac™ through a CTC does not apply to routine immunization. CTC can only be applied during campaigns, whether initial preventive mass vaccination campaigns or catch up campaigns.

2. What type of support is given to countries which may want to use CTC?

WHO can support countries implementing a CTC approach with training, supervision and/or monitoring.

3. When can countries start planning for the use of MenA in a CTC?

As soon as countries plan to conduct a MenAfriVac™ campaign, they should assess the need for a CTC approach as well as their needs for training and supervision in order to determine whether they would like to adopt a CTC approach. Planning for a CTC strategy should start at least two months prior to the start of the campaign.