HPV vaccine delivery through a controlled temperature chain

A guide for decision-makers and implementers

World Health Organization

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PREFACE

Three licensed human papillomavirus (HPV) vaccines – a bivalent, a quadrivalent and a nonavalent vaccine – are now being marketed in many countries throughout the world. With regard to cervical cancer prevention, all of these HPV vaccines provide high protection against HPV-16 and HPV-18, the HPV types which are associated with 71% of cervical cancer cases globally. The vaccines are also highly efficacious in preventing precancerous cervical lesions caused by these virus types, and have excellent safety, efficacy and effectiveness profiles.

The need to keep vaccines in a 2°C to 8°C cold chain can be a constraining factor for many immunization activities, particularly when transporting vaccines to remote populations.

In June 2016, the licensure and prequalification for the quadrivalent HPV vaccine (Gardasil®, Merck & Co., Inc., Kenilworth, NJ) were modified to allow for storage of the vaccine during three days prior to administration at temperatures of up to 42°C in a controlled temperature chain (CTC), based on a thorough review of scientific data by regulatory authorities and the World Health Organization (WHO). This labelling was further revised in June 2022 to extend CTC flexibility to four days for temperatures not exceeding 40°C.

Since June 2022, Merck's Gardasil®4 – a quadrivalent human papillomavirus (HPV) vaccine – is licensed and prequalified for use in a controlled temperature chain (CTC), allowing this vaccine to be kept outside of the traditional cold chain range of 2°-8°C, at temperatures up to 40°C for four days prior to administration.

The label variation process has resulted in a package insert for Gardasil®4, stating:

- Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.
- Data from stability studies demonstrate that the vaccine components are stable for 96 hours when stored at temperatures from 8°C to 40°C. At the end of this period, Gardasil should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Delivery of HPV vaccine through a CTC was piloted in fall 2017 in Uganda. This offered an initial opportunity to test this delivery approach and document lessons on how to optimize its implementation and ensure its successful and effective application (World Health Organization, Using the HPV vaccine in a Controlled Temperature Chain (CTC) in Uganda - a pilot project (Final Report), 2018).

OBJECTIVES OF THIS GUIDE

This document:

- defines the standard operating procedures (SOPs) for the implementation of HPV vaccine delivery using a controlled temperature chain (CTC);
- is meant to serve as a guideline document that assists country-level decision-makers and health workers through the planning, implementation, and post-outreach phases of HPV delivery using the CTC strategy;
- incorporates the lessons learned from the 2017 Uganda HPV-CTC pilot project;
- is adaptable for use with all HPV vaccines approved for administration in a CTC, irrespective of product type.

INTENDED AUDIENCE

The target audience for this document includes:

- immunization programme managers at the national level, e.g. EPI managers and logisticians;
- regional supervisors;
- health workers.

ACKNOWLEDGEMENTS

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WHO would like to thank the WHO Immunization Practices Advisory Committee (IPAC) members and participants of the WHO IPAC meeting on 10-12 July 2018 in Geneva, Switzerland and the members of the WHO Working Group on the Controlled Temperature Chain (CTC-WG) for their careful review of the multiple iterations of this document and the extensive feedback and input enabling this current version.

This guide was developed based on the findings of the 2017 Uganda CTC-HPV Pilot Project and the programmatic recommendations outlined in the WHO Guide to introducing HPV vaccine into national immunization programmes. **This guide was last updated in July 2022.**

LIST OF ACRONYMS

AEFI	adverse event following immunization
CTC	controlled temperature chain
CTC-WG	controlled temperature chain working group
EPI	Expanded Programme on Immunization
HPV	human papillomavirus
ICC	Inter-agency Coordinating Committee
IPAC	Immunization Practices Advisory Committee (WHO)
IVB	Department for Immunization, Vaccines and Biologicals, WHO Geneva
MOH	Ministry of Health
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority
PTTI	peak temperature threshold indicator
SOP	standard operating procedure
TT	tetanus toxoid
VVM	vaccine vial monitor
WHO	World Health Organization

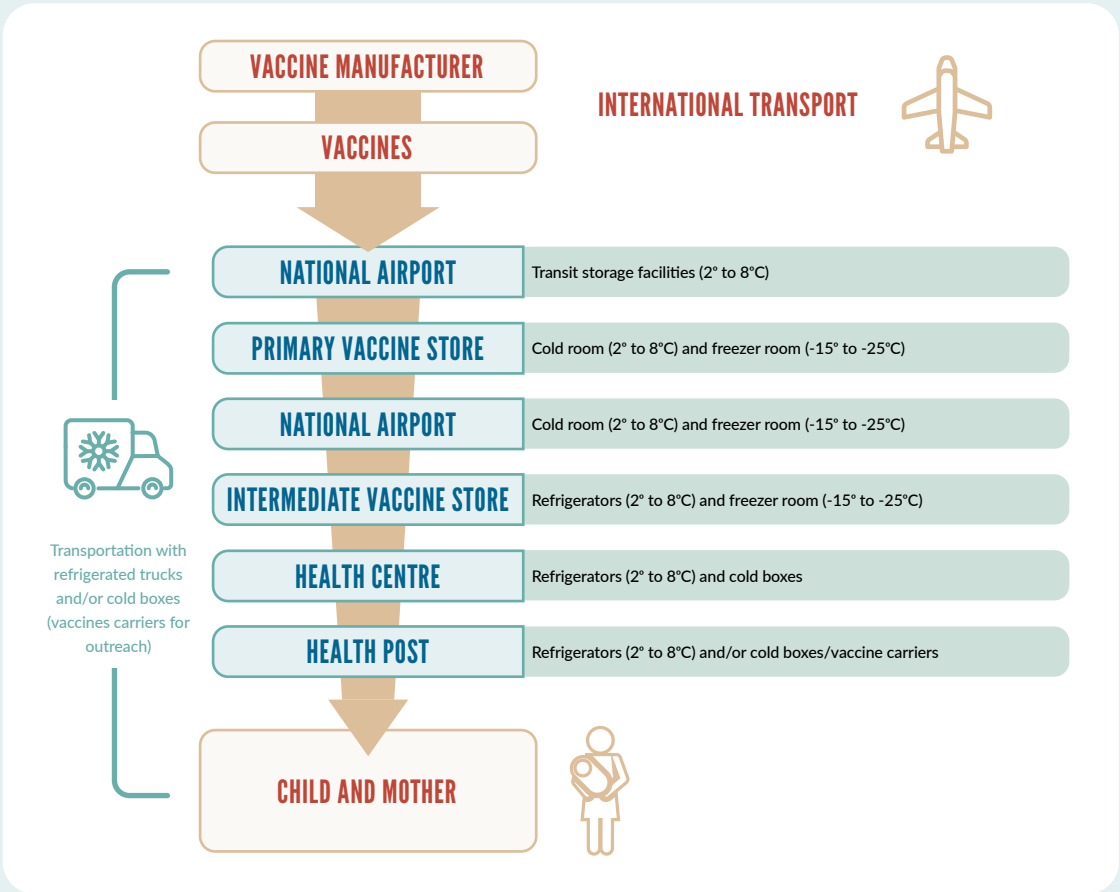
1 INTRODUCTION

1.1 THE TRADITIONAL COLD CHAIN APPROACH

Vaccines are sensitive to heat and freezing and must be kept at the recommended temperature range from the time they are manufactured until they are delivered to the recipient. The cold chain is a system that calls for an uninterrupted series of storing and transporting activities, designed to keep vaccines within an acceptable temperature range until they reach the user (Figure 1).

More information about the cold chain is available in the World Health Organization's training guide, *Immunization in Practice: A practical guide for health staff* (World Health Organization, Immunization in practice: a practical guide for health staff - 2015 update, 2015).

FIGURE 1. THE COLD CHAIN



1.2 THE CONTROLLED TEMPERATURE CHAIN

Many vaccines used in immunization programmes today are actually more heat stable than is reflected in their current labelling.[1] Keeping vaccines in a traditional 2°C to 8°C cold chain range may be challenging in settings with limited cold chain and ice pack freezing and conditioning capacity.

1.2.1 Definition of the controlled temperature chain (CTC)

The "controlled temperature chain" (CTC), an innovative approach to vaccine management, allows vaccines to be kept at temperatures outside of the traditional cold chain range of 2°C to 8°C for a limited period of time and 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 has established the following programmatic criteria for a vaccine to be labelled for and used in a CTC (World Health Organization, Controlled temperature chain: Beyond the traditional cold chain, 2017).

1. The vaccine should be used in a campaign or special strategy setting. CTC is not currently recommended for immunization through routine delivery or in combination with other non-CTC approved vaccines.
2. The vaccine must be able to tolerate ambient temperatures of at least 40°C for a minimum of three days and should be accompanied by:
    a. a vaccine vial monitor (VVM) on each vial, and
    b. a peak temperature threshold indicator (PTTI) in each vaccine carrier.
3. The vaccine must be licensed for use in a CTC by the relevant regulatory authorities, with a label that specifies the conditions.

1.2.2 How does the controlled temperature chain differ from the traditional cold chain?

There are similarities and differences between the traditional cold chain and the controlled temperature chain (Table 1.).

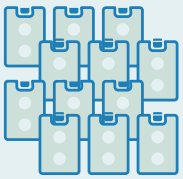
If both modalities are implemented correctly and the controlled temperature chain is used strictly for CTC-approved vaccines, the safety and potency of the vaccines are preserved. In addition, adverse events are monitored in both methods but, for the controlled temperature chain (CTC), it must be noted that the vaccine was given under a CTC.

Whereas a temperature of 2°C to 8°C must be maintained in the traditional cold chain from the time the vaccine is manufactured to the time it is given to the vaccine recipient, the CTC currently permits maintenance in ambient temperatures of up to 40°C for a specified permissible number of days prior to use. This means that no ice packs or cool water packs are needed in vaccine carriers for at least the last mile in the CTC. This reduces need for freezers and personnel needed to maintain cold chain requirements and, in turn, decreases costs compared with the traditional cold chain setting. Depending on the level at which the health system CTC is initiated – district level, health centre level, etc. – the savings may even be greater.

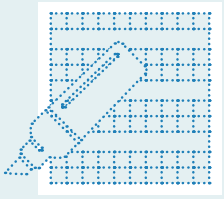
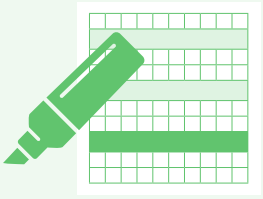
1 The term "labelling" in the context of this document is not restricted to text appearing on primary and secondary vaccine packaging but refers instead to the regulatory-approved indication and instructions appearing in a vaccine product's package insert.

In addition to the VVM, which is needed to monitor cumulative exposure to heat in both the traditional cold chain and controlled temperature chain settings, a PTTI is needed in the CTC to monitor exposure to high temperatures. Whereas the VVM is put on the vaccine vial itself by the manufacturers, the PTTI is added to the vaccine carrier or cold box at the start of the CTC. There is also the need for additional training, monitoring and supervision when implementing the CTC.

TABLE 1. COMPARING THE TRADITIONAL COLD CHAIN APPROACH WITH THE CONTROLLED TEMPERATURE CHAIN FOR HPV VACCINES

TRADITIONAL COLD CHAIN FOR HPV VACCINES	CONTROLLED TEMPERATURE CHAIN (CTC) FOR HPV VACCINES
Vaccine label indicates 2°C to 8°C for all storage and transport. 	Vaccine label/product insert indicates 2°C to 8°C for initial storage and transport,[2] and permits up to 40°C for at least 3 days prior to use. 
Vaccine vial monitors protect potency[3] and quality by monitoring cumulative exposure to heat. 	Vaccine vial monitors and peak temperature threshold indicators protect potency[3] and quality bymonitoring cumulative and peak exposure to heat, respectively. 
Conditioned ice packs[4] or cool water packs are required in vaccine carriers. 	No conditioned ice packs or cool water packs are required in vaccine carriers for the last mile.[5] Reduced risk of freezing. 
No need for additional CTC-specific training, monitoring or supervision[6]. 	Health workers need additional CTC-specific training, monitoring and supervision. 

2 Up to the level of the immediate vaccine store/health centre/health post, depending on the level where CTC is initiated.
3 Freeze-sensitive vaccines, in addition to using the VVM and PTTI to monitor cumulative and peak exposure to heat respectively, will require a shake test to test a vial that is suspected of freezing.
4 Conditioned ice packs contain a mixture of water and ice at initial temperatures of about 0°C. An ice pack is correctly conditioned when it has melted enough to allow the ice to move inside the pack.
5 The last mile is the final step or journey to reach every child, adolescent or adult who needs to be immunized. For example, from the health centre or health post to the vaccine recipient.
6 The outreach staff might need other additional training not related to CTC.

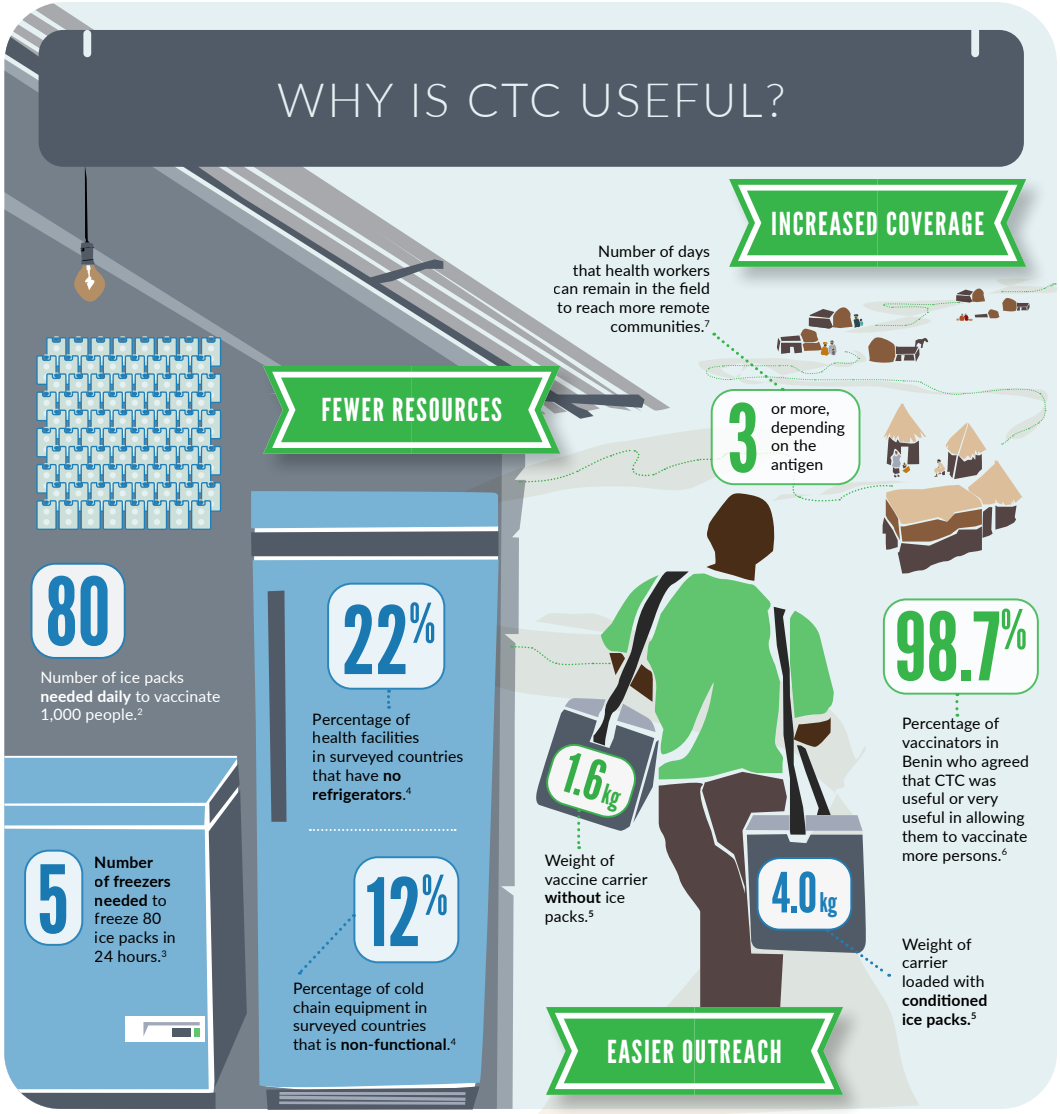
TRADITIONAL COLD CHAIN FOR HPV VACCINES	CONTROLLED TEMPERATURE CHAIN (CTC) FOR HPV VACCINES
Preserves the safety and potency of the vaccine, when implemented correctly. 	Preserves the safety and potency of the vaccine, when implemented correctly. 
Requires cooling equipment, transport and human resources at all levels to maintain cold chain. 	Halves the cost of maintaining a cold chain and logistics system.[7,8] Fewer freezers, fewer journeys and less staff time are needed to manage and maintain cold chain requirements. 
No need for extra materials such as PTTI cards, indelible markers or CTC monitoring sheets. 	Extra materials such as PTTI cards, indelible markers and CTC monitoring sheets are needed during the implementation phase. 
At the time the HPV vaccine is to be given, only two conditions must be met: the vaccine has not expired; and the VVM status shows it is useable. 	At the time the HPV vaccine is to be given, four CTC conditions must be met without exception: the vaccine has not expired; the VVM status shows it is useable; the PTTI status shows it is useable; and the vial has not been in the CTC for more than 4 days. 
Monitoring of adverse events following immunization is conducted as usual. 	Monitoring of adverse events following immunization is conducted, but it must be noted that the events occurred while following a CTC approach.[9] 

7 The calculations here assume that the controlled temperature chain starts at the level of district storage and they do not take into account the extra costs of CTC-specific training.

8 Lydon P., et al. Economic benefits of keeping vaccines at ambient temperature during mass vaccination: the case of meningitis A in Chad. WHO Bulletin. 2014; 92:86-92. Available at http://www.who.int/bulletin/volumes/92/2/13-123471/en/

9 It is good to note if CTC was used on the AEFI form, so that CTC can be ruled out or not, as being causal.

FIGURE 2. WHY IS CTC USEFUL?



Adapted from: What is a controlled temperature chain (CTC)? An infographic, available at: http://www.who.int/immunization/programmes_systems/supply_chain/resources/WHO_CTC_Infographic.pdf?ua=1

2 WHY CONSIDER A CTC?

CTC helps to address cold chain issues at the health centre level and for last-mile transport. CTC alleviates some of the need for surge cold-chain capacity required to accommodate school-based or community outreach programmes. It also provides an alternative in places where the cold chain is a challenge or icepack production is a constraining factor during outreach programmes.

Introducing the CTC approach is an opportunity to strengthen the national immunization programme and health system as it reduces some supply chain barriers and increases coverage levels by extending reach of immunization with innovative vaccines. However, there are requirements associated with this new modality, such as understanding the regional or local variations in cold chain practice and constraints; additional CTC-specific training and supervision; modification of old training/supervision materials; acquisition of new materials such as indelible markers, PTTIs and CTC monitoring forms; and proper delineation of the target population, as unused vials cannot be returned into the traditional cold chain. The 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 or regions where the flexibility offered by this innovation will simplify the logistics of the vaccination activity, for example by addressing cold chain constraints and/or challenging outreach conditions (World Health Organization, The controlled temperature chain (CTC): frequently asked questions, 2016). The World Health Organization further recommends a phased approach of establishing HPV vaccination under the traditional cold chain approach prior to adopting CTC for improved delivery.

The following tables provide some more details on the advantages of using the CTC approach (Table 2) and costs/risks of implementing a CTC (Table 3). Some relevant results from a recent pilot study have also been included in each of these tables. As Figure 3 illustrates, careful consideration must be given to the trade-offs between maintaining the traditional cold chain or delivering vaccine through a CTC. While the risks associated with the CTC are expected to be outweighed by the benefits, this is a programmatic decision that must be made by the national immunization programme, taking into account the multiple constraints with which it is confronted and assessing whether CTC will bring genuine relief and efficiency to HPV delivery activities.

TABLE 2. ADVANTAGES OF IMPLEMENTING A CTC

ADVANTAGES OF CTC	COMMENT
INFRASTRUCTURE	
Reducing cold chain needs. Removing a vaccine from the cold chain to enter a CTC reduces the space needed within the cold chain.	
No need for ice packs. No additional freezer capacity is needed for ice packs and more vaccines can be carried in one vaccine carrier.	In a recent HPV-CTC pilot study, in each of the 4 districts sampled (2 intervention and 2 control), more than 20% of the health facilities did not have functioning freezing equipment.
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 ice packs, the vaccine carrier remains dry.	In a recent HPV-CTC pilot study, at least 80% of health workers interviewed in the 2 intervention districts agreed that the CTC approach facilitated their work because the vaccine carriers remained dry.
Fewer problems with freeze-sensitive vaccines. For freeze-sensitive vaccines such as HPV, the CTC approach adds value, because it eliminates the risk of vaccines freezing if directly adjacent to an ice pack when carried in the vaccine carrier.	
NATIONAL IMMUNIZATION PROGRAMME	
Saving of staff time. There is no need to train staff to use the cold chain[10], and less time is required to plan and manage additional cold-chain requirements, such as ice pack freezing and conditioning and transportation issues. The time saved can be reallocated to supervisory and field activities.	
Increased ease of vaccine transportation. Since the vaccines can be put in the vaccine carrier without conditioned ice packs, the volume and weight that need to be transported by health workers will be reduced.	A commonly used WHO prequalified vaccine carrier has a capacity of 1.7 L and weighs 1.6 kg when empty, but 4.0 kg when fully loaded with vaccines and the required 4 conditioned ice packs.[11,12] A recent HPV-CTC pilot study found that at least 90% of interviewees in both intervention districts agreed that the CTC approach facilitated their work because the vaccine carriers were lighter.
Increased vaccine coverage. With the 4-day allowable limit for HPV under CTC, health workers can travel further, thereby reaching usually unreached remote villages and increasing coverage and equity.	A recent HPV-CTC pilot project showed that in both intervention districts, at least 90% of the interviewed health workers agreed that the CTC approach allowed them to go further with just a few vaccines to find more girls.

10 However, there will be additional training about how to deliver vaccines in CTC.
11 What is a controlled temperature chain (CTC)? An infographic , available at: http://www.who.int/immunization/programmes_systems/supply_chain/resources/WHO_CTC_Infographic.pdf?ua=1
12 Vaccine carriers, available at http://www.blowkings.co.in/vaccine-carriers.html

ADVANTAGES OF CTC	COMMENT
FINANCIAL	
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.	At least 80% of health workers interviewed in a recent HPV-CTC pilot study agreed that the CTC approach facilitated their work because they did not have to worry about the cold chain during the vaccination day.

Adapted from: The controlled temperature chain (CTC): frequently asked questions, available at: http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf

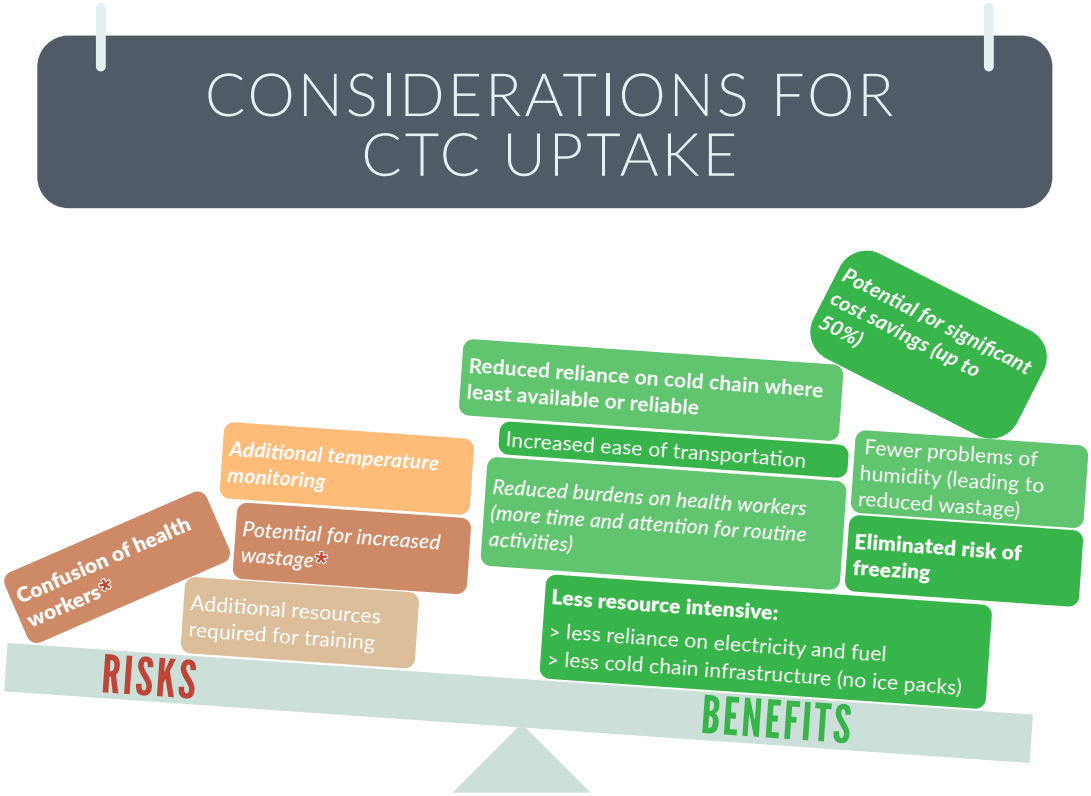
TABLE 3. COSTS/RISKS OF IMPLEMENTING A CTC

COSTS/RISKS OF IMPLEMENTING A CTC	COMMENT
Risk of confusion. As CTC is a new practice, concern has been expressed regarding the potential risk of confusion among health workers about which vaccines can be used in a CTC, especially with subsequent campaigns involving non-CTC eligible vaccines.	Possible health worker confusion is a good index to measure when delivering HPV vaccine in a CTC setting. However, experience so far has shown that health workers are able to distinguish between CTC- and non-CTC-eligible vaccines.
Start-up costs. CTC requires one PTTI per vaccine carrier or equivalent. These are low-cost paper cards with a temperature-sensitive sticker that cost under US$1 each, depending on the quantities needed. Note that PTTIs can be reused as long as they have not been damaged and the inner circle has not turned black. Other materials needed include indelible markers and monitoring forms.	
Vaccine wastage. Higher levels of closed-vial vaccine wastage may be seen in the CTC context if the vials need to be discarded because the vaccine have been exposed to temperatures above 40°C, or if the time limit (maximum number of permitted days) has been exceeded. Thus, in order to avoid unnecessary wastage, it is essential to make proper estimates of the target population and, if possible, avoid taking vials out of the cold chain at the end of the school week, since school-based vaccinations cannot occur over the weekend. In addition, good communication protocols among supervisors monitoring the various vaccination teams can ensure that teams which have completed vaccination of their target population can give their remaining marked vials in the CTC to teams that are yet to complete their vaccination sessions in order to reduce wastage.	In a recent HPV-CTC pilot study, one of the intervention districts recorded a 2.09% closed-vial wastage rate versus 6.2% in the other intervention district. Closed vial wastage was not recorded in the non-intervention districts.
Operations. Initially, additional time and resources may be required to familiarize vaccinators and supervisors with this new approach.	

Adapted from: The controlled temperature chain (CTC): frequently asked questions, available at: http://www.who.int/immunization/programmes_systems/supply_chain/resources/Controlled-Temperature-Chain-FAQ.pdf

FIGURE 3.

CTC BALANCE SCALE



* Easily mitigated through adequate training and supervision – no evidence of this problem in all CTC experience to date.

3 NATIONAL LEVEL DECISION-MAKING

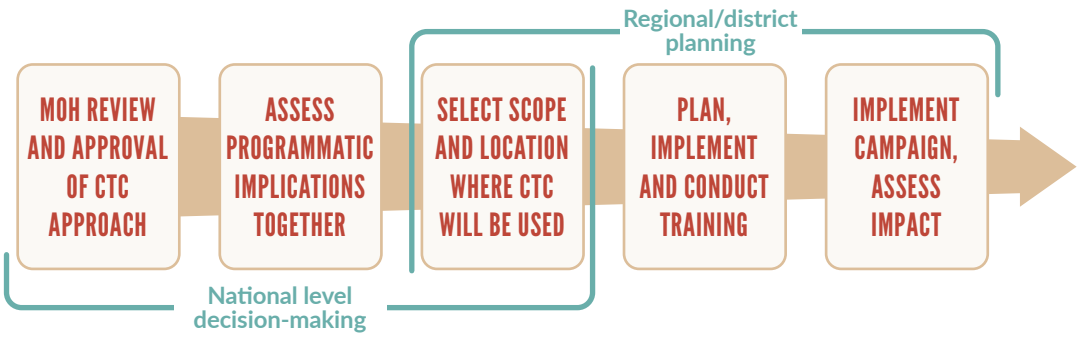
3.1 MINISTRY OF HEALTH AND NATIONAL REGULATORY AUTHORITY REVIEW AND APPROVAL

In most cases, CTC will be integrated into an existing HPV vaccination programme. The World Health Organization recommends a phased approach, calling for establishing HPV vaccination under the traditional cold chain approach prior to adopting CTC for improved delivery.

It is essential that the national immunization programme approves the use of a CTC approach in defined areas or conditions based on the recommendation of the National Immunization Technical Advisory Group (NITAG) and the licensing of the National Regulatory Authority (NRA) (if applicable). As with other decisions pertaining to the national immunization programme, the responsibility for choosing to use (or not to use) the CTC approach lies with the national government (Figure 4).

Prior to further planning, it is important to ensure that the CTC-approved HPV vaccine is approved for use in the country where the CTC campaign is to take place and that its registration includes the CTC storage conditions.

FIGURE 4. DECISION-MAKING: NATIONAL AND REGIONAL/DISTRICT LEVELS



3.2 ASSESSMENT OF PROGRAMMATIC IMPLICATIONS

3.2.1 Engagement of key decision-making bodies

Given that there are trade-offs to consider before selecting a CTC approach, it is important to consult with partner or technical coordination groups, such as the Inter-agency Coordinating Committee (ICC)[13] and/or the NITAG,[14] before choosing to undertake a CTC strategy. These groups should be asked to advise on the issues described in Table 2, "Advantages of implementing a CTC"; Table 3, "Costs/risks of implementing a CTC"; and Figure 3, "CTC balance scale".
The variety of viewpoints and expertise contained in these groups will help ensure all key considerations are fully examined. If your country does not have an ICC and/or a NITAG, consider using an existing immunization technical working group or setting up an ad hoc group to assess the CTC approach. When constituting the ad hoc group, all key immunization partners should be represented, and the group should be chaired/managed by the MOH or the Expanded Programme on Immunization (EPI).

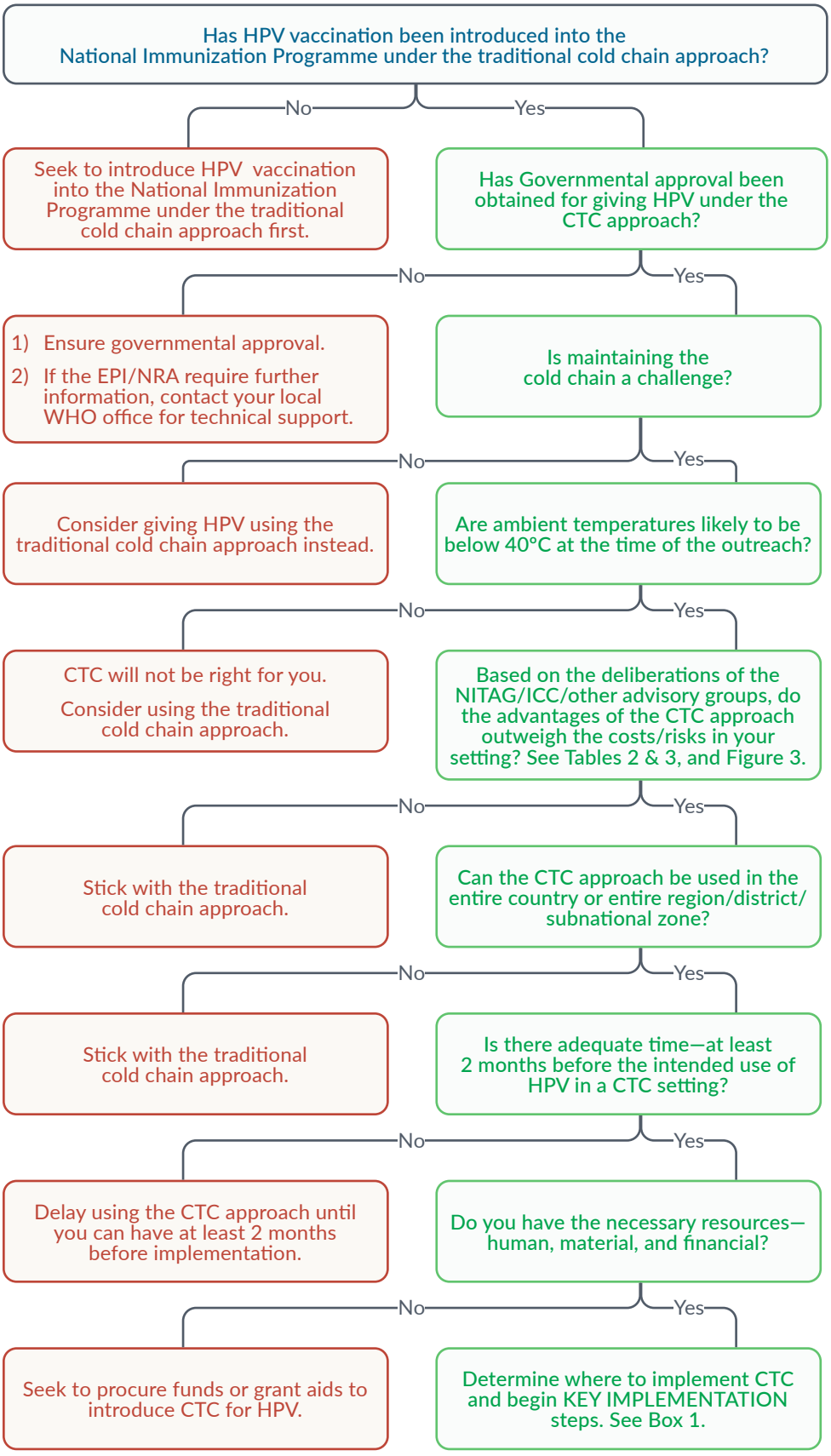
3.2.2 Factors to consider when implementing a CTC

- **A clear need.** The gains of implementing a CTC are most appreciated when there is a clear need for its implementation, such as cold chain constraints or challenging outreach conditions.
- **Capacity requirements.** To implement a CTC, there should be an existing:
  - Store vaccines for four days at up to 40°C.
  - stock of materials and vaccines
  - capacity to assess the target population
  - capacity to develop clear micro plans.
- **Resource and time requirements.** A CTC is an innovative approach that, especially when first introduced, requires resources and time for developing and distributing training and monitoring tools. If you have never conducted an outreach using CTC, and if your outreach is less than two months away, there is unlikely to be enough time to plan properly for a CTC, and a traditional cold chain approach might remain more appropriate.
- **Human resources and training.** Appropriate supervision and monitoring are key for successful CTC implementation. This requires adequate numbers of motivated, trained and committed district and regional staff members, who are able to supervise vaccinators effectively and respond to questions during the outreach.
- **Assessing the trade-offs.** While there are clearly gains and benefits to using Gardasil®4 (or other CTC-approved HPV vaccines) in a CTC, there are also costs and risks associated with it. See Tables 2 & 3 and Figure 3.

Figure 5 illustrates a decision-tree algorithm that walks you through the factors to consider before implementing a CTC (Figure 5). Box 1 gives an at-a-glance view of key CTC implementation steps. A detailed CTC implementation timeline is provided in Annex 1.

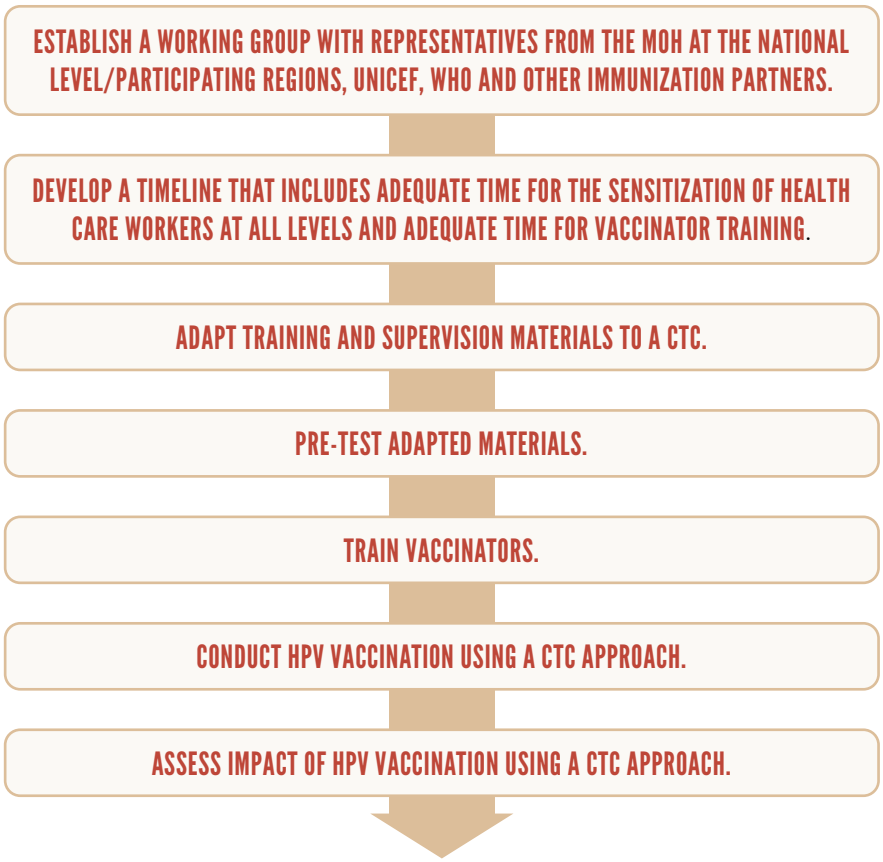
13 ICCs are made up of representatives of the Ministry of Health (MOH), WHO, UNICEF and other domestic and external partners. They improve coordination among partners for the support of the national immunization programme.
14 NITAGs are multidisciplinary groups of national experts – such as senior pediatricians, immunization and vaccine experts, epidemiologists, public health experts, health economists, health systems experts and social scientists – responsible for providing independent, evidence-informed advice to policy makers and programme managers on policy issues related to immunization and vaccines.

FIGURE 5. DECISION-TREE ALGORITHM FOR CTC IMPLEMENTATION



BOX 1.

KEY IMPLEMENTATION STEPS FOR HPV VACCINATION USING A CTC APPROACH



4 REGIONAL/DISTRICT LEVEL DECISION-MAKING

4.1 DECISION-MAKING PROCESS

Once the decision has been made to use a CTC approach for HPV vaccination, it is important to decide on where, when and how the CTC will be implemented as well as the content of the CTC training.

These decisions should be made in consultation with the ICC, NITAG, technical working groups and/or other advisory bodies. This chapter will help with decisions as to where and when the CTC can be implemented as well as the content of the CTC training. Chapter 5 will discuss how the CTC can be implemented, presenting the different scenarios for CTC implementation in detail.

Before making final decisions, it is important to conduct a mapping exercise to identify those parts of the country where equity and coverage are currently a challenge. In addition, the peak ambient temperature during the time of the vaccination period must be considered. A good starting place for ambient temperatures is the World Meteorological Organization's Africa Initiative at acmad.org or sites such as weatherbase.com, or wolframalpha.com (for WolframAlpha, please enter "climate <place name>" to get a result. For example, in determining the temperature in Nairobi, Kenya, you would need to enter: climate Nairobi, Kenya).

4.1.1 Resources to support the decision-making process

The following aspects have to be taken into consideration when deciding on where, when and how the CTC will be implemented as well as the content of the CTC training.

» **District mapping (Tables 4 & 5).** This will be helpful in identifying areas where CTC could help address challenges or concerns – such as cold chain challenges and long distances, and areas where outreach forms a large proportion of the vaccination strategy. If HPV vaccination was introduced into the national immunization programme before introducing the CTC approach, the mapping data should already be available.

TABLE 4. DISTRICT MAPPING

DISTRICT	TOTAL POPULA-TION	TARGET POPULA-TION	# OF HEALTH CENTRES WITH FREEZING CAPACITY	# OF SCHOOLS	# OF OUTREACH POSTS	DISTANCE FROM CAPITAL

TABLE 5. HEALTH FACILITY MAPPING

NAME OF HEALTH FACILITY	NAME OF SCHOOL	SCHOOLS: # OF GIRLS/ DISTANCE TO HEALTH FACILITY		STATE OF ROAD	OUTREACH POSTS: # OF GIRLS/DISTANCE TO HEALTH FACILITY	

- **Cold-chain inventory.** If a recent cold-chain inventory is available, its data can be used to assess if there are problems with cold chain capacity and ice pack conditioning. Cold-chain challenges might be heightened during the HPV vaccination activity due to the surge capacity required and the large number of ice packs needed. In areas where cold-chain equipment is non-existent, insufficient or not functioning, CTC may offer significant advantages. In addition to the cold chain inventory, it will be important to assess cold chain options in the schools where vaccination will take place.
- **Energy issues/constraints.** If your cold-chain equipment uses gas or kerosene, and if shortages are occurring in any parts of the country, CTC may be a good solution to overcome these constraints. Similarly, if the majority of equipment is electricity based, and if there are supply problems or expected interruptions, these areas may be priorities for CTC.
- **Peak ambient temperature.** A mapping of temperatures in each district, including highs and lows during the planned vaccination dates (if the HPV vaccine is delivered in a campaign mode), or throughout the year (if the HPV vaccine is delivered in Health Facilities as part of the routine programme) is essential. If the ambient temperature in certain districts is likely to reach or exceed 40°C during the planned vaccination dates, keeping the HPV vaccine at ambient temperature cannot be done safely and a cold chain will be required for vaccination in these districts.
- **Vaccine supply.** It is essential to ensure that there are enough vaccines present at the district/ regional storage facility for the intended outreach. Having sufficient vaccines, up to the target population totals for girls in school and out of school, is essential. There also should be a back-up supply, in case the vaccination teams from the health facility run out of vaccines for a given excursion.

4.2 DECIDING WHERE TO IMPLEMENT A CTC – SCOPE AND LOCATIONS FOR CTC USE

CTC may be used across the country, or it may be applied only in specific districts. At a minimum, however, it is best to implement CTC throughout an entire district, region or subnational zone. Do not select only specific areas, schools or specific health centres within a district, region or subnational zone. Implementing CTC in only parts of a district may not be cost effective, and partial implementation carries the risk that health personnel will be confused. Consider how the CTC training and supervision will be conducted. Note that, ideally, CTC supervision and monitoring should be integrated in the overall vaccination activity and should not require additional supervisory staff.

As you decide where to implement CTC, it is important to take the following into consideration.

- Rather than having isolated districts implementing CTC, it may make sense to "group" districts into CTC areas, which will make supervision and training easier.
- It is recommended to initiate the CTC approach on a small scale, e.g. one or two districts, regions or subnational zones such as states/provinces with different characteristics such as urban/rural, high/low coverage or different levels of school attendance. This planning will allow the national immunization program to:
  - finetune training, supervision, monitoring and microplanning efforts;
  - consider whether the gains of the CTC approach outweigh the costs.

4.3 WHEN TO IMPLEMENT A CTC

This section explains planning of the implementation timeline and the level at which CTC will start.

4.3.1 Planning the implementation timeline

It is important to recognize that implementing CTC-based vaccination is a departure from the standard vaccination management practice. As mentioned in Chapter 3, it is recommended that the decision to implement a CTC is made at least two months prior to the start of vaccination (see Annex 11.1 for sample CTC implementation timeline). This will allow the proper time to initiate activities at national level and at subnational, regional or district levels.

National level

- Select districts/regions/subnational zones of the country where CTC will be conducted.
- Order peak temperature threshold indicators and print the cards.
- Brief regional and district staff.

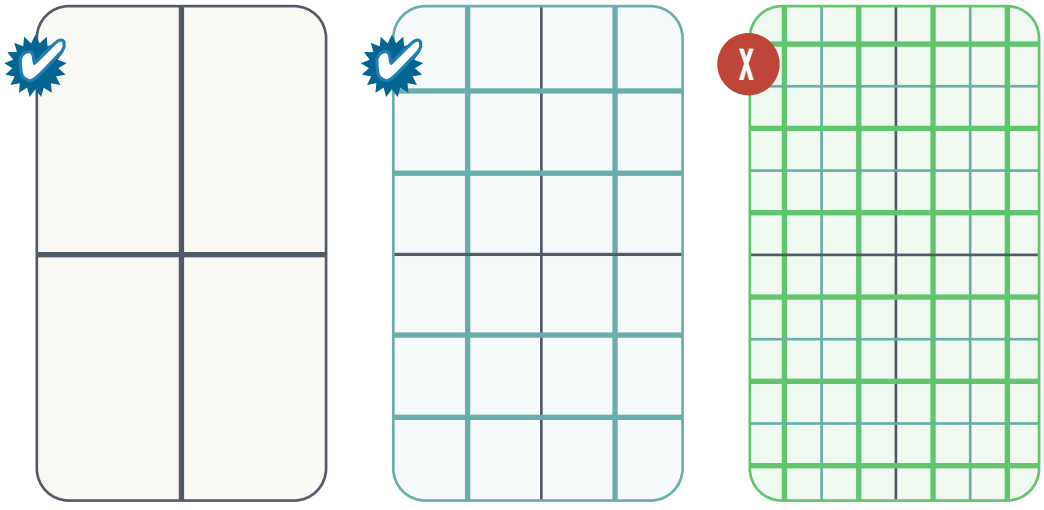
Subnational/regional/district level

- Finalize areas where CTC will be implemented within the subnational zone/region/district.
- Decide at what level of the health system to start the CTC.
- Adapt training materials for the local context.
- Develop appropriate micro plans, including guidance on transportation and running an immunization session under a CTC.
- Adapt supervision tools and forms for CTC use.
- Train subnational, regional, district and health-care worker staff.

It is worth emphasizing here that CTC should not be implemented at a level lower than the 3rd administrative division. For example, the nation, may be divided into states, which are further divided into districts. These districts may be made up of counties which contain multiple health centres and/or catchment areas. CTC should be implemented in the entire state or district, not just in certain counties in a district. Implementation at levels smaller than a district, implies a higher complexity of planning, training and supervision, as well as distribution of supplies (ie. PTTIs), which makes management and oversight too difficult. There is also a higher risk of confusion when policies vary from one county to another. Figure 6 gives a diagrammatic representation of the appropriate administrative level to conduct a CTC.

FIGURE 6.

APPROPRIATE ADMINISTRATIVE-LEVEL DIVISIONS FOR CTC IMPLEMENTATION



4.3.2 Start of CTC

It is also important to determine at which level to start the CTC. Will the vaccine stay in the standard 2°C to 8°C cold chain until the district level or the most peripheral health facility, after which it will be managed in a CTC until administration? The availability of functional cold chain capacity or refrigeration at the district level or health centre is a critical factor in determining where CTC starts. Another factor to consider in the decision will be the outreach micro-planning, and the expected transit time to service delivery site.

An economic benefit study in Chad compared a modeled CTC scenario between the initiation of district-level storage and vaccination, with the actual December 2011 mass vaccination campaigns against meningococcal meningitis which used the traditional cold chain approach. It found that the CTC scenario provided a substantial 50% savings (Lydon, et al., 2014). The exact scenario chosen for the implementation of CTC could affect the savings realized (more details on the CTC scenarios can be found in Chapter 5).

4.4 CTC TRAINING, EDUCATION AND INFORMATION

When CTC is a new practice, it is important to train supervisors and health-care workers properly. In addition, it is important to ensure all logisticians as well as partner organizations are informed and educated about CTC.

The *Guide to introducing HPV vaccine into national immunization programmes* (World Health Organization, Guide to introducing HPV vaccine into national immunization programmes, 2016), provides detailed information on conducting HPV vaccination outreach under the traditional cold chain approach and should serve as a reference material for all things pertaining to HPV vaccination. This guide on HPV vaccination through a CTC approach is complementary to the afore-mentioned guide.

Ideally, one full day should be dedicated to CTC training to make sure that all personnel involved feel comfortable and confident using this new approach. If available, HPV vaccination micro plans should be used for CTC training.

In case HPV vaccination takes place in schools, it will be important to include information about CTC in the orientation for teachers and headmasters to make sure they are aware and do not provide contradicting information about cold chain requirements for the CTC-approved HPV vaccine.

A training module of slides dedicated to HPV vaccination using the CTC approach is available on request from WHO. Training materials on CTC need to be prepared (or translated) in the appropriate local language and in sufficient quantities. Summarized reference materials and job aids should be developed and given to the participants attending training so that they have information to refer to and share with others when they return to their post. This is particularly important for cascade training. Interactive, hands-on training techniques – such as field visits, showing videos of correct practices, small group discussions, demonstrations and skills practices – are generally more successful for training adults than classroom lectures.

The following key messages need to be conveyed, should questions be raised by community leaders, teachers or others.

- ✔ The HPV vaccine is stable for use outside the cold chain for a limited period of time just prior to administration.
- ✔ There have been many tests conducted in the laboratory to ensure the HPV vaccine is still effective under these conditions.
- ✔ These tests have been validated by scientists at WHO and/or scientists in this country. The condition of the HPV vaccine is still being monitored at all times.
- ✔ Health-care workers have been specially trained in how to monitor the HPV vaccine during the vaccination in order to ensure it remains safe and potent to use before administering it.
- ✔ As part of the post-marketing and adverse events following immunization (AEFI) surveillance, the Ministry of Health, with support from WHO, is monitoring for any unexpected problems.
- ✔ This practice is only being used for the HPV vaccination. For all other immunization activities, the cold chain will still be used.

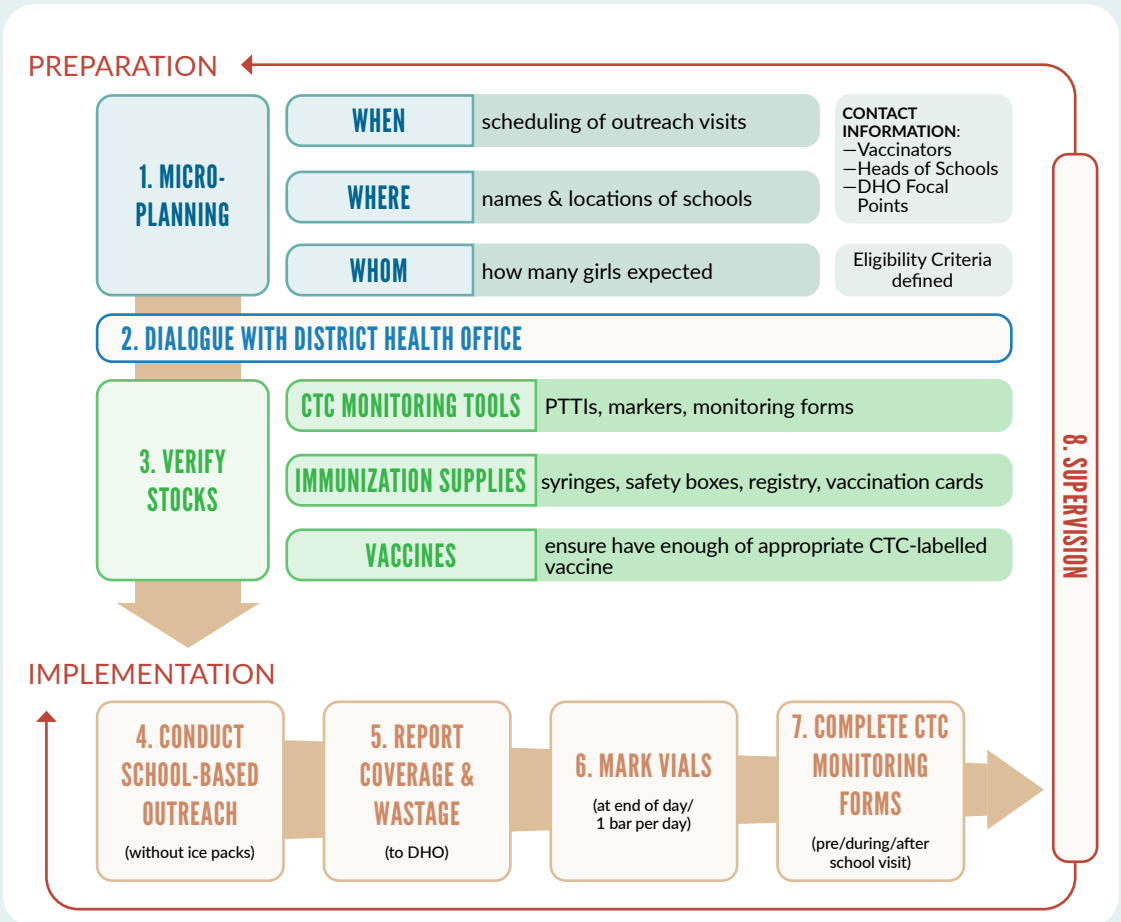
For answers to frequently-asked questions on CTC, see the section: Additional resources, located at the end of this document and which provides a link to the document *The controlled temperature chain (CTC): frequently asked questions*.

5 CTC IMPLEMENTATION AT THE HEALTH FACILITY LEVEL

As with any regular outreach immunization activities, you must carefully plan the schedule for when and where to organize the sessions if you are using the CTC (Figure 7). This is essential, as the maximum time that the vaccines can be kept in the CTC is four days, after which any unused vials must be discarded.

FIGURE 7.

CTC IMPLEMENTATION AT THE HEALTH FACILITY LEVEL



Total time allowed in a CTC = time for transport and/or storage and immunization.

5.1 PREPARATION PHASE

The preparation phase includes:

- microplanning
- dialogue with the district health office
- verification of stocks.

This section describes microplanning in detai.

5.1.1 Microplanning

The adapted microplanning checklist below takes CTC into consideration. Please refer to the *Guide to introducing HPV vaccine into national immunization programmes* (World Health Organization, Guide to introducing HPV vaccine into national immunization programmes, 2016) for the full microplanning list.

Adapted microplanning checklist: for HPV vaccine delivery at schools and outreach locations

✔ **Vaccine delivery outside of health centres, such as in schools, may result in additional costs. These costs should be planned for and associated funds secured prior to delivery.**

Costs may be reduced using CTC. For example, fuel expenses can be reduced. With CTC it will no longer be necessary to provide teams with new ice packs during the day and more vaccines can be transported at a time. The vaccine carrier's weight will also be substantially reduced, potentially allowing for the use of motorcycles or bicycles rather than cars. Additionally, teams are not obliged to return to the health facility every evening, as vaccines do not have to be put back in the cold chain at the end of the day.

✔ **Ensure that the human resources needed to carry out the outreach are arranged without disrupting services at the health centre.**

This will still apply when using CTC. However, staff time will be reduced when using CTC as health workers will not have to spend time conditioning ice packs and supervisors will not have to re-stock ice or vaccines during the day.

✔ **Map all health centres and health posts in the district, and all schools and outreach locations to be reached.**

For CTC implementation, it will be important to know the distances and travel time to the schools or other outreach locations.

✔ **Assess opportunities to combine HPV vaccination outreach with other outreach activities for integrated delivery with other health interventions.**

Please note that CTC will only be advantageous if HPV is not integrated into the delivery of other vaccines which need to be kept in the cold chain up to administration.

5.1.1.1 Preparing a work plan/microplan

The preparation of a microplan for HPV immunization usually involves the following steps.

1. **Review school-based vaccination plans.**
2. **Review the operational map of your health centre's catchment area.** If you do not already have one, you need to prepare a simple map and map all the schools.
   Consider how to reach girls living outside catchment areas of health facilities, or out-of-school and within catchment areas but geographically hard-to-reach vulnerable target-aged girls, and disadvantaged communities.
3. **Plan when to remove the vaccine from the traditional 2°C to 8°C cold chain range.** Review the different scenarios listed in 5.1.1.2 and decide which one is applicable to your situation. It is important to remember that vaccines removed from the cold chain towards the end of the week run the risk of not being used in time for the weekend and could expire prior to the beginning of the following work week.
4. **Consider the geographical situation.** Some villages might not be so far away in terms of distance. but they might be difficult to reach due to mountainous terrain or bad roads.

It is important to estimate the time it will take to immunize girls in the target age group in each immunization session. Also, take into consideration how many vaccinators there will be in each team. This will help determine how many persons the teams can immunize per session and, therefore, how many sessions they will complete in one day. It takes approximately one hour for a health worker to vaccinate 20 girls.

Planning an immunization session using CTC provides new flexibility. As you plan when and where to organize your immunization sessions during the HPV vaccination, you should consider how the CTC flexibility can allow you to reach the highest number of people in your target population and reduce transportation-related costs. The maximum time that the HPV vaccine can be kept in the CTC is four days. This is an important consideration when preparing your work plan.

It is important to note here that the WHO-approved vaccine carrier is the best mode of transportation of the vaccines. The only change when using CTC is the removal of ice packs.

If you are starting CTC from the health centre, consider the following situations as you develop your strategy.

1. **Functional cold chain at health centre**
   - HPV vaccine vials are removed from the cold chain for one day of vaccination *(no ice packs needed, no risk of freezing).*
   - The HPV vaccine can be stored in a CTC for up to four days. This should allow vaccinators to go to one school or community on the first day and then move on to the next school or community further away from the health centre without having to return to the health centre.
2. **Remote and hard-to-reach areas**
   - Teams are able to stay overnight within the timeframe of four days, enabling them to achieve higher coverage in the target population *(rather than returning each night to the health centre to replenish conditionned ice packs).*
3. **No cold chain/lack of cold-chain space at health centre**
   - Vaccines will be delivered to the health centre, and vaccination will have to start as soon as possible. HPV vaccines have to be used within four days but, during this time, it will not be necessary to return to the district level.

5.1.1.2 CTC scenarios

There are several scenarios which will enable you to make the best use of the CTC approach. Which of these you choose to use will depend on the existing cold chain and ice pack conditioning capacity at each level, transportation options and infrastructure, as well as the national vaccine supply and distribution practices.

A careful planning exercise must then take place, taking into account the maximum time the HPV vaccine is allowed to be kept in a CTC. Given that this vaccine only has a four-day window for a CTC, it is essential to ensure that you can carry out your planned CTC activities within that time. Figures 8–10 show possible scenarios for using the HPV vaccine in a CTC. As you determine which scenario to use, bear in mind the appropriate administrative divisions for CTC implementation (Figure 6). CTC should be implemented at the 3rd administrative (district) level or higher. Also note that a CTC day starts in the morning (a.m.). If vaccines are removed from the cold chain and put in the CTC in the morning, that day counts as day 1. If vaccines are put in the CTC in the afternoon, the next day counts as day 1.

SCENARIO 1 **(Figure 8 & Table 6) is best suited to situations in which ice-making capacity at district level is limited, and the distance between district and health centre involves less than a day of travel.** This scenario is suitable for health centres without functional cold chains that require more than one delivery from the district level to the health centre during outreaches. The drawback here is that the CTC timeline starts counting once the vaccines leave the district centre. So, essentially, this means only two days can be spent vaccinating.

FIGURE 8. IMPLEMENTING CTC, STARTING UPON DEPARTURE FROM THE DISTRICT LEVEL

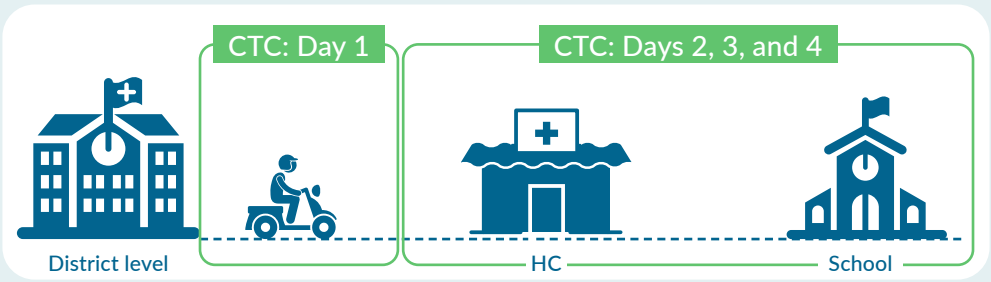


TABLE 6. VACCINES ARE REMOVED FROM THE COLD CHAIN UPON DEPARTURE FROM THE DISTRICT LEVEL

Day 1	Travel day. The vaccines are removed from the cold chain at the district level and transported to the health centre, without ice.
Days 2 to 4	The vaccines are taken to the school or outreach post for vaccination.

SCENARIO 2 (Figure 9 & Table 7) is best suited for health centres without functional cold chain capacity. The vaccines are transported from the district level to the health centre in the cold chain and taken into the CTC as soon as they reach the health centre. In this scenario, vaccination should start either the same day, if time allows, or the next day. Vaccines have to be used within four days of arrival at the health centre.

FIGURE 9. IMPLEMENTING CTC, STARTING UPON ARRIVAL AT THE HEALTH CENTRE

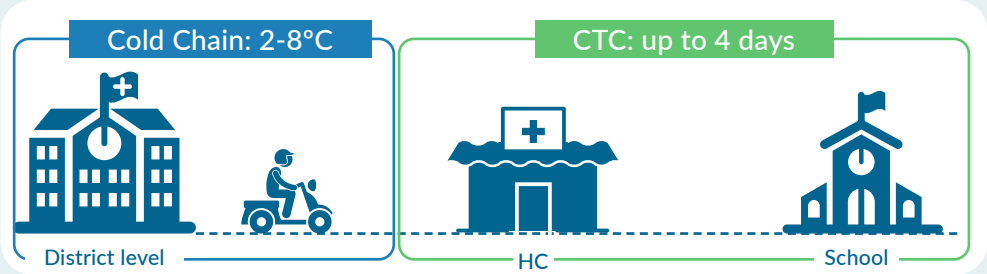


TABLE 7. VACCINES ARE REMOVED FROM THE COLD CHAIN UPON ARRIVAL AT THE HEALTH CENTRE

Day 1	The vaccines arrive at the health centre and are removed from the cold chain. Depending on the time of arrival, immunization with the vaccines in a CTC may begin today.
Days 2 to 4	The vaccines are taken to the school or outreach post for vaccination.

SCENARIO 3 (Figure 10 & Table 8) is best suited to situations in which health centres have a functional cold chain with adequate space for vaccines. There are two options for this scenario. Option A allows the team to take sufficient vaccines for a target population of four days and go to remote schools over this time frame without returning to the health centre before the end of the fourth day. Option B allows vaccination teams to take vaccines for a target group of one day and return each evening to the health centre. In both cases, if vaccines are not used in one day, they can be kept in the CTC and used the next day.

FIGURE 10. IMPLEMENTING CTC AT THE START OF VACCINATION ACTIVITIES

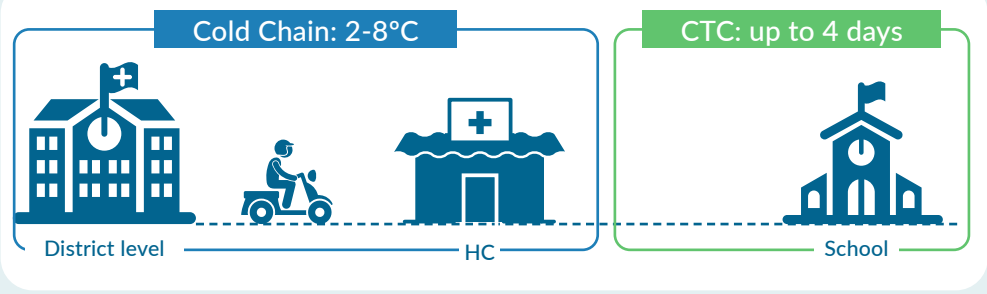


TABLE 8. VACCINES ARE REMOVED FROM THE COLD CHAIN ON THE DAY OF VACCINATION/OUTREACH

Day 1 to 3	*Option A:* Multiday overnight outreach (4 days/4 nights). *Option B:* Four days of outreach, each originating from the health centre each morning. Vaccine vials are stored overnight at ambient temperature.

CTC could also start at the school where the HPV vaccination takes place. However, this would have fewer advantages, as ice packs would still need to be prepared and carried.

Microplans from previous school-based vaccination activities will necessarily have included the need to ensure adequate cold-chain capacity and the availability of ice packs.

It is important to spend time developing new microplans that take full advantage of the flexibility offered through a CTC (Figures 11 & 12). In order to maximize CTC benefits you should do the following.

- Explore efficiencies in multi-day outreach trips. Returning to a central point each night to collect ice for the next day will no longer be necessary.
- Now that there is no need for ice in the vaccine carrier, consider whether teams could vaccinate more girls in one day by carrying extra vaccine vials.
- Now that there is no need to return for, or receive, an ice top-up during the day, consider which of the teams could travel further during the day in order to reach more remote populations.
- Explore the idea of packing vaccine carriers the night before to save time in the morning and to avoid errors resulting from the "morning rush".

Example of microplans taking advantage of the CTC flexibility:

FIGURE 11.

HPV VACCINATION MICROPLAN: REACHING SEVERAL SCHOOLS OVER FOUR DAYS

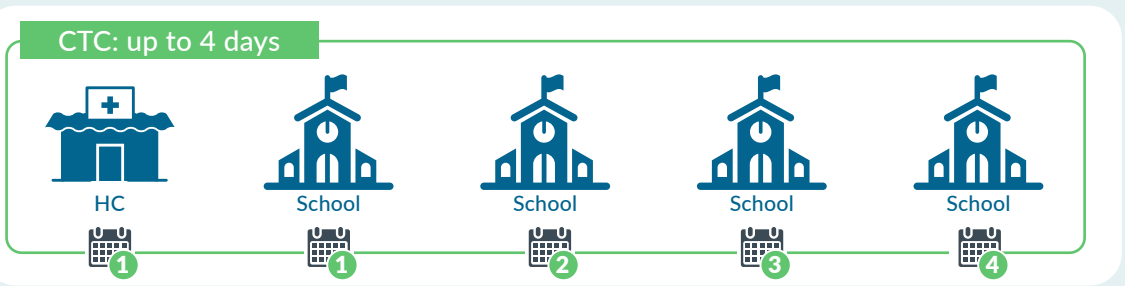
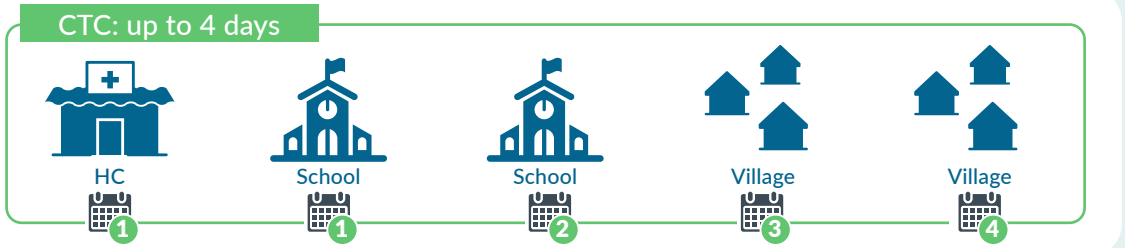


FIGURE 12.

HPV VACCINATION MICROPLAN: REACHING SCHOOLS AND CONTINUING TO VILLAGE OUTREACH OVER FOUR DAYS



How to measure a CTC day. A CTC day starts in the morning. If vaccines are removed from the cold chain in the morning and put into CTC, then that day counts as Day 1. However, if vaccines are removed from the cold chain and put in the CTC in the afternoon or later, the next full day counts as Day 1. The total allowable time for a vaccine in CTC is four days.

5.1.1.3 Estimating the size of the target population

Because vaccines cannot be returned to the refrigerator once they enter the controlled temperature chain, it is important not to remove more vaccines than can be used within three days. The number of vaccines taken out of the cold chain should be based on an accurate estimation of the size of the target population for a given excursion. The size of the target population to be immunized during HPV vaccination is different from the target population for your regular immunization sessions, as you will be vaccinating adolescent girls of one or multiple age cohorts. Should there be unused vials remaining once the target population has been fully reached, every effort should be made to locate additional girls to vaccinate in the community rather than to allow vaccine to be discarded due to the CTC excursion period/timeline expiring. When confronted with the latter scenario, consideration could exceptionally be given to vaccinating older girls who do not fit in the target profile.

It is important to verify the estimated target group, which is also referred to as "enumeration". The following steps are recommended for enumeration (World Health Organization, Guide to introducing HPV vaccine into national immunization programmes, 2016).

For school-based strategies:

- Generate an up-to-date list of all schools in the district, including private schools and special education schools which may be missing from official lists.
- Contact the schools and obtain the number of target girls who are enrolled.
- If possible, have the school pre-register or enumerate the girls who are to be vaccinated and provide a list of the girls' names and dates of birth to the health facility.
- Confirm with the schools and obtain agreement that the dates proposed for vaccination are convenient and do not conflict with school exams or holiday periods.

For community outreach strategies:

- Involve volunteer health workers and community members to generate up-to-date lists of girls of eligible age who do not attend school.

In both enumeration strategies, naturally occurring events such as seasonal migration patterns or natural disasters, as well as conflict, famine or political instability, should be accounted for as these could drastically affect the estimates of the target population.

Because vaccines cannot be returned to the cold chain once they enter the controlled temperature chain, accurately estimating the target population for a given HPV vaccination session using the CTC approach becomes one of the most critical planning steps to minimize wastage.

Other important points to note in the preparation phase can be found in Box 2.

BOX 2.

PREPARATION PHASE CHECKLIST

- ✔ Pay special attention to the timing of your immunizaation sessions so that all targets can be attained.
- ✔ Ensure unambiguous eligibility criteria for HPV immunization.
- ✔ Improve HPV vaccine forecasting based on a clearer eligibility criterion and a more accurate target population estimate thereby minimizing your chances of having unused vials at the end of the CTC cycle.
- ✔ Ensure unused vials can be used somewhere else during the CTC cycle.
- ✔ Provide more resources to strengthen the flow of information between health facilities and schools for HPV outreach planning purposes.
- ✔ Ensure realistic and detailed micro plans for HPV immunization based on active dialogue with primary schools.
- ✔ Ensure proper communication with the school and community leadership to ensure the immunization activity is expected and receives appropriate attention and turn out.
- ✔ Verify you have the stocks you need before implementing the CTC approach:
  - » HPV vaccines
  - » Immunization supplies
  - » CTC tools (Explained in detail in subsequent sections):
    - Peak temperature threshold indicators (PPTI)
    - Indelible markers
    - CTC monitoring sheet
    - WHO-approved vaccine carrier
- ✔ Refer to the Guide to Introducing HPV Vaccine into National Immunization Programmes for the general guidelines to follow in planning your immunization session.

5.2 IMPLEMENTATION DAY

This section describes recommended actions before, during and after an immunization session.

5.2.1 Before an immunization session

Before an immunization session using the CTC approach, the following steps are to be followed.

1. **Check the labels of the vaccine.** If the label is not attached, discard the vial.
2. **Check the expiry date.** You must discard vials if the expiry date has already passed.
3. **Check the vaccine vial monitor (VVM).** Discard if it has reached the discard point.
4. **Ensure that you calculate carefully** the number of vials needed based on your microplan.
5. **Check that the vaccine carrier is clean** and in an operational state.
6. **Take the vaccine vials out of the refrigerator and put them in the vaccine carrier** (without ice packs). Record the date and time that the vaccine is removed from the cold chain into your vaccine distribution or vaccine management log, noting that CTC has been initiated.
7. **Add the PTTI in a good state** (the inner circle has not turned black) to the vaccine carrier (Figure 13).
8. **Record the status of the PTTI** on your monitoring sheet and the number of vials you removed from the cold chain.
9. **Check that you have all your general immunization supplies,** which would typically consist of:
   - syringes
   - safety boxes
   - registry
   - vaccination cards.
10. **As a final check, ensure you have all your CTC tools before you depart:**
    - PTTIs
    - indelible markers
    - CTC monitoring sheets
    - WHO-approved vaccine carrier.

FIGURE 13. VACCINE CARRIER WITH VACCINE VIALS, A PEAK TEMPERATURE THRESHOLD INDICATOR AND NO ICEPACKS

5.2.2 During an immunization session

When using the CTC for outreach immunization sessions, some of the tasks that you usually carry out will be a bit different. As you are not using ice packs, there is no need to check the ice packs during the immunization session.

However, it is very important to check the following.

1. **Check the VVM** (Figure 14). If it indicates the vaccine has passed the discard point (Figure 15), you must discard that vial immediately.
2. **Check the PTTI** (Figure 16). If it indicates a peak exposure has been reached (the whole circle is black), you must discard all the vaccines that are still in the vaccine carrier, even if the VVMs have not reached their discard point. At this point, vaccinators should contact their supervisors or health facility head, who will use the monitoring sheet (Figure 17) to document the number of vials that had to be discarded because the PTTI had turned black. If you are in doubt about the reading of the PTTI, do not use the vaccines. Contact your supervisor or health facility head immediately.

5.2.3 After an immunization session

On returning to the health centre or at the completion of an immunization session, there are additional steps to be taken in the context of CTC.

1. **At the completion of the immunization session,** record the ending date and time in your vaccine distribution/management log.
2. **Check the status of the PTTI** in the vaccine carrier to make sure it has not turned black. If it has turned black, notify your supervisor and determine how best to discard all the vials in the vaccine carrier.
3. **If the PTTI remains in good status,** count the balance of unused vaccine vials.
4. **Mark those unused vials accordingly.** See Box 3 for the appropriate way to mark unused vaccine vials.
5. **Discard all vials that have reached the maximum time limit/expiry.**
6. **Complete the monitoring sheet.**
7. **Do not place the unused vials back in the refrigerator.**
8. **Report any adverse events** reportedly linked to CTC or incidents of confusion deemed linked to CTC (e.g. taking non-approved vaccines out of the cold chain) to WHO.

BOX 3.

MARKING VACCINE VIALS AFTER AN IMMUNIZATION SESSION.

Upon return to the health center or upon completion of an immunization session, vaccinators may have unopened vials. It is important to keep track of vials that have been exposed to CTC conditions, to ensure the four-day limit has not passed. Therefore, if there are unopened vials remaining, you should carry out the following steps:

- ✔ Mark the unused vials from the CTC excursion. You can use an indelible marker to make the markings (See below).
  - » If you are on a multiday outreach trip and are not returning to the health centre, you are advised to mark all remaining vials at the end of each day.
- ✔ Put all the marked vials together and store them at ambient temperature below 40°C.
  - » Be careful to keep all marked CTC vaccines together and separate from other HPV vaccine vials that have not yet been put in a CTC.
- ✔ Make sure that the marked vaccine vials are used first in the next immunization session.
- ✔ If marked vials are not used the subsequent day, add a second line to the label and pay special attention to ensuring those vials are used first the next day (See below).
- ✔ At the end of the fourth day, add a fourth mark on the vaccine vials that had three marks at the beginning of the day and then discard them (See below).

DAY ONE	DAY TWO	DAY THREE	DAY FOUR
Vaccination journey I	Vaccination journey II	Vaccination journey III	Vaccination journey IIII

Safe disposal of unused vials must occur per WHO recommendations or established national guidelines.

Redistribute, where possible, marked vaccine vials from vaccination teams that have completed their sessions for the campaign to those still on duty.

5.3 VACCINE CARRIERS AND COLD BOXES

A standard WHO-prequalified vaccine carrier (Figure 13) is the recommended option for transporting vaccines in a CTC. The vaccine carrier has the advantage of already being associated with immunization activities, both by you and the community. You are also very familiar with its operation and use. However, when using the CTC, there is no need to insert and transport ice packs. This means that there will be much more space in the vaccine carrier, and the weight will be reduced. This does not mean, however, that you should put a lot more vaccine vials in the vaccine carrier. You need to calculate your vaccine needs carefully, depending on your target population and your session plan, so that vaccines are not wasted (section 5.1.1.3).

If you choose not to use vaccine carriers, it is important to ensure that you carry the vaccine in a carrier that:

- is well insulated;
- shelters the vaccines from direct sunlight or exposure to excessive light given its light sensitivity;
- keeps the vaccines safe from breakage;
- is strongly constructed – do not use soft bags.

Vaccine carriers and containers should be dedicated specifically for vaccine transportation and not used to carry other equipment or supplies.

5.4 TRANSPORT UNDER A CTC

Before deciding to transport vaccines in a CTC, you must plan the CTC timeline. The CTC timeline starts once the vaccines are taken out of the traditional 2°C to 8°C cold chain range. This period of time can be a maximum of four days. Once the vaccine is removed from the cold chain, its CTC timeline starts.

You should put one PTTI in each vaccine carrier or cold box. The PTTI must be placed in the vaccine carrier as soon as you remove the vaccines from the traditional 2°C to 8°C cold chain range. Before placing the PTTI with the vaccines, verify that it is not damaged or that the inner circle of the indicator is not already black.

You do not need ice packs. However, to the extent possible, you should transport the vaccines in a cold box to provide additional insulation, if there is concern that peak ambient temperatures may exceed 40°C during transport. During transport do not leave the vaccine carrier exposed in direct sunlight. When parking the car in which the vaccines are transported, or your motorcycle, avoid parking the vehicle in direct sunlight for any period of time, as this can raise the temperatures inside the vehicle much higher (by 10°C to 20°C) than outdoor ambient temperatures. This dramatic rise can have an impact on the temperature inside the cold box.

The total possible time for the HPV vaccine in the CTC is four days. This includes transport, storage and immunization time.

The same procedure for the use of the CTC to transport vaccines applies in all of the following situations:

- if you are collecting vaccines at the district store and transporting them back to your health facility;
- if you are collecting vaccines at the district store and transporting them directly to the first outreach immunization site;
- if you take the vaccines out of the traditional 2°C to 8°C cold chain range at your health facility and go to the outreach immunization sites.

6 MONITORING CTC IMPLEMENTATION

To use the HPV vaccine in a CTC, you must use two kinds of temperature monitors; the vaccine vial monitors (VVM) and the peak temperature threshold indicator (PTTI). You are probably already familiar with the VVM. However, to facilitate the comparison, Section 6.1 provides a brief description of the VVM, and 6.2 provides a description of the PTTI.

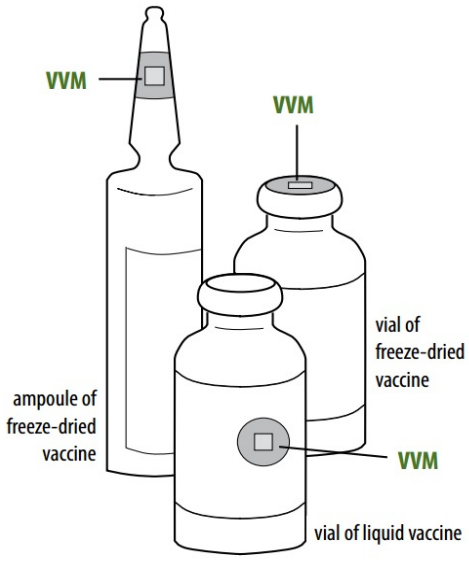
6.1 THE VACCINE VIAL MONITOR

A VVM is a label that changes colour when the vaccine vial has been exposed to heat over a period of time. Before opening a vial, you must check the status of the VVM to verify that the vaccine has not been damaged by heat. Manufacturers attach VVMs to vials of most vaccines (Figure 14).

The VVM is printed on the vial label or cap. It looks like a square inside a circle. If the vaccine vial is exposed to heat, the square becomes darker. If the vaccine has been subjected to excessive heat, which risks making it subpotent, the colour of the inner square of the VVM will be the same or darker than the outer circle.

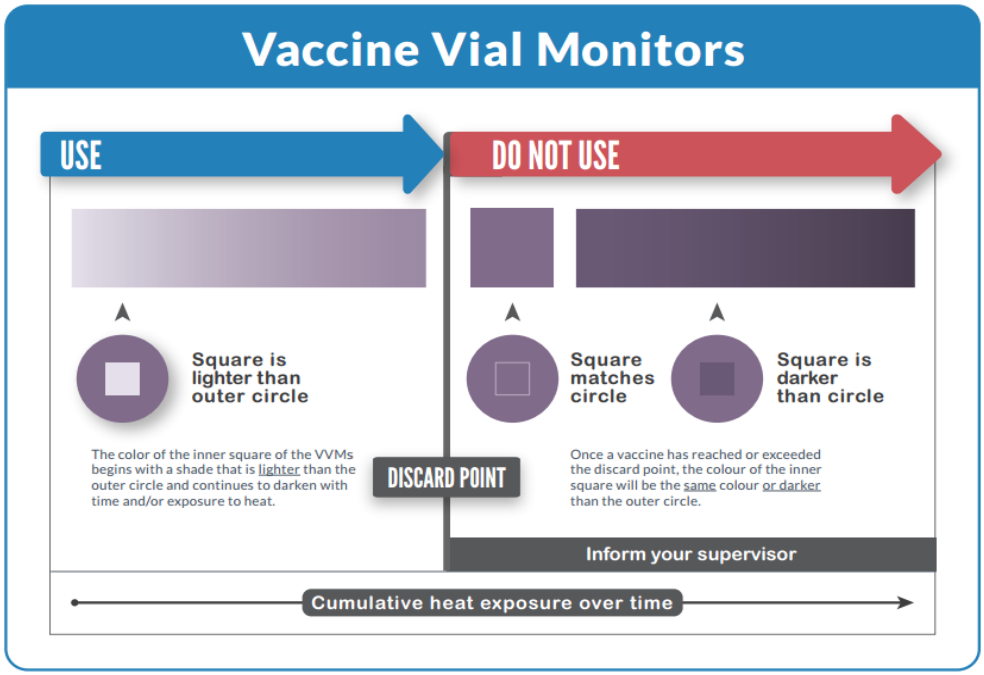
You can only use vials if the VVM's inner squares are lighter in colour than the outside circle. If the inner square of a vial's VVM has begun to darken, but is still lighter than the outer circle, the vial should be used before the vials with a lighter inner square (Figure 15).

FIGURE 14. VVM ON VIAL LABEL OR CAP



Source: Immunization in Practice. A practical guide for health staff. Module 3: The cold chain. Geneva, World Health Organization, 2004.

FIGURE 15. HOW TO READ A VACCINE VIAL MONITOR (VVM)



Source: Vaccine Vial Monitor (VVM) Infographic. Available at: http://www.who.int/immunization/programmes_systems/supply_chain/resources/tools/en/index4.html

6.2 THE PEAK TEMPERATURE THRESHOLD INDICATOR

The PTTI does not replace the VVM. The PTTI measures **PEAK** exposure to heat, while the VVM measures **CUMULATIVE** exposure to heat. Figure 16 shows a PTTI in actual size.

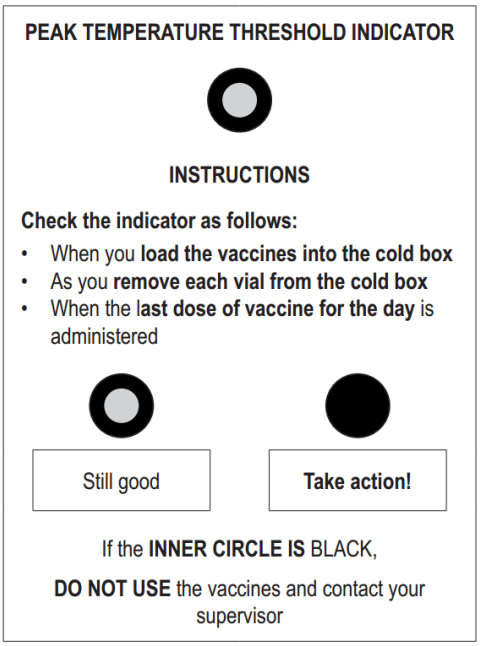
A PTTI is a small, round sticker on a card. The sticker has the form of a black circle with a grey circle in the middle. The sticker changes colour irreversibly when it is exposed to a peak temperature – the grey colour in the middle turns black and thus the whole circle is black (Figure 16). The indicator changes colour when the vaccine has been exposed to a peak temperature (i.e. a temperature over 40°C), which means the vaccine may no longer be effective and should not be used. You should immediately inform your supervisor or health facility head if this happens.

You should only implement the CTC approach if you have a PTTI. Without the PTTI, you cannot ensure that the vaccines have not been exposed to the peak upper limit of 40°C. When using the CTC, a PTTI must be placed in the vaccine carrier/container with the vaccine immediately after you remove the vaccines from the traditional 2°C to 8°C range.

Place the PTTI inside the vaccine carrier for outreach immunization activities or transport. If you are transporting the vaccine in its original cardboard box packaging, place a PTTI in the box. The indicator should be kept in the vaccine carrier/box the whole time.

In addition, the PTTI should not be exposed to direct sunlight, it should be kept in the vaccine carrier at all times or stored in a dark cool place in the health centre/district prior to use.

FIGURE 16. THE PEAK TEMPERATURE THRESHOLD INDICATOR CARD



6.2.1 How many peak temperature threshold indicators are needed?

As an estimate, one peak temperature threshold indicator (PTTI) is needed per planned vaccination team, assuming each team will be using only one vaccine carrier. A reserve stock of 50 percent is recommended, to deal with indicators that turn black or get damaged and any changes to the number of teams. Note that PTTIs can be reused as long as they have not been damaged and the inner circle has not turned black.

6.2.2 How to handle and store peak temperature threshold indicators?

Caution is required to handle PTTIs with care even before a CTC is initiated, as this remains temperature sensitive material. When not in use, it recommended that PTTIs be stored in a cool place, preferably in refrigeration. Exposure to high temperatures during non- CTC transport and handling must be avoided to preserve PTTI integrity.

6.2.3 What to do if the peak temperature threshold indicator turns black?

If the PTTI has turned black, the vaccine must be discarded irrespective of the VVM status. To not risk its getting back into the CTC pool, mark each vial with an “X” showing it should be discarded.

If the PTTI has turned black, the vaccine vial must be discarded irrespective of the VVM status. To not risk its getting back into the CTC pool, mark each vial with an to show that it should be discarded.

6.3 OTHER TEMPERATURE-MONITORING TECHNOLOGIES

WHO has a list of prequalified temperature monitoring devices, including programmable electronic data loggers. Countries may wish to consider using these devices to help gather temperature data, especially when CTC is first introduced. To review the list of prequalified electronic temperature monitoring devices, please visit http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=35.

6.4 MONITORING VACCINES IN A CONTROLLED TEMPERATURE CHAIN

It will be important for vaccinators to record key information on the CTC practices in the monitoring sheet (Figure 17), and for supervisors to check on the CTC implementation at each supervisory visit.

The monitoring sheet requires vaccination teams to count all vaccine vials that are taken into the CTC every morning and evening, indicating which vaccine vials have spent one, two, three, or four days in the CTC. This helps the teams and their supervisors make sure they use those vials that have spent the longest time in the CTC first, and it obliges vaccinators to check the PTTI on a regular basis. It further provides space for feedback from the head of the facility.

FIGURE 17. SAMPLE CTC MONITORING SHEET

HPV CTC MONITORING SHEET

(ONE SHEET PER TEAM FOR THE ENTIRE VACCINATION PERIOD)

Name of District ..... Name of Health Facility .....

	Date	Date	Date	Date	Date	Date	Date
BEFORE DEPARTURE FOR VACCINATION SESSION							
Number of vials removed from the cold chain							
Number of vials with one mark							
Number of vials with two marks							
Number of vials with three marks							
TOTAL NUMBER OF VIALS							
Peak temperature threshold indicator (white= 0 black =1) Time checked							
AT SESSION SITE, BEFORE VACCINATION							
Peak temperature threshold indicator (white= 0 black =1) Time checked							
ON COMPLETION OF OUTREACH ACTIVITY							
Peak temperature threshold indicator (white= 0 black =1) Time checked							
TOTAL NUMBER OF VIALS REMAINING							
RESERVED FOR SUPERVISOR / HEAD OF HEALTH FACILITY							
No. of unopened vials discarded due to PTTI turning black							
No. of unopened vials discarded due to max. Days (4) exceeded							
No. of unopened vials discarded due to other reasons							

Reminder: Any vials with 3 marks remaining at the end of a day should be discarded

If your Peak Threshold indicator has turned black, do not use any vaccine from that vaccine carrier and please notify your supervisor or head of health facility immediately.

OTHER COMMENTS BY SUPERVISOR / HEAD OF HEALTH FACILITY:

6.5 MONITORING ADVERSE EVENTS FOLLOWING IMMUNIZATION

Injection safety is just as important when you are using vaccines in the CTC as it is when using vaccines in the cold chain. Table 9 lists examples of incorrect immunization practices and possible severe reactions following immunization using incorrect practices. Review Table 9 and reflect upon your own practices during an immunization session.

Surveillance of adverse events following immunization (AEFI) is a key component of successful immunization activities. You should follow the same procedures to monitor and track AEFIs during immunization sessions using vaccines in the CTC, that you follow when using vaccines in the traditional 2°C to 8°C cold chain range. Using vaccines in a CTC is not expected to increase AEFIs. The major risk is loss of potency due to excessive heat exposure if the VVMs and PTTIs are not appropriately monitored. However, as a good practice, it should be noted in the comments section of the AEFI reporting form that the vaccine was kept in the CTC (Annex 11.2).

TABLE 9. EXAMPLES OF INCORRECT IMMUNIZATION PRACTICES AND POSSIBLE SEVERE REACTIONS FOLLOWING IMMUNIZATION

INCORRECT PRACTICE	EXAMPLES	POSSIBLE SEVERE REACTIONS FOLLOWING IMMUNIZATION
Non-sterile injection	Reuse of disposable syringe or needle Improperly sterilized syringe or needle	Infection, such as local abscess at injection site, sepsis, toxic shock syndrome or death
	Contaminated vaccine or diluent	Bloodborne infection transmitted, such as hepatitis or HIV
Incorrect vaccine transportation/ storage	VVM at end point	Vaccine ineffective
	PTTI indicates peak exposure has been reached (if used)	Vaccine ineffective
	Clumping of adsorbed vaccine due to freezing	Local reaction to frozen vaccine, such as injection site abscess
Incomplete history	Forgetting to ask if patient has had an allergic reaction to vaccines in general or to a component of HPV vaccine specifically	May lead to a severe anaphylactic reaction, etc., if the patient responds to a component of the vaccine.

Adapted from: Use of MenAfriVac™ (meningitis A vaccine) in a controlled temperature chain (CTC) during campaigns: guidance for immunization program decision-makers and managers. Geneva: World Health Organization; 2013 (WHO/IVB/13.04).

7 SUPERVISION

Prior to implementing a CTC, it is important to ensure that all supervisors are properly trained on, and comfortable with CTC practice, and that they are able to provide supportive supervision to vaccinators. In addition, supervisors should be trained to answer commonly asked questions on CTC from the community, should they occur.

When supervising a vaccination activity using the CTC approach, supervisors should pay special attention to the following questions.

- Are health-care workers able to explain the basic CTC principles?
  - Store vaccines for four days at up to 40°C.
  - Check the VVM, expiry date and PTTI before opening each vial.
  - No return to cold chain once the vaccines have been taken out.
- Are the vaccines being properly monitored for exposure to cumulative and peak temperature exposure?
  - Under what conditions are vaccines transported, stored and utilized during the session.
- Are the vaccines protected from direct sunlight?
- Are vaccinators able to answer commonly asked questions about CTC?
- Do vaccinators understand what to do if the PTTI shows that the peak exposure has been reached?
- Are any VVMs nearing their discard point and, if so, are they being used first?
- Is proper AEFI communication being given by vaccinators to caregivers?
- Is the CTC monitoring sheet (Figure 17) correctly filled out?
  - Check in particular the section completed by the head of the health facility, which refers to discarded vaccine vials.

It is useful to gather information on how the practice is affecting vaccinators and supervisors. This will help decision-makers assess whether or not they should replicate and/or expand the CTC practice in future immunization activities.

The following is a guide to the types of observations supervisors should make and questions they need to answer. It is suggested that these questions are answered following the first, middle and last day of the vaccination activity. This will enable supervisors to monitor how things change as the practice becomes more familiar.

Assess the impact of a CTC on immunization activities and your own supervision.

- Based on your experience, what differences do you observe between immunization sessions using the CTC approach and regular immunization sessions?
- Describe any differences you notice in your own supervision when supervising CTC practices versus regular immunization activities. Are you spending more or less time on certain topics? Are you covering more or fewer sites per day?

Assess the impact and perception of CTC practice for vaccinators.

- Ask vaccinators how they are finding the new practice. What benefits are they seeing, if any, and what challenges, if any?
- Ask vaccinators if they think the CTC practice is useful. Why, or alternatively, why not?
- Ask vaccinators to suggest things they think should be changed and/or improved, if the CTC practice is to be used again.
- Observe how the vaccinators' responses change between the first day, when practice is new, and the middle and end of the vaccination activity. Are there any differences?

7.1 ASSESSING THE CTC PRACTICE

When CTC is first used, it is particularly important for the country to document and assess the benefits and challenges of the CTC approach, in order to inform future decision-making.

In addition to existing monitoring requirements, such as the number of VVMs reaching their discard point, countries should consider monitoring:

- closed-vial wastage;
- number of PTTIs that have changed colour;
- number of people vaccinated per day by CTC teams, versus non-CTC teams.

National Immunization programmes may also consider implementing cost assessment studies to allow for an economic analysis that can contribute to the evaluation of the value CTC offers to their respective HPV vaccine delivery strategy.

8 SUMMARY OF IMPORTANT POINTS

- **Temperature chain.** The controlled temperature chain (CTC) allows vaccines to be stored and transported at temperatures outside the traditional 2°C to 8°C cold chain range for limited periods of time, under monitored and controlled conditions, as appropriate to the stability of the antigen and provided the vaccine is labelled with a vaccine vial monitor (VVM).
- **Labelling.** The latest labelling for CTC on HPV vaccine allows for the vaccine to be stored under a CTC at up to 40°C for not more than four days immediately prior to administration, provided that the vaccine has not reached its expiry date and the VVM is still valid. For programmatic purposes, WHO recommends operating with a standardized 40°C upper threshold.
- **Vaccine vial monitor.** A VVM is a label that changes colour if the vaccine vial is exposed to heat over a period of time. Before putting a vial into the CTC, you must check the status of the VVM to verify that the vaccine has not been damaged by heat. Manufacturers attach VVMs to vials of most vaccines.
- **Peak temperature threshold indicator (PTTI).** A PTTI is a small, round sticker on a card. The sticker has the form of a black circle with a grey circle in the middle. The sticker changes colour irreversibly when it is exposed to a peak temperature for a maximum period of time: the grey colour in the middle turns black and thus the whole circle is black. The indicator changes colour when the vaccine has been exposed to a peak temperature (i.e. a temperature over 40°C), which means the vaccine may no longer be effective and should not be used. You should immediately inform your supervisor or health facility head if this happens.
- **VVM plus PTTI.** The PTTI does not replace VVM. The PTTI measures peak exposure to heat, while the VVM measures cumulative exposure to heat over time.
- **Vaccine transport.** The standard vaccine carrier is still the preferred option for transporting vaccines in a CTC. The vaccine carrier has the advantage of already being associated with immunization activities, both by you and by the community.
- **Timeline.** The CTC timeline starts once the vaccines are taken out of the traditional 2°C to 8°C cold chain range. This period of time can be a maximum of four days. Once the vaccine is removed from the cold chain, its CTC timeline has started, and it cannot be put back in the traditional cold chain.
- **Immunization sessions.** The organization of your immunization sessions depends on when you are going to start using the CTC.
  - CTC starts with departure from the district storage point (transportation without cold chain) – this doesn't allow for maximization of the 4-day CTC window.
  - CTC starts with the arrival at the health centre (after transportation with cold chain).
  - CTC starts when leaving the health centre (transportation without cold chain).
  - CTC starts at the school (after transportation with cold chain)., which means fewer advantages for vaccination teams.

- **Target population.** The size of the target population to be immunized during an immunization activity with HPV vaccines is different from the target population for your regular immunization sessions. For the HPV activity, as you are vaccinating adolescent girls of one or several cohorts.
- **Advance preparation.** You need to prepare immunization activities and a route plan for when and where (which school) you are going to immunize. It is also very important to communicate in advance with schools and communities to ensure planned activities can really take place.
- **Unused vial marking.** If you come back to the health centre after your immunization sessions with unused vials, mark each unused vial with a line on the label to indicate that it has spent a day in the CTC. If you are on a multiday outreach trip and are not returning to the health centre, you are advised to mark all remaining vials at the end of each day. Put all the marked vials together and store, at ambient temperature below 40°C. Be careful to keep all marked CTC vaccines together and separate from other HPV vaccine vials that have not yet been put in a CTC. Make sure that the marked vaccine vials are used first in the next immunization session. If marked vials are not used the subsequent day, add a additional line to the label of each unused vial, indicating the number of days spent in the CTC, and pay special attention to ensuring that all those marked vials are used first the next day or discarded, in the case of 4 days. At the end of the fourth day, add a fourth mark on each vaccine vial that had three marks at the beginning of the day and then discard it.

ADDITIONAL RESOURCES

a. What is a controlled temperature chain (CTC)? An infographic, available at: https://www.technet-21.org/en/knowledge-hub/main/1190-what-is-a-controlled-temperature-chain-ctc-infographic
b. The controlled temperature chain (CTC): frequently asked questions, available at: https://www.who.int/publications/m/item/controlled-temperature-chain-(ctc)-faqs

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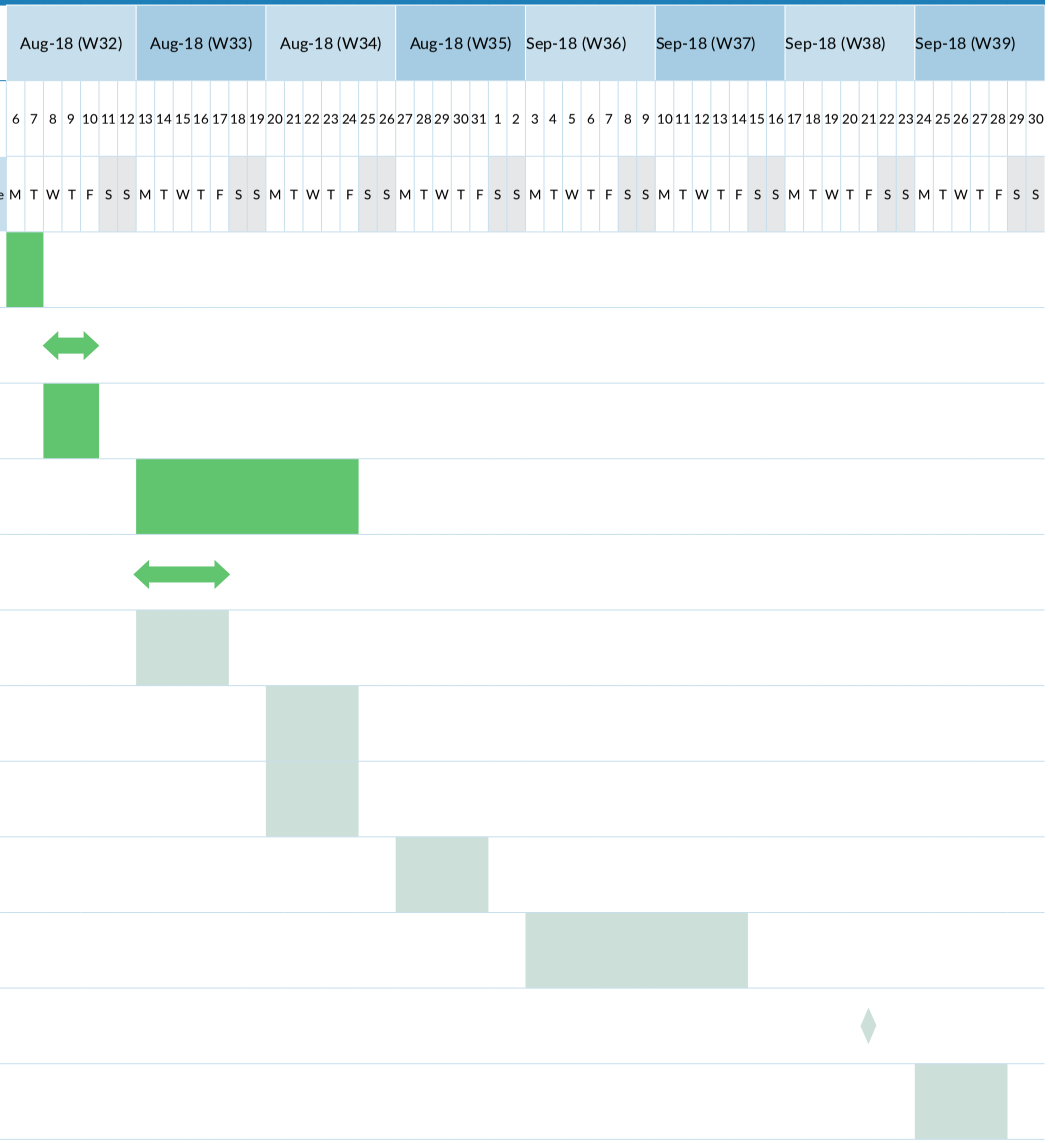
CTC Implementation Timeline

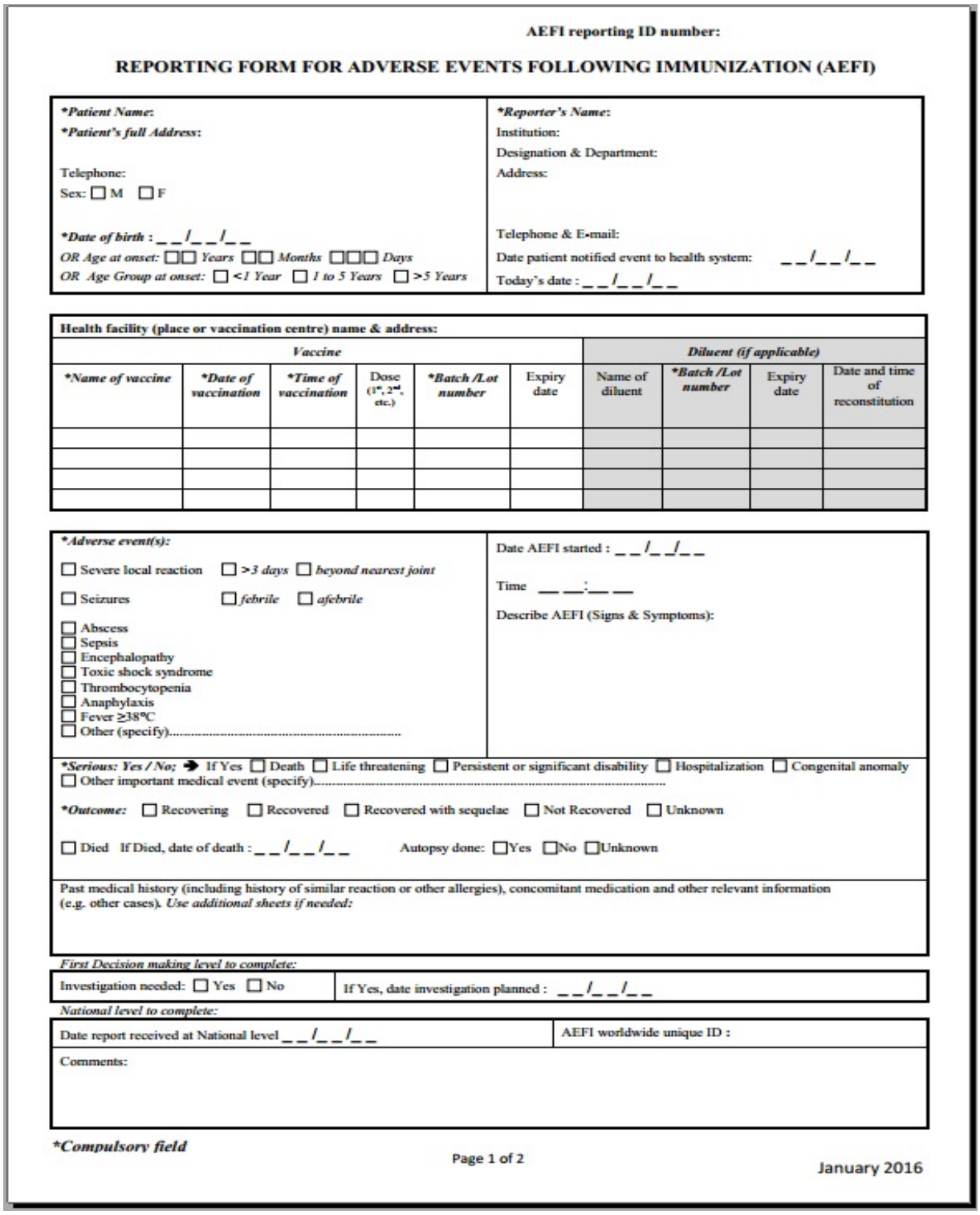
Project Lead: Double click to edit

Budget: Estimated: $0.00 | Baseline: $0.00 | **Cost**: Estimated: $0.00 | Baseline: $0.00 | Actual $0.00

WBS	Task Name	Start	Finish	Duration	% complete
1	Establish a working group	Mon 30/Jul/18	Tue 07/Aug/18	7	0%
2	Finalize areas where CTC will be implemented within	Wed 08/Aug/18	Fri 10/Aug/18	3	0%
2.1	Decide at what health system level to start CTC	Wed 08/Aug/18	Fri 10/Aug/18	3	0%
3	Order PTTI and print the cards	Mon 13/Aug/18	Fri 24/Aug/18	10	0%
4	Brief health care workers at all levels	Mon 13/Aug/18	Fri 17/Aug/18	5	0%
4.1	Set training dates	Mon 13/Aug/18	Fri 17/Aug/18	5	0%
5	Adapt training and supervision materials	Mon 20/Aug/18	Fri 24/Aug/18	5	0%
6	Develop appropriate microplans	Mon 20/Aug/18	Fri 24/Aug/18	5	0%
7	Pre-test adapted materials	Mon 27/Aug/18	Fri 31/Aug/18	5	0%
8	Train regional, district & health care worker staff	Mon 03/Sep/18	Fri 14/Sep/18	10	0%
9	Conduct HPV vaccination using a CTC approach	Mon 17/Sep/18	Fri 21/Sep/18	5	0%
10	Assess impact of HPV vaccination using CTC	Mon 24/Sep/18	Fri 28/Sep/18	5	0%



ANNEX 2: AEFI REPORTING FORM



AEFI reporting ID number:

REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Patient Name: ***Patient's full Address:*** Telephone: Sex: ☐ M ☐ F ***Date of birth :*** _ _ /_ _ /_ _ *OR Age at onset:* ☐☐ *Years* ☐☐ *Months* ☐☐☐ *Days* *OR Age Group at onset:* ☐ *<1 Year* ☐ *1 to 5 Years* ☐ *>5 Years*	***Reporter's Name:*** Institution: Designation & Department: Address: Telephone & E-mail: Date patient notified event to health system: _ _ /_ _ /_ _ Today's date : _ _ /_ _ /_ _

Health facility (place or vaccination centre) name & address:

Vaccine						*Diluent (if applicable)*			
Name of vaccine	***Date of vaccination***	***Time of vaccination***	Dose (1st, 2nd, etc.)	***Batch /Lot number***	Expiry date	Name of diluent	***Batch /Lot number***	Expiry date	Date and time of reconstitution

Adverse event(s): ☐ Severe local reaction ☐ *>3 days* ☐ *beyond nearest joint* ☐ Seizures ☐ *febrile* ☐ *afebrile* ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever ≥38°C ☐ Other (specify).....	Date AEFI started : _ _ /_ _ /_ _ Time __ __:__ __ Describe AEFI (Signs & Symptoms):

Serious: Yes / No; ➔ If Yes ☐ Death ☐ Life threatening ☐ Persistent or significant disability ☐ Hospitalization ☐ Congenital anomaly
☐ Other important medical event (specify).....

Outcome: ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Died If Died, date of death : _ _ /_ _ /_ _ Autopsy done: ☐Yes ☐No ☐Unknown

Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g. other cases). *Use additional sheets if needed:*

First Decision making level to complete:

Investigation needed: ☐ Yes ☐ No	If Yes, date investigation planned : _ _ /_ _ /_ _

National level to complete:

Date report received at National level _ _ /_ _ /_ _	AEFI worldwide unique ID :
Comments:	

Compulsory field

Page 1 of 2

January 2016

Source: Available at the WHO website at: http://www.who.int/vaccine_safety/initiative/tools/AEFI_reporting_form_EN_Jan2016.pdf

NOTES

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