Controlled Temperature Chain Working Group


# CONTROLLED TEMPERATURE CHAIN: Strategic Roadmap for Priority Vaccines

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# I. Contents

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The development of the CTC Strategic Roadmap was led by the CTC-WG Secretariat: Rachel Bauquerez (WHO), Anna-Lea Kahn (WHO), Dörte Petit (WHO) and Debra Kristensen (PATH). Overall guidance was provided by Nora Dellepiane, Chair of the Working Group.

The roadmap was reviewed and endorsed by the members of the Immunization Practices Advisory Committee.

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## ACRONYMS

| | |
|---|---|
| CDC | US Centers for Disease Control and Prevention |
| CPAD | compact prefilled autodisable device |
| CTC | Controlled Temperature Chain |
| CTC-WG | Controlled Temperature Chain Working Group |
| DT | diphtheria tetanus vaccine |
| ECTC | extended controlled temperature conditions |
| EPI | Expanded Programme on Immunization |
| GVAP | Global Vaccine Action Plan |
| HBsAG | hepatitis B surface antigen |
| Hep B | hepatitis B |
| HepB-BD | hepatitis B vaccine birth dose |
| HPV | human papillomavirus |
| IPAC | Immunization Practices Advisory Committee |
| JSI | John Snow Inc. |
| MNT | maternal neonatal tetanus |
| MSF | Médecins Sans Frontières |
| OCC | out of the cold chain |
| OCV | oral cholera vaccine |
| Q | Quarter |
| Td | tetanus diphtheria (low dose) vaccine |
| Tdap | tetanus–diphtheria–acellular pertussis |
| TSE | total system effectiveness |
| TT | tetanus toxoid |
| TT-CV | tetanus toxoid – containing vaccines |
| UNICEF | United Nations Children's Fund |
| WHO | World Health Organization |

# II. INTRODUCTION

The "Controlled Temperature Chain" (CTC) is an innovative approach to vaccine management that allows 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 a duration of a specific number of days, just prior to administration.

This strategic roadmap takes stock of progress to date and identifies the path forward (2017 to 2020) for the CTC. It reflects the consensus reached by the Controlled Temperature Chain Working Group (CTC-WG), which reports to the World Health Organization's (WHO's) Immunization Practices Advisory Committee (IPAC). The mission of the CTC-WG is to convene key stakeholders to (i) define a shared vision and strategy for CTC; and (ii) to advocate for this innovative vaccine delivery and supply chain strategy, where appropriate, with vaccine manufacturers as well as with potential implementing countries. The overall objective of the global CTC agenda remains the facilitation of vaccine delivery to achieve immunization coverage and equity targets for CTC-qualified vaccines, as per the Global Vaccine Action Plan (GVAP) for 2011 to 2020.[1,i] The CTC approach, in its licensed standards,[2] is believed to be an effective means of improving access to vaccination, especially in middle- and low-income countries with limited resources and poor infrastructures, by rendering the delivery of vaccines more efficient and with broader reach.

This document defines the necessary activities required to meet the objectives for CTC over the next four years, which consist mainly of:

- Improving stakeholder involvement, advocacy and alignment on CTC work streams;
- Increasing the base of evidence in support of CTC and characterising the value proposition of CTC with respect to improving immunization coverage and equity;
- Developing operational guidance and communication tools in support of CTC practices; and
- Supporting efforts towards the licensure and prequalification of appropriate vaccines for CTC.

This roadmap focuses primarily on four vaccine types selected by the CTC-WG and endorsed by IPAC in February 2017: vaccines against human papillomavirus (HPV), oral cholera vaccine (OCV), tetanus toxoid vaccine (including TT [tetanus toxoid] vaccine, Td [tetanus diphtheria low dose] vaccine, or other TT-CVs [tetanus-toxoid-containing vaccines]) and hepatitis B vaccine birth dose (HepB-BD). These four vaccine types are the leading priorities of the CTC programme of work between 2017 and 2020.

This document provides background information about each of the priority vaccines and the current status of CTC efforts, along with the required steps over the next four years (2017 to 2020) to effectively advance the CTC agenda. The roadmap addresses supply and programmatic issues, aiming for priority vaccines to become licensed for CTC use and facilitating uptake of the CTC vaccine delivery approach. The four-year time frame purposefully aligns with the GVAP. The roadmap also includes efforts to identify

[i] The number of vaccines that have either been relicensed or licensed for use in a CTC is one of the indicators of Strategic Objective 6 of the Global Vaccine Action Plan: Strategic Objective 6: Country, regional and global research and development innovations maximize the benefits of immunization; Indicator SO6.4: Number of vaccines that have either been relicensed or licensed for use in a CTC at temperatures greater than the traditional +2°C to +8°C range.

future vaccine candidates for CTC use and encourages a proactive approach to CTC licensure during product development.

Note that execution of the proposed activities will be contingent on effectively securing the necessary funding support.

# III. BACKGROUND ON CTC: PROGRAMME RATIONALE AND PROGRESS TO DATE

CTC has been on the global immunization agenda for many years.[1] Since 2007, WHO and PATH, with support from the Bill & Melinda Gates Foundation, have explored the possibilities of storing and transporting certain heat-stable vaccines in a CTC. Upstream, supply-level investments and initiatives gained momentum with the licensure of the first CTC-compatible vaccine, MenAfriVac® (meningitis A vaccine), which was followed by intensive downstream, programme-level work with countries to ensure successful implementation of this new approach.

Experience so far shows that CTC use of vaccines relieves health workers of many of the burdens associated with ensuring an adequate cold chain to the point of vaccination, thereby freeing health personnel time and resources, improving efficiencies and potentially enabling increased immunization coverage and equity for CTC-labelled vaccines.[3] Vaccinators in the field welcome this new option for vaccine management as it greatly facilitates their work by saving them from burdensome journeys to renew ice stocks and from carrying heavy vaccine carriers. Finally, staff time that would be required to condition ice packs during campaigns is saved and can be redirected back to maintaining routine immunization services, which often are compromised during campaigns. Today, regulatory and WHO prequalification pathways exist to label vaccines for CTC use.[4,5] Two vaccines currently bear such labels; three additional vaccine products should have CTC labels soon; and work towards CTC criteria for six other vaccines is under way. As of May 2017, close to 4 million individuals worldwide have received MenAfriVac® delivered in a CTC in six countries. WHO produced guidance materials for the planning and implementation of CTC in these countries.

This is a pivotal time for advancing CTC use of vaccines. The CTC experience to date has demonstrated that the approach entails a complex agenda of activities at multiple levels; this agenda has progressed well so far but still requires an extensive amount of work and investment. Manufacturers have confirmed their interest and commitment to qualifying vaccines for CTC use. It remains key that this is matched by an equal level of engagement and action by WHO and partners. HPV vaccine was prequalified in mid-2016 and oral cholera vaccine (OCV) is currently under review for CTC prequalification. Some manufacturers of HepB-BD and TT vaccines are preparing to seek CTC licensure. This will require focused technical and other types of support to vaccine producers and regulators to see the efforts to fruition, as well as advocacy and technical support at the country level to see beneficial uptake of CTC use of these vaccines. It is therefore essential that momentum not be lost and the investments to date not be undermined.

From an economic point of view, evaluations have been undertaken in two countries to quantify the costs and benefits of MenAfriVac® CTC use. An economic benefits study in Chad[6] showed the potential for campaign implementation cost savings of up to 50% due to CTC, and a recently published study in Togo[7] showed savings ranging from US$ 0.03 to US$ 0.107 per dose. Cost analyses to date have focused

on MenAfriVac® vaccine, which offers limited opportunities for cost savings and does not allow for the extrapolation of analysis to other vaccines, because it is a new vaccine that is introduced for a one-off campaign effort in specific geographic zones. However, CTC-related savings could be greater with other vaccines that are provided in larger and repeated outreach efforts.

While CTC use of MenAfriVac® provided an expedient and helpful CTC introduction platform, the pipeline of new CTC-labelled vaccines is expected to reap much greater and longer-term benefits, as these other vaccines will routinely be given in special settings (for example, outreach to homes or schools or outbreak response) for the foreseeable future. Investment in CTC will therefore be an important complement to supply chain investments, as the latter will not always reach all the way to the most vulnerable populations.

Further economic analyses are needed to better articulate the value of each CTC use case. Modelling the broad impact of specific future CTC-qualified vaccines will only be practical once we have evidence from countries to fuel assumptions of the models. Fortunately, newly CTC-labelled vaccine products soon will be available for pilot introductions, and economic studies are close at hand. There is still much to be learned about the benefits and impact of CTC with new antigens, in campaigns of longer duration and in diverse settings.

## A. The role of CTC in addressing immunization programme needs

The CTC approach is meant to complement supply chain investments and to help overcome burdens and constraints associated with the last mile of vaccine delivery in a traditional cold chain. Ultimately, CTC has the potential to contribute to increased immunization coverage and equity in low-income countries. More specifically, CTC can offer the following substantial benefits:

- Simplifying the logistical requirements and costs for vaccine distribution and extending outreach capabilities by allowing transport and short-term storage of vaccines without ice or refrigeration during the days immediately preceding administration;
- Decreasing the risk of freeze damage for freeze-sensitive vaccines, especially during outreach in vaccine carriers, a use case in which they are most at risk of being placed too close to ice packs;
- Improving immunization coverage and equity by facilitating the distribution of vaccines that are used in campaigns or special strategies to reach underserved populations, for example:
    - Meningitis A vaccine campaigns;
    - HPV vaccine administration in schools;
    - HepB-BD administration in homes or communities;
    - TT-CV administration in homes or communities.
    - Mobile-outbreak response with OCV in resource-poor settings; and
    - Facilitated access to under- or unimmunized urban children, particularly in slum areas, for multiple CTC-compatible vaccines.
- Improving working conditions for vaccinators by reducing weight of vaccine carriers, obviating the need to renew ice packs during long journeys and potentially avoiding the need to travel to return vaccines into the cold chain after outreach; and
- Optimizing the use of staff time by redirecting staff to routine immunization activities that ordinarily would need to be dedicated to conditioning ice packs for campaigns.

## B. Progress to date

### 1. Availability of CTC guidance for manufacturers

- **Generic extended controlled temperature conditions (ECTC) regulatory guidance has been developed for vaccine manufacturers** and endorsed by the WHO's Expert Committee on Biological Standardization.[8]
- CTC **qualification is a preferred characteristic for vaccines** in the Vaccine Presentation and Packaging Advisory Group's *Generic Preferred Product Profile for Vaccines*[9] and WHO's guidelines for *Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification*.[5]

### 2. Availability of CTC-labelled vaccines

- **Two vaccines are currently fully prequalified by WHO for CTC use.**
  - Serum Institute of India's MenAfriVac® (meningitis A vaccine) is labelled to allow use at temperatures up to 40°C for four days. A growing body of published evidence demonstrates the benefits of the use of this vaccine in a CTC. WHO has also produced specific guidelines for implementation of MenAfriVac® in a CTC.[10]
  - Merck's Gardasil®4 (quadrivalent HPV vaccine) is labelled to allow use at temperatures up to 42°C for three days. Planning for pilot use and the development of implementation guidelines are under way.

It should be noted that Pfizer's Prevnar 13® (pneumococcal conjugate vaccine) was approved for use at temperatures up to 40°C for three days. However, this indication was removed in 2016 to allow consistent labelling across Prevnar products (with different presentations/number of doses per vial) and because WHO confirmed that this particular product is not a high priority for CTC, given that it is typically delivered with other vaccines that still require the traditional cold chain.

- **Two more vaccines are expected to soon be prequalified for CTC use by WHO.** Shantha Biotechnics, a Sanofi company, has submitted additional data to WHO for prequalification of their Shanchol™ vaccine (OCV) at temperatures up to 40°C for a to-be-determined duration (likely between 7 and 20 days). Prequalification is expected by the fourth quarter of 2017. Euvichol® (OCV) from EuBiologics is currently under review for CTC labelling by the Korean regulatory authority in consultation with the WHO prequalification team. Prequalification of Euvichol® is expected by the end of 2018 with a similar outcome as Shanchol™.
- **At least five additional vaccine producers are advancing efforts to label vaccines for CTC use.** There are two manufacturers of monovalent HepB-BD that are moving forward with stability testing in support of an eventual CTC label. A TT vaccine manufacturer has been discussing the potential for CTC with WHO and partner agencies. Two other HPV vaccine products are also progressing towards CTC labelling.

## 3. Recent CTC and out-of-the-cold-chain[ii] introductions and assessments

**With meningitis A (MenAfriVac®):**

- CTC pilot study completed in Benin[11] with study of adverse events following immunization;
- Economic benefits modelling study completed in Chad;[6] and
- Official CTC implementation scaled up for national campaigns in Mauritania (with knowledge, attitudes and practices study), Togo (with economic benefits study using field data), Cote d'Ivoire, South Sudan and the Democratic Republic of the Congo.

**With TT, HepB-BD and OCV:**

- Recent out-of-the-cold-chain studies have been conducted on the use of TT by Médecins Sans Frontières in Chad, HepB-BD by the US Centers for Disease Control and Prevention in Laos, and OCV by Médecins Sans Frontières in Guinea and by WHO in Malawi.

## 4. CTC guidance and tools for national immunization programmes

- Meningitis A vaccine CTC guidance, training[12] and facilitator's[13] documents are available on the WHO website.
- A three-episode advocacy film on CTC, an infographic and a frequently asked questions document were created as tools to promote the approach among varied stakeholders. All are available in English[14] and French.[15]
- A peak-threshold temperature indicator was identified and used in CTC implementation studies.
- An evaluation of manufacturers' perceptions of CTC was completed in 2015.[iii]
- An assessment of country interest in HepB-BD use with CTC was completed in 2016.

## 5. Current barriers and issues

- There is a lack of demand for CTC-labelled vaccines by countries – possibly because few are aware of or have experience with CTC, and MenAfriVac® CTC campaign introductions were single events prior to use of the vaccine in routine settings.
- Some national health authorities view CTC as adding extra complexity or confusing staff, which may potentially undermine immunization campaigns and cold chain investments.
- The 2015/2016 evaluation of vaccine manufacturers' perceptions of CTC showed that vaccine manufacturers are seeking greater clarity on WHO's vision and strategy for CTC, as well as the relationship between CTC and ECTC.
- CTC activities sit within two separate WHO departments (Immunization, Vaccines and Biologicals and Essential Medicines and Health Products) that have different reporting structures, funding and priorities.

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

[iii] A summary report is available from WHO on request.

### 6. Strategic prioritization by the CTC-WG

The recognition of a need for more strategic coordination and improved visibility of the CTC programme led to the establishment of the CTC-WG under WHO's IPAC in mid-2016. This working group has successfully assembled the principal stakeholders for CTC to ensure a shared vision for the programme and to achieve a higher degree of respective commitment across partnering agencies, which include WHO; United Nations Children's Fund (UNICEF); Gavi, the Vaccine Alliance; and PATH as well as representatives of industry through the participation of the International Federation of Pharmaceutical Manufacturers and Associations and the Developing Countries Vaccine Manufacturers Network. A key output of the CTC-WG was the IPAC-endorsed statement[16] on the use of vaccines out of the cold chain versus in a CTC, which was also promoted by the Strategic Advisory Group of Experts on Immunization in October 2016 in the context of HepB-BD. This statement advocates strongly in favour of CTC, encouraging manufacturers to accelerate efforts towards licensing and labelling in keeping with CTC criteria.

When the CTC-WG convened in person in February 2017, a key part of its discussions concerned the identification of the vaccines that possess the most favourable combination of heat-stability potential to qualify for CTC use and likelihood for CTC use to have positive public health impact. Following a critical overview of the list of CTC candidate vaccines considered to date and their status with respect to licensure or relabelling for use in a CTC, consensus was reached to focus efforts over the next four years (2017 to 2020) around four priority vaccines, namely HPV vaccine, TT-CV, OCV and HepB-BD.

These vaccines were selected based on three criteria: (i) adequate heat stability; (ii) a delivery strategy that would benefit from CTC use/expressed country need; and (iii) technical feasibility of CTC licensure.

All four of the selected priority vaccines meet the heat stability and technical feasibility criteria required by WHO for CTC. See Annex 1 for detailed information on the delivery strategies and programmatic benefits of potential CTC use for these vaccines.

For each of the four priority vaccines, relevant technical and programmatic experts, including personnel from WHO regional and country offices, will be identified and called on for their expert guidance and input when planning antigen-specific CTC activities and interventions.

## IV. PRIORITY VACCINES FOR CTC

Only one of the four priority vaccines is fully approved and ready for use in a CTC. This is the WHO-prequalified quadrivalent HPV vaccine from Merck. As mentioned above (see III. B.2 Availability of CTC-labelled vaccines), an OCV has obtained licensure for CTC use with a National Regulatory Authority and is currently under review for WHO prequalification. The CTC focus for these two vaccines under this roadmap will be on programmatic work with countries to collect field implementation data to possibly inform future demand and guide future country decisions on the application of CTC. However, there will also be efforts to create an enabling environment at the financing and procurement levels to advance the supply of additional CTC-labelled products. The main endeavours for the other two priority vaccine types, TT-CV and hepatitis B (Hep B) vaccine, will focus on supply work with manufacturers, including country-level demand assessment and identification of candidate products and pathways to CTC licensure and prequalification. Annex 2 defines the potential contributions of key CTC stakeholders to this programme of work.

It is acknowledged that a number of activities in support of these priority vaccines cut across the four vaccine types but appear as individually listed activities or commitments under each vaccine type. However, every effort will be made to identify potential synergies across the four vaccines and apply lessons learned from one antigen to another.

## A. Human papillomavirus vaccine

### 1. Supply

Currently, five HPV vaccines exist, two of which are WHO-prequalified: Cervarix® (bivalent) and Gardasil® (quadrivalent and nonavalent). One HPV vaccine product, Gardasil®4 was licensed and prequalified for use in a CTC in June 2016. Other manufacturers are working to qualify their products for CTC licensure.

### 2. Programmatic use

As of February 2017, 93 countries have introduced HPV vaccination into their national immunization programme to date (see Fig. 1). The remaining countries are mainly in Africa and Asia and consist of highly populated countries such as China, India, Nigeria and Pakistan.

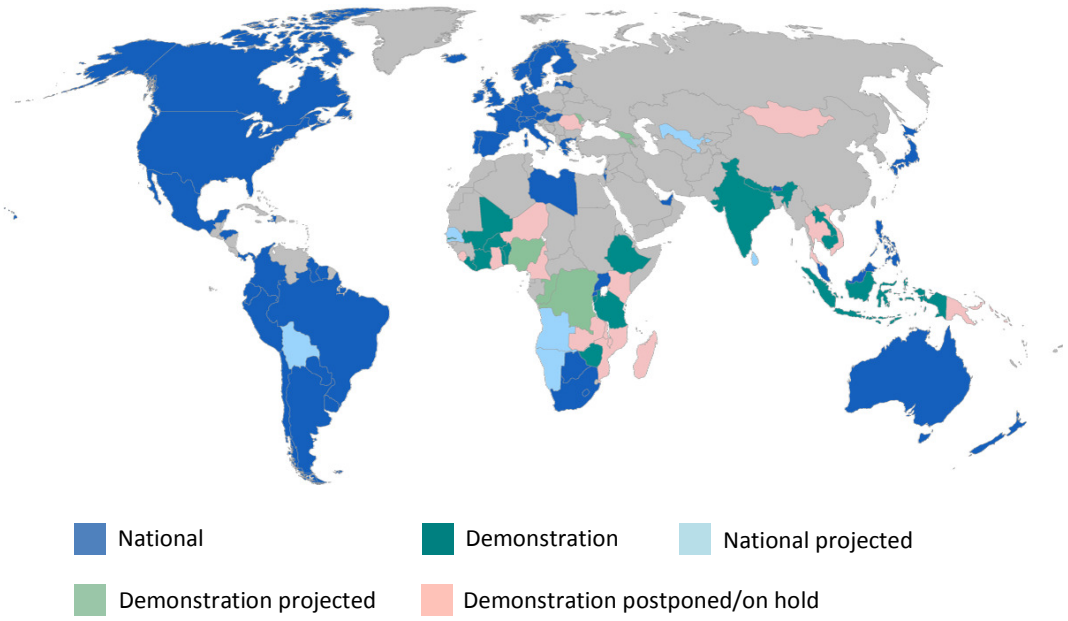



**Fig. 1. Countries with HPV vaccine in the national immunization programme**

CTC use of Gardasil®4 has not yet occurred, though planning is under way for pilot introductions in at least two initial countries between 2017 (Uganda) and 2018 (Malawi).

It is expected that CTC will bring advantages for HPV vaccination in the following settings:

- An existing school health programme that is run by the school and that takes place on a specific day or period during the school year for which vaccines are delivered for this day/period;

- A school-based delivery strategy that requires health facility staff to travel from the health centre to the schools in their catchment area;
- An outreach delivery strategy that requires health facility staff to travel from the health centre to different locations in their catchment area; and
- Vaccine delivery through campaigns (including introductory so-called catch-up campaigns) that requires health facility staff to travel from the health centre to different locations in their catchment area.

## 3. Planned achievements by 2020

- HPV vaccine will be implemented in a CTC in at least five countries between 2017 and 2020:
  - 2017 – at least one country (pilot)
  - 2018 – at least one new country (uptake)
  - 2019 – at least two new countries (uptake)
  - 2020 – at least one new country (uptake).
- Benefits for health workers and economic savings in at least two countries will be documented by the end of 2019. These outputs could be considered for incorporation into an adaptable tool that can apply to all eligible vaccines with linkages to an ongoing WHO work stream on total system effectiveness. Coverage and equity indicators will be explored as well.
- Two additional HPV vaccine products will be licensed for use in a CTC by 2020.

## 4. Proposed activities: HPV vaccine

| PLANNED ACTIVITIES FOR HPV VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| **1. Identify expert advisors (in adolescent and school health) to support advances in CTC for HPV vaccine, including strategies and outreach efforts to improve vaccine delivery** | **LEAD:** WHO/EPI CTC focal point, WHO/HPV programme focal point, PATH/CTC focal point and PATH/HPV focal point<br>**PARTNER:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ● | ― | ● | | | | | | | | | | | |
| **2. Identify countries to implement Gardasil®4 in a CTC**<br>***Note:*** *Bhutan, Botswana, Malawi, Papua New Guinea, Senegal, Seychelles, Solomon Islands, Sri Lanka, Uganda and Zimbabwe have been discussed as potential candidates* | **LEAD:** WHO/EPI CTC focal point, WHO/HPV programme focal point, PATH/CTC focal point and PATH/HPV focal point<br>**PARTNERS:** CTC-WG members<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ● | ― | ― | ― | ― | ● | | | | | | | | |
| **2.1. Develop develop selection strategy of countries and regions, number of countries and regions to have impact/ identify countries with approved Gavi, the Vaccine Alliance applications for HPV vaccine introduction and confirmed shipments** | WHO/EPI CTC focal point, UNICEF and Gavi, the Vaccine Alliance | ● *Draft guidance is already available* | | | | | | | | | | | | | | | |
| | | | | ● | ― | ― | ― | ― | ● | | | | | | | | |
| **2.2. Develop/adapt strategy on how to approach countries and regions** | WHO, PATH and UNICEF | ● | ― | ― | ― | ● | | | | | | | | | | | |
| **2.3. Identify dates for national rollouts of HPV vaccine** | | | | ● | | ● | | | | | | | | | | | |
| **2.4. Compile information pack for country-level stakeholders and share information material about CTC for HPV vaccine with countries** | WHO, PATH and UNICEF with CTC-WG members | | | ● | ― | ● | | | | | | | | | | | |

| PLANNED ACTIVITIES FOR HPV VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| **3. Develop guidance for countries on CTC with HPV vaccine implementation** | **LEAD:** WHO/EPI CTC focal point, WHO/HPV programme focal point and PATH/CTC focal point<br>**PARTNER:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | ● *Draft guidance is already available* | | | | | | | | | | | | | | | |
| **3.1. Review draft guidance** | WHO with CTC-WG members via TechNet-21 | | | ● | | | | | | | | | | | | | |
| **3.2. Pilot draft guidance and revise based on feedback from field** | WHO and PATH | | | ●—● | | | | | | | | | | | | | |
| **3.3. Finalize guidance based on experience in 2018** | | | | | | ●—● | | | ● *Final guidance available* | | | | | | | | |
| **4. Implement HPV vaccination in a CTC in at least one country (Uganda) in 2017**<br>***Note:** Discussions with multiple countries ongoing* | **LEAD:** WHO/EPI CTC focal point, WHO/HPV programme focal point and PATH/CTC focal point<br>**PARTNER:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ●—● | | ● | | | | | | | | | | | |
| **4.1. Develop study protocol and submit for ethics review at WHO, PATH and in country** | | ● *Draft study protocol available* | | ● *Final study protocol and ethics approval* | | | | | | | | | | | | | |
| **4.2. Country advocacy mission(s)** | | | | ● | | | | | | | | | | | | | |
| **4.3. Country planning missions** | | | | ●—● | | | | | | | | | | | | | |
| **4.4. Implementation and documentation** | | | | ●—● | | ● *Final report available for other countries and for manufacturers* | | | | | | | | | | | |
| **5. Implement HPV vaccination in a CTC in additional countries in 2018**<br>***Note:** Discussions with the Ministry of Health in Botswana and Malawi are under way* | **LEAD:** WHO/EPI CTC focal point, WHO/HPV programme focal point and PATH/CTC focal point<br>**PARTNER:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | | | | | | |
| **5.1. Country advocacy mission** | | | | | ●—● | ● | | | | | | | | | ●—● | | |
| **5.2. Country planning mission** | | | | | | ●—● | | | | | | | | | | ●—● | |
| **5.3. Implementation and data collection** | | | | | | | ●—● | | ● *Final report* | | | | | | | | ● |

| PLANNED ACTIVITIES FOR HPV VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 6. Document implementation results | **LEAD:** WHO/EPI CTC focal point and PATH/CTC focal point<br>**PARTNER:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | • *Other countries to be determined* | | • *Other countries to be determined* | | | | |
| 6.1. Coverage and improved access | | | | | | | | | | | | | | | | | |
| 6.2. Equity | | | | | | | | | | | | | | | | | |
| 6.3. Economic savings | | | | | | | | | | | | | | | | | |
| 6.4. Overall challenges and benefits of CTC | | | | | | | | | | | | | | | | | |
| 6.5. Lessons learned on managerial challenges and needs | | | | | | | | | | | | | | | | | |
| 7. Develop advocacy and communication materials based on implementation results and distribute | **LEAD:** WHO/EPI CTC focal point and PATH/CTC focal point<br>**PARTNER:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | | | | | | |
| 7.1. Develop advocacy strategy for countries and regions and for manufacturers: highlight coverage and equity | | | | | | | • *Advocacy material developed* | | | | • *Advocacy material published on WHO website and distributed* | | | | | | |
| 7.2. Implement advocacy strategy | | | | | | | | | | | | | | | | | |
| 7.3. CTC to be on agenda for EPI managers and regional working group meetings | | | | | | | | | | | | | | | | | |
| 8. Work with vaccine manufacturers to ensure key HPV vaccines in development are prequalified for CTC use | **LEAD:** WHO/EPI CTC focal point, WHO/ Prequalification Team and PATH/CTC focal point<br>**PARTNER:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | | | | | | |

Abbreviations: CTC, Controlled Temperature Chain; CTC-WG, Controlled Temperature Chain Working Group; EPI, Expanded Programme on Immunization; HPV, human papillomavirus; Q, quarter; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

## B. Oral cholera vaccine

### 1. Supply

Of the three OCVs prequalified by WHO – Dukoral®, Euvichol® and Shanchol™ – the latter two are under review for licensure and WHO prequalification with CTC labelling. Dukoral® is prequalified but the manufacturer has yet to seek CTC compatibility.

### 2. Programmatic use

It is expected that CTC will bring advantages for OCV immunization in the following settings:

- Periodic mass vaccination campaigns in rural, isolated areas or slums with limited infrastructure;
- Pre-emptive vaccination campaigns in rural, isolated areas or slums with limited infrastructure; and
- Reactive vaccination campaigns in rural, isolated areas or slums with limited infrastructure.

### 3. Planned achievements by 2020

- OCV will be implemented in a CTC in five countries between 2018 and 2020:
  - 2018 – at least one country (pilot)
  - 2019 – at least two new countries (uptake)
  - 2020 – at least two new countries (uptake), including one where other vaccines are administered in a CTC to examine potential synergies in coadministration.
- Benefits for health workers and economic savings in all three settings outlined above will be documented by the end 2019 and incorporated, as mentioned above, into a possibly broader tool and total system effectiveness work stream. Coverage and equity indicators will be explored as well.
- One additional OCV product will be licensed for use in a CTC by 2020.

## 4. Proposed activities: OCV

| PLANNED ACTIVITIES FOR OCV VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| **1. Identify expert advisors (in outbreak emergency) to support advances in CTC for OCV, including strategies and outreach efforts to improve vaccine delivery** | **LEAD:** WHO/EPI CTC focal point and WHO/Cholera Task Force<br>**PARTNER:** MSF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ● | | | | | | | | | | | | | |
| **2. Identify countries or settings to implement OCV in a CTC** | **LEAD:** WHO/EPI CTC focal point and WHO/Cholera Task Force<br>**PARTNER:** MSF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ● | ● | | | | | | | | | | | | |
| **2.1. Develop strategy for approach and selection of countries** | | | | ● | ● | | | | | | | | | | | | |
| **2.2. Compile and share information pack for the country level** | | | | | ● | | | | | | | | | | | | |
| **2.3. Engage country with initial dialogue, with country (Ministry of Health, WHO/ country office, PATH, UNICEF) and advocacy visits** | | | | ● | ● | ● | | | | | | | | | | | |
| **3. Develop draft guidance on CTC implementation for countries** | **LEAD:** WHO/EPI CTC focal point and WHO/Cholera Task Force<br>**PARTNER:** MSF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | ● | ● | | | | | | | | | | | |
| **3.1. Review draft guidance** | WHO with CTC-WG members via TechNet-21 | | | | | | ● | ● | | | | | | | | | |
| **3.2. Pilot draft guidance and revise based on feedback from field** | WHO and PATH | | | | | | ● | ● | | | | | | | | | |
| **4. Implement OCV vaccination in a CTC in one country in 2017 – pilot project**<br>*Note: this will depend on the timing of CTC prequalification* | **LEAD:** WHO/EPI CTC focal point and WHO/Cholera Task Force<br>**PARTNER:** MSF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | ● | ● | | | | | | | | | |
| **4.1. Develop draft study protocol and submit for ethics review at WHO, PATH and in country** | | | | | | ● *Final study protocol and ethics approval* | | | | | | | | | | | |
| **4.2. Country planning and advocacy mission** | | | | | | ● | ● | | | | | | | | | | |
| **4.3. Implementation and documentation** | | | | | | | ● | ● | ● *Final report available for other countries and for manufacturers* | | | | | | | | |

| PLANNED ACTIVITIES FOR OCV VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| **5. Implement OCV in a CTC in additional countries in 2018** | **LEAD:** WHO/EPI CTC focal point and WHO/Cholera Task Force<br>**PARTNER:** MSF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | | | | | | |
| **5.1. Country advocacy visit** | | | | ● | ● | | | | | | | | | | | | |
| **5.2. Country planning mission** | | | | | ● | ● | | | | | | | | | | | |
| **5.3. Implementation and documentation** | | | | | | ● | | | ● | ● *Final reports* | | | | | | | |
| | | | | | | | | | | | ● *Final reports* | | | | | | |
| **6. Document implementation results** | **LEAD:** WHO/EPI CTC focal point and WHO/Cholera Task Force<br>**PARTNER:** TBD<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | ● *Countries to be determined* | → | → | → | → | → | → | → | → | → | → | → | → | → |
| **6.1. Coverage and improved access** | | | | | | | | | ● | → | → | → | → | → | → | → | → |
| **6.2. Equity** | | | | | | | | | ● | → | → | → | → | → | → | → | → |
| **6.3. Economic savings** | | | | | | | | | ● | → | → | → | → | → | → | → | → |
| **6.4. Overall challenges and benefits of CTC** | | | | | | | | | ● | → | → | → | → | → | → | → | → |
| **6.5. Lessons learned on management** | | | | | | | | | ● | → | → | → | → | → | → | → | → |
| **6.6. Facilitation of self-administration of second dose through CTC as appropriate*** | | | | | | | | | ● | → | → | → | → | → | → | → | → |
| **7. Develop advocacy and communication materials based on implementation results and distribute** | **LEAD:** WHO/EPI CTC focal point and WHO/Cholera Task Force<br>**PARTNERS:** MSF, UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | ● | → | → | → | → | → | → | → | → |
| **7.1. Develop advocacy strategy for countries and regions and for manufacturers: highlight coverage and equity** | | | | | | | | | ● *Advocacy materials developed* | | | | | | | | |
| | | | | | | ● | | | | ● *Advocacy materials published on WHO website* | | | | | | | |
| | | | | | | | | | | | ● *Advocacy materials distributed* | | | | | | |
| **7.2. Implement advocacy strategy** | | | | ● | → | → | → | → | → | → | → | → | → | → | → | → | → |
| **7.3. CTC to be on agenda for EPI and regional working group meetings** | | | | ● | → | → | → | → | → | → | → | → | → | → | → | → | → |
| **8. Work with vaccine manufacturers to ensure other OCV vaccine(s) in development are/is prequalified for CTC use** | **LEAD:** WHO/EPI CTC focal point, WHO/Cholera Task Force and PATH CTC focal point<br>**PARTNERS:** MSF, UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | ● | → | → | → | → | → | → | → | → | → | → | → | → |

Abbreviations: CTC, Controlled Temperature Chain; CTC-WG, Controlled Temperature Chain Working Group; EPI, Expanded Programme on Immunization; MSF, Médecins Sans Frontières; OCV, oral cholera vaccine; Q, quarter; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

*NOTE: Studies are underway to examine the necessity and spacing options for the second dose of OCV.

## C. Tetanus toxoid containing vaccine

### 1. Supply

Currently, six WHO-prequalified TT vaccines exist, none of which are licensed for CTC. Note that WHO favours Td vaccine over TT vaccine,[17] so exploring Td vaccine for CTC should also be a consideration of this work stream.

### 2. Programmatic use

It is expected that CTC will bring advantages for tetanus vaccination in the following settings:

- Outreach activities that reach women at reproductive age who live in remote, isolated areas that are inaccessible by services or who do not come to health facilities; and
- Campaign activities that reach women of reproductive age, including those living in high-risk areas.

Opportunities for joint administration of TT-CV with other CTC-licensed vaccines such as HPV, OCV, or HepB-BD will be explored.

### 3. Planned achievements by 2020

One TT-CV product will be licensed for use in a CTC by 2020.

## 4. Proposed activities: TT

| PLANNED ACTIVITIES FOR TT VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 1. Identify expert advisors on tetanus immunization (MNT-WG), to develop strategies and outreach efforts to improve vaccine delivery | **LEAD:** WHO/EPI CTC focal point, WHO/MNT-WG and PATH CTC focal point<br>**PARTNERS:** UNICEF (as part of MNT-WG), MSF<br>**INPUT/GUIDANCE FROM:** MNT-WG members | | | ● | | | | | | | | | | | | | |
| 2. Determine if other TT-CV should/could be considered (for example, Td, Tdap, DT) | **LEAD:** WHO/EPI CTC focal point, WHO/MNT-WG and PATH CTC focal point<br>**INPUT/GUIDANCE FROM:** MNT-WG members | ● | | ● | ● | | | | | | | | | | | | |
| 2.1. Identify priorities of expert advisors on tetanus immunization | | ● | | | | | | | | | | | | | | | |
| 2.2. Identify feasibility with manufacturers | | ● | | | | | | | | | | | | | | | |
| 3. Determine the priority product formats for TT-CV used in a CTC (for example, single or multidose or CPAD) based on programmatic needs and assess demand/availability. | **LEAD:** WHO/EPI CTC focal point, WHO/MNT-WG and PATH CTC focal point<br>**PARTNERS:** MSF, UNICEF<br>**INPUT/GUIDANCE FROM:** MNT-WG members | | | | | ● | | | | | | | | | | | |
| 4. Develop a value proposition for TT-CV used in a CTC | **LEAD:** WHO/EPI CTC focal point and WHQ/ MNT working group and PATH CTC focal point<br>**PARTNERS:** MSF, UNICEF<br>**INPUT/GUIDANCE FROM:** MNT-WG members | | | | | ● | | | | | | | | | | | |
| 4.1. Seek collaboration with academic institutes | | | | ● | ● | | | | | | | | | | | | |
| 4.2. Identify appropriate study format: modelling, surveys, etc. | | | | | ● | | | | | | | | | | | | |
| 4.3. Conduct studies | | | | | | ● | ● | ● | | | | | | | | | |
| 5. Advocacy/communication with TT-CV manufacturers | **LEAD:** WHO/EPI CTC focal point, WHO/MNT-WG and PATH CTC focal point<br>**PARTNERS:** MSF,UNICEF<br>**INPUT/GUIDANCE FROM:** MNT-WG members | | | ● | ● | ● | | | | | | | | | | | |
| 5.1. Contact manufacturers that have WHO prequalified TT/Td/CPAD products individually to inform them about TT-CV being a CTC priority | | | | ● | ● | ● | | | | | | | | | | | |

| PLANNED ACTIVITIES FOR TT VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| **6. Develop an incentive scheme for CTC-licensed TT-CV products, especially linked to in-country cost reduction (total system costs)** | **LEAD:** UNICEF,<br>**PARTNERS:** WHO, PATH<br>**INPUT/GUIDANCE FROM:** MNT-WG members | | | | | ● | → | → | → | → | → | → | → | → | → | → | → |
| **7. Provide technical assistance to vaccine product developers** | **LEAD:** PATH CTC focal point<br>**PARTNERS:** WHO/EPI CTC focal point<br>**INPUT/GUIDANCE FROM:** MNT-WG members | | | ● | → | → | → | → | → | → | → | → | → | → | → | → | → |
| **8. Develop guidance for countries on the use of TT-CV in a CTC** | **LEAD:** WHO/EPI CTC focal point<br>**PARTNERS:** PATH, MSF<br>**INPUT/GUIDANCE FROM:** MNT-WG members | | | | | | | | | | | | | ● | → | → | → |

Abbreviations: CPAD, compact prefilled autodisable device; CTC, Controlled Temperature Chain; DT, diphtheria tetanus; EPI, Expanded Programme on Immunization; MNT-WG, Maternal and Neonatal Tetanus Working Group; MSF, Médecins Sans Frontières; Q, quarter; Td, tetanus diphtheria (low dose); Tdap, tetanus–diphtheria–acellular pertussis; TT-CV, tetanus-toxoid-containing vaccine; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

## D. Hepatitis B vaccine birth dose

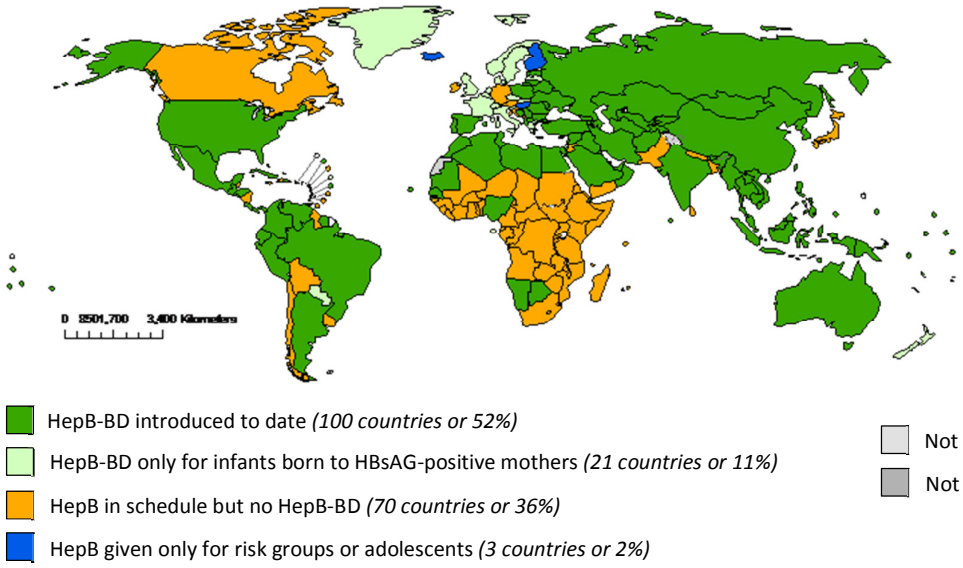
### 1. Supply

Currently, there exist seven WHO-prequalified Hep B vaccines, none of which are licensed for use in a CTC.

Package inserts for two monovalent Hep B vaccines, including one WHO-prequalified vaccine, indicate that, for one product, the vaccine is stable for one month at 37°C and, for another product, the vaccine is stable for one week at 45°C. A few manufacturers are working towards licensing Hep B vaccine products for CTC use.

### 2. Programmatic use

Ninety-seven countries have introduced HepB-BD to date (Fig. 2).a




Abbreviations: HBsAG, hepatitis B surface antigen; Hep B, hepatitis B; Hep-BD, hepatitis B vaccine birth dose.

[a] The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2017. All rights reserved.

Data source: WHO/Immunization, Vaccines and Biologicals Database as at 9 August 2017 and European Centre for Disease Prevention and Control published data at http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx; 194 WHO Member States map produced by WHO/Immunization, Vaccines and Biologicals, date of slide: 9 August

**Fig. 2. Countries with HepB-BD in their national immunization programme**

It is expected that CTC will bring advantages for HepB-BD in the following settings:

- Outreach activities that reach babies born outside of health facilities or those discharged early before vaccination can be given; and
- Provision of Hep B vaccine in small rural facilities without cold chain equipment.

It should be noted that the timely vaccination enabled by CTC could also have a beneficial effect on disease transmission. Efforts could be explored as to how to measure or predict this through potential modelling. This could be included in the definition of this vaccine's value proposition.

## 3. Planned achievements by 2020

- The value proposition will be characterized for HepB-BD use in a CTC in varied settings.
- Two Hep B vaccine products will be licensed and prequalified by WHO for use in a CTC by 2020.

## 4. Proposed activities: HepB-BD

| PLANNED ACTIVITIES FOR HepB-BD VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 1. Identify expert advisors in HepB-BD to develop strategies and outreach efforts to improve vaccine delivery | **LEAD:** WHO/EPI CTC focal point, WHO/Hep B focal point and PATH CTC focal point<br>**PARTNERS:** UNICEF, CDC<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ● | | | | | | | | | | | | | |
| 2. Determine the priority product formats for Hep B vaccine used in a CTC (for example, single or multidose or CPAD) based on programmatic needs, and assess the market. | **LEAD:** WHO/EPI CTC focal point, WHO/Hep B focal point and PATH CTC focal point<br>**PARTNERS:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ● | ● | | | | | | | | | | | | |
| 2.1. Identify appropriate study format: modelling, surveys. | | | | | | | | | | | | | | | | | |
| 3. Develop a value proposition for Hep B vaccines used in a CTC; consider use within TSE framework | **LEAD:** WHO/EPI CTC focal point, WHO/Hep B focal point and PATH CTC focal point<br>**PARTNERS:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | | | | | | |
| 3.1. Seek collaboration with academic institutes | | | | ● | ● | | | | | | | | | | | | |
| 3.2. Identify appropriate study format: modelling, surveys | | | | | ● | | | | | | | | | | | | |
| 3.3. Conduct studies | | | | | | ● | ● | ● | | | | | | | | | |
| 4. Advocacy/communication with Hep B vaccine manufacturers | **LEAD:** WHO/EPI CTC focal point, WHO/Hep B focal point and PATH CTC focal point<br>**PARTNERS:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | ● | ● | ● | | | | | | | | | | | |
| 4.1. Inform HepB-BD manufacturers | | | | ● | ● | | | | | | | | | | | | |
| 4.2. Ensure that Hep B products currently not WHO-prequalified will be reviewed for CTC prequalification | WHO, UNICEF | | | ● | ● | | | | | | | | | | | | |
| 5. Develop an incentive scheme for CTC-licensed Hep B products | **LEAD:** UNICEF; Gavi, the Vaccine Alliance<br>**PARTNERS:** WHO, PATH<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | ● | → | → | → | → | → | → | → | → | → | → | → | → |

| PLANNED ACTIVITIES FOR Hep B-BD VACCINES | LEAD AGENCY AND PARTNERS | 2017 | | | | 2018 | | | | 2019 | | | | 2020 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| **6. Provide technical assistance to vaccine product developers** | **LEAD:** PATH CTC focal point<br>**PARTNERS:** WHO/EPI CTC focal point<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | | | | | | |
| **7. Develop guidance for countries on the use of Hep B in a CTC** | **LEAD:** WHO/EPI CTC focal point, WHO/Hep B focal point and PATH CTC focal point<br>**PARTNERS:** UNICEF<br>**INPUT/GUIDANCE FROM:** CTC-WG members | | | | | | | | | | | | | | | | |

Abbreviations: CDC, US Centers for Disease Control and Prevention; CPAD, compact prefilled autodisable device; CTC, Controlled Temperature Chain; EPI, Expanded Programme on Immunization; Hep B, hepatitis B; Hep B-BD, hepatitis B vaccine birth dose; Q, quarter; TSE, total system effectiveness; UNICEF, United Nations Children's Fund; WG, working group; WHO, World Health Organization.

# V. OTHER PROPOSED ACTIVITIES

The CTC-WG agenda will carry out additional activities, which will include:

- Developing an overall communication and advocacy strategy;
- Identifying other priority vaccines in research and development for CTC licensure and adding them to the roadmap as appropriate;
- Monitoring the continuing appropriateness of the CTC designation (three days/40°C) as additional vaccines are reviewed and as programme strategies evolve to address the rural and urban hard-to-reach populations;
- Ensuring that a threshold indicator and/or vaccine vial monitor with threshold indicator is WHO-prequalified for use with CTC vaccines; and
- Documenting how the application of CTC can improve coverage and thereby contribute to herd immunity among vaccinated populations.

As the CTC work progresses, it is likely that a broader array of stakeholders will become involved. The respective roles for each of the key stakeholders in the CTC programme of work are listed in Annex 2.

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# V. ANNEX 1: Background information on initial priority vaccines for CTC licensure and use

| VACCINE | CHALLENGES THAT CTC COULD HELP TO ADDRESS | HOW CTC COMPLEMENTS SUPPLY CHAIN INVESTMENTS | POTENTIAL FOR IMPROVED COVERAGE | ECONOMIC RETURNS ON CTC INVESTMENTS | COMMENTS |
|---|---|---|---|---|---|
| HepB-BD | HepB-BD does not reach babies born in mothers' homes nor in facilities without cold chain, mainly due to logistics and cold chain challenges. The risk of Hep B infection for infants increases significantly when the first dose is not received in the first few days following birth. | Supply chain investments have the potential to equip delivery rooms and postnatal wards to have the HepB-BD available in the cold chain. However, a large percentage of births are taking place at mothers' homes, and CTC would facilitate the delivery of the vaccine to the newborns in a timely manner. Cold chain investment would not reach this level of vaccine delivery, which requires vaccines to be kept at midwives' homes. | CTC would facilitate making vaccines available in delivery rooms, postnatal wards and homes via administration of the vaccine by midwives during home birth visits, thereby increasing timely birth dose coverage. | The higher price of a single-dose presentation might be compensated by reduced wastage and reduced freeze damage. An increase in birth-dose vaccination has the potential to reduce the proportion of newborns who acquire perinatal Hep B infection, leading to savings for the health system in terms of treatment of chronic liver disease. | HepB-BD has been the vaccine most studied with OCC use. |
| TT-CV | MNT continues to be a public health problem particularly in countries with populations that are inaccessible by traditional vaccination strategies. Seventeen countries have not yet eliminated MNT, and 49 000 newborns died from tetanus in 2013 and 34 000 in 2015, according to WHO estimates. | The 70 million women of reproductive age who are not receiving TT-CV vaccination belong to the voiceless part of the population who do not come to hospitals. While supply chain investment would help equip health facilities, CTC would allow reaching out to this part of the population, which otherwise would be left behind. | CTC use of TT-CV would facilitate campaigns and outreach to women who are inaccessible by traditional strategies. In Chad, in an operational research setting, MSF kept TT vaccines inside vaccine carriers without ice packs for 30 days to be carried by teams during a mass vaccination campaign and outreach activities. | With CTC, transportation and labour costs could potentially be saved during efforts to reach the unreached in pursuit of MNT elimination. Reduced freeze damage is also a potential benefit. CTC will contribute to decreasing the disease burden, as it will help reach women who are otherwise missed, as they do not come to hospitals and therefore have to be reached at their homes. | The possibility of using TT-CV in a CTC is a major advantage for countries struggling to eliminate MNT. OCC studies with TT have demonstrated feasibility. |

| VACCINE | CHALLENGES THAT CTC COULD HELP TO ADDRESS | HOW CTC COMPLEMENTS SUPPLY CHAIN INVESTMENTS | POTENTIAL FOR IMPROVED COVERAGE | ECONOMIC RETURNS ON CTC INVESTMENTS | COMMENTS |
|---|---|---|---|---|---|
| HPV vaccine | HPV vaccine is frequently administered through activities that require complex cold chain logistics, such as outreach to schools. All too often, unorthodox practices come into play (such as use of nonvaccine certified refrigerators and other inappropriate cooling mechanisms), which threaten appropriate storage and transport of this freeze-sensitive vaccine. | Supply chain investment would contribute to the use of appropriate equipment in which HPV vaccines should be stored. At the same time, outreach activities would still require the production and transportation of ice packs. This burden would be alleviated by CTC. | CTC would ease outreach logistics and allow for longer immunization sessions on a given day, since melting ice packs would no longer be a constraint on timing. Consequently, there could be less disruption of school activities over multiple days to allow for HPV vaccination and better acceptance. | With CTC, transportation and labour costs could potentially be saved during outreach activities. Reduced freeze damage is also a potential benefit. | Initial cold chain evaluation studies have already demonstrated the potential for HPV vaccine outreach to schools within CTC temperature guidelines. |
| OCV | Cholera outbreaks often occur in areas with the least health resources (for example, rural isolated areas and slums). Governments and WHO tend to be reluctant to recommend oral cholera vaccination because, among other issues, of the need for cold chain distribution in these difficult settings. | It will be challenging to improve and maintain the supply chain in rural isolated areas and slums. CTC would therefore be a more effective investment, helping to organize immunization campaigns in these hard-to-reach areas. | Maintaining cold chain for large numbers of doses in most cholera outbreak settings is often close to impossible due to the amount of vehicle movements, need to change ice packs and temperature monitoring required. Alternative options would be facilitated by CTC. For example, in Guinea, vaccines were stored under cold chain conditions but were transported and used at ambient temperatures on the day of vaccination. This greatly facilitated campaign implementation and increased coverage. | Cold chain storage capacity is limited, often requiring reliance on other locations and sources of storage (for example, the United Nations compound in Haiti). With CTC, the additional transportation and staffing costs could potentially be saved. CTC will allow for the organization of cholera vaccination campaigns that otherwise might not be possible to conduct; therefore, CTC could potentially contribute to a decrease in the risk of further outbreaks. | Using a cold-chain-requiring product for large, rapid and reactive vaccination campaigns may seem less feasible during the chaos of epidemic disease in regions with fragile health systems. Concerns about scarcity of resources may result in an attempt to pit one public health approach against another. This can be avoided through CTC licensure and implementation. |

Abbreviations: CTC, Controlled Temperature Chain; Hep B, hepatitis b; HepB-BD; hepatitis B vaccine birth dose; HPV, human papillomavirus; MNT, maternal and neonatal tetanus; MSF, Médecins Sans Frontières; OCC, out of the cold chain; OCV, oral cholera vaccine; TT-CV, tetanus-toxoid-containing vaccine; WHO, World Health Organization.

# VI. ANNEX 2: Proposed roles and responsibilities of key CTC stakeholders

A number of stakeholders continue to be committed to the CTC agenda and have been active on the CTC-WG run jointly by WHO and PATH. The following overview outlines the proposed responsibilities of partners that are already engaged in the CTC agenda.

## World Health Organization

### Expanded Programme on Immunization/Department for Immunization, Vaccines and Biologicals

- Secretariat for the CTC-WG;
- Formulation of vision and strategy, together with immunization partners, clarifying the intent of CTC both in the short term and long term; review and endorsement of CTC priorities and strategies via advisory bodies (for example, IPAC and/or the Strategic Advisory Group of Experts on Immunization);
- Further development of global policies and guidance for CTC implementation and use;
- Identification of need and potential demand from countries for specific vaccines licensed for CTC; support to countries to analyse the potential for CTC-compliant vaccine use in their countries;
- Assessment and documentation of country experiences with CTC implementation; and
- Coordination, advocacy and technical/financial support to countries with CTC pilot studies, introductions, evaluations and vaccine procurement decisions.

### Prequalification Team/Department for Essential Medicines and Health Products

- Participation in the CTC-WG;
- Definition of prequalification requirements and approvals for CTC-labelled vaccines and peak temperature threshold indicators;
- Responsive provision of regulatory and stability-testing guidance to vaccine manufacturers to assist with CTC qualification;
- Continuous feedback to manufacturers on developments regarding intent, programmatic use, guidance and potential candidate vaccines, helping facilitate the development of business cases by manufacturers; and
- Close collaboration with national regulatory authorities in vaccine-producing and -receiving countries on an ongoing basis to orient them on CTC requirements, aiming at a harmonized approach across countries.

## PATH

- Co-Secretariat for CTC-WG;
- Technical assistance to vaccine manufacturers and vaccine delivery device (for example, microarray patch) developers to improve product heat stability, qualify for CTC labelling and liaise at appropriate time points with WHO for regulatory guidance;
- Identification of funding sources and management of financial support to vaccine manufacturers to offset the costs that are associated with the stability studies required for relabelling high-priority CTC vaccines if necessary;

- Development of a vaccine technology prioritization framework evaluation of CTC using the framework as applied to specific vaccines, vetting of results with global stakeholders and submission of results to WHO for official endorsement;
- Assistance to WHO with CTC pilot studies, introductions, evaluations and development of policies/guidance materials; leadership of specific evaluations as agreed upon with WHO;
- Field validation testing of vaccine vial monitor/threshold-indicator devices for WHO prequalification, and other technical assistance to WHO as needed to advance the availability of these devices for CTC use; and
- Advocating for CTC qualification and labelling with key vaccine development collaborators.

## UNICEF

- Participation in the CTC-WG;
- Provision of vaccine forecasting data to help clarify the future markets for CTC-labelled vaccines;
- Work with WHO to assess country demand for CTC licensed vaccines;
- Incorporation of CTC requirements into vaccine procurement processes as advised by WHO;
- In close collaboration with WHO and other partners, further development of global policies and guidance materials for CTC implementation and use;
- Identification of need and potential demand from countries for specific vaccines licensed for CTC; support to countries to analyse (economic and coverage analysis) the potential for CTC-compliant vaccine use in their countries;
- Assistance to WHO in assessment and documentation of country experiences with CTC implementation; and
- Coordination, advocacy and technical support to countries with CTC pilot studies, introductions, evaluations and vaccine procurement decisions, including in relation to use of CTC in acute emergency and other humanitarian situations.

## Bill & Melinda Gates Foundation

- Provision of funding to advance CTC work by stakeholders, including CTC qualification work and milestones in grants to key vaccine developers and manufacturers; and
- Advocacy for CTC qualification and labelling with key vaccine manufacturers directly or indirectly.

## Médecins Sans Frontières

- Participation in the CTC-WG; and
- Assistance to WHO with CTC pilot studies, introductions, evaluations and development of policies and guidance materials – particularly in relation to use of CTC in emergency aid situations; leadership of specific evaluations as agreed upon with WHO.

## Gavi, the Vaccine Alliance

- Participation in the CTC-WG;
- Market-shaping for relevant vaccines – for example, the inclusion of CTC in vaccine roadmaps; and
- Ensuring of communication and advocacy on CTC with endorsed strategies and priorities.

## CONTACT

WORLD HEALTH ORGANIZATION
DEPARTEMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS
20, AVENUE APPIA
CH – 1211 GENEVA 27
SWITZERLAND