

Brief Communication

Controlled temperature chain: Reaching the unreached in resource-limited settings

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Abstract

Geographical distance from health centre and the costs and constraints involved in cold chain maintenance are important factors influencing poor immunization coverage in remote areas of resource-limited countries. Controlled temperature chain (CTC) is an approach which uses the innate heat stability specific to certain vaccines, to reduce the dependency on cold chain and has been accepted for potential use in situations where cold chain maintenance is not feasible and limits immunization programme effectiveness. In 2012, MenAfriVac, Meningitis A conjugate vaccine became the first vaccine to be pre-qualified by World Health Organization for use under CTC. Various existing vaccines are being approved for CTC use in low-resource settings. Proper CTC labelling and effective temperature monitoring are important considerations. While cold chain is critical and should be maintained as always, CTC is a useful alternate option which needs to be explored to reach the unreached in limited-resource settings.

Keywords: Controlled temperature chain; Immunization; MenAfriVac

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In the last decade, great progress has been made in developing and introducing new vaccines and expanding the reach of immunization programmes. Despite the significant advances, vaccine preventable diseases remain an important cause of morbidity and mortality.¹ According to global immunization coverage survey in 2014, 18.7 million children under one year of age worldwide had not received third dose of Diphtheria, Pertussis and Tetanus (DPT). More than sixty percent of these children live in ten countries: Democratic Republic of the Congo, Ethiopia, India, Indonesia, Iraq, Nigeria, Pakistan, Philippines, Uganda and South Africa.² More than 20.1 million children under two years of age have not received the first dose of measles vaccine.² Reaching these underserved populations is a challenge which needs to be tackled, since these populations often carry severe disease burden.¹

Meeting vaccination coverage targets in every region, country and community is one of the main goals of the decade of vaccines (2011-2020).¹ Geographical distance from the health centre is one of the main determinants for the low immunization coverage among these populations, though other socioeconomic factors such as income, educational status also play a role.¹

Cold chain maintenance- the bottlenecks in resource-poor settings

The need for maintenance of a strict cold chain is one of the constraining elements in hampering the coverage of the unreached and underserved populations. While most developing countries have functioning cold rooms at the national level and regional levels, the ability to maintain storage and transport temperatures between 2^o C and 8^o C, at lower levels of supply chain becomes challenging

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due to lack of reliable electricity or functioning equipment.³ These factors interfere with the outreach vaccination sessions, where the health workers have to carry the vaccines in cold chain for several miles from the health post. As a result, the increasing cost and/or logistical constraints of vaccine delivery due to the cold chain requirements significantly hinder vaccination coverage in hard-to-reach areas.⁴ In addition, some vaccines freeze when carried against frozen ice packs and vial labels peel off if vials become wet. Mass immunization campaigns require an increased ice production and storage capacity. Large campaigns in distant areas necessitate transporting of freezers to make ice packs.⁵ Storing of multi-dose vials after reconstitution adds to the strain on available resources.⁵

Controlled temperature chain

Controlled temperature chain (CTC) is an approach which uses the untapped thermal stability specific to certain vaccines to reduce the dependency on cold chain and has been accepted for potential use in situations where maintaining the cold chain is not feasible and limits immunization programme effectiveness.⁴ The participants of two consultations held under the auspices of World Health Organization (WHO), on the Scientific and Regulatory considerations on the stability evaluation of vaccines under CTC: first meeting at Ottawa, Canada (4-6 December 2012) and final meeting at Langen, Germany (4-6 June 2013) recommended use of the term “Extended Controlled temperature chain” as more appropriate than CTC, but suggested the continued use of term CTC until endorsement by the concerned WHO committee.^{5,6}

The working definition of Extended CTC which may be dependent on the country in which vaccine is used, allows a specific vaccine to be kept and used at ambient temperatures upto 40°C: for a limited period of time immediately preceding vaccine administration; under circumstances where maintaining a 2°C to 8°C is not possible or extremely challenging; for vaccines meeting a number of pre-determined conditions; up until this excursion, the vaccine should continue to be kept in the traditional 2°C to 8°C cold chain or other label conditions.^{5,6}

The 2 consultations by WHO have concluded that 40°C be considered the target CTC temperature if supported by the stability profile of the vaccine; at least 3 days is the minimum time for excursion outside the cold chain for logistic reasons; temperature monitoring must be assisted by appropriate peak temperature indicators.^{5,6}

CTC: Success story of MenAfriVac

In October 2012, MenAfriVac, Meningitis A conjugate vaccine developed by Serum Institute of India became the first vaccine to be pre-qualified by WHO for use under CTC, at ambient temperatures of upto 40°C for a maximum of 4 days, following a label variation approved by Drug Controller General India.⁶ In November 2012, a pilot project was launched by PATH and WHO with MenAfriVac, delivering the vaccine to remote health posts and outreach sites in the Banikora district of northern Benin in South Africa.³ Over 155596 vaccines were administered across 150 villages and only 9 vials were discarded for surpassing the 4-day limit. Follow-up studies showed that none of the recipients of CTC vaccine contracted meningitis that season.^{7,8} An economic analysis of a mass vaccination campaign in Chad using MenAfriVac, in 2011 before WHO approval, estimated that the direct campaign-specific cold chain and logistics costs could potentially be halved if CTC strategy was implemented.⁸

CTC vaccines in pipeline

Stability studies undertaken for the following vaccines reported retention of potency and efficacy when used under CTC conditions: Biomanguinis yellow fever vaccine (for 6 months at 37°C), Hepavax-Hepatitis B vaccine (for 6 months at 37°C) and Oral Polio vaccine (for 86.9 hours at 47.1°C).^{5,6} CTC labels have been approved by countries such as Canada, European Union, South Africa and United States, for various currently used vaccines such as MenAfriVac (meningococcal vaccine), Prevnar (pneumococcal conjugate vaccine) Gardasil and Cervarix (Human papilloma virus vaccines).^{5,6}

CTC: Advantages

CTC would provide improved options for safe and effective immunization strategies for delivery of vaccines to the right target population at the right time.⁵ CTC would also reduce the costs and constraints that ice pack requirements impose on transport and the need for specialized equipment. It would also facilitate integration of supply chains for drugs and vaccines.^{5,8}

CTC: Considerations

Clear labelling is a critical issue.⁵ The use of vaccines under CTC conditions will have to be carefully planned to avoid wastage of stock as any unused vaccine has to be discarded after CTC time limit even if VVM indicates otherwise.⁵ As CTC relates to the recommended temperature conditions depending on the country, use of vaccines should be preceded by extensive clinical trials in the specified country.

Apart from using VVM to measure cumulative heat exposure, Langen Report recommends mandatory use of peak temperature threshold indicators.⁶ The standard vaccine carrier was used for transport of MenAfriVac vaccines in CTC and is the recommended and preferred option in all CTC campaigns since it is usually associated with immunization activities both by the health care personnel and the community.⁹

The way forward

There is a need to document CTC practices in various parts of the world. Effective utilization of CTC requires strengthening of temperature monitoring methods.^{5,6,9} There is a need to study more vaccines which might be used in mass campaigns or emergency diseases such as Yellow fever, cholera, meningitis,

polio, influenza, Japanese encephalitis and Dengue for use under CTC conditions.⁵

In conclusion, while cold chain is critical and should be maintained as much as possible, CTC is a useful alternate option which needs to be explored for effective delivery of vaccines in resource-poor, remote areas where cold chain maintenance is difficult, provided proper temperature monitoring systems, adequate training and guidelines are in place. As the WHO launches the theme of World Immunization week 2016, “Close the Immunization gap” CTC is an innovative approach which could aid the global progress towards achieving immunization coverage targets in every region, community and country.

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