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A cluster randomized non-inferiority field trial on the immunogenicity and safety of tetanus toxoid vaccine kept in controlled temperature chain compared to cold chain

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ABSTRACT

Background: In resource-poor settings, cold chain requirements present barriers for vaccine delivery. We evaluated the immunogenicity and safety of tetanus toxoid (TT) vaccine in "Controlled Temperature Chain" (CTC; up to 40 °C for <30 days before administration), compared to standard cold chain (SCC; 2–8 °C). Prior to the study, stability parameters of TT–CTC were shown to meet international requirements.

Methods: A cluster randomized, non-inferiority trial was conducted in Moïssala district, Chad, December 2012–March 2013. Thirty-four included clusters were randomized to CTC or SCC. Women aged 14–49 years, eligible for TT vaccination and with a history of ≤1 TT dose, received two TT doses 4 weeks apart. Participants were blinded to allocation strategy. Tetanus antibody titers were measured using standard ELISA at inclusion and 4 weeks post-TT2. Primary outcome measures were post-vaccination seroconversion and fold-increase in geometric mean concentrations (GMC). Non-inferiority was by seroconversion difference ($TT_{SCC} - TT_{CTC}$) <5% and ratio of GMCs (TT_{SCC}/TT_{CTC}) <1.5. Adverse events were monitored at health centers and at next contact with participants.

Results: A total of 2128 women (CTC = 1068; SCC = 1060) were recruited. Primary intention to vaccinate analysis included 1830 participants; 272 of these were included in the seroconversion analysis. Seroconversion was reached by >95% of participants; upper 95%CI of the difference was 5.6%. Increases in GMC were over 4-fold; upper 95%CI of GMC ratio was 1.36 in the adjusted analysis. Few adverse events were recorded.

Conclusions: This study demonstrates the immunogenicity and safety of TT in CTC at <40 °C for <30 days. The high proportion of participants protected at baseline results in a reduction of power to detect a 5% non-inferiority margin. However, results at a 10% non-inferiority margin, the comparable GMC increases and vaccine's stability demonstrated in the preliminary phase indicate that CTC can be an alternative strategy for TT delivery in situations where cold chain cannot be maintained.

1. Introduction

Effective immunization with tetanus toxoid (TT) requires a cold chain system to store and transport vaccines at 2–8 °C from manufacturer to beneficiaries. The maintenance of the cold chain ensures quality of all types of vaccines. However, it can be an obstacle to vaccine delivery, especially in resource-poor countries where

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cold chain infrastructure and electricity are not always available [1,2]. Several studies have shown the feasibility of using specific vaccines under controlled temperature chain (CTC) [3–11], where vaccines are maintained outside the standard 2–8 °C recommendation for a defined duration and temperature, depending on the vaccine's particular heat-stability profile [12]. The possibility of using specific vaccines outside storage recommendations started with the introduction of vaccine vial monitors (VVM) [13,14]. A VVM is a small sticker attached to the vaccine vial that contains a time–temperature sensitive square and an outer circle. When the square reaches the color of the circle, it indicates potential degradation and the vial should be discarded [15].

Immunization of women with TT is a central strategy of the Maternal and neonatal tetanus elimination (MNTE) initiative [16]. This initiative aims to achieve the elimination goal of <1 neonatal tetanus (NT) case per 1000 live births per year in all districts of each country by end 2015. By December 2013, 25 countries [17] had not reached the elimination goal and others may be at risk of increased NT cases if efforts to maintain high TT coverage in women of childbearing age do not continue [16]. One of the pillars of the MNTE initiative is to conduct TT supplementary immunization activities (SIA) targeting women of reproductive age in high-risk areas [16]. Delivering TT vaccine in CTC could remove one of the important barriers to reaching underserved and marginalized populations considered mostly affected by tetanus.

This study was designed to assess immunological non-inferiority of TT kept in CTC compared to standard cold chain (SCC) when administered to women of childbearing age. Additionally, the safety of TT kept in CTC was assessed. A non-inferiority design was based on the expectation that CTC would help increase vaccination coverage by facilitating activities. Allocation to CTC or SCC was done at cluster level to avoid potential confusion and administration errors if individual randomization were used, as well as to replicate actual implementation strategies.

2. Materials and methods

2.1. Study design

This study was a cluster randomized, non-inferiority field trial conducted in three health zones of Moïssala district, Chad between December 2012 and March 2013. Clusters, corresponding to a village or group of neighboring villages with an estimated population of 600–800 residents, were identified. Clusters were stratified according to distance to health centers ($\leq$ or >5 km) and to infant vaccination activities taking place at village level. Clusters were assigned to receive TT kept in CTC or SCC with equal probability and by stratum (Stata, College Station, TX, USA). All women aged 14–49 years residing in study clusters were invited to participate and were allocated to CTC or SCC according to the predefined random allocation. While vaccinators and health personnel conducting the study were aware of allocation group, village heads, participants and laboratory personnel analyzing samples were blinded to the allocation.

In this study, CTC vaccines were kept outside the cold chain, at <40 °C, from district to participant level for a maximum of 30 days.

2.2. Objectives

The primary objective of the study was to demonstrate the non-inferiority of TT kept in CTC compared to that kept in SCC in terms of seroconversion and increase in antibody titers. Non-inferiority of CTC vaccine could be claimed if, one month after vaccination, the difference ($TT_{SCC} - TT_{CTC}$) in percentage of participants reaching seroconversion was <5% and the ratio of geometric mean anti-tetanus antibody concentrations (GMCs) (TT_{SCC}/TT_{CTC}) was <1.5. The study also evaluated adverse events (AEs) following administration of TT kept in CTC and SCC.

2.3. Vaccine

In May 2012, prior to the study, TT in 10 dose-vials (Serum Institute of India Limited, Hyderabad, India) from three different batches (018B2001A, 018L1008B and 018L1024D) were exposed to CTC conditions in Moïssala district, Chad. This vaccine has a VVM 30, reaching discard point after 30 days at 37 °C. Following this, CTC vaccines were kept inside vaccine carriers without ice-packs for 30 days and carried by teams during a mass vaccination campaign and outreach activities. Teams were instructed to perform daily duties normally. A maximum ambient temperature of 43.1 °C was registered during this period. Exposure temperatures were monitored using electronic temperature recorders (LogTag® TRID30-7). Exposure temperatures in the three vaccine carriers used ranged from 24.6 °C to 40.1 °C (mean 31.2 °C; with 30 $\leq$ 35 °C for 50% of the time and $\geq$35 °C for 14%. A VVM percentage-based color intensity scale previously used [3,11], with 100% indicating discard point, showed 50% change in color suggesting that exposure to heat had not damaged the product. Control vaccines remained in the refrigerator in Moïssala district (4.8–13.2 °C, with 3% of the time >8 °C).

Exposed and control vaccines were tested for potency, pH, toxicity and adsorption following standard testing procedures [18–20] at the Belgian Scientific Institute of Public Health (WIV-ISP) in Brussels. The WIV-ISP is authorized to perform the required in-vivo tests; care of the animals was in accordance with institutional guidelines. After exposure period, laboratory results showed that vaccines still met specifications required for use and were considered stable (Table 1). The same vaccine batches were used for immunization of study participants.

2.4. Participants

Eligible participants were women 14–49 years of age living in the study area who had received a maximum of one previous TT

Table 1
Results of potency, pH and flocculation tests for vaccines kept in controlled temperature chain (CTC) and standard cold chain (SCC).

Batch	CTC			SCC		
	Potency IU/dose (95%CI)	pH	Flocculation (total Lf/ml)	Potency IU/dose (95%CI)	pH	Flocculation (total Lf/ml)
018B2001A	95 (73–124)[1]	6.56	19.2 (21 min)	94 (71–124)[1]	6.50	15.2 (23 min)
018L1008B	222 (161–308)[1]	6.63	18.4 (19 min)	147 (108–200)[2]	6.66	18.4 (24 min)
018L1024D	135 (98–185)[2]	6.53	19.2 (20 min)	92 (63–131)[2]	6.59	15.2 (30 min)

Note: The variability of potency results is related to an in-vivo testing. All batches meet international requirement. No statistical differences were observed between CTC and cold chain batches.
[1] 1st run, reference value ED50 = 118.
[2] 2nd run, reference value ED50 = 125.