



Research Paper

Safety and effectiveness of a non-electric infant warmer for hypothermia in Rwanda: A cluster-randomized stepped-wedge trial

Josee Uwamariya^a, Christian Mazimpaka^a, Leana May^{b,c}, Alphonse Nshimiyiryo^a, Henry A. Feldman^{d,e}, Felix Sayinzoga^f, Sharon Umutesi^f, Ashok Gadgil^{g,h}, Vi H. Rapp^h, Evrard Nahimana^a, Anne Hansen^{d,e,*}

^a Partners In Health/Inshuti Mu Buzima (PIH/IMB), KG9 Avenue, No. 46, Nyarutarama Cell, Remera Sector, Kigali, Gasabo, Rwanda

^b Children's Hospital of Colorado, 13123 E 16th Ave, Aurora, CO 80045, United States

^c University of Colorado School of Medicine, 13001 E 17th Pl, Aurora, CO 80045, United States

^d Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115, United States

^e Harvard Medical School, 25 Shattuck St, Boston, MA 02115, United States

^f Rwanda Ministry of Health, KN3 Rd, Kigali, Rwanda

^g University of California, 760 Davis Hall, Berkeley, CA 94720, United States

^h Lawrence Berkeley Laboratory, MS 90R2121, 1 Cyclotron Road, Berkeley, CA 94720, United States

ARTICLE INFO

Article History:

Received 27 January 2021

Revised 25 March 2021

Accepted 26 March 2021

Available online 16 April 2021

ABSTRACT

Background: Neonatal hypothermia is a common source of morbidity and mortality in low resource settings. We developed the Dream Warmer, a low cost, re-usable non-electric infant warmer to prevent and treat hypothermia.

Methods: We conducted a cluster-randomized stepped-wedge trial. The primary aim was to assess the effect on overall euthermy rates of introducing the warmer compared to standard of care in rural Rwandan hospitals. The secondary aims were to assess effects of warmer introduction on mortality, as well as the safety and feasibility of the warmer. Ten district hospitals participated in the study from November 19th 2019 to July 15th 2020. Patients were eligible to use the warmer if they were 1) hypothermic (temp < 36.5 °C) or 2) or at risk of hypothermia (weight < 2.5 kg or estimated post menstrual age < 35 weeks) when Kangaroo Mother Care was not available. An encounter was defined as the data from an individual infant on a single day. Trial of a Non Electric Infant Warmer for Prevention and Treatment of Hypothermia in Rwanda [NCT03890211].

Findings: Over the study period, 3179 patients were enrolled across the ten neonatal wards, yielding 12,748 encounters; 464 unique infants used the warmer 892 times, 79% eligible due to hypothermia. Because of limited study nurse resources, the warmer was used in only 18% of eligible encounters. Despite this low rate of warmer use, the rate of euthermy rose from 51% (95% CI 50–52%) of encounters pre-intervention to 67% (66–68%) post-intervention; $p < 0.0001$. Among the encounters in which the warmer was used, only 11% (9–13%) remained hypothermic. While mortality rates pre- and post-intervention did not change, mortality rate among those who used the warmer was significantly lower than among those who did not (0.9% vs 2.8%, $p = 0.01$). Use of the warmer did not affect hyperthermia rates. There were no safety concerns or instances of incorrect warmer use.

Interpretation: Introduction of the warmer increased rates of euthermy with no associated safety concerns.

© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

1. Introduction

Neonatal hypothermia is widely recognized to be one of the major causes of preventable morbidity and mortality, especially among the world's poorest newborns [1–3]. Though rarely listed as the direct cause of death [3], it is estimated to contribute to 40% of the

2–4 million babies who die each year, almost exclusively in Low and Middle Income Countries (LMIC) [4]. Provision of warmth is an essential element of the most basic care of small and sick infants, yet is frequently lacking [5,6]. Neonatal hypothermia is reported to occur in up to 85% of hospitalized neonates in LMIC [3]. For low birth weight (LBW) newborns in low resource setting (LRS), studies report almost universal occurrence of hypothermia whether born at home or in health care facilities [7,8].

Preterm neonates rely on external heat to maintain a normal core temperature for weeks to months. The WHO recommends that

* Corresponding author at: Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115, United States.

E-mail address: anne.hansen@childrens.harvard.edu (A. Hansen).

Research in Context

Before undertaking the development of the Dream Warmer, the authors reviewed all available sources to determine the existence of an adequate non-electric infant warming device for the low-income setting. This included a PubMed search with no date limitations for the terms newborn, low birth weight, premature, preterm, hypothermia, global, transwarmer, and conductive mattress. We also conducted general internet searches for products unrecognized in the academic literature. We found two devices that approximated our needs: Embrace and Warmilu warmers. Both had deficiencies related to preparation, ability to clean for multi-use, compatibility with KMC, accessibility of infant for medical assessment/treatment, and cost. To overcome these deficiencies, we collaborated with the Rwanda Ministry of Health (RMOH) to develop and test a non-electric infant warmer that met all of these requirements. Having conducted two pilot tests totaling 204 uses with strong safety, effectiveness and feasibility data, we were invited by the RMOH to proceed to a Stepped Wedge trial. In the process of these clinical trials, we have kept up with the literature pertaining to hypothermia in the low resource setting and have discovered no new competitive devices.

This is, to our knowledge, the first randomized trial studying a transwarmer mattress designed for and tested in the low resource setting. The Dream Warmer has the unique features of being compatible with KMC, allowing visual and physical access to the patient if needed can be easily cleaned and re-used... In this large scale, multisite study, our warmer continues to perform well, significantly improving rates of eutheria, with no safety concerns or instances of misuse.

external heat be provided as Kangaroo Mother Care (KMC) for stable babies with a birth weight ≥ 2000 g [9]. There is growing evidence of the multiple advantages of KMC including thermoregulation, bonding, and milk production [10,11]. It is a low cost, highly effective intervention that must be supported.

A supplemental external heat source is needed, however, when KMC does not provide sufficient heat, or for periods when the mother is unavailable (due to illness or need to conduct activities incompatible with KMC). Additionally, health care providers often require visual or physical access to an ill baby to conduct assessments or perform procedures. A thermoregulatory device is urgently needed to complement KMC in the LRS.

Therefore, we developed the Dream Warmer, a low-cost, non-electric reusable infant mattress based on the concept of a heating pad, incorporating a phase change material that is melted by boiled water and then remains at skin temperature for approximately 6 h. (See Supplemental Material 1 for description of infant warmer design, laboratory testing, and use.) The warmer satisfies all major qualifications put forward by UNICEF [12] and PATH [13] including ease of use, cleaning and maintenance; re-usability; durability; offering access to infant; existence of temperature indicator and low literacy instructions; and appropriateness for use on transport.

We conducted the first multicenter study of a non-electric infant mattress in hospitalized newborns in rural Rwanda. We hypothesized that introducing the warmer across ten Rwandan district hospitals would increase rates of eutheria.

2. Methods

2.1. Study design

This was a cluster-randomized stepped-wedge trial (Figs. 1 and 2). CONSORT guidelines were followed. All hospitals started in the pre-

intervention period. Ten warmers were introduced to a new hospital every two weeks, thereby transitioning from the pre-intervention or "pre phase," to the post-intervention or "post phase." After the last hospital transitioned, a final 4 weeks of data was collected at all ten hospitals.

The study was designed to provide control data in an ethical and feasible manner, while accommodating for multiple uncontrollable confounders. Because the value of preventing or treating eutheria is beyond the point of equipoise, the most ethical way to obtain data from a control group was a pre-post comparison rather than a randomized trial. The stepped wedge design [14] was chosen as robust approach to implementing a novel intervention in multiple sites in the LRS. Because of the complexity of thermoregulatory practices beyond the control of the study nurses (e.g. availability of electricity and functioning electric heating equipment, ambient temperature, willingness of individual mothers to provide KMC, availability and thickness of blankets), our primary analyses compared all the encounters in the pre phase to all of those in the post phase, regardless of whether the warmer was used.

2.2. Participants and setting

Because all hospitalized infants regardless of weight or age might develop hypothermia, rather than collecting data only on LBW or preterm infants, all patients admitted to the neonatal ward were eligible for participation in the study. Infants were eligible to receive the intervention of the warmer if they were

- i Hypothermic (temp < 36.5 °C) or
- ii At risk of hypothermia (current body weight < 2.5 kg or estimated post menstrual age < 35 weeks) at times when KMC was not available or not sufficient (temperature rising by < 0.5 °C/h).

Infants were excluded from using the warmer if they required phototherapy (due to untested interaction between phototherapy and the warmer), had a significant skin condition (to avoid confusion ascribing potential adverse effect to the warmer), an initial temperature < 35 °C with an electrical heating source available, or were deemed too unstable for inclusion by the bedside nurse. Infants were also excluded if the family was unwilling or unable to provide informed consent.

Ten district Rwandan hospitals participated in the study from November 19th 2019 to July 15th 2020 (Table 1). Hospitals were selected by the Rwanda Ministry of Health based on high neonatal admission rates and varied climates. The warmer was introduced to the ten hospitals in a random order generated by an Excel computer program. The order of introduction was not concealed, but was communicated to the investigators to facilitate planning and deployment of staff. Of note, the study was shut down from March 22nd to May 11th, 2020 due to the country-wide lockdown for COVID-19 and when it re-opened, Kirehe hospital could not rejoin.

Written informed consent translated into the local language Iki-nyrwanda was obtained from the parent of each study participant from whom we only collected data. If an infant became eligible to use the warmer, a second consent was requested specifically for warmer use. The study was approved by human research review: BCH Institutional Review Board (IRB-P00030705), the Rwanda National Ethics Committee (reference # 0076/RNEC 2018), Rwanda National Health Research Committee (reference # 514) and the Rwanda MOH. The trial was registered at ClinicalTrials.gov: NCT03890211.

2.3. Intervention

The intervention was the provision of the warmer (See Supplemental Material 2). In accordance with the Rwandan National Neonatal Care Protocol (RNNCP), mothers were encouraged to provide KMC

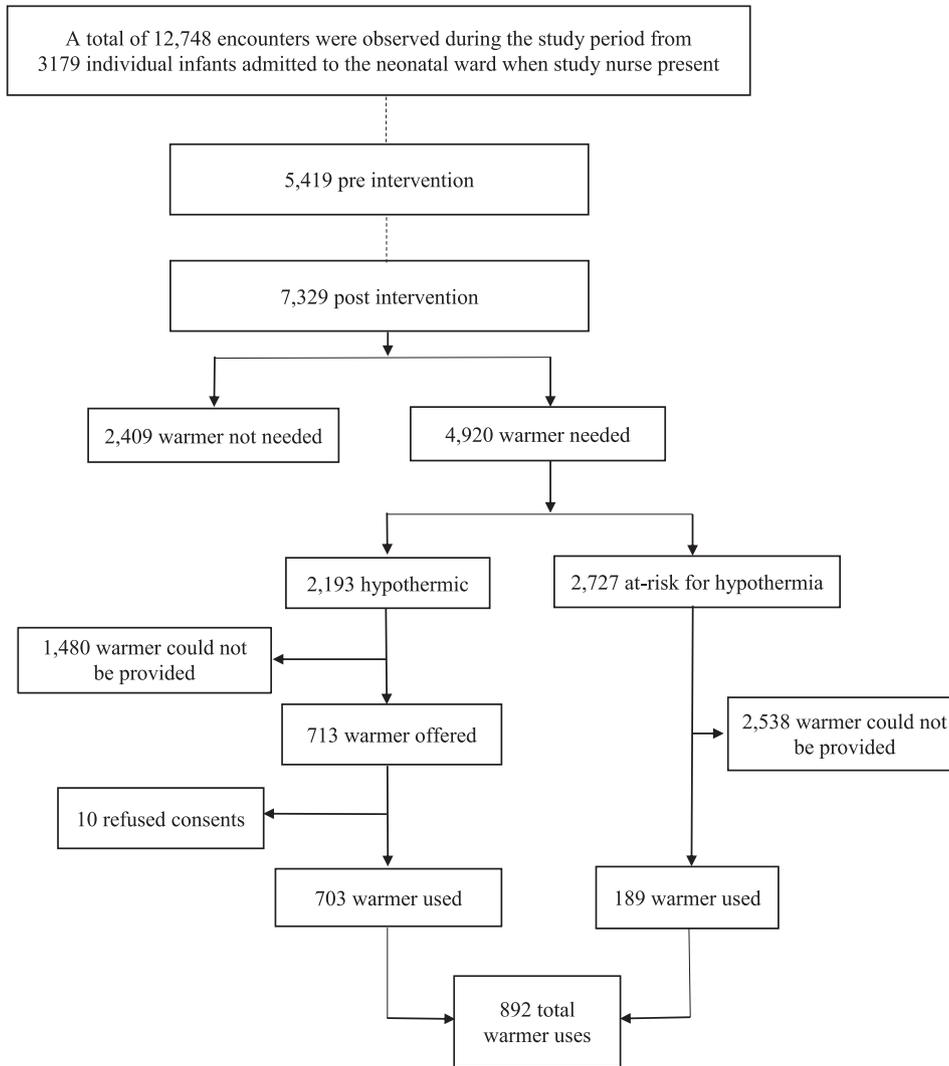


Fig. 1. CONSORT trial profile.

to hypothermic and at-risk infants whenever possible. For hypothermic infants, if the temperature was not rising by ≥ 0.5 °C/h with KMC alone, the warmer was offered as an additional heat source. In these cases, the heat was provided by placing the

warmer over the infant’s back while the mother provided KMC (Fig. 3). If the mother was not available for KMC, the infant was warmed exclusively with the warmer by being placed directly on it as it lay flat (Fig. 4). Use of a blanket, hat and socks was

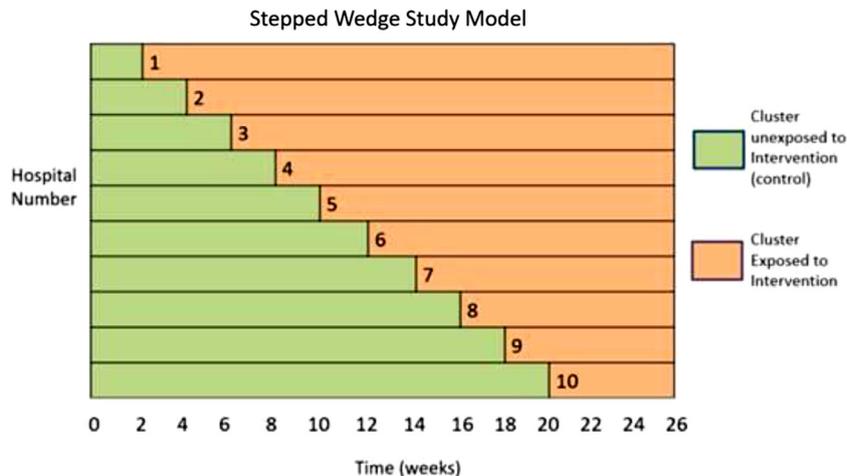


Fig. 2. Progression of new hospital enrollment every two weeks, transitioning from “pre phase” to “post phase” with four weeks of data collection at all hospital sites at the end of the study.

Table 1.
Clinical and demographic characteristics of study participants.

Variables	n	%
Hospital, N = 3179		
Nyamata	488	15.4
Mibilizi	440	13.8
Kabgayi	379	11.9
Rwamagana	377	11.9
Byumba	295	9.3
Ruhengeri	286	9.0
Nyagatare	267	8.4
Gisenyi	252	7.9
Nemba	217	6.8
Kirehe	178	5.6
Estimated gestational age, N = 3179		
<37 weeks	770	24.2
≥ 37 weeks	1075	33.8
Missing data	1334	42.0
Birth weight, N = 3179		
Normal (≥2500 g)	1759	55.3
Low birth weight (1500 to <2500 g)	1084	34.1
Very low birth weight (1000 to <1500 g)	205	6.5
Extreme low birth weight (<1000 g)	23	0.7
Missing data	108	3.4
Age at first encounter, N = 3179		
≤7 days	2377	74.8
8–31 days	672	21.1
≥32 days	38	1.2
Missing data (missing date of birth)	92	2.9
Length of hospital stay (in days), N = 2988, median (IQR)	7	(4–12)
Infant Warmer use criteria, N = 892*		
Hypothermic (<36.5 °C)	703	78.8
At risk for hypothermia, KMC not available/inadequate	189	21.2
Infant Temperature Prior to Infant Warmer Use, N = 892*, median (IQR)	36.1	(35.8–36.4)

* Total number of individual infants.

† 191 babies missing data for either missing date of admission or date of hospital exit.

* Encounters of infants placed on the non-electric infant warmer. It was possible for one infant to have multiple encounters.

encouraged but other clothes were only added by caregiver request, as they reduce heat transfer.

The study nurse trained the bedside nurses to prepare the warmer, when to remove it, and how to clean and store it. To ensure safety, bedside nurses were only allowed to use the warmer under supervision of the study nurse.

Infants were eligible to use the warmer every time they met the inclusion criteria, which may have been multiple times during their hospital stay. Only one infant was placed on each warmer with each



Fig. 3. Heat source with KMC: Pictorial representation of the dream warmer being used in conjunction with KMC and a hat.

use, but warmers were used by multiple infants over the course of the study, with thorough cleaning between uses.

Criteria for early discontinuation of the warmer: The intervention was stopped and the infant was warmed with an appropriate source of electric heat (if available) if the infant met any Early Stopping Criteria (See Supplemental Material 2).

The intervention was complete and the warmer was removed if the mother became available to resume KMC, or when the warmer dropped below phase change temperature as evidenced by its beginning to harden and turn opaque, and no longer being warm in the area under where the infant was lying.

2.4. Data collection and outcomes

A study nurse collected all data from the medical record onto paper data collection form and then transcribed them into an electronic database. The study manager audited 5% of transcribed data.

Patients not using the warmer (pre and post phase): The study nurses measured the patient's temperature in the axilla with a standard thermometer in accordance with the RNNCP, namely every hour if abnormal, then every three hours, and collected gestational age as documented in the medical record, daily weight, length of hospital stay, and mortality data. The study nurse also measured the ambient air temperature every three hours using a standard wall thermometer.

Patients using warmer: The study nurse measured the temperature of the patient and the warmer (with a thermistor) every 30 min until the infant was euthermic (36.5–37.5 °C) and then every 1 h for the remainder of use of the warmer. At each of these times, the nurse also collected data on whether the infant received the warmer with KMC, or as a stand-alone heat source, as well as whether the infant had a blanket, hat, diaper, or other clothing.

The data collected during the pre phase was the control data. The data collected during the post phase was the intervention data. Data collection and intervention were only performed when the study nurse was present, 40 h/week. An encounter was defined as the data from an individual infant on a single day.

Our primary outcome, assessed by encounter, was attainment or maintenance of euthermia, defined as the infant's temperature either (i) staying between 36.5 and 37.5 °C throughout the encounter, or (ii) at any point in the encounter where observed to be <36.5 °C, having risen at least 0.5 °C/h since the initial hypothermic measurement. This endpoint was ascertained for every encounter in enrolled infants in both the pre and post phase, regardless of whether the warmer was used.

Our secondary outcomes were mortality prior to discharge, as well as safety and feasibility of the warmer limited to infants who used the warmer.

The safety outcomes were whether an infant developed hyperthermia (temperature > 37.5 °C) and the occurrence of any adverse events including skin irritation such as rash or burn.

The feasibility of using the warmer was assessed by observer audits conducted by the study nurse of both usability (correct application of the warmer) and functionality (evidence of material breakdown). The study nurse was instructed to correct any incorrect intentions at preparation, use, or cleaning of the warmer, and document the potential error.

3. Statistical analysis

Dichotomous outcomes were analyzed by Fisher exact test. The primary outcome was analyzed by multiple logistic regression, stratified by hospital, with individual encounter as the unit of analysis and study period as the independent variable (regardless of warmer use, following the intention-to-treat principle). Alternative statistical models, employed for sensitivity analyses, both pre-specified and

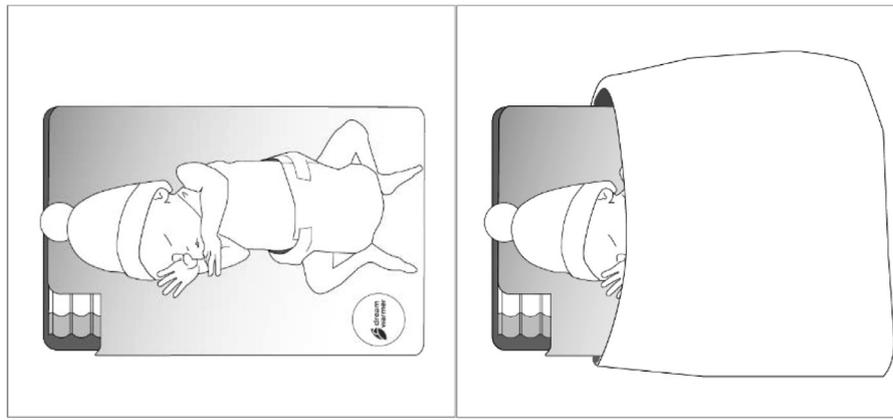


Fig. 4. Stand-alone heat source: Pictorial representation of the dream warmer, inserted into an insulating sleeve with a window that allows visualization of the phase change material. Wearing a hat, the infant is laid directly on the warmer and then covered with a blanket.

post-hoc, included warmer use as the independent variable (per-protocol analysis); clustering by infant to account for multiple encounters; adjustment for infant-level and encounter-level covariates (gestational age, initial temperature, calendar time); limiting analysis to data collected before the study paused for the COVID-19 outbreak; and excluding one hospital that provided no post-intervention data owing to the pandemic.

We used time-to-event analysis to estimate the percentage of encounters in which the Warmer maintained certain temperature thresholds over an 8 h span, using a gamma distribution to model ‘failure’ time (i.e., crossing the threshold) and interval censoring to account for the intermittent rather than continuous recording of temperature. Statistical computations were carried out with Stata (version 12, College Station, TX) and SAS (version 9.4, Cary, NC).

Sample size calculation: To calculate detectable effects for the stepped-wedge design [15], we estimated enrollment at 5 infants per hospital per 2 week study period with a control rate of 60% successful warming, varying by 10% (SD) among hospitals (intraclass correlation 0.04). An average of 2–7 encounters per infant provided 90% power with 5% type 1 error to detect an improvement of 9–16% in rate of successful warming.

Role of the funding source: The study was funded by the Banyan Gates Foundation which had no influence on study design; collection, analysis and interpretation of data; writing of the report nor decision to submit the paper for publication. The funding source has no conflict of interest in regards to the Dream Warmer. Dr. Anne Hansen had full access to all the data in the study and had final responsibility for the decision to submit for publication.

4. Results

4.1. Demographics and description of use

We recorded a total of 12,748 encounters from 3179 patients admitted to the neonatal wards of the ten participating hospitals. Roughly half the encounters were among infants < 2.5 kg (Table 1). Infants were eligible to use the warmer during 67% (4920/7329) of the encounters during the intervention period. Primarily because of the study nurses’ limited time to collect data and prepare or supervise the preparation of the warmer, the warmer was used in only 18% (892/4920) of the total eligible encounters (37% of hypothermic encounters and 7% of at risk encounters), by 464 individual patients. In ten instances the study nurse recorded that the family declined consent to participate in the intervention. Once the warmer was introduced, it was used between 1 and 21 times, but most commonly it was used only once (Table 2). The mean time of use was 5.5 h (SD 2.9 h). The eligibility criterion for warmer was hypothermia in 703

(79%) of the 892 encounters, and “at-risk” in the remaining 189 (21%) of encounters.

In 67 (7.5%) encounters, infants met criteria for early discontinuation of the warmer. Of these encounters, 62 (92.5%) had a temperature rise to > 37.5 °C while on the warmer, three had a temperature < 36.5 °C despite maximum non-electric heat exposure, and two did not have a temperature rise within 30 min. An electric heat source was not actually available for any of these five infants.

4.2. Primary outcome

The rate of attaining or maintaining eutheria rose from 51% of 5419 encounters in the pre phase to 67% of 7429 encounters in the post phase; $p < 0.0001$ (Table 3), despite the fact that the warmer was only used in 37% of hypothermic encounters. Of the encounters in which the warmer was used, only 11% remained hypothermic.

Logistic regression results for the primary outcome and sensitivity analyses are reported in Table 4. In the primary analysis (intention-to-treat), the odds of successful attainment or maintenance of eutheria were 2.12 times greater in the post-intervention than the pre-intervention period (95% CI 1.95–2.30, $p < 0.0001$). Substantially identical results were obtained for sensitivity analyses in which we accounted for within-patient clustering, patient and encounter-level covariates, and exclusion of data due to COVID-19. The odds of successful attainment or maintenance of eutheria were 2.51 times greater in encounters with warmer use than in those without (95% CI 2.12–2.97, $p < 0.0001$). Adjustment for calendar time, to address the possibility of confounding by secular trend, attenuated the intervention only slightly (Table 4).

Effectiveness: Of the 892 encounters in which the warmer was used, 79% achieved or maintained eutheria, compared to 59% when the warmer was not used (whether patient met eligibility criteria for use, or not); $p < 0.0001$ (Table 3). Of encounters in which the warmer was used due to hypothermia, 547/892 (78%) successfully attained or maintained eutheria. Of those who used the warmer

Table 2.
Number of times warmer used by individual infants.

Number of times warmer used	Infants (%)	Uses (%)
1	279 (60)	279 (31)
2	96 (21)	192 (22)
3	36 (8)	108 (12)
4	23 (5)	92 (10)
5–6	18 (4)	96 (11)
7–21	12 (3)	125 (14)
Total	464	892

Table 3.
Attainment or maintenance of eutheria,* comparing pre and post phases, warmer use and eligibility criteria.

	Encounters	Euthermia (%)	Hypothermia (%)	Hyperthermia (%)	p [†]
Total	12,748	7702 (60)	3571 (28)	1475 (12)	
Pre-intervention	5419	2767 (51)	2026 (37)	626 (12)	< 0.0001
Post-intervention	7329	4935 (67)	1545 (21)	849 (12)	
Warmer not used	11,856	6994 (59)	3475 (29)	1387 (12)	< 0.0001
Warmer used	892	708 (79)	96 (11)	88 (10)	
Indication for warmer					
Hypothermic	703	547 (78)	85 (12)	71 (10)	0.03
At risk of hypothermia	189	161 (85)	11 (6)	17 (9)	

* **Euthermia:** 36.5–37.5 °C throughout the encounter; or if <36.5° at any point, having gained ≥0.5° per h since initial measurement. **Hypothermia:** <36.5° at any point, having gained <0.5 °C per h since initial measurement. **Hyperthermia:** >37.5 °C at any point.

[†] Fisher exact test.

due to the “at-risk” criterion, 161/189 (85%) maintained eutheria. The rates of eutheria were stable when adjusted for gestational age (Table 4).

4.3. Secondary outcomes

The rate of mortality did not change significantly in the pre (2.8%) compared to post (2.3%) phase ($p = 0.37$). However, when comparing infants who did not use the warmer ($N = 2715$) to those who used the warmer at least once ($N = 464$), the mortality rate was significantly lower among those who used the warmer at least once (0.9% vs 2.8%, $p = 0.01$), (Table 5).

Ambient temperature during the recorded encounters ranged from 19.2 to 30.8 °C, with a median of 25.5 °C. Within a given hospital, the likelihood of attaining or maintaining eutheria decreased slightly but not significantly with lower ambient temperature (odds ratio 0.92 per °C, 95% CI 0.81–1.06, $p = 0.27$).

Generally, the warmer was used with a blanket and hat as recommended to minimize ongoing heat loss. There was a fairly high use of diapers, that would theoretically reduce heat transfer, but improve hygiene. The instances when the warmer was used with KMC reflected the study protocol in which “maximum heat exposure”

(defined as KMC, blanket and hat) was applied in certain circumstances of marked hypothermia (Table 6).

5. Safety

Our two safety outcomes for infants who used the warmer were rates of hyperthermia and instances of skin irritation.

Infants who used the warmer had a 10% rate of hyperthermia (mean 37.7, range 37.6–38.2). Of note, this compares with a 12% rate of hyperthermia in infants who did not use the warmer (mean, 38, range 37.6–40.9) ($p = 0.10$). The overall rate of hyperthermia (regardless of warmer use) remained at 12% throughout the study, with no change in the post compared to pre phase (Table 3).

There were zero recorded instances of any adverse events including burns, rashes or other evidence of skin irritation for the 892 instances in which the warmer was used.

6. Feasibility

Our feasibility outcomes were rates of incorrect preparation, use, and cleaning, duration of warmth provided by the warmer, and evidence of material breakdown of the warmer.

Table 4.
Primary (intention-to-treat), secondary (per protocol), and sensitivity analyses.

Analysis	Groups compared	Encounters	Euthermia,%*	Odds ratio [†]	p [‡]
By study period (intention-to-treat)	Post-intervention	7329	68 (67–69)	2.12 (1.95–2.30)	< 0.0001
	Pre-intervention	5419	50 (49–52)		
Clustered by patient	Post-intervention	7329	68 (67–69)	2.03 (1.84–2.25)	< 0.0001
	Pre-intervention	5419	51 (49–53)		
Omitting Kirehe Hospital	Post-intervention	7329	68 (66–69)	2.12 (1.95–2.30)	< 0.0001
	Pre-intervention	4706	50 (48–51)		
Omitting post-COVID data	Post-intervention	3223	68 (66–70)	2.14 (1.91–2.41)	< 0.0001
	Pre-intervention	5400	50 (48–51)		
Adjusted for gestational age [‡]	Post-intervention	4521	68 (66–69)	2.11 (1.89–2.35)	< 0.0001
	Pre-intervention	3070	50 (48–52)		
Adjusted for initial infant temperature	Per week			1.01 (0.99–1.02)	0.32
	Post-intervention	7329	68 (67–69)	2.11 (1.94–2.30)	< 0.0001
	Pre-intervention	5419	50 (49–52)		
Per °C				1.09 (1.03–1.15)	0.003
Adjusted for secular trend	Post-intervention	7329	68 (67–69)	1.86 (1.64–2.12)	< 0.0001
	Pre-intervention	5419	50 (49–52)		
	Per month				1.03 (1.01–1.06)
By warmer use (per protocol)	Warmer used	892	78 (75–81)	2.51 (2.12–2.97)	< 0.0001
	Warmer not used	11,856	59 (58–60)		
By indication for use [§]	At risk	189	84 (76–89)	1.21 (0.69–2.12)	0.51
	Hypothermia	703	81 (77–84)		

* Probability of attained or maintained eutheria, with 95% confidence interval.

[†] Odds ratio for attainment or maintenance of eutheria, as compared between groups or per unit covariate, with 95% confidence interval, from multiple logistic regression analysis stratified by hospital. p tests hypothesis that odds ratio = 1.

[‡] Smaller sample owing to unrecorded covariate data.

[§] Hypothermia: initial infant temperature ≥36.5 °C. At risk: initial temperature ≥36.5 with gestational age <35 wk, birth weight <2.5 kg, or other unspecified risk. [‡]Odds ratio per unit covariate. [§]Hypothermia: initial infant temperature ≥36.5 °C. At risk: GA <35 week, birth weight <2.5 kg, or other unspecified risk.

Table 5.
Mortality rates.

	Infants (%)		<i>p</i> [†]	Infants (%)		<i>p</i> [†]
	Pre-intervention	Post-intervention*		Warmer not used	Warmer used once or more	
Died	40 (2.8)	41 (2.3)	0.37	77 (2.8)	4 (0.9)	0.01
Discharged or remained hospitalized	1369 (97.2)	1729 (97.7)		2638 (97.2)	460 (99.1)	
Total	1409	1770		2715	464	

* Including 121 infants with encounters both pre and post.

† Proportions compared by Fisher exact test.

With a total of 892 uses, there were zero instances of incorrect preparation, use, or cleaning of the warmer. Of note, the study nurse conducted these activities in 90% of encounters, directly supervised them in 9%; the bedside nurse conducted these activities alone in only 1%. The Warmer stayed > 35 °C for at least 6 h in 72% of encounters (Fig. 5). There were 5 warmers that showed evidence of sealing-material breakdown after an unknown number of uses, in all cases due to small flakes of wax leaking outside of the plastic film.

7. Discussion

Neonatal hypothermia has been called a silent killer; [16] there is an estimated 80% increase in mortality rate for every 1 °C decrease in first measured temperature [17], and premature infants with a core temperature <35 °C have at least a tenfold increased mortality risk [7]. Survivors suffer morbidity, most tragically stunted growth [18] including brain growth with its attendant effects on neurodevelopment in this already vulnerable population.

The incidence of hypothermia is highest in premature/LBW newborns [7,19]. Over 20 million neonates are born each year weighing < 2.5 kg, over 96% in developing countries [9]. Maintaining euthermia in this large at-risk population depends on a “heat chain” starting in the delivery room and continued until the infant is mature enough to independently maintain euthermia. In high resource settings, this supplemental heat source is provided by incubators and warming tables. These are expensive, difficult to use, clean and maintain, and generally requiring a constant source of electricity. When misused, they can cause hypothermia [20,21] and hyperthermia [22]. If not properly cleaned, they can transmit infections [23,24]. In LRS, KMC is the preferred option but can be insufficient or infeasible.

Thus, appropriate thermoregulatory technologies must be developed to complement KMC for LRSs, rather than reliance on “hand-me-down” equipment [25]. The term, “frugal technologies” has been coined to describe cost-effective technologies that are thoughtfully designed and developed specifically to function well in the challenging conditions encountered in LMICs [26]. Neonatal thermoregulation is a problem ripe for “frugal technology.”

Here we report the findings of what, to our knowledge, is the first large scale study of a frugal thermoregulatory device developed and tested in the LRS. The introduction of the Dream Warmer significantly increased euthermia rates. It is unclear why rates of euthermia improved even in the infants who did not use the warmer. One potential explanation is that increased awareness of hypothermia as a treatable condition led to improved implementation of other modalities such as KMC and the use of hats. For the subset of infants who did use the warmer it was highly effective, safe and feasible.

We were surprised that the mortality rate of infants using the warmer was significantly lower than those not using the warmer despite the higher expected mortality risk of patients eligible to use the warmer. We do not attribute this finding directly to the use of the warmer because it was available for such a small minority of the total hours of the hospital course, but it deserves further exploration.

The roughly 12% rate of hyperthermia in both users and non-users of the warmer was an important finding, especially when setting expectations for what to consider as a safety concern for an infant warming device. The maximum recorded temperature in an infant using the warmer was actually lower than that recorded in an infant not using the warmer (38.2 vs 40.1 °C). Likely some of these instances of hyperthermia were due to endogenous fever rather than an effect of external thermoregulatory practices.

In order to avoid disturbing the patient, the thermistor measurements were taken at the warmer’s edge where it cools most quickly. It is a physical property of the wax that it changes phase at 37 °C. However, the phase change does not happen evenly throughout the warmer. The edges, exposed to room air, are the first to cool below 37 °C. This explains the thermistor reading of 35 °C. We are addressing the leakage of wax flakes through the plastic film with selection of a more robust plastic, and radiofrequency sealing technique. Of note, the wax is made of food grade vegetable oil which is non-toxic and theoretically edible.

Limitations: We did not see the full effects of round-the-clock euthermia because the warmer was only approved for use when a study nurse was present, thus for a maximum of 40/168 (24%) h/week. In addition, because of limited study personnel, only 18% of eligible patients, and 37% of hypothermic infants actually received the

Table 6.
Euthermia as influenced by warmer accessories.

Accessory	Used	Encounters	Euthermia,%*	Odds ratio (95% CI) [†]	<i>p</i> [*]
Kangaroo Mother Care	Yes	114	87 (78–92)	1.62 (0.82–3.19)	0.17
	No	778	80 (76–84)		
Clothing	Yes	25	45 (23–69)	0.17 (0.06–0.48)	0.001
	No	867	82 (79–85)		
Diaper	Yes	426	86 (82–90)	2.04 (1.24–3.35)	0.005
	No	466	75 (69–81)		
Hat	Yes	696	82 (78–86)	1.23 (0.64–2.37)	0.54
	No	196	79 (70–86)		
Blanket	Yes	891	81 (78–85)	—	—
	No	1	100 (— [‡])		

* Probability of attained or maintained euthermia, with 95% confidence interval.

† Odds ratio for euthermia when accessory used, with 95% confidence interval, from multiple logistic regression analysis stratified by hospital.

‡ Indeterminate, insufficient sample size.

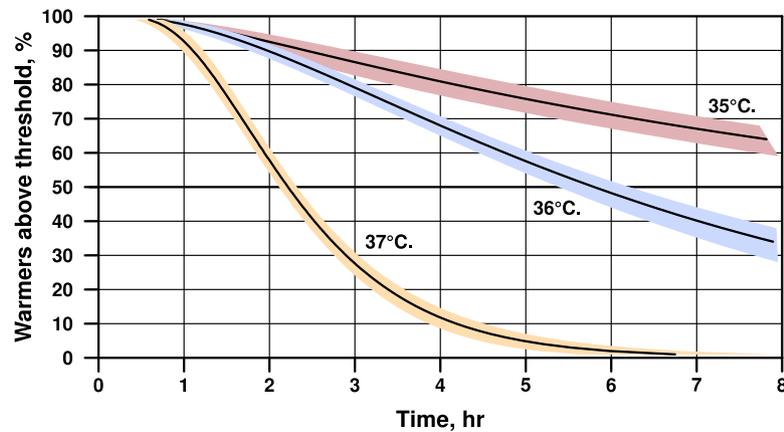


Fig. 5. Temperature of infant warmer's edge vs time from start of use. Percentage of warmers maintaining temperature above specified thresholds, decreasing with time from start of encounter. At 6 h, 72% of warmers remained above 35 °C (upper curve). Bands indicate 95% confidence interval on time axis.

intervention. We expect that the rates of hypothermia would drop in proportion to percentage of time each infant could use the warmer. Because the study nurses either directly handled the warmer, or directly supervised the bedside nurse, we do not have data on how the preparation, use and cleaning of the warmer might differ when used outside of this tightly controlled research context. Gestational age was missing in 42% of patients due to limited prenatal testing. The study was shut down for almost 2 months due to COVID-19 and one hospital was unable to rejoin the study. We adjusted for this loss in our statistical analysis.

Despite these limitations, this study demonstrated the effectiveness, safety and feasibility of the warmer now with over a 1000 uses when including our two pilot studies [26,27]. After improving the manufacturing process by incorporating a stronger plastic and sealing technique, we are confident that the Dream Warmer is ready to scale. The low use rate during the study is emblematic of the difficulties this next phase presents. The successful introduction of a novel therapy requires both demonstration of an acceptable safety/efficacy profile and then adoption of the therapy by health care providers. With use of the warmer leaving only 11% of patients hypothermic with no adverse effects observed, the remaining challenge will be that of human behavior. Because the reduction in mortality and morbidity by preventing and treating neonatal hypothermia is relatively easy given the appropriate equipment, we hope this warmer can play a significant role in reaching the Sustainable Development Goal 3.2.2 and optimizing the outcomes of survivors.

Declaration of Competing Interest

Anne Hansen is the Founder and CEO, and Ashok Gadgil is member of the Board, of Global Newborn Solutions, a nonprofit founded to manufacture and distribute the Dream Warmer. Neither has ever received any financial compensation for their role. Ashok Gadgil and Vi Rapp have a US patent application titled "Differential-melting point PCM as safety indicator for warming devices" that was filed on Aug 22, 2020, by Regents of Univ. of California with UC Berkeley reference case number B20-037-2US which is pending. Anne Hansen reports other from Banyan Gates Foundation, has a patent, Infant Warming Pad, licensed to Lawrence Berkeley National Laboratory and a Patent, Differential-Melting Point PCM as Safety Indicator for Warming Devices licensed to US Berkeley. No conflicts of interest exist for other authors.

Contributions

Drs. Gadgil, Rapp and Hansen worked on the technological design and production of the Infant Warmer. Drs. Feldman, Hansen, May,

Mazimpaka, Nahimana and Mr. Nshimiyiryo conceptualized the study design. Ms. Uwamariya and Dr. Mazimpaka coordinated and supervised all data collection. Drs. Feldman, Hansen, May, Mazimpaka, Mr. Nshimiyiryo and Ms. Uwamariya completed the data analysis while Dr. Feldman and Mr. Nshimiyiryo prepared all figures and Drs. Feldman, May, Mazimpaka, Nahimana and Mr. Nshimiyiryo interpreted all data. Drs. Feldman, May, Mazimpaka, Hansen, Gadgil, Rapp, Nahimana, Mr. Nshimiyiryo and Ms. Uwamariya contributed to writing the final manuscript and approved the final version. Dr. Sayinzoga and Ms. Umutesi critically reviewed the manuscript as experts in the field.

Data sharing statement

Drs. Henry Feldman and Alphonse Nshimiyiryo have verified all underlying data.

Funding

The study was funded by the Banyan Gates Foundation.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.eclinm.2021.100842](https://doi.org/10.1016/j.eclinm.2021.100842).

References

- [1] Kumar V, Shearer JC, Kumar A, Darmstadt GL. Neonatal hypothermia in low resource settings: a review. *J Perinatol* 2009;29(6):401–12. doi: [10.1038/jp.2008.233](https://doi.org/10.1038/jp.2008.233).
- [2] Lunze K, Bloom DE, Jamison DT, Hamer DH. The global burden of neonatal hypothermia: systematic review of a major challenge for newborn survival. *BMC Med* 2013;11(24). doi: [10.1186/1741-7015-11-24](https://doi.org/10.1186/1741-7015-11-24).
- [3] Mullany LC, Katz J, Khatri SK, LeClerq SC, Darmstadt GL, Tielsch JM. Risk of mortality associated with neonatal hypothermia in southern Nepal. *Arch Pediatr Adolesc Med* 2010;164(7):650–6. doi: [10.1001/archpediatrics.2010.103](https://doi.org/10.1001/archpediatrics.2010.103).
- [4] UNICEF. Levels & Trends in Child Mortality: Estimates Developed by the UN Inter-Agency Group for Child Mortality Estimation. UNICEF; 2020. [accessed 2021] Available from: <https://www.unicef.org/reports/levels-and-trends-child-mortality-report-2020>.
- [5] Moxon SG, Lawn JE, Dickson KE, et al. Inpatient care of small and sick newborns: a multi-country analysis of health system bottlenecks and potential solutions. *BMC Pregnancy Childbirth* 2015;15(Suppl2):S7. doi: [10.1186/1471-2393-15-S2-S7](https://doi.org/10.1186/1471-2393-15-S2-S7).
- [6] Department of Reproductive Health and Research. *Managing Newborn Problems: A Guide for Doctors, Nurses, and Midwives*. Geneva: World Health Organization; 2003. [accessed 2020]. Available from https://www.who.int/maternal_child_adolescent/documents/9241546220/en/.
- [7] Mullany L. Neonatal hypothermia in low-resource settings. *Semin Perinatol* 2010;34(6):426–33. doi: [10.1053/j.semperi.2010.09.007](https://doi.org/10.1053/j.semperi.2010.09.007).
- [8] Briend A, de Schampheleire I. Neonatal hypothermia in West Africa. *Lancet* 1981;1:846–7. doi: [10.1016/s0140-6736\(81\)92730-6](https://doi.org/10.1016/s0140-6736(81)92730-6).

- [9] World Health Organization; Systematic review summary. kangaroo mother care to reduce morbidity and mortality in low birthweight infants. [accessed 2020]. Available at: https://www.who.int/elena/titles/review_summaries/kangaroo-care-lbw/en/.
- [10] Boundy EO, Dastjerdi R, Spiegelman D, et al. Kangaroo mother care and neonatal outcomes: a meta-analysis. *Pediatrics* 2016;137(1). doi: [10.1542/peds.2015-2238](https://doi.org/10.1542/peds.2015-2238).
- [11] Conde-Agudelo A, Belizán JM, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2016(8). doi: [10.1002/14651858.CD002771.pub2](https://doi.org/10.1002/14651858.CD002771.pub2).
- [12] UNICEF Supply Division. Target product profile: conductive warmer - thermal management. UNICEF & NEST 360; 2020. [accessed 2020]. Available at: <https://www.unicef.org/supply/documents/target-product-profile-newborn-care>.
- [13] Thermoregulation devices: Guide to selection. Seattle: program for appropriate technology in health (PATH) & United States agency for international development (USAID); 2014. [accessed 2020]. Available at: https://path.azureedge.net/media/documents/DT_guide_to_select_thermo_dev.pdf.
- [14] Hemming K, Haines TP, Chilton PH, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ* 2015;350:h391. doi: [10.1136/bmj.h391](https://doi.org/10.1136/bmj.h391).
- [15] Baio G, Copas A, Ambler G, Hargreaves J, Beard E, Omar RZ. Sample size calculation for a stepped wedge trial. *Trials* 2015;16:354.
- [16] Cavallin F, Segafredo G, Pizzol D, et al. Thermal effects of a woolen cap in low birth weight infants during kangaroo care. *Pediatrics* 2018;141(6). doi: [10.1542/peds.2017-3073](https://doi.org/10.1542/peds.2017-3073).
- [17] Mullany LC, Katz J, Subarna K, et al. Risk of mortality associated with neonatal hypothermia in Southern Nepal. *Arch Ped Adolesc Med* 2010;164:650–6. doi: [10.1001/archpediatrics.2010.103](https://doi.org/10.1001/archpediatrics.2010.103).
- [18] Kumar V, Shearer JC, Kumar A, Darmstadt GL. Neonatal hypothermia in low resource settings: a review. *J Perinatol* 2009;29(6):401–12. doi: [10.1038/jp.2008.233](https://doi.org/10.1038/jp.2008.233).
- [19] World Health Organization. Maternal & newborn health/safe motherhood unit. Thermal Protection of the Newborn: A Practical Guide. Geneva: World Health Organization; 1997. [accessed 2020]. Available at: https://www.who.int/maternal_child_adolescent/documents/ws42097th/en/.
- [20] Ibe OE, Austin T, Sullivan K, Fabanwo O, Disu E, Costello AM. A comparison of kangaroo mother care and conventional incubator care for thermal regulation of infants <2000 g in Nigeria using continuous ambulatory temperature monitoring. *Ann Trop Paediatr* 2004;24(3):245–51. doi: [10.1179/027249304225019082](https://doi.org/10.1179/027249304225019082).
- [21] Bergman NJ, Linley L, Fawcus SR. Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200- to 2199-gram newborns. *Acta Paediatr* 2004;93(6):779–85. doi: [10.1111/j.1651-2227.2004.tb03018.x](https://doi.org/10.1111/j.1651-2227.2004.tb03018.x).
- [22] Amadi HO, Olateju EK, Alabi P, Kawuwa MB, Ibadin MO, Osibogun AO. Neonatal hyperthermia and thermal stress in low- and middle-income countries: a hidden cause of death in extremely low-birthweight neonates. *Paediatr Int Child Health* 2015;35(3):273–81. doi: [10.1179/2046905515Y.0000000030](https://doi.org/10.1179/2046905515Y.0000000030).
- [23] Abdel-Hady H, Hawas S, El-Daker M, El-Kady R. Extended-spectrum beta-lactamase producing klebsiella pneumoniae in neonatal intensive care unit. *J Perinatol* 2008;28(10):685–90. doi: [10.1038/jp.2008.73](https://doi.org/10.1038/jp.2008.73).
- [24] Iregbu KC, Anwaal U. Extended spectrum beta-lactamase-producing klebsiella pneumoniae septicaemia outbreak in the neonatal intensive care unit of a tertiary hospital in Nigeria. *Afr J Med Med Sci* 2007;36(3):225–8 PMID: 18390061.
- [25] Howitt P, Darzi A, Yang GZ, et al. Technologies for global health-executive summary. *Lancet* 2012;380(9840):507–35. doi: [10.1016/S0140-6736\(12\)61127-1](https://doi.org/10.1016/S0140-6736(12)61127-1).
- [26] Nahimana E, May L, Gadgil A, et al. A low cost, re-usable, electricity-free infant warmer: evaluation of safety, effectiveness and feasibility. *Public Health Action* 2018;8(4):211–7. doi: [10.5588/pha.18.0031](https://doi.org/10.5588/pha.18.0031).
- [27] May L, Nshimiyiryo A, Kubwimana M, et al. Performance of a non-electric infant warmer in Rwandan health centers. *Glob Pediatr Health* 2019;6. doi: [10.1177/2333794X19884820](https://doi.org/10.1177/2333794X19884820).