Effectiveness of kangaroo mother care before clinical stabilisation versus standard care among neonates at five hospitals in Uganda (OMWaNA): a parallel-group, individually randomised controlled trial and economic evaluation

Victor Tumukunde, Melissa M Medvedev*, Cally J Tann, Ivan Mambule, Catherine Pitt, Charles Opondo, Ayoub Kakande, Ruth Canter, Yiga Haroon, Charity Kirabo-Nagemi, Andrew Abaasa, Wilson Okot, Fredrick Katongole, Raymond Ssenyonga, Natalia Niombi, Carol Nanyunja, Diana Elbourne, Giulia Greco, Elizabeth Ekirapa-Kiracho, Moffat Nyirenda, Elizabeth Allen†, Peter Waiswa†, Joy E Lawn†, on behalf of the OMWaNA Collaborative Authorship Group‡*

Summary

Background Preterm birth is the leading cause of death in children younger than 5 years worldwide. WHO recommends kangaroo mother care (KMC); however, its effects on mortality in sub-Saharan Africa and its relative costs remain unclear. We aimed to compare the effectiveness, safety, costs, and cost-effectiveness of KMC initiated before clinical stabilisation versus standard care in neonates weighing up to 2000 g.

Methods We conducted a parallel-group, individually randomised controlled trial in five hospitals across Uganda. Singleton or twin neonates aged younger than 48 h weighing 700–2000 g without life-threatening clinical instability were eligible for inclusion. We randomly assigned (1:1) neonates to either KMC initiated before stabilisation (intervention group) or standard care (control group) via a computer-generated random allocation sequence with permuted blocks of varying sizes, stratified by birthweight and recruitment site. Parents, caregivers, and health-care workers were unmasked to treatment allocation; however, the independent statistician who conducted the analyses was masked. After randomisation, neonates in the intervention group were placed prone and skin-to-skin on the caregiver's chest, secured with a KMC wrap. Neonates in the control group were cared for in an incubator or radiant heater, as per hospital practice; KMC was not initiated until stability criteria were met. The primary outcome was all-cause neonatal mortality at 7 days, analysed by intention to treat. The economic evaluation assessed incremental costs and cost-effectiveness from a disaggregated societal perspective. This trial is registered with ClinicalTrials.gov, NCT02811432.

Findings Between Oct 9, 2019, and July 31, 2022, 2221 neonates were randomly assigned: 1110 (50·0%) neonates to the intervention group and 1111 (50·0%) neonates to the control group. From randomisation to age 7 days, 81 (7·5%) of 1083 neonates in the intervention group and 83 (7·5%) of 1102 neonates in the control group died (adjusted relative risk [RR] 0·97 [95% CI 0·74–1·28]; p=0·85). From randomisation to 28 days, 119 (11·3%) of 1051 neonates in the intervention group and 134 (12·8%) of 1049 neonates in the control group died (RR 0·88 [0·71–1·09]; p=0·23). Even if policy makers place no value on averting neonatal deaths, the intervention would have 97% probability from the provider perspective and 84% probability from the societal perspective of being more cost-effective than standard care.

Interpretation KMC initiated before stabilisation did not reduce early neonatal mortality; however, it was cost-effective from the societal and provider perspectives compared with standard care. Additional investment in neonatal care is needed for increased impact, particularly in sub-Saharan Africa.

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Introduction

An estimated 2·3 million neonates died worldwide in 2022, more than 1 million of whom were in sub-Saharan Africa, a number unchanged for 20 years.[1] Currently, 64 countries are off track to meet the Sustainable Development Goal 3·2 target for neonatal survival by 2030. Most neonatal deaths occur in the first week of life and around 36% occur within 24 h of birth.[2] Each year,

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*Joint first authors

†Joint senior authors

‡Members listed at the end of the Article

Department of Infectious Disease Epidemiology and International Health (V Tumukunde MMed, M M Medvedev PhD, Prof C J Tann PhD, Prof J E Lawn PhD), **Department of Global Health and Development** (C Pitt PhD, G Greco PhD), **and Department of Medical Statistics** (C Opondo PhD, R Canter MSc, Prof D Elbourne PhD, Prof E Allen PhD), **London School of Hygiene & Tropical Medicine, London, UK; Non-Communicable Disease Programme, Medical Research Council–Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit, Entebbe, Uganda** (V Tumukunde, Prof C J Tann, I Mambule MPH, A Kakande MSc, Y Haroon BSc, C Kirabo-Nagemi MHEcon, A Abaasa PhD, W Okot MBChB, F Katongole MBChB, R Ssenyonga MBChB, N Niombi MBBS, C Nanyunja MSc, G Greco, Prof M Nyirenda PhD); **Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA** (M M Medvedev); **Department of Neonatal**

Medicine, University College London Hospitals NHS Trust, London, UK (Prof C J Tann)**; Department of Health Policy, Planning, and Management, Makerere University, Kampala, Uganda** (E Ekirapa-Kiracho PhD, P Waiswa PhD)**; Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden** (P Waiswa)

Correspondence to: Prof Joy E Lawn, Department of Infectious Disease Epidemiology and International Health, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
joy.lawn@lshtm.ac.uk

Research in context

Evidence before this study

Despite a new Sustainable Development Goal to specifically address newborn survival, 64 countries remain off track for the target in 2030, with 2·3 million neonatal deaths globally in 2022. The iKMC trial was conducted by WHO to investigate the effect of immediate kangaroo mother care (KMC) in five tertiary-level hospitals with neonatal intensive care (WHO level 3) in India and sub-Saharan Africa. The trial reported no reduction in the primary outcome of early mortality (<72 h), but a reduction in the secondary outcome of 28-day mortality among neonates weighing 1000–1799 g who had received immediate KMC compared with those who had received standard care. Reductions in hypothermia and suspected sepsis were also found. A similar trial in a hospital providing neonatal special care (WHO level 2) in The Gambia did not report a significant 28-day mortality effect; however, it was underpowered largely because of improvements in the overall quality of care, which contributed to a 50% reduction in mortality in the control group compared with pre-trial rates. In 2022, WHO guidance changed to recommend initiating KMC as soon as possible after birth. Neither of the aforementioned trials has reported on cost and infrastructure requirements for successful implementation. We searched PubMed, without language restrictions, for published studies on KMC initiated before stabilisation from Jan 1, 1990, to July 1, 2023, using the following search terms: "kangaroo mother care" [MeSH], or "care method, kangaroo mother" [MeSH], or "skin-to-skin contact" [MeSH], or "skin-to-skin care" [MeSH], and "intervention costs," or "incremental costs," or "cost-effectiveness". We found no relevant additional trials. Although previous economic evaluations have explored the financial costs to health-care providers and households of KMC for stable neonates, no published study has considered household opportunity costs nor compared the incremental costs of KMC initiated before stabilisation relative to standard care.

Added value of this study

This parallel-group, individually randomised, controlled trial in five government hospitals across Uganda addresses a crucial evidence gap on the effects and economic costs of KMC initiated before stabilisation in the context of WHO level 2 care typical in sub-Saharan Africa, where neonatal mortality is highest. Pragmatic improvements in the quality of care for small and sick newborns, notably hospital infrastructure, were required to ensure safe implementation of KMC before clinical stabilisation. Similar to the previous trials, no difference in early mortality (<7 days) was observed; however, there was a non-significant relative reduction in mortality of 12% at 28 days (relative risk [RR] 0·88 [95% CI 0·70–1·09]; p=0·23) and a pooled relative reduction in 28-day mortality of 14% across the sub-Saharan African sites of all three trials (RR 0·86 [95% CI 0·74–1·00]; p=0·043). There was evidence of a benefit linked to higher duration of KMC. We observed a lower risk of day-7 mortality (0·17 [0·07–0·43]; p=0·0001) and day-28 mortality (0·19 [0·10–0·38]; p<0·0001) among babies in the intervention group who had received 12–24 h of KMC daily compared with those who had received up to 12 h of KMC daily. Additional important benefits of KMC initiated before stabilisation included reductions in hypothermia (0·76 [0·70–0·83]; p<0·0001) and improvements in daily weight gain at 28 days (adjusted mean difference 0·75 g [95% CI 0·01–1·49]; p=0·047). Our economic evaluation indicated that KMC before stabilisation was cost-effective compared with standard care from the societal and provider perspectives. The intervention would be expected to be cost-saving to both providers (adjusted mean difference –US$57·0 [–69·9 to –44·1]; p<0·0001) and society (–$66·2 [–85·7 to –46·7]; p<0·0001) in settings where KMC before stabilisation significantly reduced length of stay from 7·3 days to 6·1 days.

Implications of all the available evidence

A pooled analysis of the three trials of KMC before stabilisation in sub-Saharan Africa showed a clear benefit of the intervention for 28-day survival, with remarkably consistent effects across five of the six participating sites in Africa, although one reported a non-significant increase in mortality. Notably, all these trials anticipated early mortality reduction (eg, 2–7 days) with early KMC, yet found greater impact at 28 days. These findings might also be affected by the cohort of neonates; for example, there are more small-for-gestational-age neonates in south Asian settings. It is crucial that appropriate neonatal care is in place before the implementation of immediate KMC. Improvements in infrastructure, including the number and skill level of nursing and medical staff, as well as context-specific neonatal devices, remain crucial for these vulnerable newborns whose survival depends on high-quality neonatal care, including respiratory support. Further research is important, particularly regarding the implementation of neonatal care and KMC at different levels of health facilities, such as tracking quality of care through routine data, and how to operationalise follow-up and family support for newborns at risk. Given these findings, effective scale-up requires planning, budget impact analysis, and greater investment, especially across sub-Saharan Africa.

approximately 13·4 million newborns are born preterm (<37 weeks of gestation) and one in four newborns worldwide are born small and vulnerable, including preterm and small-for-gestational-age.[3] Preterm birth is the leading cause of death in children and of long-term loss of human capital.[3] Mortality risk is highest in low-income and middle-income countries (LMICs) due to gaps in neonatal care.[4]

Kangaroo mother care (KMC), involving continuous skin-to-skin contact between a caregiver and a newborn immediately after birth, has been shown to decrease mortality among clinically stable neonates.[5] One trial

coordinated by WHO (the iKMC trial),[6] which recruited newborns weighing 1000–1799 g in five tertiary-level hospitals with neonatal intensive care (level 3) in sub-Saharan Africa and India, reported that immediate KMC led to a 25% reduction in their secondary outcome of mortality within 28 days, compared with those who had received standard neonatal care plus KMC after stabilisation. Another trial conducted in a level 2 neonatal unit in The Gambia found no reduction in mortality with KMC before stabilisation compared with standard care; however, this study was underpowered because of improvements in the quality of standard care that contributed to a 50% reduction in neonatal mortality compared with baseline.[7] The findings of these two trials left an evidence gap regarding the effects of immediate KMC at facilities without neonatal intensive care, where most births in LMICs occur, and questions regarding possibly lower impact in sub-Saharan Africa. In 2022, WHO changed its guidelines to include the recommendation that KMC should be initiated as soon as possible after birth at all levels of facility-based care and in all countries, including in high-income contexts.[8] However, resource requirements were not well defined, including the incremental costs of initiating KMC before stabilisation and necessary facility infrastructure. Indeed, there are few economic evaluations of KMC overall.[5,8] Although previous studies have explored the financial costs of KMC to health-care providers and households,[9–16] no report has considered household opportunity costs or focused on KMC among neonates before stabilisation.

We aimed to compare the effectiveness and safety of KMC initiated before stabilisation versus standard care among neonates up to 2000 g in sub-Saharan Africa. Additionally, we aimed to assess the incremental costs and cost-effectiveness of this intervention from the societal perspective.[17]

Methods

Study design

The OMWaNA trial was a parallel-group, individually randomised controlled trial conducted in the neonatal units (WHO level 2) of five government hospitals across Uganda (appendix p 6). Improvements to infrastructure and equipment and training of doctors and nurses were required before trial initiation, as described previously.[18] All hospitals were provided with essential equipment and supplies to support the provision of KMC and level 2 newborn care. Details regarding study context and methods have been published in the trial protocol.[17] In Uganda, maternity and newborn care should be provided free of charge in government health facilities;[19] however, families are expected to support caregivers to meet essential needs, such as meals, and to occasionally buy drugs and supplies outside of the hospital in the event of a stockout.

This trial is reported in accordance with CONSORT guidelines (appendix p 4).[20] The study was approved by the Research Ethics Committees of Uganda Virus Research Institute (GC/127/19/06/717), Uganda National Council of Science and Technology (HS 2645), and London School of Hygiene & Tropical Medicine (16972). The trial was overseen by a steering committee and an independent data and safety monitoring board.

Participants

All liveborn neonates aged younger than 48 h and weighing 700–2000 g, who were admitted to participating hospitals and for whom the indication for KMC was uncertain according to WHO guidance concerning clinical stability,[21] were eligible for inclusion. Clinical stability was defined as receiving at least one type of therapy: oxygen; continuous positive airway pressure (CPAP) where available; intravenous fluids; therapeutic antibiotics; or anti-seizure medication. Exclusion criteria included triplet or higher multifetal pregnancy (unless pregnancy resulted in the death of at least one fetus) and the parent or caregiver being unable or unwilling to provide consent, perform KMC, or attend follow-up visits. Neonates with life-threatening instability, severe jaundice requiring immediate management, active seizures, or major congenital malformations were also excluded.

All admitted neonates weighing up to and including 2000 g were screened for eligibility by study staff. Neonates considered to be stable (meeting WHO 2019 criteria for KMC eligibility) were excluded and remaining neonates were assessed for eligibility. Neonates who met the criteria for life-threatening instability or who had conditions precluding KMC (eg, seizures or jaundice) were reassessed every 3 h for up to 48 h, after which they were excluded. Written informed parental consent was obtained for all participants.

Randomisation and masking

Eligible neonates were randomly assigned (1:1) to receive either KMC initiated before clinical stabilisation (intervention group) or standard care (control group). A random allocation sequence was computer-generated with permuted blocks of varying sizes, stratified by birthweight (700–1000 g, 1000–1499 g, or 1500–2000 g) and recruitment site.

See Online for appendix

Allocation concealment was done by programming the allocation sequence into the screening database and revealing treatment group only when screening of eligible neonates was complete. The independent statistician programmed the allocation sequence into the REDCap screening database. Treatment group was revealed only after the study medical officer or study nurse had entered all required screening data into REDCap. Neonates from multiple births were allocated to the same group according to the allocation of the firstborn.[22] Masking of parents, caregivers, or health-care workers was not possible due to the nature of the KMC intervention; however, the independent statistician who

conducted the analyses was masked to treatment allocation.

Procedures

In the intervention group, KMC was initiated as soon as possible after randomisation, following education to caregivers on its benefits and how to perform it. Neonates were naked, except for hat and nappy; placed prone and skin-to-skin on the caregiver's chest; and secured using a KMC wrap. Adjustable beds were provided to facilitate continuous skin-to-skin care. KMC duration was charted by caregivers and verified by study staff. When not in KMC (eg, during maternal bathing), neonates received incubator or radiant heater care. Study personnel and hospital staff encouraged caregivers to practise near-continuous KMC throughout the hospitalisation.

Neonates in the control group were cared for in an incubator or radiant heater, as per hospital practice. Caregivers could have physical contact with their newborn, but skin-to-skin contact was not initiated until stability criteria were met.[17] Once stable, caregivers could practise KMC (≥1 h per session). Neonates in both groups received standard clinical care according to hospital guidelines.[17]

Outcomes

The primary outcome was all-cause neonatal mortality from randomisation to age 7 days. Secondary outcomes were all-cause neonatal mortality to age 28 days; hypothermia at 24 h (axillary temperature <36·5°C); time to stabilisation;[17] time to death; time to exclusive breastmilk feeding; duration of hospital admission; and readmission frequency, daily weight gain (g per kg per day), and women's wellbeing and maternal responsiveness at 28 days. Stability was defined as having met all of the following criteria continuously for at least 24 h: breathing spontaneously with oxygen saturation (SpO_2) of more than 90% in room air, no need for supplemental oxygen or CPAP, respiratory rate 40–60 breaths per min, absence of apnoea, heart rate 80–180 beats per min, axillary temperature 36·0–37·4°C, and no need for intravenous fluids. Women's wellbeing was assessed by use of the Women's Capabilities Index, which was developed in Malawi and subsequently adapted to Uganda,[23] and maternal responsiveness was measured with the Maternal-Infant Responsiveness Instrument.[24] Both tools were administered by Ugandan study staff. Outcome data were collected by the same procedure for all participants. Outcome data at day 28 were collected at follow-up visits or by oral report from the caregiver, if attendance was not possible (eg, during the COVID-19 pandemic). Data were captured electronically in REDCap by use of trial-specific care report forms, with inbuilt ranges and consistency checks, and were synchronised and backed up daily over a secure connection.[25] Identifiable data were password-protected and stored separately on computers or in locked cabinets in secure rooms at each study site.

Statistical analysis

A sample size of 2188 neonates (1094 per group) was estimated to be required to detect an absolute reduction in 7-day mortality of 5·6% (22·4% relative reduction) at a 5% significance level (two-sided) and 80% power, allowing for 20% attrition. This calculation assumed a 7-day mortality rate of 25% in the control group on the basis of perinatal audit data. The data and safety monitoring board conducted a prespecified interim analysis when 50% of neonates had been enrolled (appendix p 7).

Baseline demographic and clinical characteristics were collected by treatment group. All randomly assigned neonates with complete data at trial endpoints were included in the analysis to provide an unbiased estimate of the intention-to-treat effect, assuming missingness at random. Risk ratios (RRs) with 95% CI were estimated for 7-day and 28-day mortality and were compared between the intervention group and the control group with modified Poisson regression models. Modified Poisson regression was preferred over binomial regression for obtaining RRs[26] given that binomial regression is prone to non-convergence.[27]

Additionally, the complier average causal effect on mortality was obtained to estimate the efficacy of KMC among babies who had received KMC within 24 h of stabilisation,[28] and a dose–response analysis was conducted in the intervention group to compare the effect of KMC duration on mortality. Median time to stabilisation, time to death, time to exclusive breastmilk feeding, and hospital discharge were estimated as the 50th percentile of distribution of event times, and hazard ratios (HRs) with 95% CIs comparing between the intervention and control groups were calculated with Cox proportional hazards regression models. Mean differences in admission duration, readmission frequency, daily weight gain, and Women's Capabilities Index and Maternal-Infant Responsiveness Instrument scores between groups were estimated by use of linear regression models.

For all regression models, robust SEs were used to account for clustering of outcomes with multiple births. All models included adjustment for stratification factors (ie, birthweight category and hospital site) and sex. Subgroup analyses explored the effect of KMC on mortality by gestational age, birthweight, size for gestational age, singleton versus twin birth, hospital site, neonatal mortality risk (NMR)-2000 score,[29] and mode of delivery. Tests of interaction were conducted to evaluate evidence of subgroup effects. Only neonates with complete data at trial endpoints were included in the analyses. All statistical analyses were performed with Stata (version 18.1). This trial is registered with ClinicalTrials.gov, NCT02811432.

Economic evaluation

The economic evaluation is reported in accordance with CHEERS guidelines (appendix p 5)[30] and was conducted

from a disaggregated societal perspective (provider and household combined), consistent with recommendations.[31] An analysis plan was reported with the trial protocol.[17] We examined both financial costs which reflect actual expenditure, and economic costs which reflect the full value of resources used, as well as estimated costs incurred during hospitalisation.

Data on resource use were collected for each neonate regarding medicines administered, type of care received (ie, KMC or incubator or radiant heater), duration of hospital admission, and individual-level medical supplies used (appendix p 9). Costs of setup (described previously[18]), staff time, electricity, water, generic medical supplies, and non-medical supplies were assessed with top-down methods to estimate the unit cost of each night spent in hospital per neonate by type of care and hospital. These unit costs were applied to individual neonates on the basis of the duration of each type of care received. The salaries of hospital staff were obtained from the 2020 Uganda Health Service Commission Circular scale. Staff time was allocated across neonates receiving different types of care with a time and motion study[32] (appendix p 8) and staff consultation. Household costs were collected through caregiver surveys at hospital discharge and at 28 days. Costs were collected in the currency in which they were incurred, inflated to 2020 values, and converted to US$ on the basis of average exchange rates in 2020 (US$1=£0·72=Uganda Shilling 3641).[33] Setup costs and capital goods were annualised over their useful life at a 3% discount rate in the base case analysis.[31] Parameter input values and sources are described in the appendix (pp 9–11).

We estimated mean differences (with 95% CIs) in cost per neonate between groups by intention to treat for each hospital, for all hospitals combined, and for a subset of hospitals with broadly homogeneous results (appendix pp 12–13). Mean differences were estimated with linear regression models,[34] which included adjustment for stratification factors and sex. Robust SEs were used to account for clustering by multiple births. Societal economic costs comprised provider economic costs, household financial costs, and household opportunity costs (eg, foregone income) for each neonate. We also estimated mean costs per neonate by group and by hospital and described the distribution of these costs using percentiles. Multiple imputation was used to impute missing values for societal and household costs; household cost data were log-transformed before imputation to address non-normality (appendix p 8).[35–37] The effects of alternative assumptions about missing primary outcome data were also explored. Household costs are presented per neonate and per household because of the high rate of non-singleton neonates (38%). We examined major cost drivers and heterogeneity by birthweight category, vital status at discharge, and singleton versus multiple birth. We conducted one-way sensitivity analyses to explore the robustness of our findings to uncertainty in key parameters. Based on our analysis of cost drivers, we recalculated the difference in costs between groups for the lowest and highest plausible values of parameters which had the potential to influence our decision recommendation. Our protocol stated that we would only estimate incremental cost-effectiveness ratios if the intervention was more effective and more costly than standard care. These conditions were not met, so we used an incremental net benefit framework to calculate the probability that choosing KMC instead of standard care would be cost-effective over a conservative range of monetary values that policy makers could be willing to pay to avert a neonatal death ($0–1200).[38–40] All analyses were performed with Microsoft Excel and Stata (version 18.1).

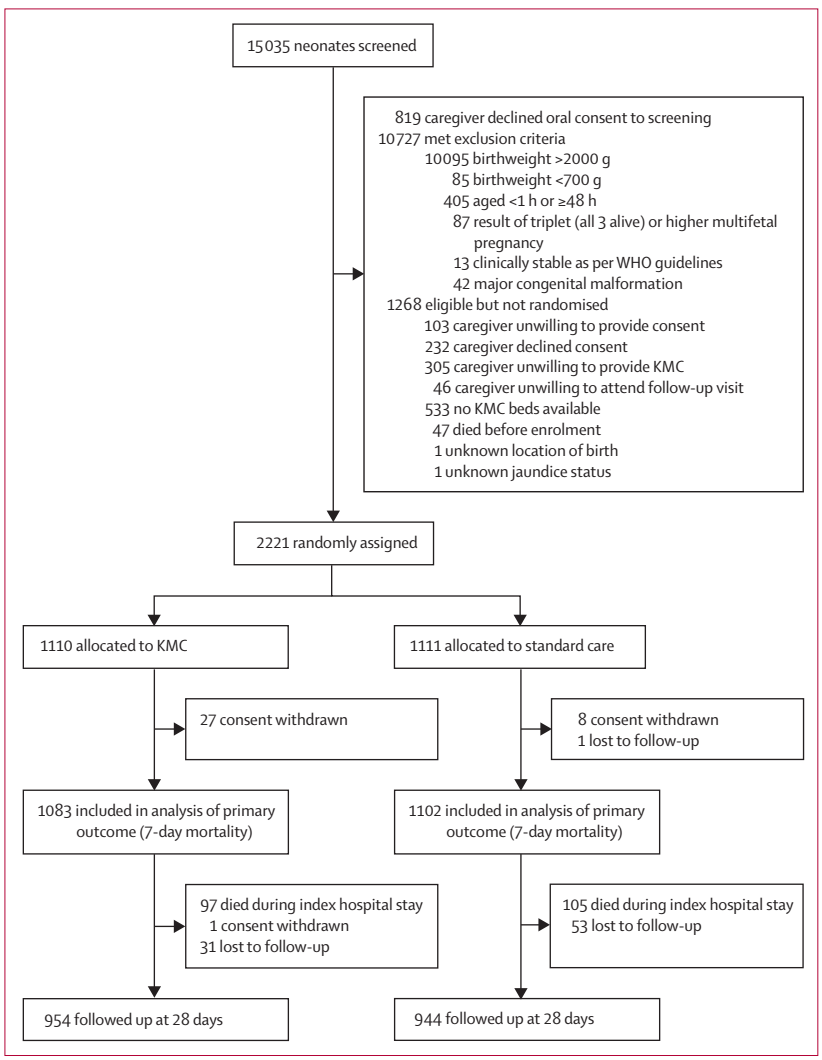

Figure 1: **Trial profile**
KMC=kangaroo mother care.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Intervention group	Control group
Neonates		
Total number	1110	1111
Age at screening, h	20·3 (11·6)	21·5 (11·5)
Gestational age at screening, weeks*	32·3 (2·4)	32·3 (2·2)
Data missing	5 (0·5%)	3 (0·3%)
Weight at screening, kg	1·5 (0·3)	1·5 (0·3)
Sex		
Female	558 (50·3%)	561 (50·5%)
Male	552 (49·7%)	550 (49·5%)
Multiple birth		
Singleton	693 (62·4%)	694 (62·5%)
Individual twin enrolled	75 (6·8%)	79 (7·1%)
Pair of twins enrolled	336 (30·3%)	336 (30·2%)
Individual triplet enrolled	2 (0·2%)	0
Two triplets enrolled	4 (0·4%)	2 (0·2%)
Mode of delivery		
Spontaneous vaginal delivery	903 (81·4%)	885 (79·7%)
Instrumental vaginal delivery (forceps or vacuum-assisted)	4 (0·4%)	2 (0·2%)
Caesarean delivery	198 (17·8%)	222 (20·0%)
Birth location		
Hospital 1	14 (1·3%)	12 (1·1%)
Hospital 2	111 (10·0%)	100 (9·0%)
Hospital 3	128 (11·5%)	124 (11·2%)
Hospital 4	406 (36·6%)	413 (37·2%)
Hospital 5	191 (17·2%)	177 (15·9%)
Other hospital or facility	207 (18·6%)	231 (20·8%)
En route to hospital	13 (1·2%)	16 (1·4%)
Home	40 (3·6%)	38 (3·4%)
Hospital of enrolment		
Hospital 1	16 (1·4%)	16 (1·4%)
Hospital 2	143 (12·9%)	145 (13·1%)
Hospital 3	165 (14·9%)	169 (15·2%)
Hospital 4	537 (48·4%)	524 (47·2%)
Hospital 5	249 (22·4%)	257 (23·1%)
Mothers		
Total number	941	942
Age (actual or estimated), years	25·6 (6·0)	25·6 (6·2)
Data missing	8 (0·9%)	2 (0·2%)
Highest level of education		
Primary school	332 (35·3%)	349 (37·0%)
Secondary school	503 (53·5%)	506 (53·7%)
University degree	68 (7·2%)	60 (6·4%)
None	27 (2·9%)	20 (2·1%)
Data missing	11 (1·2%)	7 (0·7%)
Monthly income, US$†	9·4 (0·0–54·9)	5·5 (0·0–54·9)
Data missing	37 (3·9%)	29 (3·1%)

Data are n (%), mean (SD), or median (IQR). Additional baseline characteristics are provided in the appendix (pp 18–19). *Calculated by Ballard score.[41] †Income standardised assuming 220 days of work annually and 5 days of work per week, in line with previous studies.[42]

Table 1: **Baseline characteristics**

Results

Between Oct 9, 2019, and July 31, 2022, a total of 15 035 neonates were screened for participation, of whom 3489 (23·2%) were eligible. 2221 (63·7%) neonates of 1883 mothers were randomly assigned: 1110 (50·0%) neonates of 941 mothers to the intervention group and 1111 (50·0%) neonates of 942 mothers to the control group. In total, 1083 (97·6%) neonates in the intervention group and 1102 (99·2%) in the control group were included in the analysis of the primary outcome at 7 days; 1051 (94·7%) in the intervention group and 1049 (94·4%) in the control group were included in the 28-day analysis (figure 1). The data and safety monitoring board considered interim data on three occasions, and recommended continuation. The trial concluded when target enrolment was reached.

Neonatal and maternal characteristics were similar at baseline between the two groups (table 1; appendix pp 12–13). Mean age of neonates at screening was 20·3 h (SD 11·6) in the intervention group and 21·5 h (11·5) in the control group. In both groups, mean gestational age, measured by Ballard score,[41] was 32·3 weeks and mean birthweight was 1·5 kg (table 1). Except for data on maternal income, which were missing for 3·0% of neonates, data for covariates were missing for up to 0·8% of neonates and were balanced between groups.

From randomisation to 7 days of age, 81 (7·5%) of 1083 neonates in the intervention group and 83 (7·5%) of 1102 in the control group died (adjusted RR 0·97 [95% CI 0·74–1·28]; p=0·85). From randomisation to 28 days of age, 119 (11·3%) of 1051 neonates in the intervention group and 134 (12·8%) of 1049 in the control group died (0·88 [0·71–1·09]; p=0·23; table 2). Most deaths were attributed to preterm birth complications, including neonatal sepsis and respiratory distress syndrome.

There was no evidence of effect modification for any of the prespecified subgroup categories (ie, birthweight, gestational age, size for gestational age, singleton *vs* twin birth, hospital site, NMR-2000 risk score, or mode of delivery) on the primary outcome. There was evidence of effect modification on 28-day mortality by gestational age (p=0·012), with the intervention showing a greater effect than standard care for neonates with gestational age up to 28 weeks (appendix pp 21–22). The complier average causal effect analysis found weak evidence of a reduced risk of 7-day mortality (RR 0·60 [95% CI 0·35–1·05]; p=0·072) and strong evidence of a reduced risk of 28-day mortality (0·63 [0·44–0·90]; p=0·0011) among babies who received KMC within 24 h of randomisation (appendix p 23). Among babies in the intervention group who received KMC, those receiving a median of 12–24 h of KMC per 24 h had lower risk of mortality at 7 days (0·17 [0·07–0·43]; p=0·0001) and at 28 days (0·19 [0·10–0·38]; p<0·0001) than did babies receiving up to 12 h of KMC daily.

Results differed significantly between the intervention and control groups for six of 13 secondary outcomes

	Intervention group (n=1110)	Control group (n=1111)	Crude effect	Crude p value	Adjusted effect*	Adjusted p value
Risk ratio (95% CI)						
Primary						
Mortality at 7 days	81/1083 (7·5%)	83/1102 (7·5%)	0·99 (0·74 to 1·33)	0·96	0·97 (0·74 to 1·28)	p=0·85
Secondary						
Mortality at 28 days	119/1051 (11·3%)	134/1049 (12·8%)	0·89 (0·70 to 1·12)	0·307	0·88 (0·70 to 1·09)	p=0·23
Hypothermia at 24 h	448/1096 (40·9%)	585/1101 (53·1%)	0·77 (0·70 to 0·84)	p<0·0001	0·76 (0·70 to 0·83)	p<0·0001
At least one episode of hypothermia within first 24 h	833/1096 (76·0%)	913/1101 (82·9%)	0·92 (0·88 to 0·96)	0·0001	0·91 (0·88 to 0·95)	p<0·0001
At least one readmission following index hospital discharge	20/848 (2·4%)	32/840 (3·8%)	0·62 (0·36 to 1·07)	0·088	0·63 (0·36 to 1·09)	p=0·10
Hazard ratio (95% CI)						
Time to stabilisation, days†	5·1 (4·1–6·7); 1081 (97·4%)	4·9 (3·8–6·5); 1100 (99·0%)	1·02 (0·90 to 1·17)	0·73	1·31 (1·13 to 1·53)	p=0·0004
Time to exclusive breastmilk feeding, days‡	7 (5–8); 1075 (96·8%)	5 (3–7); 1089 (98·0%)	0·79 (0·73 to 0·85)	p<0·0001	0·75 (0·69 to 0·82)	p<0·0001
Time to hospital discharge after randomisation, days	6·9 (4·5–7·9); 1083 (97·6%)	5·1 (3·1–7·1); 1102 (99·2%)	0·79 (0·73 to 0·86)	p<0·0001	0·75 (0·69 to 0·82)	p<0·0001
Time to death, days§	5·0 (2·5–10·7); 1083 (97·6%)	5·9 (2·8–13·9); 1102 (99·2%)	0·90 (0·70 to 1·15)	0·41	0·87 (0·68 to 1·12)	p=0·30
Mean difference (95% CI)						
Duration of hospital admission, days	7·3 (0·2); 1083 (97·6%)	6·1 (0·1); 1102 (99·2%)	1·12 (0·73 to 1·52)	p<0·0001	1·13 (0·75 to 1·50)	p<0·0001
Frequency of readmission	0·02 (0·01); 848 (76·4%)	0·04 (0·01); 840 (75·6%)	–0·016 (–0·033 to 0·001)	0·070	–0·015 (–0·032 to 0·002)	p=0·077
Daily weight gain at 28 days, g per day	7·8 (0·3); 761 (68·6%)	7·1 (0·3); 731 (65·8%)	0·78 (0·02 to 1·55)	0·045	0·75 (0·01 to 1·49)	p=0·047
Women's wellbeing at 28 days (Women's Capabilities Index)¶	0·69 (0·01); 624/941 (66·3%)	0·68 (0·01); 602/942 (63·9%)	0·013 (–0·003 to 0·029)	0·104	0·013 (–0·002 to 0·029)	p=0·097
Maternal responsiveness at 28 days‖	85·4 (0·3); 758 (68·3%)	85·0 (0·3); 725 (65·3%)	0·48 (–0·29 to 1·26)	0·11	0·57 (–0·19 to 1·33)	p=0·14

Data are n/N (%), n (%), median (IQR), or mean (SD). *Effects adjusted for stratification factors (ie, birthweight category and hospital site) and sex of neonate. †Defined as the first time at which a neonate met all of the following criteria for a continuous period of at least 24 h: breathing spontaneously with oxygen saturation, >90% in room air; no need for supplemental oxygen or continuous positive airway pressure; respiratory rate 40–59 breaths per min; no apnoeic episodes; heart rate 80–179 beats per min; axillary temperature 36·0–37·4°C; and no need for intravenous fluids. ‡Defined as the first time a neonate received breastmilk, either directly from the breast or by nasogastric tube, bottle, cup, or spoon after expression from the breast, as the sole source of nutrition. §Calculated as the 50th and 25th to 75th percentile of the distribution of event times among neonates who died. ¶Assessed with the Women's Capabilities Index in 624 of 941 mothers in the intervention group and 602 of 942 mothers in the control group (duplicate entries removed for mothers of enrolled twins or triplets). This index has a scale of 0–1, with higher scores indicating greater wellbeing. ‖Assessed with the Maternal Infant Responsiveness Instrument, which has a scale of 0–110, with higher scores indicating greater responsiveness.

Table 2: **Primary and secondary outcomes**

(table 2). The proportion of neonates with hypothermia at 24 h was 40·9% (448 of 1096) in the intervention group and 53·1% (585 of 1101) in the control group (adjusted RR 0·76 [95% CI 0·70–0·83]; p<0·0001). The prevalence of hypothermia in the first 24 h was 76·0% (n=833) in the intervention group and 82·9% (n=913) in the control group (adjusted RR 0·91 [0·88–0·95]; p<0·0001). Median time to stabilisation was 5·1 days (IQR 4·1–6·7) in the intervention group and 4·9 days (3·8–6·5) in the control group (adjusted HR 1·31 [1·13–1·53]; p=0·0004; appendix p 23). The HR for time to stabilisation was driven exclusively by hospital 4. Median time to exclusive breastmilk feeding was 7 days (IQR 5–8) in the intervention group and 5 days (3–7) in the control group (adjusted HR 0·75 [0·69–0·82]; p<0·0001; appendix p 23). Median time to hospital discharge was 6·9 days (IQR 4·5–7·9) in the intervention group and 5·1 days (3·1–7·1) in the control group (adjusted HR 0·75 [0·69–0·82]; p<0·0001; appendix p 24). Mean weight gain at 28 days was 7·8 g per day (SD 0·3) in the intervention group and 7·1 g per day (0·3) in the control group (adjusted mean difference 0·75 [0·01–1·49]; p=0·047). Time to death (appendix p 24) and readmission frequency, women's wellbeing, and maternal responsiveness at 28 days were similar in both groups (table 2). Serious adverse events were balanced between neonates in both groups (table 3).

Skin-to-skin contact was initiated within 24 h of randomisation in 891 (82·7%) of 1078 neonates with data in the intervention group and in 89 (8·2%) of 1082 in the control group (table 4). Median daily duration of skin-to-skin contact in the KMC position was 10·1 h (IQR 5·9–13·0) in the intervention group and 0·0 h (0·0–4·8) in the control group. Median total duration of skin-to-skin contact in the KMC position during hospitalisation was

	Intervention group (n=1110)	Control group (n=1111)
Total		
Number of non-serious AEs	300	172
Number of SAEs	144	149
SAEs*		
Suspected or confirmed neonatal sepsis	34 (23·6%)	35 (23·5%)
Respiratory distress syndrome	21 (14·6%)	16 (10·7%)
Neonatal jaundice	4 (2·8%)	6 (4·0%)
Death with unknown cause	16 (11·1%)	16 (10·7%)
Apnoea of prematurity	29 (20·1%)	37 (24·8%)
Suspected or confirmed aspiration pneumonia	8 (5·6%)	9 (6·0%)
Neonatal seizures	6 (4·3%)	6 (4·1%)
Suspected or confirmed necrotising enterocolitis	10 (6·9%)	7 (4·7%)
Abdominal distension	1 (0·7%)	0
Intraventricular haemorrhage	1 (0·7%)	2 (1·3%)
Oedema	1 (0·7%)	0
Haemorrhagic disease of the newborn	7 (4·9%)	6 (4·0%)
Severe anaemia	0	4 (2·7%)
Hyperthermia	0	2 (1·3%)
Aspiration	1 (0·7%)	1 (0·7%)
Intracranial haemorrhage	1 (0·7%)	0
Acute kidney injury	1 (0·7%)	0
Intestinal obstruction	1 (0·7%)	0
Gangrene	1 (0·7%)	0
Neonatal meningitis	0	1 (0·7%)
Suspected congenital heart disease	0	1 (0·7%)
Oxygen desaturation	1 (0·7%)	0
Number of participants who experienced at least one SAE	124 (11·2%)	125 (11·3%)
Unexpected and related SAE	1 (0·7%)	0
SAEs by site		
Hospital 1	2 (1·4%)	1 (0·7%)
Hospital 2	12 (8·3%)	19 (12·8%)
Hospital 3	21 (14·6%)	18 (12·1%)
Hospital 4	69 (47·9%)	75 (50·3%)
Hospital 5	40 (27·8%)	36 (24·2%)
SAEs with fatal outcomes	95 (66·0%)	106 (71·1%)

Data are n (%). AE=adverse event. SAE=serious adverse event. *Percent values represent the proportion of SAEs with the total number of SAEs in each group as the denominator.

Table 3: **AEs and SAEs**

	Intervention group (n=1110)	Control group (n=1111)
Participants with data*	1078 (97·1%)	1082 (97·4%)
KMC† commenced within 24 h of randomisation	891 (82·7%)	89 (8·2%)
Daily duration of KMC, h	10·1 (5·9–13·0)	0·0 (0·0–4·8)
Total duration of KMC, h	60 (36–85)	0 (0–26)
KMC stopped at least once	372 (34·5%)	21 (1·9%)
Total number of stoppages	674	28
Reason stopped‡		
Severely unstable for >10 min	69 (10·2%)	4 (14·3%)
Severe jaundice requiring immediate management	407 (60·4%)	8 (28·6%)
Severe anaemia requiring blood transfusion	6 (0·9%)	1 (3·6%)
Active seizures	1 (0·2%)	1 (3·6%)
Severe abdominal distention	11 (1·6%)	4 (14·3%)
Omphalitis or infection of umbilical cord	24 (3·6%)	1 (3·6%)
Widespread skin infection of neonate or caregiver providing skin-to-skin contact	11 (1·6%)	2 (7·1%)
Mother or caregiver not available or not willing to provide continuous skin-to-skin contact	145 (21·5%)	7 (25·0%)

Data are n (%) or median (IQR). Additional results by hospital site are provided in the appendix (p 20). KMC=kangaroo mother care. *Excludes 43 neonates who died, three participants who were discharged, and 15 neonates who were withdrawn, all within 24 h of randomisation. †The skin-to-skin contact aspect of KMC. ‡Multiple observations per neonate (collected daily until day 7, then on days 14 and 21; therefore, will vary per neonate).

Table 4: **Initiation and duration of KMC between neonates and mothers or caregivers**

60 h (36–85) in the intervention group and 0 h (0–26) in the control group.

A pooled meta-analysis of the OMWaNA trial, WHO's iKMC trial, and the eKMC trial in The Gambia showed a relative reduction of 19% in 28-day mortality (95% CI 0·71–0·93; p=0·0019; figure 2A). A meta-analysis including African sites only across the three trials showed a relative reduction of 14% in 28-day mortality (0·74–1·00; p=0·043; figure 2B; appendix p 25). 28-day mortality was the only mortality outcome that was measured consistently in all trials.

Across all five hospitals in the OMWaNA trial, the mean economic cost to society per neonate (n=2221) was similar between the intervention group (US$359·1) and the control group ($365·9; adjusted mean difference –$7·2 [95% CI –21·5 to 7·2]; p=0·33; appendix pp 26–29). There was weak evidence that provider economic costs were lower in the intervention group ($273·3) than in the control group ($282·4; –$9·4 [–19·0 to 0·3]; p=0·058). Applying the assumption that policy makers place no value on averting neonatal deaths, the intervention would have a 97% probability from the provider perspective and an 84% probability from the societal perspective of being more cost-effective than standard care. If policy makers were willing to pay $400 to avoid a neonatal death, the probability of cost-effectiveness would increase to 98–99% from the provider perspective and to 88–91% from the

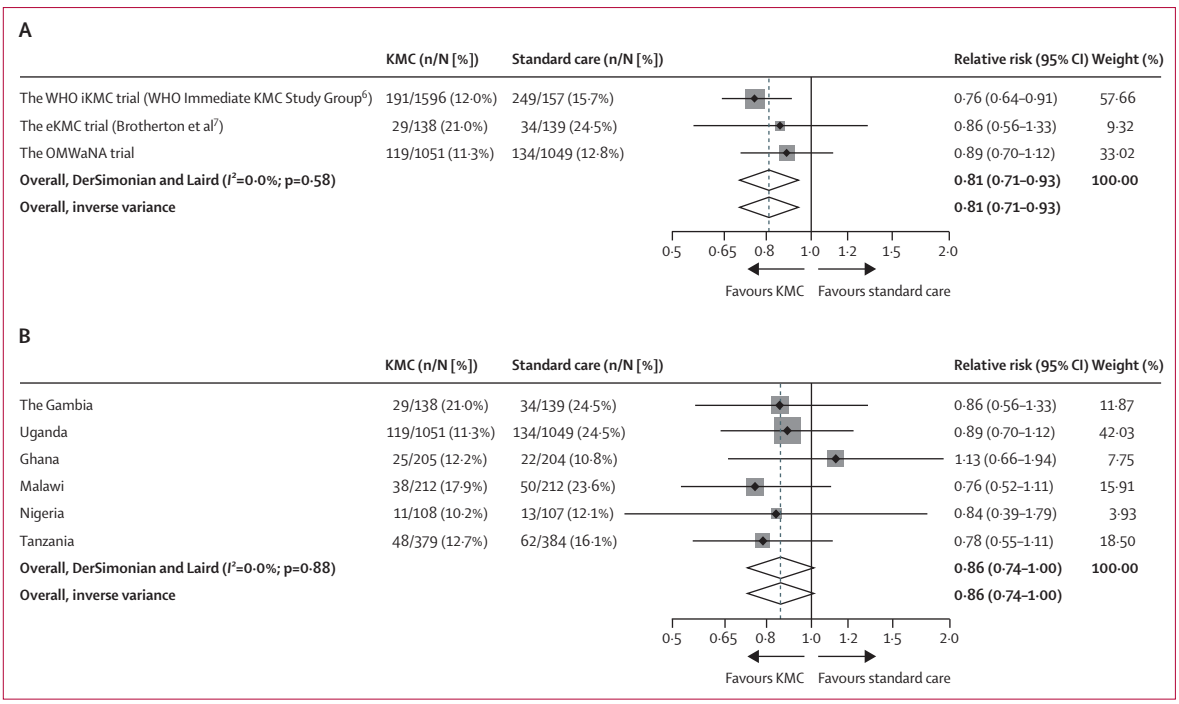

Figure 2: **All-cause mortality at 28 days for published trials on early or immediate KMC**
Meta-analysis for the pooled results of all three trials (A) and for trial sites across six sub-Saharan African countries from all three trials (B). KMC=kangaroo mother care.

societal perspective (figure 3; appendix p 30). There was no evidence of overall differences in household costs for financial expenditures ($2·8 [–1·3 to 6·8]; p=0·18) or for foregone income (–$0·5 [–8·6 to 7·5]; p=0·90), whether measured per neonate or per household (appendix pp 26–27, 32). Findings were broadly consistent at four of the hospitals; however, at hospital 4, which was overcrowded, length of stay was significantly shorter among babies in the control group than among those in the intervention group. Costs per neonate at hospital 4 were, therefore, higher in the intervention group than in the control group for provider economic costs ($42·8 [28·9 to 56·6]; p<0·0001), household financial costs ($11·1 [5·0 to 17·3]; p<0·0001), and societal economic costs ($57·4 [36·9 to 77·8]; p<0·0001; appendix pp 26–27).

Staff time comprised 62·7% ($171·4) in the intervention group and 63·7% ($179·8) in the control group of provider costs (appendix pp 33–34). Staff time (–$8·4) and electricity (–$5·7) cost less in the intervention group than in the control group, and outweighed the slightly higher provider costs of hospital setup, water, drugs, therapies, supplies, and transport ($4·8) in the intervention group. Duration of hospitalisation was similar between groups at four hospitals, where provider and societal costs were consistently higher in the control group; however, at hospital 4, neonates were hospitalised for longer in the intervention group, which drove higher provider and societal costs in this group (appendix p 35). Associations between hospitalisation duration and household costs were unclear (appendix p 36). Across all hospitals, there was evidence of effect modification in provider economic and household financial costs for subgroup analyses by birthweight category (p<0·0001), singleton birth versus multiple births (p<0·0001 for provider costs and p=0·011 for household costs), and vital status at hospital discharge (p<0·0001 for provider costs and p=0·0012 for household costs). There was strong evidence of effect modification in societal economic costs by birthweight category (p<0·0001) and vital status at discharge (p<0·0001; appendix p 37).

Uncertainty in several variables had a small effect on estimates of incremental economic costs to society and did not change conclusions about the cost-effectiveness of the intervention (appendix p 38). However, if it were assumed that staff allocated their time equally each shift across neonates regardless of type of care (ie, KMC, incubator, or radiant heater), costs would be higher in the intervention group than the control group (adjusted mean difference $31·0 [95% CI 16·9 to 45·1]; p<0·0001). By contrast, if neonates in the control group at hospital 4 (n=524) were admitted for the same mean duration (7·1 days) as were neonates in the control group across the other four hospitals (n=587), the overall cost across all five hospitals would be even lower in the intervention group than we estimated in our base case analysis (–$71·0 [–83·9 to –58·2]; p<0·0001). If the difference in electricity cost between KMC and incubator or radiant heater were doubled, the overall cost would be lower in the intervention group than in the control group (adjusted mean difference –$21·6 [–35·0 to –6·2]; p=0·0050).

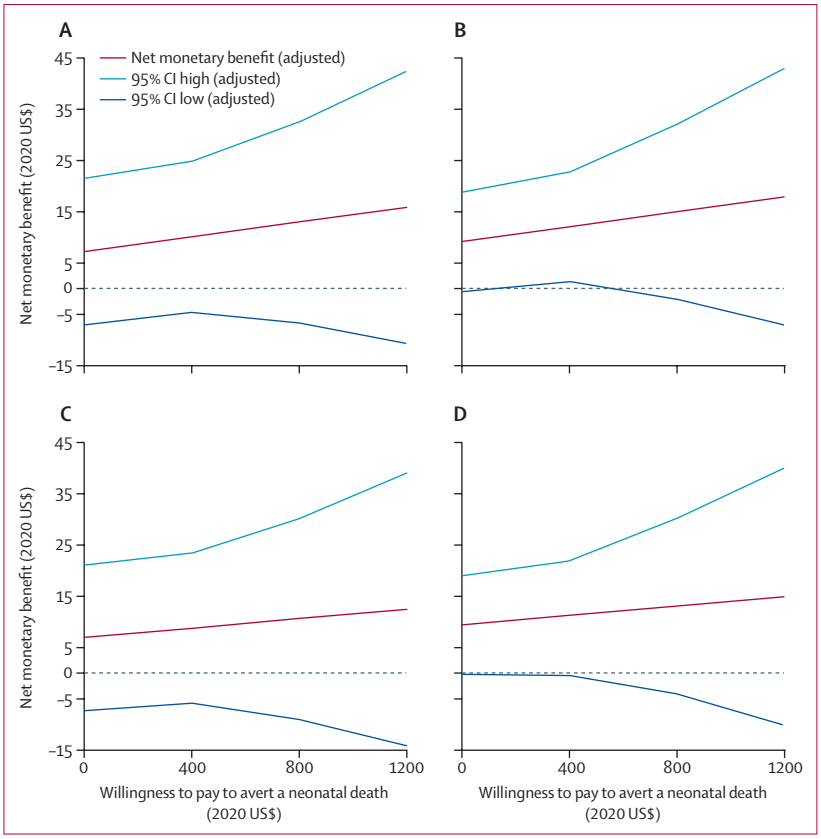

Figure 3: **Incremental net monetary benefit analysis**
All costs in 2020 US$. Adjusted incremental net monetary benefits for societal and provider economic costs. Effects adjusted for stratification factors (ie, birthweight category and hospital site) and sex of neonate. Additional details are provided in the appendix (p 30). (A) Total societal economic costs: scenario A. (B) Total provider economic costs: scenario A. (C) Total societal economic costs: scenario B. (D) Total provider economic costs: scenario B. In scenario A, the mortality rate among the 27 babies with missing data on the primary outcome in the intervention group is half the observed rate in the intervention group. In scenario B, the mortality rate among the 27 babies with missing data on the primary outcome in the intervention group is double the observed rate in the intervention group. In both scenarios, the mortality rate among the nine babies with missing data on the primary outcome in the control group is equal to the observed rate in the control group.

Discussion

We found that KMC initiated before stabilisation had no effect on the primary outcome of early neonatal mortality (<7 days) and had a non-significant relative reduction in 28-day mortality of 12% compared with standard care among 2221 neonates in Uganda. Secondary outcomes, including hypothermia at 24 h and daily weight gain at 28 days, were significantly improved among neonates in the intervention group. A meta-analysis pooling the results from the OMWaNA trial with those of other relevant trials showed a significant relative reduction in 28-day mortality of 19% overall and of 14% across trial sites in sub-Saharan Africa only. Our economic evaluation found that, compared with standard care, KMC initiated before stabilisation decreased the economic cost of neonatal care to society and providers. No overall differences were observed in the financial or opportunity costs to households. In economic terms, KMC initiated before stabilisation would be considered to dominate standard care, being the more cost-effective policy choice even if no value was placed on avoiding neonatal deaths.

Early neonatal mortality was the primary outcome for all three trials (WHO's iKMC trial, the eKMC trial in The Gambia, and the OMWaNA trial), but was not significantly reduced following intervention in any of these trials. However, the iKMC trial[6] reported a significant relative reduction of 25% in their secondary outcome of 28-day mortality (95% CI 11–36%) among 3183 neonates. This observed reduction seemed to have been primarily driven by the trial site in India (RR 0·66 [95% CI 0·50–0·89]), comprising 1372 babies.[6] We observed a non-significant relative reduction in 28-day mortality of 12% (range 11–22), which is consistent with four of the five African sites. In the iKMC trial, a subgroup analysis showed improved but non-significant point estimates for 28-day survival at the sites in Malawi, Nigeria, and Tanzania, and a slight increase in mortality at the site in Ghana.[6] The eKMC trial in The Gambia, involving 277 neonates, found a similar non-significant reduction of 16% in the relative risk of mortality at 28 days (RR 0·84 [95% CI 0·55–1·29]).[7] Possible reasons for the observed variation in mortality effects at 28 days between the iKMC trial and the other two trials include case-mix differences (notably more small-for-gestational-age newborns in south Asia), the context of care, the intensity or daily duration of skin-to-skin contact in the intervention group (16·9 h in the iKMC trial *vs* 9·5 h in the OMWaNA trial *vs* 6·7 h in the eKMC trial), and duration of admission (15 days in both groups in the iKMC trial *vs* 6–7 days in the OMWaNA trial).[3] Our complier average causal effect analysis found strong evidence of reduced mortality at 28 days among babies who had received KMC within 24 h of randomisation. Neonates in the intervention group who received an average of 12–24 h of skin-to-skin contact in the KMC position daily had a lower risk of mortality at both day 7 and day 28 than did those receiving up to 12 h of KMC daily.

Although the eKMC trial[7] reported no difference in the prevalence of hypothermia at 24 h between neonates in the intervention group and in the control group, lower rates were observed in the intervention group in both the OMWaNA trial (RR 0·76) and the iKMC trial (RR 0·65),[6] albeit assessed at different endpoints (at 24 h *vs* at hospital discharge). Additionally, the iKMC trial reported a lower rate of suspected sepsis among neonates in the intervention group than among those in the control group (RR 0·82).[6] By contrast, the eKMC trial found no difference in suspected sepsis at 28 days between groups.[7] Neither the iKMC trial nor the eKMC trial found any differences between groups in prespecified feeding outcomes, such as exclusive breastfeeding and daily weight gain at 28 days, whereas the OMWaNA trial reported a significant improvement in daily weight gain at 28 days in the intervention group. In all three trials, a substantial proportion of newborns met birthweight and other

inclusion criteria (40–75%), but were ineligible or unable to be enrolled.

The findings from our economic evaluation are consistent with those from previous studies in South America and central America,[9–13] sub-Saharan Africa,[9,14] south Asia,[9,15] and Europe,[16] which all found that KMC resulted in cost savings from the health service provider perspective; however, these studies did not evaluate KMC initiated before stabilisation. Only one previous study, a randomised controlled trial in India involving 141 stabilised neonates born weighing up to 1100 g, considered costs from the household perspective.[15] The study found that the immediate shifting of neonates to the KMC ward, where care was provided by mothers, led to financial cost savings for parents (Indian rupee –13 519 [–US$205] per neonate; p<0·001) and the hospital (–20 278 [–$307]; p<0·001) compared with intermediate intensive care, and that these cost savings were driven by reduced length of hospitalisation.[15] We found that duration of hospitalisation was a key driver of provider and societal costs. Overall, across the five hospitals in this trial, we found no evidence of differences in household financial or opportunity costs because at hospital 4, the largest site, participants in the control group were discharged much sooner than those in the intervention group, lowering the costs of care for neonates in the control group. These discharge decisions might have been driven by overcrowding in the neonatal unit or could be a trial artefact, with staff possibly wishing to ensure the effectiveness of the intervention.

The OMWaNA trial had many strengths as a parallel-group, individually randomised controlled trial with an embedded full economic evaluation, pragmatically and robustly implemented in five hospitals providing neonatal care in settings typical of sub-Saharan Africa. We provided pragmatic infrastructure improvements and minimal additional human resources.[18] The planned sample size was achieved, despite substantial disruption from the COVID-19 pandemic. Our embedded economic evaluation is the first to evaluate the costs of KMC among neonates before clinical stabilisation and the first to assess the societal economic costs of KMC, including opportunity costs to households.

This trial also had limitations. Our sample size assumed a baseline mortality rate of 25% and the trial was powered to detect a relative risk reduction in the primary outcome (mortality at 7 days). Our sample size would have been sufficient to detect an absolute reduction of 4·8% (relative reduction of 26·7%), even with an 18% mortality rate. However, we observed lower reductions in mortality rate than were expected from baseline data in both the control and intervention groups, which reduced our power to detect the prespecified relative reduction of 5·6%. This reduced mortality rate was plausibly related to improvements in the quality of neonatal care and monitoring, with infrastructure and device upgrades, notably with CPAP in preparation for the trial. Variation between sites for some aspects of care, such as KMC duration and CPAP availability, could have affected our findings. Given the nature of KMC, it was impossible to mask participants and hospital staff to treatment allocation, but the independent statistician who conducted the analyses was masked to treatment allocation. We were unable to include household costs at 28-day follow-up because few data were collected. Furthermore, because of a scarcity in follow-up data, we have not modelled costs over a lifetime horizon, which could be useful to consider differences in long-term morbidities, life expectancy, and associated costs.

WHO's updated guidelines on preterm neonates, revised following the iKMC trial, recommend initiating KMC as soon as possible after birth at all levels of neonatal care and in all income contexts.[8] Global uptake of immediate KMC is being actively advocated.[43] Our findings underline that neonatal care, including safe respiratory support, needs to be in place before the implementation of KMC for small, vulnerable newborns, who are sensitive to the quality of hospital care, which is affected by neonatal unit infrastructure, nursing ratios, and essential devices. Mortality outcomes might also be affected by neonatal case mix (eg, the high prevalence of small-for-gestational-age newborns in south Asia) and other factors. Our novel economic results suggest that KMC initiated in neonates before clinical stabilisation could reduce costs compared with standard care, even when considering the investments in floor space and devices that are required to improve the quality and safety of neonatal care from current practice.[18]

Research priorities include a focus on how to implement KMC among neonates before clinical stabilisation in contexts with the highest risk of neonatal deaths, in newborn wards and maternity units, and at different levels of the health system. Indicators for tracking national coverage and quality of care through routine data collection will be crucial, otherwise scale-up will not be measurable. Operationalisation of follow-up care and family support for newborns at risk is crucial, given that we found earlier than expected discharge times for such vulnerable newborns. Because of the investment needed, budgeting tools, national investment cases, and budget impact analyses are already in demand to inform scale-up of neonatal care,[44] including immediate KMC, especially across sub-Saharan Africa where rates of neonatal mortality are highest globally.

OMWaNA Collaborative Authorship Group
Rolland Mutumba, Harriet Nambuya, Irene Nayiga, Mary Nyanzi, Oyella Sheila Sherine, Diana Nabawanuka, Maburuka Anguparu, Agnes Batani, Gladys Bingi, Emmanuel Byaruhanga, Mugoya Dauda, Onyachi Nathan, Kyebambe Peterson, Alfred Yayi, and Janet Seeley.

Contributors

MMM, JEL, and PW conceptualised the OMWaNA trial with EA. VT, IM, and CJT coordinated the trial, with support from MMM, MN, PW, and JEL. WO, FK, RS, NN, and CN collected clinical data and monitored participant safety. AK, YH, and AA coordinated data management, with oversight from RC, CO, and EA. VT, IM, CJT, and MMM oversaw monitoring for adverse events. CK-N collected economic data, with support from EE-K, MMM, GG, and CP. CO and RC analysed clinical

data, with input from VT, MMM, CJT, DE, EA, and JEL. MMM conducted the economic analysis, with oversight by CP and input from GG and EE-K. VT, MMM, CJT, and CO co-wrote the manuscript, with CP and JEL. All authors interpreted the data, critically reviewed the manuscript, and approved the final version. RC, CO, and MMM accessed and verified the data. VT, MMM, and JEL were responsible for the decision to submit the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data sharing and transfer agreements were jointly developed and signed by all collaborating partners. Data from the study will be deposited online at LSHTM Data Compass (https://datacompass.lshtm.ac.uk/), with access subject to approval.

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References

1 United Nations Inter-agency Group for Child Mortality Estimation. Levels & trends in child mortality: report 2023. New York, NY: United Nations Children's Fund, 2024. https://data.unicef.org/wp-content/uploads/2024/03/UNICEF-2023-Child-Mortality-Report-1.pdf (accessed March 19, 2024).

2 Oza S, Cousens SN, Lawn JE. Estimation of daily risk of neonatal death, including the day of birth, in 186 countries in 2013: a vital-registration and modelling-based study. *Lancet Glob Health* 2014; **2:** e635–44.

3 Lawn JE, Ohuma EO, Bradley E, et al. Small babies, big risks: global estimates of prevalence and mortality for vulnerable newborns to accelerate change and improve counting. *Lancet* 2023; **401:** 1707–19.

4 WHO. Born too soon: decade of action on preterm birth. 2023. https://www.who.int/publications/i/item/9789240073890 (accessed Dec 4, 2023).

5 Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database Syst Rev* 2016; **8:** CD002771.

6 WHO Immediate KMC Study Group. Immediate "kangaroo mother care" and survival of infants with low birth weight. *N Engl J Med* 2021; **384:** 2028–38.

7 Brotherton H, Gai A, Kebbeh B, et al. Impact of early kangaroo mother care versus standard care on survival of mild-moderately unstable neonates <2000 grams: a randomised controlled trial. *EClinicalMedicine* 2021; **39:** 101050.

8 WHO. WHO recommendations for care of the preterm or low-birth-weight infant. 2022. https://www.who.int/publications/i/item/9789240058262 (accessed Dec 4, 2023).

9 Cattaneo A, Davanzo R, Worku B, et al. Kangaroo mother care for low birthweight infants: a randomized controlled trial in different settings. *Acta Paediatr* 1998; **87:** 976–85.

10 Ruiz JG, Charpak N, Castillo M, et al. Latin American Clinical Epidemiology Network Series - paper 4: economic evaluation of kangaroo mother care: cost utility analysis of results from a randomized controlled trial conducted in Bogotá. *J Clin Epidemiol* 2017; **86:** 91–100.

11 Broughton EI, Gomez I, Sanchez N, Vindell C. The cost-savings of implementing kangaroo mother care in Nicaragua. *Rev Panam Salud Publica* 2013; **34:** 176–82.

12 Lima G, Quintero-Romero S, Cattaneo A. Feasibility, acceptability and cost of kangaroo mother care in Recife, Brazil. *Ann Trop Paediatr* 2000; **20:** 22–26.

13 Sloan NL, Camacho LW, Rojas EP, Stern C. Kangaroo mother method: randomised controlled trial of an alternative method of care for stabilised low-birthweight infants. *Lancet* 1994; **344:** 782–85.

14 Memirie ST, Tolla MT, Desalegn D, et al. A cost-effectiveness analysis of maternal and neonatal health interventions in Ethiopia. *Health Policy Plan* 2019; **34:** 289–97.

15 Sharma D, Murki S, Oleti TP. To compare cost effectiveness of 'kangaroo ward care' with 'intermediate intensive care' in stable very low birth weight infants (birth weight <1100 grams). *Ital J Pediatr* 2016; **42:** 64.

16 Lowson K, Offer C, Watson J, McGuire B, Renfrew MJ. The economic benefits of increasing kangaroo skin-to-skin care and breastfeeding in neonatal units: analysis of a pragmatic intervention in clinical practice. *Int Breastfeed J* 2015; **10:** 11.

17 Medvedev MM, Tumukunde V, Mambule I, et al. Operationalising kangaroo Mother care before stabilisation amongst low birth Weight Neonates in Africa (OMWaNA): protocol for a randomised controlled trial to examine mortality impact in Uganda. *Trials* 2020; **21:** 126.

18 Medvedev MM, Tumukunde V, Kirabo-Nagemi C, et al. Process and costs for readiness to safely implement immediate kangaroo mother care: a mixed methods evaluation from the OMWaNA trial at five hospitals in Uganda. *BMC Health Serv Res* 2023; **23:** 613.

19 Lindberg C, Nareeba T, Kajungu D, Hirose A. The extent of universal health coverage for maternal health services in eastern Uganda: a cross sectional study. *Matern Child Health J* 2022; **26:** 632–41.

20 Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340:** c869.

21 WHO. Kangaroo mother care: a practical guide. 2003. http://www.who.int/maternal_child_adolescent/documents/9241590351/en (accessed Dec 4, 2023).

22 Shaffer ML, Kunselman AR, Watterberg KL. Analysis of neonatal clinical trials with twin births. *BMC Med Res Methodol* 2009; **9:** 12.

23 Greco G, Skordis-Worrall J, Mills A. Development, validity, and reliability of the Women's Capabilities Index. *J Human Dev Capabil* 2018; **19:** 271–88.

24 Nanyunja C, Sadoo S, Kohli-Lynch M, et al. Early care and support for young children with developmental disabilities and their caregivers in Uganda: the baby Ubuntu feasibility trial. *Front Pediatr* 2022; **10:** 981976.

25 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377–81.

26 Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res* 2013; **22:** 661–70.

27 Williamson T, Eliasziw M, Fick GH. Log-binomial models: exploring failed convergence. *Emerg Themes Epidemiol* 2013; **10:** 14.

28 Sommer A, Zeger SL. On estimating efficacy from clinical trials. *Stat Med* 1991; **10:** 45–52.

29 Medvedev MM, Brotherton H, Gai A, et al. Development and validation of a simplified score to predict neonatal mortality risk among neonates weighing 2000 g or less (NMR-2000): an analysis using data from the UK and The Gambia. *Lancet Child Adolesc Health* 2020; **4:** 299–311.

30 Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *BMJ* 2022; **376:** e067975.

31 Wilkinson T, Sculpher MJ, Claxton K, et al. The international decision support initiative reference case for economic evaluation: an aid to thought. *Value Health* 2016; **19:** 921–28.

32 Lopetegui M, Yen PY, Lai A, Jeffries J, Embi P, Payne P. Time motion studies in healthcare: what are we talking about? *J Biomed Inform* 2014; **49:** 292–99.

33 World Bank. Official exchange rate (LCU per US$, period average). https://data.worldbank.org/indicator/PA.NUS.FCRF (accessed Nov 11, 2021).

34 El Alili M, van Dongen JM, Esser JL, Heymans MW, van Tulder MW, Bosmans JE. A scoping review of statistical methods for trial-based economic evaluations: the current state of play. *Health Econ* 2022; **31:** 2680–99.

35 Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *PharmacoEconomics* 2014; **32:** 1157–70.

36 MacNeil Vroomen J, Eekhout I, Dijkgraaf MG, et al. Multiple imputation strategies for zero-inflated cost data in economic evaluations: which method works best? *Eur J Health Econ* 2016; **17:** 939–50.

37 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011; **30:** 377–99.

38 Hoch JS, Hay A, Isaranuwatchai W, et al. Advantages of the net benefit regression framework for trial-based economic evaluations of cancer treatments: an example from the Canadian Cancer Trials Group CO.17 trial. *BMC Cancer* 2019; **19:** 552.

39 Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of "community acquired" syncope. *BMC Health Serv Res* 2006; **6:** 68.

40 Hounton S, Newlands D. Applying the net-benefit framework for assessing cost-effectiveness of interventions towards universal health coverage. *Cost Eff Resour Alloc* 2012; **10:** 8.

41 Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. *J Pediatr* 1991; **119:** 417–23.

42 Pitt C, Ndiaye M, Conteh L, et al. Large-scale delivery of seasonal malaria chemoprevention to children under 10 in Senegal: an economic analysis. *Health Policy Plan* 2017; **32:** 1256–66.

43 WHO. Kangaroo mother care: implementation strategy for scale-up adaptable to different country contexts. 2023. https://apps.who.int/iris/handle/10665/367625 (accessed Dec 4, 2023).

44 Kamuyu, R, Tarus, A, Bundala, F et al. Investment case for small and sick newborn care in Tanzania: systematic analyses. *BMC Pediatr* 2023; **23** (suppl 2)**:** 632.