

## ORIGINAL ARTICLE

# Immediate “Kangaroo Mother Care” and Survival of Infants with Low Birth Weight

WHO Immediate KMC Study Group\*

## ABSTRACT

**BACKGROUND**

“Kangaroo mother care,” a type of newborn care involving skin-to-skin contact with the mother or other caregiver, reduces mortality in infants with low birth weight (<2.0 kg) when initiated after stabilization, but the majority of deaths occur before stabilization. The safety and efficacy of kangaroo mother care initiated soon after birth among infants with low birth weight are uncertain.

**METHODS**

We conducted a randomized, controlled trial in five hospitals in Ghana, India, Malawi, Nigeria, and Tanzania involving infants with a birth weight between 1.0 and 1.799 kg who were assigned to receive immediate kangaroo mother care (intervention) or conventional care in an incubator or a radiant warmer until their condition stabilized and kangaroo mother care thereafter (control). The primary outcomes were death in the neonatal period (the first 28 days of life) and in the first 72 hours of life.

**RESULTS**

A total of 3211 infants and their mothers were randomly assigned to the intervention group (1609 infants with their mothers) or the control group (1602 infants with their mothers). The median daily duration of skin-to-skin contact in the neonatal intensive care unit was 16.9 hours (interquartile range, 13.0 to 19.7) in the intervention group and 1.5 hours (interquartile range, 0.3 to 3.3) in the control group. Neonatal death occurred in the first 28 days in 191 infants in the intervention group (12.0%) and in 249 infants in the control group (15.7%) (relative risk of death, 0.75; 95% confidence interval [CI], 0.64 to 0.89;  $P=0.001$ ); neonatal death in the first 72 hours of life occurred in 74 infants in the intervention group (4.6%) and in 92 infants in the control group (5.8%) (relative risk of death, 0.77; 95% CI, 0.58 to 1.04;  $P=0.09$ ). The trial was stopped early on the recommendation of the data and safety monitoring board owing to the finding of reduced mortality among infants receiving immediate kangaroo mother care.

**CONCLUSIONS**

Among infants with a birth weight between 1.0 and 1.799 kg, those who received immediate kangaroo mother care had lower mortality at 28 days than those who received conventional care with kangaroo mother care initiated after stabilization; the between-group difference favoring immediate kangaroo mother care at 72 hours was not significant. (Funded by the Bill and Melinda Gates Foundation; Australian New Zealand Clinical Trials Registry number, ACTRN12618001880235; Clinical Trials Registry-India number, CTRI/2018/08/015369.)

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\*A complete list of the collaborators in the WHO Immediate KMC Study is provided in the Supplementary Appendix, available at NEJM.org.

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INFANTS WITH LOW BIRTH WEIGHT WHO are born preterm, are small for their gestational age, or both constitute approximately 15% of all neonates worldwide but account for 70% of all neonatal deaths. Reducing mortality among these infants, particularly those born in low- and middle-income countries in Asia and sub-Saharan Africa, is therefore key to the achievement of the United Nations Sustainable Development Goals target of reducing neonatal mortality to a level at least as low as 12 deaths per 1000 live births in all countries by 2030.<sup>1-3</sup>

“Kangaroo mother care,” defined as both continuous skin-to-skin contact of the infant with the chest of the mother (or another caregiver when not possible with the mother) and feeding exclusively with breast milk, is among the most effective interventions for preventing death in infants with low birth weight.<sup>4</sup> World Health Organization (WHO)<sup>5</sup> guidelines currently recommend initiation of short, intermittent sessions of kangaroo mother care when the infant’s condition begins to stabilize and continuous kangaroo mother care when the infant’s condition has stabilized. In a meta-analysis of eight hospital trials involving a total of 1736 infants, infants who received kangaroo mother care after stabilization had a 40% lower mortality than those who received conventional care in an incubator or a radiant warmer (3.2% vs. 5.3%; risk ratio, 0.60; 95% CI, 0.39 to 0.92).<sup>6</sup> This meta-analysis also showed that infants who received kangaroo mother care had fewer infections, higher rates of exclusive breast-feeding, and better weight gain than those who did not. In studies included in the review, the mean age at randomization (when the condition of the infants was considered to be stable) ranged from 10 hours to 24.5 days of life. Approximately 45% of neonatal deaths occur within 24 hours after birth and 80% during the first week of life<sup>7</sup>; thus, the majority of deaths among infants with low birth weight typically occur before kangaroo mother care can be initiated.

The effect of initiating kangaroo mother care immediately after birth on physiological stabilization has been evaluated in two randomized, controlled trials conducted in South Africa<sup>8</sup> and Vietnam.<sup>9</sup> In both trials, skin-to-skin contact that was initiated soon after birth in infants with low birth weight resulted in earlier stabilization than conventional care.

There is a critical knowledge gap regarding the effect of initiating continuous kangaroo mother care soon after birth and before stabilization with respect to mortality in infants with low birth weight. We conducted a large, multicenter, randomized, controlled trial to evaluate the safety and efficacy of continuous kangaroo mother care initiated immediately after birth in infants with a birth weight between 1.0 and 1.799 kg.

## METHODS

### STUDY DESIGN AND PARTICIPANTS

The trial was conducted in five tertiary-level hospitals in Ghana, India, Malawi, Nigeria, and Tanzania. All live-born infants in the participating hospitals whose birth weight was between 1.0 and 1.799 kg, regardless of gestational age, type of delivery, or singleton or twin status, were eligible for inclusion. Mother–infant pairs were excluded if the mother was younger than 15 years of age, was unable or unwilling to provide consent, had given birth to three or more infants in this pregnancy, was sick and unlikely to be able to provide kangaroo mother care within the first 3 days after birth, could not be enrolled within 2 hours after childbirth, or resided outside the study area. Infants who were unable to breathe spontaneously by 1 hour after birth or who had a major congenital malformation were also excluded.

The trial was approved by the ethics review committee at WHO and at each study site. The study was overseen by a steering committee and a data and safety monitoring board. Drs. Bahl, Rao, Yoshida, and Minckas vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The details of the study methods have been published previously and are briefly summarized here.<sup>10</sup>

### PROCEDURES

Three independent teams, trained in the standard operating procedures of the study, were responsible for the conduct of screening and enrollment, the provision of support for the mothers providing kangaroo mother care, and the measurement of outcomes at each site. Pre-screening of all pregnant women admitted for childbirth was conducted to identify women at

high risk for delivery of a low-birth-weight infant, and consent for study participation was sought. All infants born in the hospital were weighed and screened for eligibility. If the mother and infant were eligible for study participation, consent was confirmed if it had already been obtained before birth. If consent had not been obtained before birth, it was obtained after birth. At enrollment, mothers were asked to identify one or two adult women who could act as surrogate providers of kangaroo mother care; only women are permitted to stay in the postnatal areas in all study hospitals.

Randomization was performed with the use of computer-generated blocks. The blocks were variable in size and were stratified according to site and birth weight (1.0 to 1.499 kg or 1.5 to 1.799 kg). The assignments were sealed in serially numbered, opaque envelopes prepared at WHO and delivered to the sites. Research assistants conducted randomization as they opened each numbered envelope sequentially. Twins were allocated to the same group. The nature of the intervention prevented blinding, but the outcome assessment was conducted by an independent team whose members were not involved in intervention delivery.

Changes in the nature of obstetrical and neonatal care as well as structural changes in the neonatal intensive care units (NICUs) were necessary for mothers providing immediate kangaroo mother care. These NICUs (hereafter referred to as Mother–NICUs), which included mothers' beds and reclining chairs, were built or converted from existing NICUs. All equipment, staff, and care provision in the Mother–NICUs remained the same as in the control NICUs. At two sites, completely new Mother–NICUs were built in a nearby location and the existing NICUs were retained as the control NICUs. At the other three sites, modifications were made to convert half the existing NICUs to Mother–NICUs, and the other half served as the control NICUs. Infants receiving kangaroo mother care were secured firmly to the mother's chest with a binder that ensured a patent airway.<sup>11</sup> All care of the mother and infant was provided while skin-to-skin contact was maintained, if possible, and all interruptions in kangaroo mother care were documented. Obstetricians supervised essential postpartum care provided to mothers in the Mother–NICUs,

just as they did for mothers in the control NICUs.

Infants who were assigned to the control group were transferred to the control NICU without their mother, in accordance with standard practice. Mothers provided expressed breast milk and participated in brief sessions of kangaroo mother care when their infant began to recover from preterm birth complications and was at least 24 hours old.

Hospital staff provided care for all infants enrolled in the study, in accordance with the WHO minimum-care package for small infants.<sup>12</sup> In both the intervention and control groups, once infants were clinically stable (as determined on the basis of prespecified criteria)<sup>10</sup> for 24 hours, they were transferred from the Mother–NICU or the control NICU to the kangaroo mother care ward, where continuous kangaroo mother care was provided for all infants until discharge.

#### OUTCOMES

The primary outcomes were mortality from enrollment to 28 days of age and mortality from enrollment to 72 hours of age. The secondary outcomes included hypothermia (any axillary temperature <36°C), hypoglycemia (any blood glucose level of <45 mg per deciliter, measured when clinically indicated), suspected sepsis, time to clinical stabilization, exclusive breast-feeding (only by suckling) at the time of discharge, exclusive breast-feeding at the end of the neonatal period (at 28 days of age), maternal satisfaction with care, and maternal depression (see Table S1 in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org)).<sup>10</sup> In addition, death from the time of birth to 72 hours in unenrolled infants weighing between 1.0 and 1.799 kg, was documented. The only serious adverse event assessed according to the protocol was death.

Outcome data were collected with the use of the same methods and procedures for all enrolled infants. Clinical monitoring was conducted every 6 hours for all infants while they were in the Mother–NICU or the control NICU. Information on the duration of skin-to-skin contact and the duration of hospital stay was collected by research assistants. A home visit was conducted on day 29 to obtain data on survival, breast-feeding, and maternal depression.

**STATISTICAL ANALYSIS**

We estimated that 4200 infants were needed to detect 20% lower mortality in the intervention group than in the control group (16.8% vs. 21.1%), with a 95% confidence level, 90% power, and a 10% loss to follow-up. The data and safety monitoring board conducted interim analyses when 50% and 75% of the participants had been enrolled. After the second interim analysis, the data and safety monitoring board recommended stopping enrollment in the trial because of the clear benefit in neonatal survival in the infants receiving immediate kangaroo mother care (see the Supplementary Appendix).

Intention-to-treat analyses were performed for the primary and secondary outcomes,<sup>10</sup> and risk ratios and 95% confidence intervals were calculated for these outcomes. Adjusted risk ratios were estimated with the use of log-binomial regression modeling controlled for clustering due to multiple births and other important baseline characteristics that had the potential to be confounders. Hazard ratios were calculated with the use of multivariable Cox survival analysis to compare the times to clinical stabilization in the two groups. We used marginal mean imputation for missing values in continuous covariates and the most frequent response to impute categorical variables. No imputation was made for the primary outcomes.

Prespecified subgroup analyses were performed to explore modification of effect of immediate kangaroo mother care on primary outcomes according to birth weight (1.0 to 1.199 kg, 1.2 to 1.499 kg, and 1.5 to 1.799 kg), gestational age (<31 weeks, 31 to <34 weeks, 34 to <37 weeks, and ≥37 weeks), type of delivery (vaginal birth or cesarean section), singleton or twin gestation, and size for gestational age (small for gestational age or not small for gestational age).<sup>10</sup> Subgroup analyses according to site were conducted post hoc. In the intervention group, we examined the primary outcomes in subgroups according to compliance with kangaroo mother care (skin-to-skin contact for ≥20 hours, 10 to <20 hours, or <10 hours per day). To address reverse causality in this analysis, we excluded infants with any sign of severe illness in the first 6 hours of life. Causes of death were assigned by investigators on the basis of clinical information regarding hospital deaths and of interviews with

mothers in their homes for deaths that occurred after discharge.

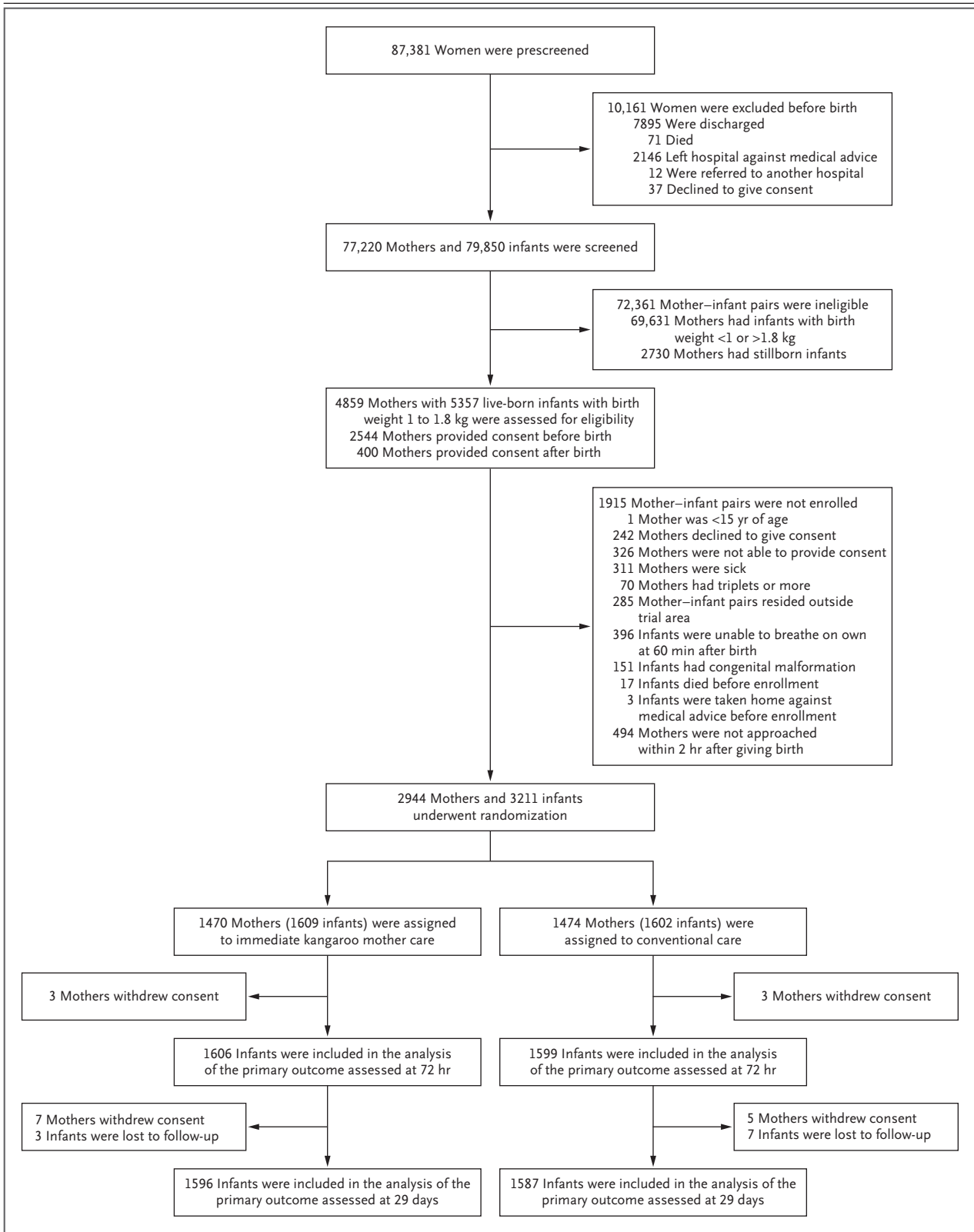
Post hoc analyses were conducted to explore the effect of the intervention on breast-feeding during the hospital stay. These analyses included assessments of the proportion of newborns by group who initiated breast-feeding within 24 hours, were put to breast in the first 72 hours, reached full breast-feeding within 7 days, and were discharged on exclusive feeding with breast milk.

**RESULTS**

A total of 87,381 pregnant women were prescreened for participation in the study, and a total of 77,220 mothers and 79,850 infants were screened for eligibility between November 30, 2017, and January 20, 2020; 5357 infants from 4859 mothers met the weight criteria for enrollment. Among them, 2944 mothers and 3211 infants underwent randomization, with 1470 mothers and 1609 infants assigned to immediate kangaroo mother care and 1474 mothers and 1602 infants assigned to conventional care, including kangaroo mother care after stabilization (Fig. 1).

Table 1 and Table S2 show the baseline characteristics of the infants and mothers in the study population as well as those of their families. Sociodemographic, newborn, and maternal characteristics were similar in the two groups. The mean gestational age at birth was 32.6 weeks and the mean birth weight 1.5 kg in both groups. With the exception of information on family income, which was missing for 8% of infants, observations for covariates were missing for only 0.3% of infants.

The median time to initiation of skin-to-skin contact in the intervention group was 1.3 hours (interquartile range, 0.8 to 2.7) and that in the control group was 53.6 hours (interquartile range, 33.8 to 101.4). The median duration of NICU stay was 6.4 days in both groups. During the NICU stay, the median daily duration of skin-to-skin contact in the intervention group was 16.9 hours and that in the control group was 1.5 hours. The daily duration of skin-to-skin contact on each day in the first 2 weeks is shown in Table S3. The main reasons that skin-to-skin contact was interrupted in infants in the intervention group were medical procedures, infant



**Figure 1 (facing page). Screening, Randomization, and Care.**

There may have been more than one reason that a mother–infant pair was not enrolled in the trial.

care, and routine activities of the mother. The median daily duration of skin-to-skin contact in the kangaroo mother care ward was similar in the intervention and control groups (20.2 hours and 19.0 hours, respectively) (Table 2).

From enrollment to 28 days of age, 191 infants

(12.0%) in the intervention group and 249 infants (15.7%) in the control group died (risk ratio, 0.75; 95% confidence interval [CI], 0.64 to 0.89;  $P=0.001$ ). The number needed to treat to prevent one death was 27 (95% CI, 17 to 77). From enrollment to 72 hours of age, 74 infants (4.6%) in the intervention group and 92 infants (5.8%) in the control group died (risk ratio for death, 0.77; 95% CI, 0.58 to 1.04;  $P=0.09$ ) (Table 3).

The intervention had similar effects across the categories of birth weight, gestational age,

**Table 1. Baseline Characteristics of the Infants and Mothers and Their Households.\***

Characteristic	Intervention	Control
Total no. of mother–infant pairs	1609	1602
<b>Infants</b>		
Median age at enrollment (IQR) — min	35 (20–55)	33 (20–54)
Mean birth weight — kg	1.5±0.2	1.5±0.2
Mean gestational age at birth — wk†	32.6±3.0	32.6±2.8
Male — no. (%)	752 (46.7)	748 (46.7)
Infants born as twins — no. (%)	430 (26.7)	430 (26.8)
Delivery by cesarean section — no. (%)	559 (34.7)	614 (38.3)
Site of birth — no. (%)		
Ghana	205 (12.7)	205 (12.8)
India	695 (43.2)	682 (42.6)
Malawi	217 (13.5)	222 (13.9)
Nigeria	108 (6.7)	107 (6.7)
Tanzania	384 (23.9)	386 (24.1)
<b>Mother and household</b>		
Total no. of mothers	1470	1474
Age of mother — yr	26.7±5.8	26.7±5.8
Median yr of schooling (IQR)‡	10 (7–12)	10 (7–12)
Monthly family income in U.S. dollars — median (IQR)	168 (110–285)	176 (110–280)
Piped water as main source of drinking water — no. (%)	934 (63.5)	953 (64.7)
Households with indoor toilet — no./total no. (%)	1288/1465 (87.9)	1343/1471 (91.3)

\* Plus–minus values are means±SD. A total of 534 infants of 267 mothers were born from multiple pregnancies. All these infants were eligible for inclusion in the study and were enrolled, with 278 infants assigned to the intervention group and 256 infants assigned to the control group. In addition, there were 325 mothers with multiple pregnancies in whom only one of the infants was eligible for inclusion in the study (152 infants in the intervention group and 173 infants in the control group). IQR denotes interquartile range. Additional baseline characteristics are provided in Table S1 in the Supplementary Appendix.

† Gestational age was based on ultrasonographic findings in the first or second trimester. If such data were not available, gestational age was based on the mother’s last menstrual period. If such data were not available, gestational age was based on Ballard score, which is determined on the basis of the neonate’s physical and neuromuscular maturity.<sup>13</sup> Information on gestational age at birth was missing for 27 infants in the intervention group and 18 infants in the control group.

‡ Data on the mother’s education were missing for two mothers in the intervention group and two mothers in the control group.

**Table 2. Initiation and Duration of Skin-to-Skin Contact of Infants with Mothers or Surrogates.\***

Variable	Intervention (N=1609)	Control (N=1602)
Median time to initiation of skin-to-skin contact (IQR) — hr*	1.3 (0.8–2.7)	53.6 (33.8–101.4)
Time to initiation of skin-to-skin contact by category — no. (%)		
<2 hr	1084 (67.4)	4 (0.2)
2 to <6 hr	314 (19.5)	14 (0.9)
6 to <12 hr	94 (5.8)	13 (0.8)
12 to <24 hr	65 (4.0)	75 (4.7)
24 to <168 hr	35 (2.2)	1176 (73.4)
≥168 hr to end of neonatal period	1 (0.1)	142 (8.9)
Never initiated	16 (1.0)	178 (11.1)
Median duration of skin-to-skin contact in control NICU or Mother–NICU (IQR) — hr/day		
With mother	12.3 (6.8–16.5)	1.5 (0.2–3.2)
With surrogate	2.3 (0.1–6.5)	0 (0–0)
Duration of skin-to-skin contact in kangaroo mother care ward — hr/day		
Total no. of hr	1300	1224
Median (IQR) — hr/day	20.2 (18.6–21.3)	19.0 (16.3–20.4)
With mother	19.4 (14.8–20.6)	18.0 (14.1–19.9)
With surrogate	0 (0–0.85)	0 (0–0)

\* If skin-to-skin contact was never initiated and the infant died, the data were censored at the time of death; if the infant was taken home against medical advice or if the mother refused to provide consent, the data were censored at time that the mother and infant left the hospital or at the time that consent was refused; if the mother and infant were discharged during the study, the data were censored at time of discharge; if the mother and the infant remained in the hospital at the end of the neonatal period, the data were censored at day 28.

weight for gestational age, type of delivery, and singletons or twins (Fig. 2 and Fig. S1). Benefit in point estimates was reported at all sites except Ghana. In the intervention group, the risk of death was lower in infants who received more hours of skin-to-skin contact per day (Table S4). Most deaths were caused by sepsis or preterm birth complications. Sepsis-associated mortality was 4.4% in the intervention group and 6.9% in the control group (risk ratio for death, 0.64; 95% CI, 0.48 to 0.86) (Table S5). Among 2146 infants with a birth weight of between 1.0 and 1.799 kg who were not enrolled in the trial, 340 (15.8%) had died by 72 hours.

Results for secondary outcomes are shown in Table 3. The proportion of infants with suspected sepsis was 22.9% in the intervention group and 27.8% in the control group (adjusted risk ratio, 0.82; 95% CI, 0.73 to 0.93); hypothermia was documented in 5.6% and 8.3% of infants, re-

spectively (adjusted risk ratio, 0.65; 95% CI, 0.51 to 0.83). The time to stabilization and the incidence of hypoglycemia, feeding fully by suckling at the time of discharge, and exclusive breast-feeding at the end of the neonatal period were similar in both groups. In post-hoc analyses, breast-feeding was initiated within the first 24 hours after birth in 58.5% of infants in the intervention group and 45.5% of infants in the control group; full breast-feeding occurred within 7 days in 78.4% and 69.0% of infants, respectively (Table S6).

## DISCUSSION

In this multicenter trial, the initiation of continuous kangaroo mother care soon after birth in infants with a birth weight between 1.0 and 1.799 kg improved neonatal survival by 25% as compared with kangaroo mother care initiated

**Table 3. Primary and Secondary Outcomes.\***

Outcome	Intervention (N = 1609)	Control (N = 1602)	Risk Ratio, Hazard Ratio, or Difference (95% CI) <sup>†</sup>	P Value
<b>Primary</b>				
Death between enrollment and 28 days — no./total no. (%)	191/1596 (12.0)	249/1587 (15.7)	0.75 (0.64–0.89)	0.001
Death between enrollment and 72 hr after birth — no./total no. (%)	74/1606 (4.6)	92/1599 (5.8)	0.77 (0.58–1.04)	0.09
<b>Secondary<sup>‡</sup></b>				
Exclusive breast-feeding at end of neonatal period — no./total no. (%)	1208/1401 (86.2)	1140/1336 (85.3)	1.01 (0.98–1.05)	
Fully breast-fed (i.e., by suckling) at hospital discharge — no./total no. (%)	62/1435 (4.3)	55/1376 (4.0)	1.06 (0.73–1.53)	
Hypothermia — no./total no. (%) <sup>§</sup>	90/1609 (5.6)	133/1602 (8.3)	0.65 (0.51–0.83)	
Median time to clinical stabilization — hr (IQR) <sup>¶</sup>	73.8 (26.8–138.5)	74.8 (25.3–140.6)	0.98 (0.90–1.07)	
Suspected sepsis — no./total no. (%) <sup>**</sup>	361/1575 (22.9)	434/1561 (27.8)	0.82 (0.73–0.93)	
Hypoglycemia at any time between 0 and 36 hr after birth — no./total no. (%) <sup>††</sup>	82/799 (10.3)	66/651 (10.1)	1.15 (0.85–1.56)	
Mean duration of hospital stay — days <sup>‡‡</sup>	14.9±0.2	15.2±0.2	1.07 (0.99–1.16)	
Mean score for maternal satisfaction <sup>§§</sup>	9.2±1.0	9.1±1.2	0.11 (0.03–0.19) <sup>¶¶</sup>	
Maternal depression — no./total no. (%) <sup>  </sup>	2/1276 (0.2)	7/1231 (0.6)	0.23 (0.05–1.14)	

\* Plus-minus values are means ±SD.

<sup>†</sup> All the values are adjusted risk ratios, except where noted. Risk ratios were adjusted for clustering due to multiple births and in accordance with study site, type of delivery, multiple pregnancies, mother's age at randomization, infant's sex and weight, mother's years of schooling and age, household with toilet, and family income.

<sup>‡</sup> The 95% confidence intervals for secondary outcomes were not adjusted for multiplicity and should not be used to infer definitive intervention effects.

<sup>§</sup> Hypothermia was defined as any instance of an axillary temperature of less than 36°C at any time from 2 hours after randomization until hospital discharge.

<sup>¶</sup> The time to clinical stabilization was defined as the first time at which an infant had all signs of clinical stability (i.e., no need for continuous positive airway pressure therapy, no episodes of apnea, an oxygen saturation of more than 90%, a respiratory rate of 40 to 59 breaths per minute, a heart rate of 80 to 179 beats per minute, a temperature of 36.0 to 37.4°C, and no need for intravenous fluids).

|| This value is the hazard ratio with a 95% confidence interval.

<sup>\*\*</sup> Suspected sepsis was defined as one or more of the following signs or symptoms: temperature of 35.5°C or more than 38°C, no movement or movement only on stimulation, in-drawing of the chest, and convulsions. Signs and symptoms were not reported for the first 24 hours of life. After that time, the infant should have been well for at least 24 hours before becoming sick. The denominator excludes infants who died, whose parents took them home against medical advice, or who were discharged before reaching 48 hours of age.

<sup>††</sup> Hypoglycemia was defined as a blood glucose level of less than 45 mg per deciliter (2.5 mmol per liter), measured when clinically indicated.

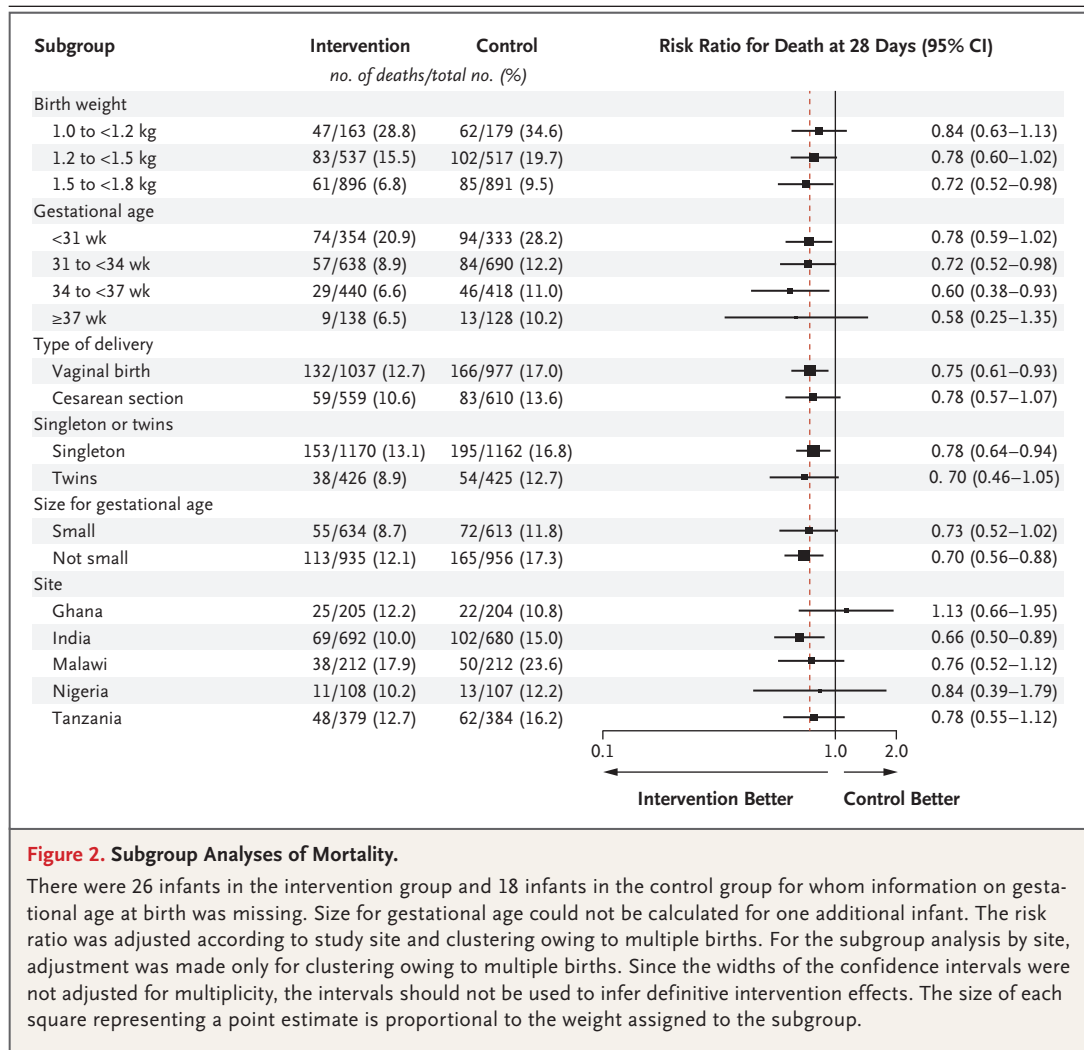
<sup>‡‡</sup> The duration of hospital stay was a prespecified process outcome.

<sup>§§</sup> The score for maternal satisfaction with health care in the hospital was assessed at discharge in 1282 mothers in the intervention group and 1233 mothers in the control group on a scale of 1 to 10, with higher scores indicating greater satisfaction.

<sup>¶¶</sup> This value is the mean difference with a 95% confidence interval.

||| Maternal depression was defined as a score of 15 points or more on the PHQ-9 Patient Depression Questionnaire. On this questionnaire, scores of 0 to 4 indicate no depression, 5 to 9 mild depression, 10 to 14 moderate depression, 15 to 19 moderately severe depression, and 20 to 27 severe depression.





**Figure 2. Subgroup Analyses of Mortality.**

There were 26 infants in the intervention group and 18 infants in the control group for whom information on gestational age at birth was missing. Size for gestational age could not be calculated for one additional infant. The risk ratio was adjusted according to study site and clustering owing to multiple births. For the subgroup analysis by site, adjustment was made only for clustering owing to multiple births. Since the widths of the confidence intervals were not adjusted for multiplicity, the intervals should not be used to infer definitive intervention effects. The size of each square representing a point estimate is proportional to the weight assigned to the subgroup.

after stabilization, the approach that is currently recommended. In order to prevent one neonatal death, the intervention would have to be provided to 27 infants (95% CI, 17 to 77). Implementation of the intervention required the mother or a surrogate to be with the infant 24 hours a day for the duration of stay in the NICU, which required the establishment of Mother-NICUs. The lower observed rates of hypothermia and suspected sepsis, though not adjusted for multiplicity, are consistent with results for the primary outcome and may at least in part explain the lower mortality among the infants receiving immediate kangaroo mother care.

Findings for the primary outcome and for infection and hypothermia were similar to those reported in earlier trials of the use of kangaroo

mother care in clinically stable infants.<sup>6</sup> However, we did not find significant differences between the intervention and control groups in the two prespecified feeding outcomes — being fully breast-fed by suckling at discharge and being fed exclusively through breast-feeding at the end of the neonatal period — despite post-hoc analyses suggesting that in the intervention group there were higher rates of initiating breast-feeding within 24 hours, putting the baby to the breast within 72 hours after birth, and reaching full breast-feeding within 7 days of birth. Nor did we find a material difference between groups in the time to stabilization, unlike two previous studies involving a similar intervention.<sup>8,9</sup> As compared with the studies that achieved intermittent kangaroo mother care in

the Cochrane review,<sup>6</sup> we achieved high compliance with the intervention — that is, approximately 17 hours of skin-to-skin contact per day.

There are several possible mechanisms by which immediate kangaroo mother care might confer benefit. Since the mother and baby are in close contact from birth, the baby is more likely to be colonized by the mother's protective microbiome and more likely to receive early breastfeeding. There is also less handling of the baby by other persons, thus reducing the risk of infection.<sup>14-20</sup> Constant monitoring of the infant by the mother, more frequent monitoring of the infant's glucose levels, and absence of stress<sup>21</sup> related to mother–infant separation may also have contributed to reduced mortality. Further studies in well-resourced settings could help to determine to what extent these enhanced survival results in low- and middle-income countries are relevant to settings in which mortality is low and intensive infant monitoring is provided. We observed that the risk of death was lower in infants who received more hours of skin-to-skin contact per day. However, this association is subject to confounding by medical issues in the infant that may have precluded prolonged skin-to-skin contact.

The results of the study are generalizable to most hospitals in low-resource settings in which immediate kangaroo mother care can be implemented as described here. Challenges in scaling up of the intervention include the involvement of multiple stakeholders, the establishment of Mother–NICUs, the need for strong collaboration between the obstetrics and neonatal departments, and changes in policy that would allow surrogates to provide kangaroo mother care.

Some limitations merit discussion. The nature of the intervention made blinding impossible. However, ensuring allocation concealment until the completion of enrollment, rigorous adherence to a predefined protocol, and the choice of mortality as a primary outcome minimize measurement bias. The open-label design may have resulted in measurement bias in some of the

secondary outcomes, which were more subjective, but would not affect our primary outcomes regarding mortality. The heterogeneity in the infrastructure, staff, and practices and possible differences in patient profiles across sites should increase the generalizability of our findings. It is not possible to partition the beneficial effect of the intervention between immediate initiation of kangaroo mother care and the simple presence of the mother with her baby because both are integral parts of the intervention. Finally, approximately 20% of the infants weighing between 1.0 and 1.799 kg who were born in study hospitals were not enrolled because the mother or the newborn was determined to be too sick to participate; this limitation needs to be considered when estimating the potential public health effects of the intervention.

In this large, multisite, multicountry study conducted in low-resource hospitals, continuous kangaroo mother care initiated immediately after birth in infants with a birth weight between 1.0 and 1.799 kg resulted in a significantly lower risk of neonatal death than the currently recommended initiation of kangaroo mother care after stabilization.

This study was reviewed and approved by the World Health Organization Ethics Review Committee and the institutional review boards at the five study sites: the School of Medical Science–Komfo Anokye Teaching Hospital, Ghana; Vardhman Mahavir Medical College and Safdarjung Hospital, India; the Malawi College of Medicine, Malawi; the Obafemi Awolowo University Teaching Hospitals Complex, Nigeria; and the National Institute for Medical Research, Tanzania.

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#### APPENDIX

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