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Community-Based Kangaroo Mother Care to Prevent Neonatal and Infant Mortality

Nancy L. Sloan, Dr.P.H.

Columbia University Mailman School of Public Health
Department of Epidemiology

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SUMMARY

Kangaroo Mother Care (KMC) is a method whereby the hospital-born stabilized low weight newborn is held in constant skin-to-skin (STS) contact on the mother's breast, breastfed as promptly and exclusively as possible and provided family and institutional support as needed. Traditional KMC significantly reduces the incidence of serious morbidity, particularly serious respiratory conditions (Sloan et al, 1994; Charpak et al, 1997; Caettano et al, 1998). However, KMC in hospital settings is typically provided to "stabilized" newborns and does not affect mortality (NMR) as most deaths (85% in Sloan et al, 1994) occur prior to that "stabilization." Prior to this study, a single adequately controlled study measuring mortality (Charpak et al., 2001) found a statistically insignificant lower infant mortality rate in analyses adjusted for socio-economic and demographic characteristics associated with traditional KMC. We posited that immediate postnatal KMC as a promising mechanism for thermal regulation and prevention of neonatal and infant mortality in low-income countries where most births occur at home, neonatal intensive care is virtually unavailable, and the incidence of low birth weight and newborn and infant mortality is high. Bangladesh has the highest incidence (~33%) of low birth weight (LBW) in the world. At the time the study was designed, infant and neonatal mortality rates (IMR and NMR) were 8.0% and 5.0% (Niport, Mitra and Associates, ORC Macro, 2001) for Dhaka and Sylhet divisions where the study was implemented. Acute respiratory infection (ARI) accounted for 23% of all infant deaths. Over 95% of infants were predominantly breastfed. Most (95%) rural births occurred at home and 82% were assisted by an untrained traditional birth attendant or relative (Niport, Mitra and Associates, ORC Macro, 2001).

Together with the Bangladesh Rural Advancement Committee (BRAC), Mitra and Associates (M&A), Ecuadorian and Bangladeshi physicians, nurse-midwives and KMC experts, we adapted KMC for community-based implementation (CKMC) in a manner that does not require birth weight or clinical judgment as measurement of birth weight is not routine in home deliveries in resource poor countries. To deliver CKMC in a feasible, replicable manner, we elected to train a single category of existing community-based workers, called community nutrition promoters, from the Bangladesh Integrated Nutrition Programme (BINP), which served approximately one-third of Bangladesh. We trained 22 community-based nutrition workers and their 2 supervisors and pilot tested the simplest approach, teaching CKMC to all late (≥7.5 months) gestation and recently postpartum women as frequently as possible. Nutrition workers informed but did not train others, including voluntary women's groups who help the nutrition workers, and traditional birth attendants about CKMC. CKMC and its differences from traditional KMC are specified in detail in Quasem et al, 2002. The key messages include: Hold your baby skin-to-skin (STS) between your breasts 24 hours a day to improve thermal regulation of the baby and promote prompt and exclusive breastfeeding and maternal-infant bonding, engage family support to help the mother when she needs short breaks (to go to the bathroom, etc.), take the baby to the nearest health center for a check-up when the baby does not want to breastfeed/or a woman feels she has no breastmilk, if the baby becomes purple, pale or cold, is very agitated or is lethargic. One component, to delay

immersion in water to bathe the baby, was added to CKMC as this is standard hospital practice for LBWs and as such is not normally considered an element of traditional, hospital-based KMC. Another critical difference was the promotion of CKMC for all babies rather than LBWs as 1) STS improves early breastfeeding which is critical to the establishment of breastfeeding as well as provision of immunologically important colostrum, and 2) babies weight on the day of birth is not routinely measured where the incidence of home births, LBW and NMR is high. In addition, the incidence of hypothermia, a cause of substantial newborn mortality, in normal weight babies, while lower than that of low birth weight (LBW) babies, is also high particularly in winter months (Darmstadt et al, 2006). We adapted KMC for immediate postnatal community-based (CKMC) application in rural Bangladesh where the incidence of home delivery, LBW and NMR is high and neonatal intensive care unavailable. In the small pilot study (n=35), we found the adaptation successful; 77% of women provided skin-to-skin care (STS) and 85% of those with LBW babies did so. Most (69%) in the pilot study gave STS ≥7 hours a day in the first two days of life, when most newborn mortality occurs.

We then conducted a randomized controlled cluster trial to test whether CKMC reduces overall NMR by 27.5%, IMR by 25%, and LBW-specific NMR by 30% assuming 85% of NMR occurs in LBWs and the incidence of LBW is 35%. Our sample included all 42 unions where BRAC supervised the National Nutrition Programme (NNP, which was the ensuing program to BINP) in two Bangladesh divisions with the highest IMRs. Stratified by distance to the sub-district capitol and population size, half of 42 unions were randomly assigned to CKMC and half not. One village per union was randomly selected proportionate to union population size. A baseline survey identified the sample of 39,849 eligible consenting women and their socio-demographic characteristics. Community-based workers were taught to teach CKMC to all expectant and postpartum women in the intervention villages. 4,165 live births were identified and enrolled. Newborns were followed at 30 to 45 days of age and infants are being followed quarterly through their first birthday to record infant care, feeding, growth, health and vital status.

The intervention and control groups are similar. Except for care seeking, CKMC behaviors (STS, prompt breastfeeding, delayed bathing, sleeping together) were more common in the intervention than control group (p=<.0001), but only 24% received STS ≥7 hours daily in the first two days of life compared with 69% in the pilot study. There was no difference in the babies' weight, head or arm circumference or in reported morbidity at the 30-45 day follow-up, except that fewer CKMC than control babies were reported to have become pale (0.4% v. 1.1%, p=0.018). Throughout infancy, more CKMC babies were reported to have experienced diarrhea (43.6% v 39.3%, p=.006); while statistically significant, the absolute difference is small and may reflect that mothers who hold their babies skin-to-skin observe and report more occurrences, particularly those that affect their body and cleanliness. Mothers of CKMC babies reported less postpartum bleeding (73.3% v. 76.8%, p=.039), possibly a consequence of more immediate breastfeeding. There was no difference in overall NMR or IMR (NMR: CKMC 4.6% v control 4.3%, p=0.68; IMR: CKMC 6.9% v control 6.6%, p=0.74). The slightly higher rates in the CKMC group reflect differences in baseline NMR (CKMC 6.1% v control 5.6%, p=0.68), i.e., virtually no relative difference between study groups

in NMR change since baseline, and IMR (CKMC 7.5% v control 6.5%, p=0.09), indicating a greater CKMC reduction in IMR since baseline (13% CKMC relative reduction compared with a 3% control relative reduction, p=.000). In babies weighing ≤2,000 g at birth NMR was 9.5% in the CKMC compared with 22.5% in the control group (design adjusted p=0.02). However, the lower NMR in babies weighing ≤2000 grams subgroup is difficult to interpret, since birthweight was missing on over 40% of live births and on nearly 65% of those dying in the newborn period, and was differential by study group. Few (but more than expected), 7.1% of CKMC and 7.2% of control group mothers, experienced subsequent pregnancy within one year of the first study enrolled pregnancy (OR=0.97, 95% ci 0.76-1.23, p=0.80). Slightly more CKMC mothers reported using contraceptives within that period (54.2% CKMC v. 50.0% control, p=0.009). Excluding women who used contraception in that time, 4.5% of CKMC and 3.3% of control group mothers experienced subsequent pregnancy within one year of the first study enrolled pregnancy (OR=1.31, 95% ci 0.79-2.17, p=0.29).

In light of the extensive missing birthweight information and its potential bias, the study's data safety and monitoring board (DSMB) and investigators conclude that the sole existing evidence of benefit based on the observed lower NMR among babies weighing ≤2000 grams at birth is insufficient to justify implementing the intervention at this point in time. This conclusion takes into account the results of two small African studies of early ("birth") KMC in hospitals (Lincetto, Nazir and Cattaneo, 2000; Worzu and Kassie, 2005), and what is known from a subsequent study of CKMC and other essential newborn care interventions in India (Vishwajeet et al, 2006). Estimating missing birthweight by statistical modeling of the study's data may help clarify the results. Further experimental evaluation ensuring baseline similarity of study groups and complete, reliable assessment of birthweight is necessary to determine whether CKMC improves survival. CKMC training or taking CKMC to scale at this time is ill-advised before establishing its benefits and optimal methods of implementation. Suboptimal implementation (where the majority of women provide less than seven hours a day of skin-to-skin care in the first two days of life and possibly early discontinuation of skin-to-skin care) results in no overall benefit. If CKMC, which quickly becomes popular, is set in place in a manner that is ineffective, it will be difficult or impossible to improve implementation and effect at a later date.

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HYPOTHESES

As CKMC had been rapidly and popularly accepted in the pilot study, we proposed to test the effects of CKMC on prevention of newborn and infant mortality through a randomized controlled cluster trial. CKMC training was piggy-backed on to an existing government community-based nutrition program in which both intervention and control groups participated. Based on an α=0.05 and 1-β=80%, adjusting the sample for approximately 10% loss to follow-up at 1 month and a 25% loss at one year, with an estimated baseline NMR of 6.5% and IMR of 7.5%, a sample of 2,000 deliveries per group (total 4,000 livebirths) was necessary to test a one-tailed hypothesis that CKMC would reduce NMR by 27.5%, IMR by 25% and/or low birth weight specific NMR by 30%, assuming birth weight would be available for 80% of the sample, a 35% incidence of LBW and a concentration of 85% of neonatal deaths in LBW babies. We posited that, by averting neonatal and infant mortality, CKMC would increase the proportion of women with surviving infants, continuation of breast feeding, and thus may reduce subsequent pregnancy. The sample has >80% statistical power to detect a difference in subsequent pregnancies of 4% in the control group and 2.5% in the intervention group within the one year follow-up period.

METHODS

We selected 42 unions where BRAC supervised the implementation of the National Nutrition Programme (NNP, the ensuing program to the Bangladesh Integrated Nutrition Programme) with the highest recent IMRs. Half of the 42 sample unions were assigned, stratified by union population size and distance to the upazila hospital, to receive CKMC instruction. The remaining unions served as the control group. Because we were testing a behavioral intervention and between-country diffusion of traditional KMC has been extensive, one village was randomly selected proportionate to population size from each union to prevent contamination between study groups. As each union contains an average of 30-35 villages, no other mechanism to prevent contamination believed necessary or was employed to prevent contamination except separate standardization of birth weight measurement for control and intervention group community nutrition workers. The villages were mapped and study numbers assigned to each household. A baseline survey of the nearly 25,000 households in the sample villages was conducted from March 2004 through September 2004 by Mitra and Associates to retrospectively determine the study villages IMR and NMR, enroll consenting women between the ages of 12 and 50, and initiate a system of quarterly household surveillance to identify pregnancies in these women. All consenting women were advised of the follow-up interview schedule (neonatal, and quarterly though the infants first birthday thereafter). At each follow-up, women were again asked if they consented to interview. Mitra and Associates then continued the quarterly household pregnancy identification for fifteen months to achieve enrollment of 4,000 live newborns. Women, particularly primiparous women, commonly deliver at a relative's house and later return to their own village. The sample, however, only includes consenting eligible women who were identified as living

in the household during the baseline survey. Newborns were followed up at 30 to 45 days to record vital events, reported morbidity, nutritional status (i.e., newborn weight, head and arm circumference, maternal postpartum weight), breastfeeding, STS, sleeping contact, contact with the community based workers and others, and health care utilization. Socio-demographic and reproductive health information was collected at baseline or as possible, at later pregnancy identification from consenting women for whom this information was not previously obtained. Data were directly recorded into MS Access databases on handheld computers and immediately reviewed for inconsistencies in MS Excel programs to prompt their resolution prior to departure from the household, which facilitated monthly transfer and review of data. All presented results are unadjusted except for the outcome data (NMR, IMR and subsequent pregnancy) for which analyses are adjusted for cluster design unless otherwise specified. Intent-to-treat bivariate (Chi-square and Student's t-tests for categorical and continuous data, respectively) comparisons and logistic regression analyses adjusted for cluster design effect were conducted to test the effectiveness of CKMC on NMR and IMR, birth weight specific NMR and IMR, and incidence of subsequent pregnancy. Odds ratios from logistic regression analyses using generalized estimating equations (GEE) with robust variance estimation in adjusted to account for design effects due to stratification and clustered allocation that represent the effect of CKMC as implemented in the study are presented on all outcomes (NMR, IMR and subsequent pregnancy). Odds ratios of less than one represent a preventive effect (for example, an odds ratio of 0.85 indicates a 1-.85 or 15% preventive effect). Upper and lower 95% confidence intervals that jointly do not surpass the value of 1 indicate a statistically significant result (i.e., $p \leq 0.05$). Two-tailed statistical significance is presented for all study group comparisons. In addition, a small (n=47), representative qualitative study was conducted in a sub-sample of women to further elucidate the factors that prompted and inhibited provision of different aspects of neonatal care, including those associated with CKMC. This qualitative study was not powered to determine significant differences between study groups and was implemented in an unsystematic manner. A nested study of in-depth interviews was subsequently conducted (described below).

At the completion of the baseline survey, groups of 6 to 22 community based nutrition promoters and their supervisors participated in one of five CKMC training sessions held over a period of two months. In total, 63 community-based nutrition promoters and their supervisors serving the 21 intervention group villages were taught CKMC by the BRAC project coordinator and a BRAC supervisor using a training manual and procedures that were modified by the BRAC project coordinator from those used in the pilot study. These modifications included replacing experienced trainers who were to provide initial short term intensive training of community workers followed by monthly retraining with the full time engagement of supervisors (individuals with previous experience in data collection) and some unplanned emphasis on provision of CKMC for low birth weight (LBW) babies in the training and later in supervision by various supervisors. The planned training process documentation was not conducted by the BRAC project coordinator, thus there is little quantification of the extent or impact of these modifications beyond that obtained by the nested in depth study. All 122 community nutrition promoters serving the study villages were separately (by intervention or control

group) standardized in measurement of birth weight. All received a small monthly compensation (approximately $7.50 a month) for collecting newborn weight, a standard duty under the National Nutrition Programme except for the instruction that newborn weight be measured as soon as possible and within 72 hours of birth. To avoid implementation bias between the study groups, no additional compensation for teaching CKMC was provided to the nutrition workers. Local BRAC activity monitoring in May-June, 2005 found the nutrition workers had increased government chores under NNP than they had under BINP, thereby not meeting their originally planned availability and participation. To make implementation as close to that planned as possible for the remainder of the study, 35 part time BRAC school teachers and community workers with similar qualifications to the nutrition promoters were employed and trained to teach CKMC for the last six months of the study. The teachers were also paid $7.50 per month to supplement the community nutrition workers in the intervention villages. At that time, two experienced trainers participating in the pilot study were temporarily (for a period of 3-4 months) integrated into the study (one on a full and one on a part-time basis) as planned to lead the monthly refresher training sessions, and the BRAC project coordinator was replaced. Refresher CKMC training and birth weight standardization which had been conducted sporadically for the initial six months of the study, was provided monthly for the final nine months of intervention as planned.

As discussed below in the results section, the randomized controlled cluster trial (RCCT) found CKMC significantly lowers 63% of mortality in newborns weighing ≤2000 grams at birth, but there was no difference in total sample (overall) NMR or IMR between CKMC and control group babies. The observed lower NMR in small babies may reflect a concentration of CKMC benefit in those most likely to be premature, unplanned but reported local emphasis of CKMC for small babies and other potential weaknesses in the trial's CKMC training and intervention delivery, or bias in missing birthweight availability. For example, given the observed association between duration of skin-to-skin care in the first two days of life and neonatal mortality, had 69% (instead of the observed 24%) of women in the trial held their babies skin-to-skin ≥7 hours/day in the first two days of life (69% was observed in the pilot study), a reduction in overall NMR of ≥40% would be expected. Slightly more CKMC babies delivered in health care facilities and they had an unexpectedly higher NMR than institutionally-born control group babies. Thus the first of the two study DSMB meetings recommended that new information was necessary to better understand the implementation process and to improve the CKMC manual to attempt to overcome potential weaknesses.

In response to this recommendation, a nested study of in-depth interviews in a sample of CKMC group mothers of the 93 babies dying in the newborn period, a village, (±1) month and place of birth matched CKMC survivor (n=93), a similarly matched CKMC institutionally born survivor (n=21), the mothers of the 8 institutionally born control newborns who died and 3 matched institutionally (n=24) and 3 matched community (n=24) born survivors was conducted. The information was collected to determine: 1) the extent of, mechanisms and messages to overcome neonatal illness prior to death or postpartum weakness deterring CKMC, 2) the messages women received regarding provision of CKMC and interactively identify messages to improve CKMC

implementation, and 3) the extent to which a chance differential in pregnancy complications and/or delay in care seeking accounts for the unexpected elevated NMR in CKMC institutionally born babies and mechanisms to prevent this. The information is being used to modify the generic CKMC manual to ensure the best CKMC implementation (and thus effect) possible.

All data collection for the trial and nested in depth interviews, including attempts to obtain missing birthweight data, was completed by June 30, 2007.

RESULTS

Study Group Comparability

Of the nearly forty thousand age-eligible women (12 – 50 years old) living in the study villages at the time of the baseline survey, 35 (0.1%) refused participation in the baseline survey. The study groups are basically similar, although the stratified allocation of unions resulted in some geographic imbalance between the study groups. Of the eight study villages in Sylhet, only two were randomly allocated to the intervention group and the remaining six to the control group. While the sample villages in Dhaka division are geographically similar to each other, they are somewhat socio-demographically distinct from those in Sylhet division. This imbalance led to small differences in previous neonatal and infant mortality in women who had previously given birth. The baseline survey found NMR in the prior two years was 5.9% overall; 6.1% in the intervention group and 5.6% in the control. The baseline IMR in the prior two years was 7.1% overall; and somewhat different 7.5% in the intervention group and 6.5% in the control. The incidence of stillbirth was 2.8% overall and in the intervention group, and 2.9% in the control group.

During the follow-up period, two women (one in each group) refused any participation and four women (0.1%) refused participation partially through the follow-up period. All liveborn babies were followed up through 28 days of life or through death. All but 5% were followed through 365 days of life. This reflects a much smaller loss to follow-up than expected, likely attributable to careful supervision of data collection and the use of handheld computers which facilitated longitudinal linkage of the data.

In consenting women, 4,325 births were encountered of which 3.7% were reported as stillbirths. The slight geographic imbalance in study group allocation apparent in the baseline survey also led to small differences in socio-demographic and reproductive health indices between the study groups, many of which were statistically significant due to the large sample. For example, 32.0% of women in the control group were assisted by skilled attendants at delivery compared with 36.6% of women in the CKMC group, a difference of only 4.6% but highly significant (p=.002) due to the large sample. Parity was 1.9±1.9 in the control group and 1.7 ±1.8 in the CKMC group (p=.02). The largest differences were observed in religion (86.1% control v. 95.8% CKMC were Muslim, p=.000), proportion ever attended school (66.5% control v. 73.1% CKMC, p=.000) and speaks other language (7.3% control v. 0.5% CKMC, p=.000 as Sylheti dialect is mostly spoken in Sylhet). The effect of these differences is controlled in the logistic regression

analyses adjusted for design effect (presented below), and directly (not presented, as adjustment for design effectively controlled for these differences).

CKMC Behaviors

The incidence of CKMC behaviors (STS, breastfeeding, delayed bathing, sleeping with the baby) was significantly greater in the intervention than control group. There was virtually no intervention contamination between the study groups. Over three quarters (76.9%) of women delivering in the CKMC group reported giving STS ever compared with 0.5% (n=9) women in the control group (p=.000). Sixty-one percent of intervention group women gave STS within 12 hours of birth, however only 23.4% gave STS ≥7 hours per day in the first two days of life (the most critical period, when 61% of NMR occurred). The average hours of STS provision in the CKMC group (including those who never gave STS) was less than ideal; 4.5±4.8 in the first 2 days of life, 2.7±3.4 in the next 5 days of life, 1.2±2.4 in the second week of life, and 0.5±1.4 hours in the remainder of the first month of life. The greatest predictor of STS was the frequency of contact with the community-based nutrition promoter in the last month of pregnancy. Women in the CKMC group had 6.0±7.5 contacts with the community nutrition promoters/teachers in the last month of pregnancy compared with 3.1±6.3 contacts in the control group. In the CKMC group, 87.3% of women who had contact with the community-based nutrition promoter/teacher in the last month of pregnancy reported providing skin-to-skin care. Women's reports verify that community nutrition promoters serving the intervention group villages discussed breastfeeding (64.8% CKMC v 16.7% control), how to hold the baby (71.6% CKMC v. 0.2% control), cleaning the baby (64.6% CKMC v. 9.3% control) and sleeping with the baby (64.5% CKMC v 1.9% control) with significantly more pregnant women than those serving the control group (all p=.000). However, 55.4% of women reporting no contact with the promoter/teacher in the last month of pregnancy or first month postpartum reported providing STS; 91.8%% of those not reporting contact but providing STS had received the CKMC message reminder leaflet. In the small sample of CKMC mothers providing qualitative interviews, one third reported teaching KMC to others, and 30% of those mothers taught more than one other woman. All who taught KMC to others taught them about STS and to avoid complementary fluids.

Women in the CKMC group also initiated breastfeeding sooner after birth (5.1±11.2 hours v. 8.5±15.3) than those in the control group (p=.000). Mothers in the CKMC group reported first bathing their babies by immersing them in water at 5.7±5.9 days after birth compared to 2.0±2.4 days after birth in the control group (p=.000). As with traditional hospital-based KMC, fewer mothers (38.4%) reported sleeping STS with their babies than providing STS in the CKMC group (only 0.1%, i.e., 2 mothers reported doing so in the control group, p=.000).

Growth and Morbidity

There was no difference in the babies' weight, head or arm circumference or in reported morbidity at the 30-45 day follow-up, except that fewer CKMC than control babies were reported to have become pale (0.4% v. 1.1%, p=0.018). Throughout infancy, more CKMC babies were reported to have experienced diarrhea (43.6% v 39.3%, p=.006); while statistically significant, the absolute difference is small and may reflect that

mothers who hold their babies skin-to-skin observe and report more occurrences, particularly those that affect their body and cleanliness. Mothers of CKMC babies reported less postpartum bleeding (73.3% v. 76.8%, p=.039), possibly a consequence of more immediate breastfeeding as lactation stimulates maternal production of oxytocin which stimulates uterine contraction and could reduce postpartum blood loss.

Newborn Mortality

The incidence of neonatal mortality (death from birth through 28 days of life) was 4.6% in the CKMC v 4.3% in the control group (p=0.68) and virtually the same when adjusted for design effect. The slightly higher rate in the CKMC group reflects differences in baseline NMR (CKMC 6.1% v control 5.6%, p=0.68). There was virtually no relative difference between study groups in NMR change since baseline (25% lower NMR in the CKMC group and 23% lower NMR in the control group, p=.048 due to the large combined sample). There was a non-significant 7% lower (OR=0.93, 95% ci 0.53-1.63) NMR among those delivering in their own home and 13% lower NMR (OR=0.83, 95% ci 0.54-1.28) in women delivering in their own or others homes, which may provide estimates of CKMC efficacy (effect under more ideal circumstances) compared to effectiveness (under more real life circumstances).

A high incidence of missing birth weight in babies who die is expected as much NMR occurs on the first day of life (61% in this study) and it is generally culturally unacceptable to measure the weight of babies born at home after demise in rural Bangladesh. Birth weight is also relatively unavailable from women who did not deliver in their own village and for institutional deliveries. In Bangladesh, when newborn weight is measured it is also often obtained after the date of birth when it is more culturally acceptable for families to permit outsiders in the home. As newborn weight loss is observed in most countries under most conditions,[1] weight measured within 7 days of birth was modeled using internal (study) data to adjust for initial postnatal weight loss and subsequent weight gain in the first week of life. Too few data in the next few days of life were available to reliably model weight on the day of birth beyond 7 days of age. Weight was measured within 7 days of birth in 59.0% of CKMC and 54.2% of control group live born babies (p=.002), and on the day of birth in only 23.7% of CKMC and 18.5% of control babies. In babies who died in the neonatal period, weight was measured within 7 days of birth for 33.0% of CKMC babies compared with 38.6% of control babies (p=.42). In those whose modeled weight was ≤2000 grams at birth (the usual eligibility criteria for hospital-based KMC), NMR was 9.5% in the CKMC group compared with 22.5% in the control group, representing an unadjusted 64% lower NMR (p=.024). NMR was 63% lower in the CKMC group in analysis adjusted for design effect (OR=0.37, 95% ci 0.16-0.86; p=.020) that mitigates the effect of confounding (baseline dissimilarities between study groups) and sampling, but which cannot overcome bias. In those for whom newborn weight was ≤2000 grams as measured on the day of birth, NMR in the control group was 23.7% compared with 12.5% in the CKMC group (OR=0.44, 95% ci=0.19-1.00; p=.05), very similar to the modeled birthweight results. The difference in

[1] Although there are a few small studies in low birthweight, breastfeeding populations that have found no postnatal weight loss, which is subdued in low birthweight and breastfed infants.

availability of birth weight data between the study groups may reduce the validity of the results. Similarity of effect in those with modeled weight and weight measured on the day of birth is reassuring (the latter are statistically significant even though few babies were weighed on their day of birth) and indicates there is little bias in the modeling of birth weight from weight obtained in the first seven days of life. However the extent of missing birthweight and the between study group bias in the availability of weight within 7 days of birth may affect the magnitude and statistical significance of the observed effect. It is difficult to determine the extent or direction of the bias in birthweight data. More CKMC babies had birthweight in general and on the day of birth, which would indicate an underestimate of effect. However in those who died in the neonatal period, fewer CKMC babies had measured birthweight, indicating an overestimate of effect. Modeling birthweight from subsequent newborn and infant weight has been suggested to better estimate the effect of CKMC on NMR in small babies. In the intervention (CKMC) group, NMR was concentrated in those who did not receive STS in the first 2 days of life (58.3% of CKMC newborn deaths) and only five (6.0%) of CKMC newborn deaths occurred in those receiving STS≥7 hours per day. The association between daily duration of STS and NMR is smaller but persists as strong even after removing deaths occurring in the first hour or on the first day of birth (deaths that likely have etiology unassociated with gestation and birthweight and may be less or unresponsive to CKMC).

Rates of institutional delivery were similar between the study groups (CKMC 14.9% v control 13.4%, p=.16). However, in those delivering institutionally, NMR was unexpectedly nearly twice as high, 7.5% in the CKMC compared with 3.3% in the control group (p=.03).

Infant Mortality

Similar to NMR, IMR was slightly higher, 6.6% in the CKMC group compared with 6.3% in the control group (p=0.70), but unlike NMR a larger reduction in CKMC IMR since baseline was observed. IMR was 7.5% in the CKMC (13% relative reduction) compared with 6.5% (3% relative reduction) in the control group (p=.000). There was a non-significant 2% lower (OR=0.98, 95% ci 0.68-1.51) infant mortality rate among those delivering in their own home and 9% lower (OR=0.92, 95% ci 0. 62-1.35, p=0.67) in women delivering in their own or others homes, which may provide estimates of CKMC efficacy (effect under more ideal circumstances) compared to effectiveness. In those weighing ≤2000 grams at birth, IMR was 18.0% in the CKMC and 27.5% in the control group (OR=0.56, 95% ci 0.30-1.05, p=0.07), indicating that some of the deaths potentially averted in the neonatal period occurred (were deferred to later) in infancy. This weight specific analysis suffers the same weaknesses and potential biases associated with missing birthweight of the NMR analysis, discussed above. In institutional deliveries, IMR continued to be higher, though considerably less so than with NMR, in CKMC than control group babies. IMR was 38% higher in CKMC than control group babies born in health care institutions (OR=1.38, 95% ci 0.74-3.75, p=0.22).

Subsequent pregnancy

We posited that, in the absence of intervention, the rate of subsequent pregnancies within one year would be 4%. The observed rates were higher, with 7.1% of CKMC and 7.2%

of control group mothers experiencing subsequent pregnancy within one year of the first study enrolled pregnancy (OR=0.97, 95% ci 0.76-1.23, p=0.80). This represents a 3% (not statistically significant) lower rate, whereas this rate was expected to be 37.5% lower in CKMC than control mothers had CKMC improved newborn and infant survival as hypothesized. Slightly more CKMC mothers reported using contraceptives within that period (54.2% CKMC v. 50.0% control, p=0.009). Excluding women who used contraception in that time, 4.5% of CKMC and 3.3% of control group mothers experienced subsequent pregnancy within one year of the first study enrolled pregnancy (OR=1.31, 95% ci 0.79-2.17, p=0.29). In those using contraception, CKMC mothers were less likely (though not statistically significantly so) to become pregnant within 12 months (OR=0.76, 95% ci 0.50-1.15, p=0.20).

Nested In Depth Study to Clarify Results

The in depth study's first objective was to determine the extent of, mechanisms and messages to overcome neonatal illness prior to death or postpartum weakness (reverse causality) deterring CKMC. The data indicate that 37% of CKMC group mothers whose newborns died did not provide STS because the baby died too soon after birth. Death soon after birth also accounted for 16% of CKMC group mothers whose newborns died providing <7 hours STS in the first 2 days of life. Similarly, neonatal illness shortly after birth deterred 31% and 16% of mothers whose newborns died from providing STS ever or ≥7 hours' in the first 2 days of life. Postpartum maternal illness or weakness (and other factors such as having chores to do) seemed to deter more mothers of surviving newborns than those whose newborns died from providing STS. Postpartum illness or weakness was commonly sited as a reason for not providing (47%) or providing <7 hours skin-to-skin care in the first 2 days of life (50%) in mothers of surviving newborns and was respectively reported by 20% and 40% of CKMC mothers whose newborns died for not providing STS or providing it <7 hours skin-to-skin care in the first 2 days of life. CKMC group mothers felt that explicit messages encouraging women to provide CKMC to all babies, whether ill or well, and encouraging women, whether weak or well, to provide STS immediately and consistently (24 hours a day), and explaining the potential benefits to mothers and their babies will convince women to give CKMC properly.

The in depth study's second objective was to elicit the messages women received regarding provision of CKMC and interactively identify messages to improve CKMC implementation. Only 36% and 37.5% of CKMC group mothers of newborns who did not and did survive, respectively, were taught to provide CKMC to babies that were ill. Twenty-six percent to 30% were erroneously taught to breastfeed on schedule (not on demand), 35%-38% were erroneously taught that STS was to be provided to LBW or premature (not to all) babies, and only 29%-31% were correctly taught to hold STS all, including average size or large babies. The open-ended qualitative segment of the interviews revealed women had numerous views about the number of daily hours women should provide STS, when women should stop STS, and which babies should be given STS. This reflects the study's quantitative data that indicate women received various (not standard and frequently incorrect) messages from the community workers and supervisors teaching them CKMC.

The in depth study's third objective was to determine the extent to which a chance differential in pregnancy complications and/or delay in care seeking accounts for the unexpected elevated NMR in CKMC institutionally born babies and mechanisms to prevent this. The trial found that CKMC newborns born institutionally had twice the NMR of control group babies (p=.03). While the illness of 11% control group newborns who died started during birth, compared with none in the CKMC group, more CKMC newborns who died started having problems after the first hour of birth (34% in the control and 50% in the CKMC groups). There was no difference in the percent of women whose newborns died whose institutional delivery was unplanned. However, in the small group of those born in health care facilities who died in the newborn period, 85.7% of control group and 100% of CKMC group mothers reported having had pregnancy complications (p=.093). In this group, CKMC women took ~1.5 days longer to recognize they had a problem and nearly a day longer to decide they needed to seek health care. However, for those who sought care, CKMC mothers sought treatment ~ 0.75 days earlier, had slightly shorter times to reach and receive care and reported their babies were ill on average 1 day less before death than the control group. Most importantly, in the trial, 24.4% of CKMC mothers whose newborns died sought care and delivered in health care facilities compared to 9.4% (p=.009) in the control group.

CONCLUSIONS/DISCUSSION

This study is the first to demonstrate the impact of CKMC on newborn and infant survival and on subsequent pregnancy. The sole effect observed was that in newborns weighing ≤2000 grams at birth. The result demonstrates a strong, statistically significant, biologically and temporally plausible lower neonatal mortality that is consistent with results from two African studies of early ("birth") KMC conducted in hospitals with limited neonatal intensive care capacity. Lincetto et al (2000) found an 86% reduction in 24 hour mortality in a small sample of babies ≤1800 g at birth in a hospital with almost no neonatal intensive care capacity. Worku and Kassie (2005) found a 33% reduction in mortality through hospital discharge associated with early KMC (however neonatal care capacity was not described and mean age at discharge and other important study group differences were not controlled in analysis). However, both studies have methodologic flaws that challenge their validity.

We attempted to clarify the results as per the recommendations of the DSMB by conducting the nested in depth study. Based on the information obtained in the in depth study, the CKMC manual was modified (Appendix 3) to best ensure implementation and effect, however further methodologically rigorous evaluation is necessary to ensure adequate implementation and effect.

In light of the extensive missing birthweight information and its potential bias, the study's data safety and monitoring board, investigators and journal reviewers conclude that the existing evidence of benefit based on the observed lower NMR among babies weighing ≤2000 grams at birth is insufficient to justify implementation of CKMC at this

point in time. This conclusion takes into account the results of the two small African studies and what is known from a subsequent study of CKMC and other essential newborn care interventions in India (Vishwajeet et al, 2006). Estimating missing birthweight by statistical modeling of the study's data may help clarify the results. Further experimental evaluation ensuring baseline similarity of study groups and complete, reliable assessment of birthweight is necessary to determine whether CKMC improves survival. CKMC training or taking CKMC to scale at this time is ill-advised before establishing its benefits and optimal methods of implementation. Suboptimal implementation (where the majority of women provide less than seven hours a day of skin-to-skin care in the first two days of life and possibly early discontinuation of skin-to-skin care) results in no overall benefit. If CKMC, which quickly becomes popular, is set in place in a manner that is ineffective, it will be difficult or impossible to improve implementation and effect at a later date.

There was some concern at the final DSMB meeting that the excess NMR in the CKMC group who delivered in hospitals or clinics might reflect a sense of false confidence in CKMC and consequential delay in seeking care. The nested in depth information indicates that, in those whose babies died in the newborn period, CKMC mothers on average actually sought care earlier than control mothers because so many more CKMC than control group mothers whose newborns had problems and died sought and received institutional care for delivery.

DATA SAFETY AND MONITORING BOARD MEETINGS

Two data safety and monitoring board (DSMB) meetings were held by the Principal Investigator. The DSMB includes the chair, Dr. James Tonascia (biostatistician/trial specialist), Johns Hopkins University, Dr. Paul Hewett (political/social scientist), Population Council, Dr. Ana Langer (neonatologist and researcher), Engender Health and Dr. Kayode Oyegbite (health policy expert and epidemiologist). The first DSMB was held in January, 2006, and the final DSMB meeting was held in June, 2007. The two DSMB reports are attached in Appendices 1 and 2.

DISSEMINATION

A. Presentations

April 2006: Columbia University Epidemiology Seminar, New York. Audience ~60: Public health faculty, students and guests.

May 2006: Pediatric Academic Society, San Francisco. Audience ~60: International pediatricians and neonatologists.
Population Council, New York. Audience ~30: Demographic and reproductive health researchers, public relations and staff

June 2006: Global Health Council, Washington, DC: Audience 8 (round table attendees): NGO program managers.
SNL Dissemination, Dhaka. Audience ~25. Audience NGO program managers, pediatricians/obstetricians, researchers working in Bangladesh.

July 2006: South Asia Neonatal Network, New Delhi. Audience ~100. NGO representatives, program managers, neonatologists, researchers from South Asia and elsewhere.

October, 2006: International Kangaroo Mother Care Meeting, Cleveland. Audience ~45. KMC experts, program managers, neonatologists and neonatal nurses, WHO representatives.

March, 2007: Saving Newborn Lives Newborn Health Symposium at the World Bank, Washington, DC. Audience ~250 Essential newborn care experts, program managers, policy makers, donors.

July 2007: Population Council Symposium on Community-based Kangaroo Mother Care, Dhaka. Audience ~70 Bangladesh Ministry of Health, essential newborn care experts, program managers, policy makers, donors.

September, 2007: USAID Asia/Near East meeting on Essential Newborn Care, Bangkok. Audience ~100 (an additional session was requested and held due to demand) Essential newborn care experts, program managers, policy makers, donors.

B. Publications

None. The main neonatal effects article has been submitted and accepted subject to revision. Further minor revisions were requested. The article will be resubmitted before the end of October, 2007.

C. Additional Dissemination Plan

Other manuscripts will be composed and submitted for journal publication.