little marginal benefit with small changes in implementation, but that does not reduce their importance if they are still addressing sizable causes of death. In fact, achievement of high coverage of interventions like immunization increases the plausibility of rapid scale-up of other vaccines or interventions that can be added to the immunization platform, and these effects can be modelled in LiST.

In relation to the past mortality reduction associated with established interventions, we have clearly stated that one of the criteria used for the inclusion of the interventions in LiST was to incorporate those that are not likely to have an impact on mortality because of its current high coverage, but that would probably result in an increase in mortality where coverage levels are not sustained (e.g. measles and Diphtheria, Pertussis and Tetanus (DPT) vaccines). Moreover, we believe that the two figures on ‘estimated lives saved’ and ‘estimated lives lost’ are misleading. The latter shows that lives lost reduces from 97 to 0% in 1 year, while the figure on lives saved presents a slow increase, from 97 to 100% in 5 years. It is unrealistic to model a drop from 97 to 0% coverage of any well-established intervention especially immunizations. In the current version of LiST, if users do lower coverage of an intervention, there is an explicit warning that this should not be done, although the users can ignore the warning and continue with their model run.

Users can obviously make use of the tool in both ways: looking at future and past gains as Steinglass et al. have done. If a lower coverage for a preventive intervention is entered, LiST still gives priority to preventive interventions but some of the possible deaths that have not been prevented are subsequently averted by therapeutic interventions. There is no question that successful interventions that have already reached high coverage and saved an important number of lives not only need to at least maintain but also increase their levels of coverage. However, there are still about 9 million children under 5 years, including almost 4 million babies <28 days of life, dying every year, even with the high-level coverage of such interventions. There is an imperative need to focus on what more can be done to save these millions of lives. For example, it is urgent to set clear and achievable targets, estimate the likely impact of different interventions and delivery channels, implement effective strategies and monitor progress of their achievement, according to the needs and availability of interventions in different settings. There is need for flexibility and specificity; not for the one-size-fits-all models or packages. This is what LiST is designed to facilitate. Consideration of the costs of interventions is also important. As stated in at least two papers included in the series,2,3 work is underway to include costing modules in the tool, which will allow for the estimates of cost-effective interventions as well as for the costs of increased coverage of specific interventions in different scenarios. In fact, in the current version of LiST one can output data files that can be read into the Marginal Budgeting for Bottlenecks software (MBB) that allows one to link the coverage and deaths averted estimates from LiST to MBB for costing and bottleneck analysis.

References

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Comment on: ‘Kangaroo mother care’ to prevent neonatal deaths due to pre-term birth complications

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Kangaroo mother care (KMC) is a promising way to prevent a portion of neonatal mortality associated with prematurity and infection. Lawn et al.,1 have conducted meta-analyses to summarize the available
information on the effects of KMC in the first week of life, called ‘early KMC’ (EKMC) in pre-term babies (weighing ≤2000 g at birth). Meta-analysis, with its summary and simple to understand statistics and user-friendly free software to conduct the analyses, has become progressively more popular. At the same time, meta-analysis has become increasingly misused, conducted in a manner that opposes its basic tenet by aggregation of incomparable studies.

Regrettably, the meta-analysis by Lawn et al. is an example of aggregating incomparable data and drawing definitive conclusions in the absence of definitive data. The first step in conducting a meta-analysis is to clearly define the PICO (Patient, Intervention, Comparison and Outcomes) criteria. The studies included in these meta-analyses follow the PICO format, but only superficially. The significant deviations from the PICO criteria essentially render the articles inappropriate for aggregation, negating the validity of the meta-analyses and their conclusions. None of the studies was designed to be statistically powered to measure the effects of EKMC on neonatal mortality. Neonatal mortality is defined in the literature as death occurring within the first 28 days of life. The patients are neonates, yet they were neither systematically ≤2000 g at birth nor systematically eligible to receive EKMC (the PICO criteria of patient and intervention). Neither were the babies systematically followed through the neonatal period, 28 days of birth (the PICO criterion of outcome). Comparability between the experimental (KMC) and control groups is the real meaning of the PICO criterion of comparison, not simply that a comparison group exists. However, many of the study groups are not comparable. Further, the article’s quality assessment grade table (Table 3) does not provide the standard Cochrane Review information about the methodological quality of each study. These criteria include random assignment method, adequacy of allocation concealment, selection, attrition, performance and detection bias.

**Meta-analysis of mortality in randomized controlled trials**

Lawn et al. excluded neonates who did not initiate KMC in the first week of life. Charpak’s study of traditional KMC was included in this analysis. Regarding their PICO intervention criterion, Charpak et al. state, ‘Major problems of adaptation to extrauterine life were overcome at a median postpartum age of 4 days (95% confidence interval [CI]:3–5)’. Using similar eligibility criteria, three studies, Sloan et al. (Ecuador), Charpak et al. (Colombia) and Cattaneo et al. (multi-site) are the sole soundly designed and statistically powered studies to assess the effect of traditional KMC on neonatal and infant morbidity (not mortality), and as such are appropriately included in the Cochrane Review meta-analysis of traditional KMC. The exclusion of the only other published studies included in the Cochrane Review by Conde Agudelo et al. cannot simply be that KMC was, on average, started later in these trials, because KMC was also started later for many of the babies in Charpak et al. Babies from the Ecuador and multi-site trials who were KMC eligible in the first week of life are as valid for inclusion as their counterparts in Charpak et al. Lawn et al. state their concern that the inclusion of the Ecuador and multi-site studies will produce an estimated risk ratio closer to that of no difference. Surely, studies cannot be selected or excluded from meta-analysis because one likes or dislikes the results.

The outcome, neonatal death, is defined as death in the first 28 days of life. However, the study by Worku and Kassie followed neonates only through hospital discharge, not through 28 days of life, and thus could not, even if asked, provide the outcome information required by PICO. Although the neonatal mortality rate (NMR) is highest in the first few days of life, a considerable amount occurs later in the neonatal period. Lawn et al. state that 75% of newborn mortality occurs in the first week of life, but this is extremely variable. Studies that do not follow neonates through 28 days of life are different from those that do. Yet, in Worku’s and Kassie’s study, duration of hospitalization and observation of NMR was nearly one-fifth shorter in the EKMC (4.6 days), than control group (5.4 days). Logic is not an acceptable substitute for observation. In the absence of observation through 28 days of life, the number of neonatal deaths experienced in the EKMC and control groups is unknown. EKMC or conventional care, or both, could have deferred rather than prevented mortality within the neonatal period. Substantial deferral of death beyond the neonatal but within the infant period was evident in Charpak’s cohort of babies initiating KMC in the first week of life, with 8 control and 15 KMC post-neonatal infant deaths.

Excellent similarity, PICO’s comparability, of study groups within studies, is a basic tenet and key requirement for including a study in a meta-analysis. In Worku and Kassie, the study groups have important dissimilarities such as known gestation, age at admission and the proportion of infants with birth weight ≤1200 g, which was 7/22 (32%) in the KMC and 5/10 (50%) in the control group. Logically, this would imply the EKMC babies were at substantially lower risk of NMR than the control babies. However, logic is just an assumption and cannot replace observation for ascertainment of knowledge. The initial, observational study of Rey and Martinez suffered this type of incomparability, where their control group included stabilized and unstable babies, all weighing ≤2000 g at birth and born in the year before KMC was introduced at the
Maternal Child Institute in Bogotá. Their intervention group included only stabilized babies deemed eligible for KMC weighing \( \leq 2000 \text{ g} \) at birth born in the year after KMC was introduced. Thus, they compared a group of stabilized and unstable babies (i.e. survivors and non-survivors) with a group of stabilized babies (i.e. mostly survivors) and found a difference in survival.

Charpak provided the authors with data on their entire cohort of 746 infants and on a cohort of 332 babies. The Figure 2a description indicates that only babies eligible to initiate early KMC were included from Charpak’s data.\(^3,4\) However, it is difficult to determine which data were used because the meta-analysis does not present the standard information, including the sample size of each study group for each included study. The information provided in Figure 2a does not explain how the Worku and Kassie study\(^8\) accounts for 71.17% of the subject weight contribution with a much smaller sample \((n = 123)\) than that of Charpak et al., which only accounts for 15.10% of the subject contribution. This weighting gives disproportionate influence to smaller but more statistically significant differences in mortality observed by Worku and Kassie\(^8\) and under-counts the larger, but more variable and thus less statistically significant, difference in mortality in Charpak’s data.\(^3,4\) This raises the question of why Worku and Kassie’s study was weighted this way.

However, it may be argued that none of the randomized controlled trials (RCTs) of traditional KMC (a different intervention) should be included in any analysis of early KMC because subsamples of study participants can be biased. Comparability of baseline characteristics is attained when the full study sample is enrolled. Randomization blocked on important participant characteristics, such as that implemented by Charpak et al.,\(^3,4\) reduces but does not remove the bias incurred by retroactive exclusion of study subjects. For this reason, limiting neonates to those eligible for EKMC does not fairly reflect the survival effects of studies designed to evaluate EKMC.

The referenced Udani poster,\(^10\) which provides no information on study group comparability, sample size per study group or NMR, reports on neonates weighing \( \leq 1800 \text{ g} \) at birth, representing neonates with higher NMR than those weighing \( \leq 2000 \text{ g} \) at birth, and thus superficially but not satisfactorily meeting the PICO patient criterion. If this study was otherwise qualified, it could have been retained, however, by creating a separate outcome for neonates weighing \( \leq 1800 \text{ g} \) at birth.

We agree with the decision by Lawn et al. that the Bangladesh community-based RCT\(^11\) has important limitations, and we support its exclusion from the meta-analyses. In-patient (hospital) EKMC, where babies promptly have access to some formal and stabilizing neonatal care, is a profoundly different intervention from community-based KMC (CKMC), where babies have no access to immediate formal and stabilizing care (other than KMC). Exclusion of the community-based RCT is also merited by incomplete assessment of birth weight, but not incomplete assessment of vital status. Vital status was obtained in \( > 96\% \) in the total sample and \( > 95\% \) in those weighed within 7 days of birth, comparable with the best of longitudinal studies.\(^11\) In contrast, quality was not systematically moderate to high in the RCTs that Lawn et al. included in their meta-analysis. In the Suman Rao et al. report,\(^12\) loss to follow-up in the control group was 34% of their eligible 112 subjects compared with 10% of the 108 eligible in the KMC group. As previously noted, although it may be argued that the loss to follow-up in the control group infers it is likely that even more deaths were not identified in that group, in fact these babies were not followed and their vital status is unknown. While attrition bias is discussed as a study limitation, such an extent of incomparability at follow-up would exclude this study from any sound meta-analysis of NMR.

Meta-analysis of morbidity in RCTs

Contrary to their correct exclusion in the analysis of mortality, both the Sloan et al.\(^5\) and Cattaneo et al.\(^6\) trials were then inappropriately included in the Figure 2b morbidity analysis. This was inappropriate because the data were not limited to those eligible for KMC in the first week of life (different interventions). This might be an example of including data in the meta-analysis because the data agree with the authors’ desired results. The Rao\(^12\) and Udani\(^10\) data do not merit inclusion in the analysis for different reasons—they do not meaningfully meet the patient or comparison criteria as previously discussed.

Meta-analysis of mortality in observational studies

The study of Lincetto et al.,\(^13\) included in the meta-analysis of observational studies, observed mortality for an abbreviated, albeit at least standard, period of 24 h and does not meet the Outcome criterion. Lincetto et al.\(^13\) report on neonates weighing \( \leq 1800 \text{ g} \) at birth and Kambarami et al.\(^14\) report on neonates weighing \( \leq 1600 \text{ g} \) at birth, e.g. neonates with higher NMR than those weighing \( \leq 2000 \text{ g} \) at birth, thus superficially but not meaningfully meeting the PICO patient criterion. Comparability of study groups is rarely met in small studies and not met in Lincetto et al.,\(^13\) with 22 neonates in the KMC and 10 neonates in the control group. Meta-analysis of observational studies is in itself almost a contradiction in terms because observational studies, particularly small ones, rarely achieve adequate comparability of study groups (the comparison criterion) because the subjects are not randomized to groups. For this reason,
observational studies using a historical control group such as the before and after study of Pattinson et al.\textsuperscript{15} should not be included in meta-analyses. Better survival of babies weighing 1000–1999 g at birth far beyond that expected with change over time has been observed in various before and after studies of EKMC.\textsuperscript{16} However, extremely large temporal swings in mortality of babies weighing 1000–1999 g at birth have been observed elsewhere without any such intervention.\textsuperscript{17} Large numbers of subjects do not always compensate for other methodologic limitations.

### Misinterpretation of study statistics

The conclusions by Lawn \textit{et al.},\textsuperscript{1} that early KMC substantially reduces neonatal mortality among hospital-born infants weighing \(\leq 2000\) g at birth, are based upon statistics of an invalid aggregation of data. Saving Newborn Lives sent a mass e-mail on 10 April 2010 summarizing the findings as ‘Kangaroo Mother Care [not Early KMC] cuts newborn mortality [not pre-term] in half’. The studies included in the meta-analyses of mortality refer only to EKMC in the first week of life and only to mortality experienced in pre-term babies weighing \(\leq 2000\) g at birth. Even if EKMC reduced pre-term newborn mortality, it will not reduce all pre-term newborn mortality. Only a portion of newborns weighing \(\leq 2000\) g at birth are typically considered eligible for EKMC. For example, only 62.5\% of neonates weighing \(\leq 2000\) g at birth were considered eligible for EKMC in the report of Rao \textit{et al.}\textsuperscript{12} Over one-third of babies weighing \(\leq 2000\) g at birth in that study were never considered eligible for EKMC.

Meta-analyses also do not provide an effect that is globally generalizable. For example, 28\% of neonates weighing \(\leq 2000\) g at birth in Charpak \textit{et al.}\textsuperscript{3,4} and 47\% in Sloan \textit{et al.}\textsuperscript{5} were ineligible for study at all, excluding most neonates who died in the first few days of life. Babies ineligible for study include those who were considered too unhealthy for KMC. Consistency of direction (e.g. positive effect) across studies and analyses is one of various epidemiologic criteria to judge the causality of an association.\textsuperscript{18} Although Lawn \textit{et al.} observed consistency across studies, this observation might reflect only a biased selection of studies that produce the desired effect.

Study quality matters. The Cochrane Reviews have taken great care to systematically review traditional KMC\textsuperscript{7} and early skin-to-skin (ESTS) care in healthy babies.\textsuperscript{19} They stringently restrict studies eligible for analysis by adequately implementing a PRISMA (the standard) approach.\textsuperscript{20} Only one study is included in most of their analyses due to differences in outcome definition, however slight. Unlike Cochrane Reviews, in general, most outcomes for the comparisons made by Lawn \textit{et al.}\textsuperscript{1} are based on small trials with large biases, and their discussion of possible over- and under-estimation of effect is an inadequate and inappropriate mechanism to attempt to compensate for the mis-aggregation of dissimilar data. One positive and helpful result of this critique is that future meta-analyses can be conducted keeping these points in mind. When studies include incomparable Patients, Interventions and Outcomes, lack internal validity (study group Comparability) or have other serious methodologic limitations, meta-analyses are not a reasonable substitute for ‘old-fashioned’ epidemiologic review. In such circumstances, epidemiologic review can be fraught with complexities and methodologic discussion regarding the caveats of whether a causal association exists.

We agree that EKMC has potential for averting some neonatal mortality associated with prematurity and infection. We wish sufficient evidentiary data existed to quantify and qualify the effects of EKMC in institutional as well as community settings. However, to date, there is no single adequately designed and implemented trial to demonstrate the effect of early KMC on newborn or infant mortality. The mortality benefit of EKMC may prove substantial or limited; however, sufficient data of minimally adequate quality do not currently exist to demonstrate that EKMC reduces mortality compared with conventional neonatal care.

As Lawn \textit{et al.} correctly state, currently there is insufficient evidence to recommend CKMC, and there are many other aspects of EKMC, CKMC and traditional KMC that require further investigation. Adequately designed and statistically powered individual RCTs of early KMC using the CONSORT guidelines,\textsuperscript{21} that can be included in future meta-analyses, are urgently needed to guide policy and programme planning.

### References


\textsuperscript{2} van Loveren C, Aartman IH. [The PICO (Patient-Intervention-Comparison-Outcome) question]. \textit{Ned Tijdschr Tandheelkd} 2007;\textbf{114}:172–78.


We are writing in response to the letter by Sloan et al. regarding our review of ‘Kangaroo mother care’ to prevent neonatal deaths due to pre-term birth complications.1 We are happy to see the ongoing interest in this publication and thank these colleagues for their views follow a standard methodology developed by United Nations colleagues, as well as by external reviewers for the journal, including members of the Child Health Epidemiology Reference Group (CHERG) and investigators, review at meetings of the Child Health Epidemiology Reference Group (CHERG) and by United Nations colleagues, as well as by external reviewers for the journal, including members of the Cochrane Collaboration.

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