Under-five mortality according to maternal survival: a systematic review and meta-analysis
Lana Clara Chikhungu, Marie-Louise Newell & Nigel Rollins

Abstract

Although child mortality has declined substantially since 1990, it remains a global health challenge, especially in resource-constrained settings. About 17 000 children die every day, the majority in sub-Saharan Africa and southern Asia. Socioeconomic status is central to a child’s survival because it affects several relevant maternal and environmental factors, nutritional status and risk of injury. The leading causes of mortality among those younger than five years are diarrhoea, low birth weight, prematurity, neonatal infections and respiratory infections.

In 2013, 2% of global mortality among children younger than five years was attributed to human immunodeficiency virus (HIV) infection in the child. However, the successful roll-out of programmes for the prevention of mother-to-child transmission of HIV has led to fewer infants and children becoming infected with the virus each year. Attention is turning to the health and survival of the large numbers of children born to HIV-infected mothers who are themselves not infected with the virus. Compared with children born to HIV-uninfected mothers, such children still appear to show increased mortality. This may be associated with suboptimal infant feeding, which may be an adverse effect of attempts to prevent mother-to-child transmission and/or a consequence of maternal death or illness or other factors associated with the mother’s HIV infection.

In one review, which examined the effect of parental death on child survival in all settings, maternal death was found to significantly increase the risk of death in childhood and, especially, death in infancy. However, this review did not stratify the children’s levels of survival by parental HIV status, even though this may be an important confounder.

To help elucidate the association between maternal death and the risk of mortality in HIV-uninfected children born to HIV-infected women, we conducted this systematic review. Our aim was to compare, in so-called general populations, the risk of death among children who were motherless as a result of maternal mortality to that of other children. We failed to identify any prior systematic reviews on this topic. Our hope was that the results of our review would help to determine whether the increased mortality reported among children following the deaths of their HIV-infected mothers can be entirely attributed to HIV or might be at least partially attributable to loss of maternal care.

Methods

We conducted a systematic review based on a Population, Intervention, Comparison and Outcome framework. Our aim was to investigate whether, in populations not affected by HIV, maternal death increased mortality among children younger than five years. Our review included both experimental and observational studies – i.e. cohort, cross-sectional, longitudinal and randomized controlled studies – in which the study participants were mothers and children younger than five years from so-called general populations. Death and illness of the mother were considered as separate exposures. The primary outcome was death in children younger than five years. The time interval between the maternal death and the corresponding child death was a secondary outcome measure. We excluded studies that specifically recruited mothers living with HIV, studies that did not provide estimates of mortality for children younger than five years and studies that focused...
systematic reviews
Mortality of motherless young children

Box 1. Database search strategy to find studies on mortality among children younger than five years

Titles and abstracts of articles published in English were searched for the following terms: (((((((“maternal mortality”[All Fields] OR “maternal death”[All Fields] OR “maternal survival”[All Fields]) OR (“mothers”[MeSH Terms] OR “mothers”[All Fields] OR “maternal”[All Fields]) AND vital[All Fields] AND status[All Fields]) OR “mother* death”[All Fields]) OR “mother* survival”[All Fields] OR “parental death”[All Fields] OR “parental survival”[All Fields]) OR “parent’s death”[All Fields]) OR “parent’s survival”[All Fields]) AND (“mortality”[Subheading] OR “mortality”[All Fields] OR “survival”[All Fields] OR “survival”[MeSH Terms])))) AND (((“child mortality”[All Fields] OR “under-five mortality”[All Fields]) OR “child death”[All Fields]) OR “infant death”[All Fields]) OR “infant survival”[All Fields]) OR “child survival”[All Fields] NOT (“hiv”[MeSH Terms] OR “hiv”[All Fields]) AND (“1990/01/01”[PDAT]: “2016/11/30”[PDAT])

Results

Data on maternal and child deaths in publications were captured and summarized using version 5.3 of the Review Manager software package. For each of the studies included in the analysis, odds ratios (OR) and standard errors were either extracted from the published reports or computed from the raw data. Studies with a similar measure of effect, study design and children's age groups were pooled. Random-effects analysis models were used to obtain summary estimates of the children's odds of dying and the corresponding 95% confidence intervals (CI). These results were used to produce a forest plot. Heterogeneity was assessed using the I² statistic and values of this statistic between 50% and 90% were considered indicative of considerable heterogeneity. We conducted a sensitivity analysis by assessing each study’s contribution to the heterogeneity score and its risk of bias. A narrative qualitative analysis was adopted for the relevant studies that could not be summarized through a meta-analysis. The quality of the body of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation criteria and summarized in evidence profiles. The small number of studies included in our review meant that it was not appropriate to use funnel plots to explore the potential for publication bias. However, since the deaths of mothers and children occur naturally, we considered the potential for such bias to be small.

Ethics statement

The study was exempted from ethics review as all the data used had already been published.

Fig. 1. Flowchart showing the selection of studies on mortality among children younger than five years

To evaluate the quality of the included studies, we used a Cochrane tool for assessing risk of bias. In the development of the review and in the preparation of the final manuscript, we were guided by the AMSTAR tool.

Statistical analysis

Data on maternal and child deaths in publications were captured and summarized using version 5.3 of the Review Manager software package. For each of the studies included in the analysis, odds ratios (OR) and standard errors were either extracted from the published reports or computed from the raw data. Studies with a similar measure of effect,
tion on background maternal and child mortality rates obtained from the World Health Organization’s (WHO’s) Global Health Observatory website30 are available from the corresponding author.

The quality of the relevant evidence provided by all seven studies included in our systematic review was initially categorized as low because of the studies’ observational design. The quality of evidence provided by two of the studies27,28 was subsequently downgraded to very low because data from the birth and death registers used may have missed children that were not registered or those that died before they could be registered (available from the corresponding author). All seven studies were considered to have a medium risk of bias because they could not be considered comparable to a well-performed randomized trial (Table 2). No studies could be assessed in terms of the selection of participants, departures from intended interventions or missing data – mainly because death of mother could not be treated as if it were an intervention.

Mortality of children

According to maternal survival

Due to differences in the ages of the children studied, measures of effect and study design, only four studies could be included in the pooled analysis of the odds of dying for children younger than five years.23–26 The results of the meta-analysis are presented in Fig. 2.

For children whose mothers had died, the overall risk of dying before they reached an age of five years was more than four times higher than the corresponding risk for children whose mothers survived (OR: 4.09; 95% CI: 2.40–6.98). However, there was considerable statistical heterogeneity (I²: 83%) between the four studies included in the meta-analysis. In our sensitivity analysis, we found that removal of one study24 from the meta-analysis reduced heterogeneity considerably (I² = 26%) and reduced the corresponding OR – for the death of motherless children before an age of five years, compared with that of other children – to 3.16 (95% CI: 2.27–4.38). However, since there was no difference in the risk of bias across the four studies, we decided to leave data from all four in the final meta-analysis.

It was not possible to undertake a meta-analysis according to the age group of the children involved – e.g. of children younger than six months, younger than

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<th>Table 1. Summary of the seven studies included in the systematic review of under-five mortality according to maternal survival status</th>
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<td>Sear et al.27</td>
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* Participants were randomized to receive or not to receive a nutritional supplement. They were not randomized according to maternal survival.

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<th>Table 2. Assessment of risk of bias in studies on mortality among children younger than five years</th>
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N/A: not applicable.

a The risk of bias assessment with respect to “Selection of participants,” “Departures from intended interventions” and “Missing data” were not relevant to this study due to death of mother not being a typical intervention undertaken by nonrandomized studies.

Note: Risk of bias was assessed using the ROBINS–I tool.16
The odds of child death were highest in the month of the mother’s death (aOR: 12.6; 95% CI: 6.2–25.3).25

Similar findings were reported from Guinea-Bissau.25 In urban Guinea-Bissau, the mortality rate ratio for children whose mothers had died – compared with children whose mothers were still alive – was estimated to be 3.09 (95% CI: 1.27–7.49) over the period from the death of the mother to five months later. If the child was still alive six months after the maternal death, then the child’s subsequent mortality risks were not significantly different from those of children whose mothers remained alive. In rural areas of Guinea-Bissau, the mortality rate ratios over the period from the death of the mother to five months later and from six months after the maternal death were 5.93 (95% CI: 3.44–10.26) and 2.56 (95% CI: 1.29–5.09), respectively.25

**Discussion**

We found only seven papers suitable for inclusion in our systematic review and only four of these were considered eligible for meta-analysis. All of the latter demonstrated that children younger than five years were at an increased risk of death after their mothers died.23–26 Although this pattern was also reflected in the narrative analysis of age-related child mortality, the corresponding pooled estimates could not be made because of the differences in study design.24,26–29 Mortality risks were especially increased for motherless infants younger than six months. The increased likelihood of a child dying, as an apparent consequence of maternal death, was statistically significant among children aged between one and two years but not for children aged between two and four years. Results from two studies strongly indicated that children were more likely to die around the time of a maternal death23,25 than six or more months after the mother’s death.

The increased risk of death we observed for children left motherless in the first six months of their lives may reflect the particular vulnerability of infants32 and explain why maternal sickness in the first six months postpartum may have such serious consequences.32 Mothers who are ill may not be able to provide adequate care for their children – e.g. they may be unable to provide optimal breastfeeding – and this may jeopardize the children’s health and nutritional status.32–35 Premature weaning, which is associated with higher mortality rates, especially for younger infants, may occur.2,23,33,36 In settings where infant survival is highly dependent on continued breastfeeding, the loss of a father may not increase the risk of a child dying to the same extent as the loss of the mother.2,36 Even though adoption and remarriage may protect children left motherless as a result of maternal mortality, the quality of care received by such children may be lower than the care they would have otherwise received from their biological mothers.31,39–41

Although access restrictions prevented us from searching Embase, we believe that our careful search of the CINAHL, Delphis, PubMed and Web of Knowledge databases, our follow-up of the reference lists from potentially relevant articles and our scrutiny of abstracts from a large, international and relevant conference means that we are unlikely to have missed any important publications.

The considerable variation in child mortality risks observed across the studies we reviewed could reflect differ-
ences in background infant and child mortality rates related to demographic, environmental and/or socioeconomic factors and/or differences in the health and social support systems available. The quality of data may also have been variable. Civil registration data in developing countries are often incomplete and may not capture deaths as well as data from demographic surveillance sites. Similarly, historical data – e.g. data from church death registers in developed countries – are likely to have missed pre-baptism deaths. Differences in the methodological approaches followed may also account for some differences in the estimated risks. For example, Sear et al. used multilevel modelling to obtain the median odds of dying within Gambian households while other studies modelled the odds of dying at the individual level. The quality of the data in our included studies also ranged from low to very low. Despite the variations between the studies we investigated, the estimates of increased risk following maternal death were consistent and all in the same direction – even if, in some settings, the small sample sizes may have prevented statistical significance being reached.

In conclusion, between birth and an age of five years, children in so-called general populations who are left motherless as a result of maternal mortality are more likely to die than other children. The vulnerability of these children is highest in infancy, especially in the first six months of life. If the care and nutrition of motherless young children can be targeted by their communities and national health systems, the survival of such children could be improved.

Acknowledgements
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Résumé
Mortalité des enfants de moins de cinq ans en fonction de la survie maternelle: revue systématique et méta-analyse

Objectif Étudier, au sein de la population dans son ensemble, la relation entre la survie maternelle et la mortalité des enfants âgés de moins de cinq ans.

Méthodes Nous avons effectué une revue systématique des écrits publiés entre janvier 1990 et novembre 2016 qui contenaient des données sur la survie des mères et la mortalité des enfants de moins de cinq ans.

Résultats Nous avons inclus sept études dans notre revue systématique. Les résultats montrent que la mortalité chez les enfants de moins de cinq ans est plus élevée chez ceux dont la mère est décédée, surtout dans les premiers mois de vie. La mortalité chez les enfants de moins de deux ans est encore plus élevée, avec une augmentation significative du risque de mort dans les six premiers mois de vie. Ces résultats suggèrent que la mortalité infantile est fortement influencée par la survie maternelle.

Conclusion La mortalité infantile est fortement influencée par la survie maternelle. Les efforts de santé publique doivent être axés sur la prévention de la mortalité maternelle pour réduire la mortalité infantile.
Смертность среди детей в возрасте до пяти лет в зависимости от материнской выживаемости: систематический обзор и метаанализ

Цель: Изучить в рамках так называемых общих групп населения соотношение между материнской выживаемостью и смертностью детей в возрасте до пяти лет.

Методы: Авторы провели систематический обзор литературы, опубликованной в период с 1990 года по ноябрь 2016 года, в которой имеются данные о жизненном статусе матерей и смертности детей в возрасте до пяти лет. Семь исследований были включены в качественный анализ, и четыре — в метаанализ с использованием модели случайных эффектов. На основе материнской выживаемости были получены сводные оценки шансов смерти и была дена оценка статистической неоднородности. Качество включенных исследований и фактических данных оценивалось с помощью Кокрановского инструмента для оценки риска системной ошибки и критериев системы градации качества анализа, разработки и оценки рекомендаций (GRADE) соответственно.

Результаты: Было обнаружено, что у детей в возрасте до пяти лет, чья мать умерла, в 4,09 раза (95%-й доверительный интервал, ДИ: 2,40–6,98) больше шансов умереть, чем у детей с выжившими матерями. По причине неоднородности (I²: 83%) дальнейшее проведение объединенной оценки было невозможным. Для детей, оставшихся без материи в результате материнской смерти, повышенные шансы смертности колебались от 1,40 (95%-й ДИ: 0,47–4,21) до 2,92 (95%-й ДИ: 1,21–7,04) среди детей в возрасте от двух до четырех лет, от 6,1 (95%-й ДИ: 2,27–16,77) до 33,78 (95%-й ДИ: 24,21–47,14) для детей младше одного года и от 4,39 (95%-й ДИ: 3,34–5,78) до 51,68 (95%-й ДИ: 20,26–131,80) для детей младше шести месяцев.

Вывод: Утрачена матери была сопряжена с повышенной смертностью среди детей, особенно когда материнская смерть наступала в течение первого года жизни ребенка.

Resumen

La mortalidad de niños menores de cinco años según la supervivencia materna: una revisión sistemática y un metaanálisis

Objetivo: Investigar, dentro de la denominada población general, la relación entre la supervivencia materna y la mortalidad de niños menores de cinco años.

Métodos: Se llevó a cabo una revisión sistemática de documentos publicados entre enero de 1990 y noviembre de 2016 que registraban el estado vital materno y la correspondiente mortalidad de niños menores de cinco años. Se incluyeron siete estudios en un análisis cualitativo y cuatro en un metaanálisis de efectos aleatorios. Se obtuvieron estimaciones de resumen de las probabilidades de fallecimiento por supervivencia materna y se estimó la diversidad estadística. Se evaluó la calidad de los estudios y las pruebas incluidos utilizando una herramienta de Cochrane para evaluar el riesgo de sesgo y los criterios de la Clasificación de la evaluación, desarrollo y valoración de las recomendaciones (GRADE), respectivamente.

Resultados: Entre los niños menores de cinco años, aquellos cuyas madres murieron resultaron ser 4,09 veces (intervalo de confianza, IC, del 95%: 2,40–6,98) más propensos a morir que los niños cuyas madres sobrevivieron. Debido a la diversidad (I²: 83%), no fue posible realizar más estimaciones combinadas. Para los niños que quedaron sin madre debido a la mortalidad materna, el aumento de las probabilidades de muerte varió de un 1,40 (IC del 95%: 0,47–4,21) a un 2,92 (IC del 95%: 1,21–7,04) en aquellos niños de entre dos y cuatro años, de un 6,1 (IC del 95%: 2,27–16,77) a un 33,78 (IC del 95%: 24,21–47,14) en los menores de un año y de un 4,39 (IC del 95%: 3,34–5,78) a un 51,68 (IC del 95%: 20,26–131,80) en los menores de seis meses.

Conclusión: La pérdida de la madre se asoció al aumento de la mortalidad infantil, sobre todo cuando el fallecimiento de la madre se produce en el primer año de vida del niño.


