Author's response to reviews

Title: Young and vulnerable: Spatial-temporal trends and risk factors for infant mortality in rural South Africa (Agincourt), 1992-2007

Authors:

Benn KD Sartorius (bennsartorius@hotmail.com)
Kathleen Kahn (Kathleen.Kahn@wits.ac.za)
Penelope Vounatsou (penelope.vounatsou@unibas.ch)
Mark Collinson (mark@agincourt.co.za)
Stephen Tollman (stephen.tollman@wits.ac.za)

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Author's response to reviews: see over
**Response to comments - round 2 (Infant paper – BMC Public Health)**

Please note some of the minor, grammatical or spelling changes may not be highlighted or in track changes as they have already been accepted. Additional references and changes have also been included.

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Comments</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom Nkhululeko Gumedze</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td>Carla Machado</td>
<td>Minor revisions:</td>
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<td></td>
<td>I believe that the negative binomial model is not a replacement to the Poisson model, but an alternative to that. Therefore, instead of &quot;The negative binomial is a replacement for the commonly used Poisson distribution&quot; I would say &quot;The negative binomial is an alternative for the commonly used Poisson distribution&quot;.</td>
<td>The methods have been amended as follows (page 6): “The negative binomial is an alternative for the commonly used Poisson distribution, often regarded as the default distribution for integer count data.”</td>
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<td></td>
<td>This is my only point and I congratulate the authors. I believe they made a quite good job in answering all the raised questions.</td>
<td>Many thanks Carla</td>
</tr>
<tr>
<td>James Berkley</td>
<td># Major Compulsory Revisions</td>
<td></td>
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<tr>
<td></td>
<td>Abstract: Results: the main text says that 30% of maternal deaths for infants were due to HIV/TB. The abstract should therefore say '(most commonly due to HIV)' rather than '(mostly due to HIV)'</td>
<td>The abstract/results has been amended as follows (page 2): “Significant risk factors for all-cause infant mortality were mother’s death in first year (most commonly due to HIV),…”</td>
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</table>
Results: under Cause of death (1992-2006), the percentage of the total for the 230 deaths of unknown cause should be given.

Results: I think the graph of the proportion of mothers dying in the infants first year shown in the authors comments to reviewers is very striking and should be included in the article as it shows a clear temporal change in one of the main risk factors for infant death along the causal pathway of HIV.

This sentence now has the following inclusion (page 8): “During 1992-2006, 230 (33.6%) infants had an unknown cause of death.”

Following has been included in the results under “Temporal trends by cause” section (page 8,9): “A significant (IRR=1.14, p<0.001) and striking increase in the mortality rate of mothers dying in the infants’ first year was also observed (Figure 3), again from 1998 onwards.”

The following has been added to the concluding section (page 10):

Conclusions: I think that one key conclusion is
that it is insufficient to think about maternal health and neonatal/infant health separately. Policy should have much more emphasis on interventions aimed at the mother/infant dyad.

19): "From our study, it is clearly inadequate to consider maternal health separately from infant and neonatal health. This is consistent with other studies which showed that maternal health directly affects infants' health [66]. Policy should thus have greater emphasis on interventions targeting the mother-infant pair."


The following addition to the background section has been made (page 4): “Inequalities in health outcomes or access to services and benefits can occur across space and time. In some situations this can reflect a compositional effect with variations merely reflecting the different groups that inhabit different locations [24]. However, certain inequalities in child health outcomes are avoidable and unjust. These may reflect underlying inequities in the distribution of wealth, resources and social privilege in a given society, rather than an individual’s choice or behaviour. To be fair, society must strive to achieve equal opportunities for all children regardless of parental status (education, SES) and geographical location. High-quality services for children that bridge the social divide are an important means of achieving equity goals. If South Africa is to achieve the Millennium Development Goals by 2015, including MDG 4 to reduce child mortality, then there is need to scale-up coverage rapidly with access to high
quality health care and social support, particularly in the most poor and marginalised communities [25]. When population-wide intervention programmes are too costly to implement, it becomes necessary to target such efforts to high risk areas where adverse health events are the most likely to occur [26]. To address inequity in child survival, service planners need to understand the underlying socio-demographic profile and other factors contributing to high risk. Spatial-temporal mapping of high risk communities identifies those with greatest need, rather than those that are easiest to reach [27]. This provides evidence on where to target interventions for greatest impact [28] and generates hypotheses on the determinants of increased risk.”

28. Antunes J, Waldman E. Trends and spatial distribution of deaths of children aged 12–60 months in Sa˜o Paulo,
I feel a significant attempt has been made by the authors to address Dr Macassa’s queries. However, we would add in the same vein that as one of the aims of the study is to identify factors associated with infant mortality risk; access to health care is an important factor as the authors pointed out in the manuscript. However, even more than access to healthcare, presumably by this the authors mean availability of healthcare; quality of the available health care is just as important. This could include level of care and/or whether the care is paid for by the patients (by cash or insurance), subsidised by the government, etc.

Discussion (page 16) amended as follows:
“We examined health service access with respect to primary health care generally and antenatal care specifically. Distance to nearest primary health care facility was not a risk factor in this study. Antenatal clinic attendance and number of ANC visits was significantly protective, with no difference between South Africans and former Mozambican refugees. These finding suggest that factors other than geographic access may be key to understanding the risks associated with health care utilisation. These could include quality of care, level of available care (primary versus secondary), cost and social barriers. In South Africa, primary health care for children under the age of six is free, as is antenatal care. However, financial costs associated with transport and opportunity costs associated with lengthy waiting time [50] are some of the barriers described in this setting [51,52]. Twine et al showed that the poorest households were less likely to apply for social support grants than those in higher socioeconomic strata due to barriers such as distance from government offices, lack of official documentation and education of caregiver and household head [51].”

Results

"(a) The authors find that maternal migration status had impact (protective initially but negative through out the time). I wonder if the authors thought of perform separate analysis of all cause neonatal and infant mortality for children born to South African citizens and for those born to migrants to better investigate the trends among the 2 groups. It would be interesting to have such a graph, as this one of the interesting findings of the study."

This query from Dr Macassa has still not been addressed adequately. The comparison is thus not as rigorous as we suspect Dr Macassa would wish.

In response to Dr Macassa’s original comments, we produced various graphs comparing trends in infant and neonatal mortality by permanent and migrant mothers (see below for text description and figures). These figures did not show any significant difference. Based on your comments, we have deepened this analysis by examining differences in other socio-demographic factors between these two groups (see after figures).

“We agree this was a good suggestion and so have done the suggested analyses (annual infant and neonatal mortality rates by South African mother or former Mozambican refugee; and by mother migrancy status). No distinct differences in infant and neonatal rates were observed by these sub-groups over time and so were not included in the analysis. There was also no distinct difference in all cause infant and neonatal mortality trends by mother migrant status during the study period (see figures below). Slightly elevated mortality was evident among permanently resident mothers during 1998-2003, but thereafter the rates were almost identical. [Note: definition of mother a temporary migrant = she is recognised as a member of the


household, but lived less than 6 months in the area over the previous year. A permanent resident lived more than 6 months of the previous year in the area.”

See next page
Factors worth mentioning are:

--Migrant mothers are significantly more educated than permanently resident mothers (p<0.001)

--Migrant mothers come from households with a significantly higher SES than permanent mothers (p=0.0025)

--No significant difference in attendance at antenatal clinic between migrant and permanent mothers

-- However, the proportion of migrant mothers dying, irrespective of the child’s age, was significantly higher (p=0.013 [01]) when compared to permanent mothers; and marginally higher among migrant mothers for death in an
infant’s first year (p=0.054)

Whereas we have not included the graphs in the revised manuscript, we have enriched the results by the inclusion of these analyses as follows (page 10):

“Further, migrant mothers were found to be significantly more educated than mothers permanently resident in the study site (p<0.001) and from households with a significantly higher SES (p=0.0025). No significant difference was found in antenatal clinic attendance between permanent and migrant mothers.”

The following has also been added to the discussion on page 17:

“Mothers’ physical presence or absence had a significant impact on infant mortality: mother a temporary migrant (largely work-related) proved significantly protective, while conversely increasing number of months spent resident by the mother in the rural site was a risk. Brockerhoff [54] describes how maternal rural-urban migration may affect children through three types of living arrangement: children may remain in the village as foster-children in the care of their fathers or other relatives; children may accompany or follow their mothers to towns or cities; and children born after migrant mothers settle in an urban area may remain there through the first few years of life. (Note that in this study, infants born to mothers in urban areas would not be captured onto the HDSS[04] database unless they later migrated into the rural household). Bledsoe et al [55] reviewing evidence from
West Africa, suggest that while fostered children may be disadvantaged compared to biological children (in terms of access to health care and nutrition), they may still be better off than if they had accompanied their migrant mothers. By staying home, these children avoid exposure to infectious diseases during a vulnerable period of their life, have continued access to economic resources of a non-migrant father, and benefit from remittances received from the migrant mother [55] as well as better health care, nutrition and enhanced maternal health knowledge [56]. In our study, migrant mothers had significantly higher education and came from households with significantly higher SES which may explain the protective effect of mothers’ migration. According to Collinson et al, [57] since 1997 there has been an increasing trend in the number of temporary female labour migrants in the Agincourt sub-district, a poor area with limited employment opportunities with resulting pressures to migrate and remit wages back to the rural household.”

56. Hildebrandt N, McKenzie D. The effects of migration on child health in Mexico. Mimeo. Stanford University,
When talking about HIV, it would be useful to mention when the PMTCT and ARV rollout in the area started and whether this has made any difference in the prevalence of the disease ought to be mentioned.

TB appears for the first time in the methods section. It ought to be mentioned in the background as well.

In Agincourt, community-based roll-out of HAART (highly active anti-retroviral therapy) began in 2007 so would not have impacted on infant/maternal mortality rates over the time frame of this study (1992-2007). This issue is discussed as follows: please note addition highlighted in bold.

Page 18: “HAART for HIV began in 2007 in this district and its impact cannot thus be captured during the time frame of this study. This research does, however, provide useful insight into spatial-temporal mortality patterns before HAART rollout and will allow post-rollout assessment of its impact on infant mortality. Such evaluation has the potential to identify areas needing improved access to treatment, specifically prevention of mother-to-child transmission and anti-retroviral therapy.”

Page 5: We have removed mention of TB specifically from the methods section as we do not deal with TB separately from HIV. This is because the verbal autopsy has a lower sensitivity when diagnosing HIV/AIDS and TB as separate conditions due to the overlap between AIDS and TB-related symptoms. Most published work based on verbal autopsy diagnosis.
In the discussion, suddenly the authors suggest that some of the deaths were from unknown causes; could this be related to stigmatisation of HIV? Do the authors have a feel as to whether stigmatisation is still an issue?

# This means that the paper does not explain the South African environment as well as it could, but in our view this is not a reason for publication being refused.

"(b) In Page 10 the authors discuss the high clustering of diarrhoeal/malnutrition related mortality south east of the site and they give some reasons for that finding (mainly environmental conditions - source of water supply). Nowhere in the discussion or manuscript the authors mention breastfeeding or breastfeeding patterns in the surveillance site. If the authors were not able to collect information on breastfeeding status for the children included in the sample at least they should bring the issue while discussing their findings regarding diarrhoea and malnutrition."

# This query too has not been addressed. We feel that this remains a genuine deficit in the combines HIV and TB into a single category (HIV/TB).

The following has been incorporated on page 19: “The significant increase in number of infant deaths attributed to unknown causes since the late 1990s (Figure 2) is concurrent with the rise in HIV-related mortality in the area. Levels of stigma associated with HIV are high in South Africa, particularly prior to the introduction of HAART. The ability to make a diagnosis on VA depends, in large part, on the quality of information provided by the respondent. This may have been compromised in some cases in an effort to disguise HIV as a likely cause of death, partly explaining the increase in unknown causes.”

Data on breastfeeding patterns have now been extracted. A univariate analysis of this and birth weight has been included in results (page 10):

“Breast feeding had a protective influence on all-cause as well as diarrhoea and malnutrition-related infant mortality (Table 1). Increasing infant weight at birth also had a significantly protective effect.”

These univariate findings[06] are listed in Table 1 on page 10:

<table>
<thead>
<tr>
<th>Breast feeding and birth weight</th>
<th>23,890/25,697</th>
<th>0.21</th>
<th>&lt;0.001</th>
</tr>
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<tbody>
<tr>
<td>Breast fed (diarrhoea &amp; malnutrition)</td>
<td>23,890/25,697</td>
<td>0.38</td>
<td>0.001</td>
</tr>
<tr>
<td>Increasing birth weight (kilograms)</td>
<td>15.2357</td>
<td>0.42</td>
<td>&lt;0.001</td>
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</tbody>
</table>
The discussion around the impact of breastfeeding on the clustering of diarrhoeal/malnutrition-related mortality was added following the first round of reviewer comments and has been expanded as follows:

Page 18: “Breastfeeding had a protective effect on all-cause as well as diarrhoeal and malnutrition-related infant mortality (Table 1). Breastfeeding protects infants through decreased exposure to contaminated water and food, optimal nutrition, and improved resistance to infection however there is risk of HIV transmission through breast milk. In South Africa, Ministry of Health policy on breastfeeding by HIV positive mothers has evolved in response to emerging research [59]; current recommendations are to breastfeed exclusively during the first 6 months with administration of anti-retrovirals to HIV positive mothers [60], especially those with low CD4 counts. Mothers or infants receiving highly active anti-retroviral therapy (HAART) prophylaxis should continue prophylaxis for one week after breastfeeding has ended [60]. Infant mortality due to diarrhoea, malnutrition and their interaction is a complex problem in poor, HIV prevalent African settings. Addressing this requires a multifaceted approach including provision of clean water and sanitation, promoting infant nutrition, and strengthened primary care services for mothers and infants to reduce the risk of HIV transmission through breast milk [61].”

“59. Coovadia H, Rollins N, Bland M, Little K, Coutso...
