Early evidence of reduction in all-cause and malaria attributed deaths at health facilities following scale-up of malaria interventions in Uganda 2004-2010

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Abstract
Following increased financial investment in malaria control efforts, the Uganda Ministry of Health has been scaling-up a combination of malaria interventions since 2000 under two national malaria control strategic plans. It is important to evaluate whether intervention scale-up and resources invested in malaria control have translated into significant reduction in malaria burden. Our aim was to assess the impact of scaling-up of a combination of interventions on malaria burden at health facilities in Uganda. Proportions of all-cause deaths and malaria attributed deaths among children < 5 were compared between two time periods 2004-2006 and 2008-2010. We considered the period 2004-2006 and 2008-2010 coinciding with the first and second malaria control strategic plans to be the pre and post-intervention periods respectively. Effect size of interventions on malaria indicators between the two periods was detected by comparison of two proportions using chi-square statistical test with Yates correction for continuity at 95% Confidence Interval. In 2010, all-cause under 5 deaths had decreased by 54.4% [95% CI: 54.3-54.5], p < 0.05. Malaria attributed deaths had fallen by 7.1% [CI: 6.9-7.2], p < 0.025 in children under five. In ≥ 5 age groups all-cause deaths reduced by 48.4% [CI: 47.8-48.2], p < 0.025 and 3.9% [CI: 3.8-4.0], p < 0.025 for malaria attributed death. Intervention coverage in 2010 was 64%, 7.8%, 65% and 32% for insecticide Treated nets, Indoor Residual Spraying, Artemisinin-based Combination Therapy and Intermittent Preventive Treatment during pregnancy respectively. Our analysis of the changes in malaria related indicators between the pre-and post-intervention periods show that Uganda has achieved significant improvement in reducing malaria burden as indicated by the decline in our primary outcome indicator of all-cause mortality among children < 5 and a corresponding decline in the secondary indicator of malaria attributed deaths.

Key Words: Admissions, all-cause deaths, Malaria deaths, impact of interventions, donor funding

INTRODUCTION
Uganda has been categorised as a high malaria burden and is ranked 6th in the number of malaria cases and 3rd in the number of malaria deaths [1, 2, 3]. Hospital records suggest that malaria is responsible for 30 to 50% of outpatient visits, 15 to 20% of admissions, and 9 to 14% of inpatient deaths [2, 3]. Over the past five years, increased funding by the government of Uganda and partners such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the President’s Malaria Initiative (PMI), the World Bank and the United Kingdom Department For International Development (DFID), have enabled the scale-up of four proven malaria control interventions: indoor residual spraying (IRS), insecticide-treated nets...
(ITNs), artemisinin-based combination therapy (ACTs), and intermittent preventive treatment of pregnant women (IPTp). As a result of the scale-up, Uganda has recorded improvement in malaria intervention coverage from 2006-2010 compared to earlier time periods [6].

Over the past ten years, malaria control interventions in Uganda have been guided by two strategic plans; 2000-2005 and 2006-2010. The first strategic plan period (2000-2005) was characterised by implementation of interventions with chloroquine monotherapy that was associated with high treatment failure rates of 76% in children under 5 years [4,5], very low ITN coverage of about 9.7%, and limited IRS and IPTp [6,22]. Although there are no nation-wide figures on IPTp, isolated studies indicated that the risk of malaria parasitemia in pregnant women was high (62%) and was associated with a high risk of maternal anaemia and perinatal mortality during this period [3,4]. In this study, we have referred to the 2000-2005 period as the pre-intervention period. During the second strategic plan period (2006-2010), there was increased Uganda government and donor funding, and increased in-country focus on the goals of the Roll Back Malaria (RBM) partnership to reduce the number of malaria cases and deaths by 50% by the year 2010. All these efforts led to accelerated scale up and increased coverage of malaria control interventions [6]. During this period, there was a landmark change in malaria treatment policy with introduction of highly effective ACTs that replaced chloroquine as first line treatment for uncomplicated malaria [3,4,5]. ACTs were provided free of charge to all malaria patients at health facilities. At community level, Village Heath Teams (VHT) formerly called community medicine distributors were trained to recognize, and refer cases of severe malaria to the nearest health facility. Between 2007 and 2011, significant scale up of ITNs through mass distribution campaigns was realised and a coverage of 64% was achieved [2,3]. By 2010, the Ministry of Health (MoH) achieved universal coverage in 5 districts of mid-Western Uganda [3,6]. Currently, IRS has been expanded showing additional impact [22]. Community surveys have also demonstrated progressive achievements of IPTp uptake and correct knowledge on IPTp use among pregnant women with the proportion of pregnant women that take at least 2 doses of IPTp rising from 0 in 2001 to 18% in 2006 and to 32% in 2009 [3,6].

Measuring the impact of malaria interventions determines the extent to which malaria disease burden changed over-time as a result of scaling up recommended interventions. However, monitoring and evaluation systems in Uganda are weak and unable to show whether malaria intervention scale-up has had an impact on malaria mortality and morbidity at health facilities in Uganda. Standard impact measures have been set by the RBM Monitoring and Evaluation Reference Group (MERG) [7]. The MERG recommends all-cause childhood mortality (ACCM) as the primary indicator for evaluating the impact of malaria control efforts where the malaria burden is high and vital registration systems are weak [7,8,9,10]. Several published studies have documented the relationships between ACCM and malaria specific mortality; and malaria intervention scale-up and coverage in high malaria endemic countries [7,8,16,17,18,19].The aim of this study was to evaluate the impact of increased scale-up of malaria control interventions on malaria morbidity and ACCM at health facilities in Uganda. We used the Uganda Health Management Information System (HMIS) data to estimate the all-cause under-five mortality and the proportions of in-patient and out-patient malaria cases at health facilities in Uganda.

Study design

This was a retrospective analysis of HMIS health facility records conducted from January to May 2012. Two time periods of January 2004 to December 2006 and January 2008-December 2010 coinciding with the first and second national malaria control strategic plans were considered as pre-intervention and post-intervention periods respectively. To estimate the impact of control interventions on malaria burden, a retrospective analysis of two indicators of all-cause under five mortality and malaria attributed deaths before and after the interventions was carried out. The study aim was to determine whether there was a reduction in the proportion of all-cause under five and malaria attributed deaths, among children admitted for malaria at public health facilities in Uganda. The study was approved by the School of Medicine Research and Ethics Committee.

Study area and setting

We analysed malaria data available at the central HMIS database collected from 29 districts that met the criteria for data completeness and reporting. All districts in Uganda transmit health information data through HMIS to the MoH monthly. Districts were selected based on HMIS data availability and completeness, transmission intensity and regional representation. Malaria endemicity and epidemiological mapping categorises the country into low, moderate and high malaria transmission areas. As the malaria endemicity can have influence on the effect of control interventions and therefore seriously confound our findings, we ensured that districts from all the different malaria transmission zones were included. Uganda has undergone intense decentralization since 2000 with creation of administrative units up to 112 districts by 2012. To ensure geographical similarity of the pre and post-intervention period we re-constructed districts to reflect the 56 districts exactly the way they were in 2004 (Fig 1).
**Figure 1**: Map of Uganda showing the selected study districts and malaria endemicity with all the three different malaria transmission zones represented, 2004-2010

**Key** = Districts selected

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**Study participants**

Participants included in this analysis were patients who presented to health facilities between 2004-2006 and 2008-2010 and whose records were captured in the national HMIS database. Although the biggest malaria burden is seen in children under 5 years of age and was the primary target for this study, the entire population in Uganda is at risk of malaria infection since 96% of the country is malaria endemic. Therefore we included individuals ≥ 5 years in our analysis.

**Indicators**

Monthly records of inpatient cases and inpatient deaths, stratified by age ≤ 5 and ≥5 years old, all-cause and malaria attributed deaths were used. Deaths and inpatient malaria cases consisted those that were parasitologically-confirmed and those admitted based on clinical suspicion as both the WHO and national malaria policy
recommended so during the period under study. Malaria attributed deaths was defined as deaths during admission with a confirmed diagnosis of malaria.

**Statistical analysis**
Impact was evaluated by comparing Proportions of all-cause under-five mortality and malaria attributed deaths for the pre and post intervention periods using a Chi-square test for comparison of two proportions. Impact was shown by significant difference in proportions all-cause under 5 mortality and malaria attributable deaths between pre and post intervention periods as indicated by p-value at significance level of 0.05 and 95% confidence interval.

**Results**
A total of 764,680 and 2,907,819 all-cause admission cases were extracted from the central HMIS database of which 70.4% (95% CI: 70.2%–70.5%) and 48.8% (95% CI: 48.7%–48.8%) were in children under five years of age during the pre-intervention and post-intervention periods respectively. For malaria attributable admissions, a total of 240,839 and 1,198,790 were obtained of which 65.2% (95% CI: 65.0%–65.4%) and 66.5% (95% CI: 66.3%–66.5%) occurred in children under five years of age during the pre-intervention and post-intervention periods respectively. There were a total of 451,585 and 170,542 all-cause deaths of which 73.8% (95% CI: 73.7%–73.9%) and 61.6% (95% CI: 61.4%–61.8%) occurred in children under five years of age in the pre and post-intervention periods respectively. There were a total of 15,777 and 6,790 malaria attributed deaths of which 76.6% (95% CI: 75.9%–77.3%) and 70.4% (95% CI: 69.3%–71.5%) occurred in children under five years of age in the pre and post-intervention periods respectively.

**Table 1:** Reported malaria-attributed deaths, malaria admissions, all-cause deaths and all-cause admissions in the study districts stratified by age in Uganda, 2004-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;5-All</th>
<th>≥5 all</th>
<th>&lt;5 Malaria</th>
<th>≥5 Malaria</th>
<th>&lt;5-All</th>
<th>≥5 all</th>
<th>&lt;5 Malaria</th>
<th>≥5 Malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>179637</td>
<td>90514</td>
<td>49005</td>
<td>45855</td>
<td>3153</td>
<td>39359</td>
<td>4030</td>
<td>1229</td>
</tr>
<tr>
<td>2005</td>
<td>197574</td>
<td>60604</td>
<td>60420</td>
<td>35609</td>
<td>44550</td>
<td>49359</td>
<td>5031</td>
<td>1329</td>
</tr>
<tr>
<td>2006</td>
<td>179700</td>
<td>75201</td>
<td>2581</td>
<td>1369</td>
<td>285805</td>
<td>29359</td>
<td>1130</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>538911</td>
<td>225769</td>
<td>157006</td>
<td>383833</td>
<td>333508</td>
<td>138077</td>
<td>12089</td>
<td>3688</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;5-All</th>
<th>≥5 all</th>
<th>&lt;5 Malaria</th>
<th>≥5 Malaria</th>
<th>&lt;5-All</th>
<th>≥5 all</th>
<th>&lt;5 Malaria</th>
<th>≥5 Malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>325296</td>
<td>636480</td>
<td>161443</td>
<td>92631</td>
<td>35026</td>
<td>21821</td>
<td>1594</td>
<td>670</td>
</tr>
<tr>
<td>2009</td>
<td>403969</td>
<td>646797</td>
<td>254043</td>
<td>111957</td>
<td>34046</td>
<td>25818</td>
<td>1269</td>
<td>457</td>
</tr>
<tr>
<td>2010</td>
<td>690715</td>
<td>654682</td>
<td>318428</td>
<td>972185</td>
<td>36006</td>
<td>11816</td>
<td>1082</td>
<td>882</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1419980</td>
<td>1487389</td>
<td>396414</td>
<td>401846</td>
<td>105076</td>
<td>2615</td>
<td>7662</td>
<td>2338</td>
</tr>
</tbody>
</table>

**Table 2:** Percentage reduction in malaria and all-cause deaths in 2004-2006 (pre-intervention) periods compared to 2006-2010 (post-intervention) period in selected districts in persons < 5 years and ≥5 years, in Uganda

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-intervention (%)</th>
<th>Post-intervention (%)</th>
<th>% Difference</th>
<th>95% CI</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>335350 (61.8)</td>
<td>105076 (74.6)</td>
<td>54.4</td>
<td>54.3–54.5*</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>≥5 All</td>
<td>118077 (52.3)</td>
<td>65464 (4.3)</td>
<td>48.0</td>
<td>47.8–48.2*</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Malaria</td>
<td>12089 (7.7)</td>
<td>4781 (0.6)</td>
<td>7.1</td>
<td>6.9–7.2*</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>≥5 Malaria</td>
<td>3688 (4.4)</td>
<td>2009 (0.5)</td>
<td>3.9</td>
<td>3.8–4.0*</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Admissions</td>
<td>538911 (70.6)</td>
<td>1419980 (48.3)</td>
<td>21.7</td>
<td>21.5–21.8*</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>≥5 All</td>
<td>225769 (30)</td>
<td>1487389 (51)</td>
<td>21.0</td>
<td>20.9–21.1*</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Malaria</td>
<td>157006 (65.5)</td>
<td>796944 (66.2)</td>
<td>0.7</td>
<td>0.49–0.91*</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>≥5 Malaria</td>
<td>83833 (34.8)</td>
<td>401846 (33.5)</td>
<td>1.3</td>
<td>0.95–1.65*</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

* A 95% CI not including the 0% value indicates that the difference is statistically significant.
Discussion

Our study aimed to assess the impact of scaling-up of a combination of interventions on malaria burden at health facilities in Uganda. We found a reduction of 54.4 % (95% CI: 54.3-54.5), p-value <0.05 in all-cause under five mortality and 7.1% (95% CI: 6.9-7.2) in malaria deaths between the pre and post intervention periods.

The reduction of 54.4 % seen in all-cause under 5 mortality is consistent with the recent population-based Uganda Demographic Health Survey in which Uganda’s under 5 child mortality significantly dropped from 137 in 2006 to 90 per 1,000 live births in 2011 [14]. Several other studies conducted elsewhere in malaria endemic countries in sub-Saharan Africa have reported similar findings [23, 24, 25]. In Zanzibar where similar interventions of ITNs, IRS and ACTs were scaled-up, an assessment of the impact indicated that all-cause < 5 mortality had reduced significantly from 46% in 1999-2003 to 12% in 2008, p<0.025 [11]. Another study in Zanzibar, reported evidence of a reduction of 75% in malaria attributable deaths following malaria intervention scale up between 2002 and 2006 [14]. In Zambia, increased coverage was consistent in time and place with reductions of 38% in under 5 child mortality between 2001 to 2007 following increased health financing and increased coverage of malaria interventions [15]. This reduction in all-cause < 5 mortality is corroborated further by epidemiological modelling that have predicted an achievement of more than 50% reduction in all-cause <5 years mortality if malaria intervention coverage is scaled-up to 70% [16].

A review of temporal data for over seven malaria endemic countries to assess malaria programme progress and impact on malaria related indicators for the period between 2000 to 2009 showed that all the countries had reported progress on at least one impact indicator (typically on mortality); with most observing a decline of more than 20% in under-five year mortality rates [8, 9, 17, 18, 19, 20]. Majority of published studies demonstrate reduction in all-cause under 5 deaths and corresponding decline in malaria specific mortality in most malaria endemic countries especially in Africa. Findings in this study are consistent with the general trend in sub-Saharan African malaria endemic countries.

There are plausible explanations for the reduction in both all-cause and malaria attributable deaths seen in Uganda. During the pre-intervention period, Uganda experienced the worst anti-malarial treatment failure due to wide spread chloroquine resistance [4, 5]. The risk of clinical treatment failure adjusted by genotyping in children ≤ 5 years of age peaked at 76% [4, 5]. Malaria treatment failure is strongly associated with progression to severe malaria, malaria related complications and deaths [4]. The risk of developing malaria complications and deaths is higher in children ≤ 5 years of age as compared to other age groups. In the post-intervention period, there was a change in malaria treatment policy from chloroquine to the highly efficacious ACTs [5]. Although the treatment policy was changed in 2005, full implementation took place in the latter years within the post-implementation period. This could have largely contributed to improved child survival and mortality reduction in the post-intervention period.

In endemic areas, scaling-up a combination of ITNs and ACTs is demonstrated to reduce under five mortality. However during the pre-intervention period in Uganda there was very limited coverage of ITNs and ACTs were not readily accessible in public health facilities. However during the post-intervention period, coverage levels of ITNs reached significant levels at an average figure of 64% with some districts reaching universal coverage [3, 6]. All other major malaria interventions including IRS, IPTp, health promotion and surveillance sentinel sites were implemented largely after 2006 in the post-intervention period. Improvements in mortality indicators in children ≤ 5 years of age in later years of post-intervention period may have resulted from the mass distribution of ITNs that started from late 2007 [22]. Specifically, donors including GFATM, PMI and United Nations International Children’s Emergency Fund started ITNs mass distribution campaigns in the post-intervention period. This could have had greater bearing in improving child survival in the post-intervention period and Uganda is likely to witness further improvement in malaria related indicators if ITN, IRS and ACT coverage levels are further scaled-up.

During the post-intervention period, there have been several other new innovations by the MoH such as Child Days Plus that offer a comprehensive health care package including immunization, de-worming, health education and promotion. These additional interventions could have had further impact on improving child survival in the post intervention. Increase in health financing was much better in the years after 2006 [6]. Increased funding may have improved access and availability of health services and strengthening health systems for better service delivery. Improved funding is likely to have led to implementation of additional interventions such as immunization, nutritional, and child health programs all of which directly impact on survival of children under five years of age. This study may not be completely free of the known documented biases and limitations affecting all facility-based studies. We included only those deaths that occurred in public health facilities in the 29 districts included in the study. This could have caused either underestimation or overestimation of outcomes due to lack of information on deaths occurring outside the health facility setting. However, use of HMIS data minimised this since HMIS collects health data from as low as Health Centre II which is closest to the communities. It is therefore likely that the HMIS under-five death estimates may not differ
significantly from the population-based findings. Alternative designs using surveys that measure impact of intervention on malaria mortality using verbal autopsy have well documented serious limitations [8, 16, 17, 18, 19, 20]. Sentinel surveillance sites could have provided malaria-attributed mortality and all-cause mortality, however key disadvantages with approach have been identified and published earlier that include the fact that sentinel sites are not representative of larger populations and might not be “similar enough” to national populations to justify generalization of results as documented earlier [8, 9, 11, 16-21]. Routinely collected health facility records or country’s health information system is an acceptable source of data on malaria mortality and provide close reflection of community mortality trends [8, 16, 17, 18]. Therefore we believe that the estimates obtained from this study are close to the true values of the current malaria related indicators in Uganda.

Another important limitation is the fact that though malaria is still one of the leading causes of mortality among under-fives in malaria endemic countries, there are other known co-morbidities contributing to under five mortality that may confound the relationship between intervention scale up and under five child mortality, which were not controlled in this study. However, in high malaria burden countries studies have documented the dominance of malaria in under five mortality compared to other co-morbidities. Such studies have also documented a strong relationship between all-cause < 5 mortality and malaria-specific mortality [8, 16, 17, 18]. Although both national and WHO malaria treatment guidelines recommended clinical diagnosis and parasite confirmation as acceptable methods for malaria diagnosis, clinical diagnosis was the dominant method during the study period 2004-2008. However, clinical diagnosis is non-specific and has limitations [26, 27]. In Uganda it has led to over diagnosis of malaria as most fever if not all are treated as malaria. Parasite confirmation by microscopy or Rapid Diagnostic Tests could have improved the specificity of measurement of our outcomes. Clinical diagnosis therefore could lead to an overestimation of outcomes.

### Conclusion and Recommendation

Our analysis of the changes in mortality indicators show that there has been a decline in all-cause under 5 mortality and a corresponding decline in malaria-attributed deaths between the pre- and post-intervention periods. While this study provides invaluable insights for malaria control, we recommend that a larger and well controlled study using multiple data sources be conducted to attribute interventions to the observed improvements in malaria indicators in time and place.

### List of abbreviations


### Competing interests

All other authors have no conflicts of interest.

### Author Contributions

AB carried out the study design, data collection, analysis and coordination for writing the paper. CK was very instrumental in supervision of the work, reviewing and shaping up the manuscript and the final paper.

MK assisted supervision of the work, reviewing the manuscript and the final paper.

AG participated in reviewing the study design.

JK reviewed the paper.

KD, JN, EM, SC, AK, PBK, DM, PN all provided scientific support in study design and critical review of the paper. All authors read and approved the manuscript.

### References


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