Under-utilized approaches to control anaemia in developing countries
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2. Reducing childhood mortality in poor countries. Anaemia prevention for reduction of mortality in mothers and children

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ABSTRACT

The relationship of anaemia as a risk factor for child and maternal mortality is described. Maternal case fatality rates, mainly from hospital studies vary from <1% to >50%. These large differences in risk were related primarily to differences in available obstetric care for women living in areas with inadequate antenatal and delivery care facilities. The relative risk of mortality associated with moderate anaemia (haemoglobin 40-80 g/l) was 1.35 (95% CI : 0.92-2.00), and for severe anaemia (<47 g/l) was 3.51 (95% CI : 2.05-6.00). Nutritional-related anaemia mortality is likely to be greater than malarial anaemia-related mortality. With good antenatal and obstetric care most anaemia-related deaths are preventable, and policies to reduce anaemia prevalence should not be divorced from efforts to provide adequate antenatal and delivery facilities for women in developing countries. In children although mortality was increased with anaemia (<50 g/l), the evidence for increased risk with less severe anaemia was inconclusive. A survival analysis of Malawian infants indicated that if haemoglobin decreased by 10 g/l after 6 months of age, the risk of dying before 12 months of age increased 1.72 times. Evidence from a number of studies suggests that mortality due to severe malarial anaemia in children is greater than that due to iron deficiency anaemia. Primary prevention of nutritional and malarial anaemia in young children could lead to reductions in child mortality.
INTRODUCTION

Although the prevention of anaemia is an important priority for mothers and children (Beard and Stoltzfus, 2001), to what extent is it correct to say that anaemia prevention will reduce maternal and/or child mortality? The relationship of anaemia as a risk factor for maternal or child mortality have recently been reviewed (Brabin et al 2001a; Brabin et al, 2001b). One of the major problems with previous studies is that there are no randomised controlled trials conducted to establish the effect of interventions on cause-specific mortality. As anaemia is usually multifactorial in developing countries it becomes difficult to establish attributable risk for specific causes. In particular it has proved difficult to estimate malaria and nutritional risk components of anaemia-related mortality.

The definitions of anaemia across different studies vary, as do the methods for estimation of haemoglobin and the type of study sample, which may be either hospital or community. This considerable variation between studies complicates comparative analyses.

ANAEMIA AND PAEDIATRIC MORTALITY

Figure 1 (courtesy of Dr P. Kazembe) shows the distribution of causes of paediatric hospitalisation and death for children in southern Malawi in the early 1990’s and illustrates the substantial contribution of anaemia to hospital practice. Although anaemia may be specifically identified in hospital records as a cause of admission or death, it is unclear whether it is a direct or an indirect cause. The fact that anaemia, as a cause of death in hospitalised children in developing countries, has been reported to vary from 2.8% to 58% (Brabin et al, 2001b) illustrates the uncertainty in directly attributing causation. For many studies anaemia as a cause of mortality refers to severe anaemia which is usually based on a haemoglobin value of <50 g/l.

Global estimates of the number of deaths attributed to anaemia (all forms) in hospital and non-hospital settings, have been summarised by the Global Burden of Disease Group (Murray and Lopez, 1994); younger males and older females showed higher risks. The global estimate of death rates for children aged 0-4 years was 20.1 per thousand for males and 6.2 per thousand for females, and for children aged 5-14 years the rates were 6.2 per thousand for males and 23.2 per thousand for females. The assumptions on which these estimates were derived are unclear. The variation in reported case fatality rates is substantial and ranges from 2% to 29%. Most studies report case fatality in relation to the haemoglobin cut-off point of <50 g/l and as a result it is difficult to examine whether a dose-response relationship is present. Within the limitation of the data there is little to suggest a dose-response relationship between haemoglobin values of less than 50 g/l and less than 80 g/l (Brabin et al, 2001b). With hospital data of this type it is difficult to compare mortality in children with better iron status but equivalent co-morbidity and underlying risk of death.
Figure 1. Distribution of causes of deaths and admissions in southern Malawi in the early 1990s.
From a public health point of view, it is necessary to know the risk factors in the different studies for developing severe anaemia. Malaria and malnutrition are frequent contributors. In western Kenya malaria and bacteraemia were the primary diagnoses in 38.3% and 27.2% of 81 anaemia-related deaths in hospitalised children (Zucker et al, 1996). This data would suggest that mortality due to severe malarial anaemia in children is greater than that due to iron-deficiency anaemia, although it is difficult to partition iron deficiency anaemia as a contributor to those deaths. Given the weakness in the causal evidence relating iron deficiency anaemia in young children to mortality, it is not possible to generate projections regarding population attributable risk.

There is little data available on survival analysis in anaemic children and only two community studies were identified from Malawi. In the Shire Valley results for a community cohort of 216 infants who had Hb values at 6 months and who did not receive iron supplements before 6 months have been reported (Brabin et al, 2001b). The analysis indicated that if Hb decreases by 10 g/l the risk of dying becomes 1.72 times higher (p = 0.012) during the following 6 months. In a separate study of 253 infants from Mangochi, Malawi, it was reported that amongst 64 infants with haematocrits below 25%, 7 (11%) died during the one year period of follow-up compared with 10 (5%) deaths among 189 children who had haematocrit values of 25% or greater, (relative risk 1.7, p = 0.15), (Steketee et al, 1995). Survival analysis showed a higher rate of death in children who were anaemic at the first follow-up visit, but the difference in the two hazard curves was not statistically significant.

From a public health perspective it is necessary to know the prevalence of severe anaemia in children in communities. Table 1 shows summary data from children living in villages in the Shire Valley, Malawi, which is an area with year round malaria transmission and high HIV seroprevalence in adults (Verhoef et al, 2000). Severe anaemia prevalence is higher in children aged 1-6 years and in infants. Increasingly the contribution of P. falciparum-associated severe anaemia to paediatric mortality in these young children is being recognised, even though the causal relationship between malaria parasitaemia and Hb concentrations is difficult to establish because most young children in highly malarious areas are harbouring parasites continuously. Menendez et al (1997) estimated the incidence of first episodes of severe anaemia (haematocrit <25%) in Tanzania in a cohort of infants randomised to receive iron supplements and/or antimalarials. A summary of these findings is shown in Table 2. This randomised trial supports evidence for an important contribution of malaria as well as iron deficiency in causing moderately severe anaemia. What is of concern is that 20% of infants still developed this degree of anaemia despite being offered regular iron supplements between 3 and 6 months of age and a weekly antimalarial (maloprim) from 2 to 12 months of age. The results of this study arise from an intention to treat analysis and possibly not all children included in the analysis took the interventions. These infants may have continued to be anaemic due to lack of compliance with the intervention.
Table 1. Severe anaemia prevalence in rural Malawian children from the Shire Valley

<table>
<thead>
<tr>
<th>Age</th>
<th>Number</th>
<th>6 months</th>
<th>1-6 years</th>
<th>6-11 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>311</td>
<td></td>
<td></td>
<td>111</td>
</tr>
<tr>
<td>10.3</td>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 g/l (%)</td>
<td>1.6</td>
<td>4.3</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>&lt;70 g/l (%)</td>
<td>10.3</td>
<td>22.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Incidence of first episode of severe anaemia* in Tanzanian infants

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Incidence per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No iron supplements</td>
<td>3 in 5</td>
</tr>
<tr>
<td>Iron supplements†</td>
<td>2 in 5</td>
</tr>
<tr>
<td>Antimalarial prophylaxis‡</td>
<td>1 in 4</td>
</tr>
<tr>
<td>Iron and antimalarials</td>
<td>1 in 5</td>
</tr>
</tbody>
</table>

* Haematocrit <25%
† 2 mg/kg daily ferrous glycine sulphate from 8 to 24 weeks
‡ Pyrimethamine and dapsone weekly from 8 to 48 weeks

Source: Menendez et al, Lancet 1997

These data illustrate that children became at risk of deaths from anaemia from an early age and that primary prevention of iron deficiency and malaria in young children could have substantive effects on reducing child mortality from severe anaemia.

Current UNICEF/WHO guidelines for anaemia prevention (Stoltzfus and Dreyfuss, 1998) are difficult to implement in poor areas of developing countries as they are based essentially on routine iron supplementation strategies. More innovative approaches to anaemia prevention are required including such methods as the use of iron pots for household cooking.

ANAEMIA AND MATERNAL MORTALITY

With good obstetric care there is no risk of death from anaemia in pregnant women. In the developing world, maternal mortality rates as high as 700 per 100,000 live births are reported in many parts of Africa and in some countries in south Asia. The large differences in risk are related primarily to differences
in available obstetric care for women living in areas with inadequate antenatal and delivery care facilities. Acute onset of anaemia during pregnancy will greatly increase the risk of death because this can lead to rapid cardiac decompensation.

Case fatality varies from less than 1% to 55% in studies from Nigeria, from which there is most published data, and between less than 1% to 32% for non-Nigerian studies (Brabin et al, 2001a). Early Nigerian studies report that mortality increases markedly with extremely low Hb levels (<30 g/l), (Lawson and Lister, 1954). Most reports on case fatality provide few details on aetiology of anaemia, the relative contribution of acute and/or chronic disease, co-existing conditions, exclusions, percentage transfused and other aspects of obstetric care. Many reports are from malarious areas, and malaria is an important contributor to severe pregnancy anaemia, especially in primigravidae (Brabin and Rogerson, 2001).

Rush (2000) considered it a reasonable working assumption that maternal mortality is greatly increased with severe anaemia and the strength of the relationship made it appropriate to assume a causal association with severe anaemia, but that the association with moderate anaemia was less clear. The relative risks for severe (less than 47 g/l) and moderate anaemia (40-80 g/l) have been calculated for five Nigerian studies with adequate data (Brabin, 2001a). The sample sizes for some of these studies are small. The pooled data estimates a relative risk of 1.35 (95% CI : 0.92-2.00) for moderately anaemic women and 3.51 (95% CI : 2.05-6.00) for severely anaemic women. In these Nigerian studies HIV infection was very unlikely to be a contributing factor anaemia, because all of the surveys were completed before 1985. Nutritional deficiencies and malaria were therefore the major contributors. Estimates of attributable risk for severe anaemia related deaths in malarious areas suggest that despite the contribution of P. falciparum infection to anaemia, nutritional anaemia is the major component (Brabin et al, 2001a). The converse is more probable in African children whose mortality from severe malarial anaemia is likely to be greater than that due to nutritional deficiency anaemia. (Brabin et al, 2001b)

CONCLUSION

Would improving Hb levels by whatever means lead to reductions in child or maternal mortality? In children we have no direct evidence supporting this conclusion. Even the benefits of blood transfusion in clinically stable children with severe malarial anaemia and without respiratory distress, are unclear (Brabin et al, 2001b; Meremikwu and Smith, 1999). In women there is limited evidence that prevention of anaemia other than treatment with exchange transfusion (Fuller and Turner, 1962), judicious use of blood transfusion (Lawson and Lister, 1954), or treatment of acute severe malarial anaemia (Gilles et al, 1969) lowers risk of maternal mortality. With good antenatal and obstetric care most anaemia related maternal deaths are preventable and policies to reduce anaemia prevalence should not be divorced from efforts to provide adequate antenatal and delivery facilities for women in developing countries.
There is little evidence to support a causal association of mild-to-moderate anaemia with mortality because there is no data available to examination this association. In view of the high prevalence of mild-to-moderate anaemia, it is critical to know whether this increases mortality in areas with or without malaria. For young children, Hb screening might be useful to identify those most at risk of death, but further research is necessary to answer this question. Primary prevention of malaria and iron deficiency anaemia in young children could have substantive effects on reducing child mortality from severe anaemia.
REFERENCES


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