Under-utilized approaches to control anaemia in developing countries
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9. Discussion

This thesis presents data on anaemia as a public health problem. Although this has been recognised as a major problem for many years, little progress has been achieved and the global prevalence remains unacceptably high (joint WHO, UNICEF statement).

1. Iron-based interventions for reducing anaemia

Conclusions and interpretation
Consuming food cooked in iron pots significantly increased the mean haemoglobin levels in adults and decreased the severity of iron deficiency in children in Malawi (chapter 4). A follow-up survey at 28 months to assess continued use of iron pots was undertaken. This was conducted by a Malawian field worker who was familiar with the villages and had assisted in the previous surveys (Medison Matcheya). The results of this survey are shown in table 1 and 2. Only 2 (6.3%) households were still using the iron cooking pot at 28 months. This was considerably lower than the 51.1% observed during the second survey, undertaken five months after initial introduction.

| Table 1. Household use of cooking pots between 5 to 28 months after initial distribution |
|-----------------------------------------------|---------------|
|                                      | Aluminium     | Iron            |
|                                      | cooking pot   | cooking pot    |
|                                      | (n)           | (n)             |
| Households with follow up data       | 40            | 32              |
| Households without follow-up data    | 21            | 20              |
| Stopped using pot before 5 months    | 0             | 25              |
| Stopped using pot between 5 months and 1 year | 0       | 2               |
| Stopped using pot after one year or longer | 0       | 3               |
| Is still using pot                   | 40            | 2               |

The low number of households continuing to use the iron cooking pots could be biased by a number of factors. The sample is not representative as no follow-up data was available in 20 households, and secondly precise recall of time of discontinuing usage may not be reliable. Nevertheless a few households maintained usage of the iron pots at 28 months. The characteristics of these households are not known, but their presence suggests that for a minority iron cooking pots are acceptable on a long-term basis. In contrast all households which received aluminium pots were still using these, indicating their acceptability. The high acceptability of these probably reflects their quality and familiarity with their use for cooking. Conversely the very low continued long-term usage of the iron pots would indicate considerable household concerns with weight and rusting. Another explanation could be that during the second survey false data was given
to the interviewers for reasons that are not completely clear (ie a willingness of seeming to comply). The observed effect on the haemoglobin and iron deficiency could be interpreted as regression to the mean. This seems improbable because the participants were requested repeatedly during the interviews that it was important to answer the questions honestly. Also the criteria that were used to select the sub-group (that showed the significant increase in mean haemoglobin change for adults and consistent pot users) seemed logical and based on empirical criteria. Other studies have also shown the efficacy of consuming food prepared in iron pots in preventing or treating iron deficiency anaemia in humans (chapter 6). Numerous laboratory studies, including the one in this thesis on Malawian foods (chapter 7) have shown that cooking in iron pots increases the iron content of foods. Martinez and Vannucchi amongst others have reported, using a rodent model, that this added iron was bioavailable.

Acceptability of an intervention by a population is of crucial importance and this is especially true for the present intervention, using iron cooking pots to reduce iron deficiency. A good knowledge of the factors which positively or negatively effect acceptability is important in order to understand ways in which the intervention may be modified. These issues are discussed in chapter five. The survey at 28 months showed that 14 of the 57 responses for non-use of an iron cooking pot had no relationship with the characteristics of the cast iron (table 2). The reasons for discontinuing use (rust, weight and effect on food) were also mentioned in the previous surveys. Social marketing could help to improve usage (chapter 5). The success of social marketing for an intervention has been clearly shown by Schellenberg et al (2001) in Tanzania, who evaluated coverage of insecticide-treated mosquito nets (ITBN). The coverage percentage of infants using an ITBN increased following the introduction of social marketing from 10% to 50% over three years.

Table 2. Reasons related to use of iron cooking pots at 28 months

<table>
<thead>
<tr>
<th>Non-use</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rust (%)</td>
<td>Consumes less firewood</td>
</tr>
<tr>
<td>18 (31.6)</td>
<td>1</td>
</tr>
<tr>
<td>Weight (%)</td>
<td>Appropriate family size</td>
</tr>
<tr>
<td>11 (19.3)</td>
<td>1</td>
</tr>
<tr>
<td>Effect on food (%)</td>
<td>Total</td>
</tr>
<tr>
<td>14 (24.6)</td>
<td>57 (100)</td>
</tr>
<tr>
<td>Other (%)</td>
<td></td>
</tr>
<tr>
<td>14 (24.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>57 (100)</td>
<td></td>
</tr>
</tbody>
</table>


**IMPLICATIONS FOR PUBLIC HEALTH**
Consuming food prepared in iron pots could be a valuable, low cost and sustainable intervention to reduce iron deficiency in some developing countries. For unclear reasons, but most likely related to acceptability, this intervention is not advocated in proportion to its potential. Compliance with iron pot use is an important constraint, and will be a challenge to overcome. It is a concern that low compliance is frequently accepted as an unchangeable fact and not worthy for further study. As appropriate marketing of other interventions (ITBN) has shown improved uptake, then a more positive approach to the value of using iron cooking pots might be beneficial.

**FUTURE RESEARCH**
There is an immediate need for further research to identify factors which influence positively or negatively compliance with the community use of iron pots. Only when these factors are better understood could tailored interventions with iron cooking pots appropriately be planned. In this way the relative value of this intervention, compared to fortification, food based approaches and iron supplementation strategies targeting iron deficiency, can be determined. It is also essential to establish whether there is a risk for iron overload in people using cast iron cooking pots on a daily basis, especially with regard to long-term use. From laboratory studies it is known that not all food stuffs increase in iron content, or increase to the same extent. This is due to several known factors although some still unknown factors could play a role. Before starting an intervention with iron pots, it is important to determine if the iron content of the staple local foods consumed by the targeted population increases with preparation in cast iron pots.

2. *Malaria chemoprophylaxis, or intermittent preventive treatment for reducing anaemia in children*

**CONCLUSIONS AND INTERPRETATION**
The meta-analysis (chapter 8) showed that childhood malaria chemoprophylaxis reduced the number of clinical malaria episodes, outpatient visits and hospital admissions. It also raised haemoglobin concentration and reduced anaemia, especially in younger infants or children. Mortality amongst children receiving malaria chemoprophylaxis was significantly reduced in studies conducted in the Gambia. Other studies did not report any significant difference in mortality which could be due to several factors, for example, a shorter period of malaria chemoprophylaxis, or a smaller number of participants. Despite reductions in humoral immunity, clinical immunity seemed not to be reduced significantly following the period of malaria chemoprophylaxis in children. Malaria chemoprophylaxis may lead to a higher incidence of rebound attacks of clinical malaria after malaria chemoprophylaxis during infancy (chapter 8). This effect was however only reported in one study which was conducted in Tanzania.
Implications for Public Health

The review of studies conducted over the last fifty years reporting the effects of malaria chemoprophylaxis in children came to exciting and promising conclusions. It seems that malaria chemoprophylaxis given to children is an under-utilized intervention which could have a great potential, providing drug resistance is not a limiting factor. In the interpretation of the findings it is important to make two distinctions. One with regard to the age of the individuals who will receive malaria chemoprophylaxis, and another with regard to the kinds of intervention (malaria chemoprophylaxis or intermittent malaria treatment). These two distinctions are necessary to make because their implications for practice are of critical importance.

In infants regular malaria chemoprophylaxis could reduce acquired immunity to malaria and for this reason it may be preferable to use intermittent malaria treatment. This means that a full treatment dose of an antimalarial drug is given on an intermittent basis. Intermittent treatment would be expected to have a lesser effect on reducing immunity than continued chemoprophylaxis, as with intermittent treatment malaria parasitaemias may occur more frequently. This view is supported by studies of Menendez et al (1997), Schellenberg et al (2001) and Massaga et al (2003).9

Amongst children the most important causes of death due to malaria are: severe anaemia and cerebral malaria. The prevalence of severe malaria anaemia amongst children <5 years in Africa is estimated at 1.4-5.7 million annually and causes between 190,000 to 974,000 deaths. The prevalence of cerebral malaria amongst children <5 years is estimated at 575,000 deaths annually.8 Intermittent malaria treatment in infancy, although beneficial in reducing anaemia, may not substantially reduce the risk of cerebral malaria due to the sub-optimal protection. This could be an argument for malaria chemoprophylaxis instead of intermittent malaria treatment for infants. In view of the potential for rebound malaria attacks with chemoprophylaxis, careful long-term surveillance of such an intervention, is required. In older children this may be less critical as they may have acquired a greater degree of age dependent immunity. Despite the basis for chemoprophylaxis the current priority internationally is to evaluate intermittent malaria treatment in areas of differing malaria endemicity, because of indications that it can be linked, in younger children, to vaccine delivery.

Future Research

The promising intervention of malaria chemoprophylaxis and intermittent malaria treatment should be systematically analysed in appropriate settings. Large-scale studies over a number of years are needed to establish the place of chemoprophylaxis and/or intermittent malaria treatment in the overall antimalarial armamentarium.

Overall, for both intervention strategies, it is necessary to determine if the reduction in morbidity is also accompanied by a reduction in mortality. Such studies require large sample sizes. It is also important to conduct trials in areas of differing malaria transmission in order to see to what extent this influences
the effectiveness of these interventions. This was clearly shown by Verhoeef et al in Kenya who found little effect of intermittent malaria treatment alone on anaemia compared to the studies of Schellenberg et al and Massaga et al in Tanzania who did.67,9 This could relate to a number of causes, of which two important ones are: differences in malaria transmission and age of children enrolled in these studies. A further recent study in West Kenya confirmed the benefit of iron supplementation over that of intermittent malaria treatment in children 2-36 months of age.10

In future trials it will be of the utmost importance to monitor for drug resistance. Compliance with these interventions needs to be studied in detail. With regard to intermittent malaria treatment in infants, plans for implementation are already in an advanced stage, as studies are currently being conducted to assess this intervention. The focus at the moment is to combine intermittent malaria treatment within the Expanded Programme on Immunisation (EPI). WHO and UNICEF mention some other specific issues that need to be resolved prior to implementation. These include whether intermittent malaria treatment compromises serological responses to EPI vaccines. Also a liquid preparation of the relevant antimalarial drug(s) is required to minimize disruption of the routine implementation of the EPI programmes.11 The main drug under consideration at the moment is sulfadoxine-pyrimethamine which has a long half-life and offers both a treatment and prophylactic effect, but the long-term use of this drug is limited because of current high parasite resistance. Alternative currently available drugs require 3 days treatment courses and compliance with the use of these for intermittent preventive treatment in infants may be problematic.

3. Reducing mortality due to anaemia through integrated strategies

Conclusions and interpretation
In children mortality is increased with severe anaemia (Hb < 50 g/L), but the evidence for increased risk with less severe anaemia is inconclusive (chapter 2). It seems that mortality due to severe malarial anaemia in children is greater than that due to iron deficiency anaemia (chapter 2). Primary prevention of iron deficiency and malaria in young children has substantial benefits. A significant proportion of severe anaemia episodes in infants (20%) were not prevented by these measures,9 due to lack of compliance and/or because of multiple causes of anaemia in addition to iron deficiency and/or malaria (chapter 2).

Maternal mortality is increased in case of severe anaemia RR 3.51 (95% CI 2.05-6.00), but the association between maternal mortality and moderate anaemia is unproven RR 1.35 (95% CI 0.92-2.00). Maternal severe anaemia seems to be caused more by nutritional deficits than malaria. With good antenatal and obstetric care most maternal anaemia related deaths should be preventable (chapter 2), which highlights the essential need for good health service delivery in addition to chronic prevention strategies.

A clear age-specific trend was found in the prevalence of anaemia, with infants showing a 100% prevalence falling to 32.4% amongst adult males. This is
accompanied by a decreasing malaria parasite prevalence. However despite this reduction a high proportion of adults still remain anaemic. This is indicative of the multifactorial aetiology for their anaemia. Other factors which most likely played a role, in addition to iron deficiency, are HIV infection and vitamin A deficiency (chapter 3). The peak in prevalence of iron deficiency, and malaria in adolescent pregnant girls living in the Lower Shire Valley preceded a peak in prevalence of severe anaemia, (chapter 3).

G6PD deficiency is common in the Shire Valley with a frequency of 36% for female heterozygotes, one of the highest estimates in Africa (Chapter 3).

Thalassaemia was not uncommon as $-\alpha^7$, with a gene frequency calculated at 0.29. (chapter 3). The frequency of sickle haemoglobin genotypes in infants was high, with a calculated gene frequency of 0.11. Genotypes AS and SS compared to AA genotypes had a significantly increased malaria prevalence in infants (chapter 3).

This is a new finding and could be a mechanism providing enhanced immunity to malaria in older children with the AS genotype. Other recent studies in West Kenya do not confirm this observation, but the analysis was based on different age group classes.\textsuperscript{12}

Implications for Public Health

The relationship of child or maternal mortality with severe anaemia highlights that anaemia is not simply the measurement of a haemoglobin value, in relation to an arbitrary cut-off value. Anaemia causes enormous morbidity and increases mortality risk and sustained efforts are required for its control.

It has been shown in the studies conducted in the Shire Valley that anaemia is of multifactorial aetiology and, as seen amongst adolescent pregnant girls, the prevalence varies throughout the year. The multifactorial aetiology and varying prevalence of anaemia, occurs in many situations and countries in the developing world and this has been described by Weatherall & Kwiatkowski (2002).\textsuperscript{13}

These findings highlight the need for obtaining a haematological profile of the population in question. A haematological profile is an important tool to establish priorities with regard to interventions that target anaemia. It helps to establish whether integrated interventions should be considered, for example malaria chemoprophylaxis and interventions to prevent iron deficiency, other micronutrient deficiencies and helminth control strategies. It also helps in evaluating the risk associated with such interventions and the importance of targeting specific age groups. An appropriate example is the use of sulphadoxine-pyrimethamine in EPI and its potential side effects related to G6PD deficiency.

Combined interventions targeting anaemia have the advantage of greater effect, because of the multiple causes that are being targeted simultaneously. Also there may be less need for separate delivery systems if a single system is sufficient. However it is important to carefully access and monitor if an existing system can be used, or continue to be used, since the increased workload could have negative effects on that system.

Olds et al has studied, for example, a combined approach for the control
of schistosomiasis and geohelminths and found no increase in side effects from the combination of the drugs praziquantel and albendazole compared to praziquantel alone.\textsuperscript{14} However their study was designed to measure cure rates and not haematological responses. Hathirat et al reported that giving iron supplementation after deworming gave a more rapid rise in haemoglobin.\textsuperscript{15}

Food-based approaches will also be of critical importance, related both to dietary practices and the availability of foods with improved iron and micronutrient content. A further example of a combined strategy would be the use of late umbilical cord clamping together with malaria intermittent preventive treatment in infants.\textsuperscript{16}

\textbf{Future research}

It is important to determine if there is a relationship between moderate anaemia and mortality since this would effect the targeting and or the scale of interventions required to reduce anaemia.

Comparative haematological profiles covering all age groups in a population should be more systematically measured in order to establish a broader population basis for anaemia interventions and how they should be targeted. Both single and combined intervention strategies need to be evaluated as responses will vary in different populations due to variation in haematological profiles and risk groups between different communities. Developing national policies will need to take into consideration these variations. The translation of the results of clinical research trials into a programmatic framework will require community effectiveness trials.

It will be important to study when and why extra beneficial effects occur if interventions targeting anaemia are to be integrated, as some studies have shown that anaemia prevention is limited by the occurrence of a significant number of residual cases in young children.\textsuperscript{59} These studies demonstrated, in the different intervention groups, severe anaemia or anaemia, indicative of other underlying causes for anaemia.
REFERENCES


