Relative versus absolute risk of dying reduction after using insecticide-treated nets for malaria control in Africa

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Summary   Four recently completed large-scale randomized controlled trials have assessed the impact of insecticide-treated bednets and curtains on overall child mortality in Africa. These results have sparked numerous discussions among implementing agency representatives and researchers about the public health significance of the results. For the interpretation of impact, most of the arguments have been based on the observed decrease in protective efficacy (a relative measure of impact) with increasing malaria transmission (range: 14–29%, regression for trend: F = 245 on 1,2 DF, P < 0.003). However, an analysis of the absolute measure of impact (the risk difference) showed a different pattern. The impact ranges from 3.8 to 6.9 lives saved per 1000 children protected per year, without a significant trend (F = 2.8 on 1,2 DF, P = 0.2) and with equally high values in both low and high transmission sites. When assessing the public health importance of an intervention, both relative and absolute decrease in risk should be considered.

keywords Malaria, Africa, insecticide-treated bednets (mosquito nets), mortality, malaria prevention and control

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Introduction

Insecticide-treated nets (ITNs) – including bednets and curtains – are a promising tool for reducing the morbidity and mortality from malaria in endemic areas, especially when associated with effective case-management practices (WHO 1996). One review showed a clear impact in reducing the number of malaria infections experienced by children: for the studies comparing insecticide-treated nets with untreated bed nets, the summary incidence rate ratio for an episode of fever plus parasitaemia was 0.76 (95% CI 0.61–0.94), representing a reduction of 24%; for the studies comparing insecticide-treated nets with controls not sleeping under bed nets, the summary incidence rate ratio was 0.50 (95% CI 0.42–0.59), representing a reduction of 50% (Choi *et al*. 1995). Similar results were found in a recently completed Cochrane Review for African trials: a reduction of 48% (95% CI 41–54) in the number of mild episodes if the controls did not use any nets and a reduction of 34%

(98% CI 26–42) when the controls used untreated nets (Lengeler 1998).

However, the yardstick of public health in resource-poor countries remains child survival. In 1991 a trial in The Gambia observed a reduction of up to 63% in child mortality associated with the use of ITNs (Alonso *et al*. 1991). Unfortunately, this trial was not randomized, and the intervention and control groups were not strictly comparable. Although the likelihood of a serious bias as a result of these methodological limitations was small, it was difficult to accept this result alone as a basis for recommending the large-scale implementation of ITN programs. In response to this situation, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), in collaboration with 20 other donor agencies, decided to support four additional large-scale randomized controlled trials to replicate these findings in areas with different ecological and socio-economic conditions.

The recent release of the results from these trials (D'Alessandro *et al*. 1995, Binka *et al*. 1996; Nevill *et al*. 1996; Habluetzel *et al*. 1997) started a lively discussion about the interpretation of these findings and their importance for public health in Africa. At the centre of the debate was the question: What impact should ITNs have to make them a worthwhile public health intervention? Essentially, there has been uncertainty among implementing agency representatives and researchers whether a reduction in overall mortality in children aged 6–59 months of 17% in Ghana (Binka *et al*. 1996) and 15% in Burkina Faso (Habluetzel *et al*. 1997) was sufficient to justify large-scale ITN programs, which are likely to be costly and complex operations. By contrast, the larger reductions reported from the Gambia (25% in 1–9 year-olds) (D'Alessandro *et al*. 1995) and Kenya (33% in 1–59 month-olds) (Nevill *et al*. 1996) were felt to justify such programs. One recent editorial questioned whether ITNs could have any impact at all in the most highly endemic areas in Eastern Africa (Curtis 1996).

We wanted to draw attention to the fact that this discussion has so far concentrated exclusively on *relative risk reduction* (measured through the relative risk – RR), and that *absolute risk reduction* (measured through the risk difference) is an important additional measure for the public health interpretation of the trial results.

We do not enter the current debate over whether the short-term impact on overall mortality that is measured in trials of 1–2 years duration can be maintained over a longer period of time (Snow & Marsh 1995; Trape & Rogier 1996; Greenwood 1997; Lengeler *et al*. 1997; D'Alessandro *et al*. 1997; Snow *et al*. 1997; Molineaux 1997). Similarly, the issue of how the impact measured in the frame of scientific trials (efficacy) will translate into impact under programme conditions is not touched upon. The latter point was raised recently by the team from the Burkina Faso trial because of their concern that the impact observed under trial conditions could maybe only by achieved with a high ITN coverage rate resulting in a mass killing of mosquitoes (Dr. A. Habluetzel & Prof. F. Esposito, personal communication). This area is still unexplored and indeed methodologically difficult to tackle (Lengeler & Snow 1996). There is general agreement among researchers that only the long-term follow-up of children using ITNs will provide a meaningful answer to these questions and at least three sites are currently collecting such long-term data.

Methods

The four TDR trials were carried out between 1992 and 1996 and were all large-scale (56,000–125 000 people covered), randomized and controlled. Three trials looked at the impact of insecticide-treated bednets, while one trial (in Burkina Faso) investigated the impact of treated windows, eaves and door curtains. While three trials attempted to measure efficacy (impact under ideal conditions) the Gambian trial (D'Alessandro *et al*. 1995) aimed rather at measuring effectiveness (impact under programme or 'real world' conditions) and its results reflect therefore a rather low estimate of potential impact in that setting. Technical aspects such as type of netting, insecticide dose, and mortality measurement procedures were standardized initially to an extent that it is very unlikely that such factors can explain differences between trials. The main outcome in all trials was overall mortality rather than malaria-specific mortality.

In the presentation of the essential results (Table 1) the four TDR trials have been arranged by increasing endemicity, as measured by the entomological inoculation rate (EIR). The EIR expresses the number of infective bites an unprotected

Table 1 Summary results of the four TDR trials in Africa to measure the impact of insecticide-treated nets on overall child mortality (children aged 1–59 months). EIR, Entomological Inoculation Rate. Protective efficacy calculated as 1- relative rate (incidence intervention group/incidence control group)

Country (Reference)	Intervention	Transmission intensity (EIR)	Intervention group death rate (/1000/year)	Control group death rate (/1000/year)	Unadjusted protective efficacy (95% CI)	Rate difference (deaths averted/ 1000/year)
Gambia (D'Alessandro *et al*. 1995)	Treatment of existing nets	1–30	18.7	24.3	23% (1–41%)	5.6 (2.0–9.2)
Kenya (Nevill *et al*. 1996)	Bednets + insecticide	10–30	9.4	13.2	29% (3–47%)	3.8 (1.1–6.6)
Ghana (Binka *et al*. 1996)	Bednets + insecticide	100–300	28.2	34.2	18% (1–30%)	6.0 (2.3–9.5)
Burkina Faso (Habluetzel *et al*. 1997)	Curtains + insecticide	300–500	41.8	48.7	14% (− 8–30%)	6.9 (2.0–11.8)

person is likely to experience during one year and is therefore a classical and convenient way of expressing the intensity of malaria transmission. The EIR was found to be 1–30 in The Gambia (Thomson *et al.* 1995), 10–30 in Kenya (Mbogo *et al.* 1995), 100–300 in Ghana (Armah *et al.* 1997) and 300–500 in Burkina Faso (Habluetzel *et al.* 1997). Transmission in the four sites therefore spanned more than an order of magnitude. These trials represent largely the main transmission areas on the continent, with the exception of epidemic zones. The following EIR values were used in the trend analysis: 10 for Gambia, 20 for Kenya, 300 for Ghana and 500 for Burkina Faso. Currently, a fifth trial is ongoing in Western Kenya in an area of year-round high transmission (Dr. P. Philips-Howard, personal communication).

The overall mortality rates presented in Table 1 differ slightly from previously published results because we used a standard age group of 1–59 months rather the differing age groups reported for each trial. For this comparison 1–59 months was felt to be closer to 'under-five mortality', the most commonly used indicator in child survival programs. Neonatal mortality (0–1 months) was excluded because malaria was not thought to represent an important risk in that age group.

Epidemiological concepts were used as defined in the *Dictionary of Epidemiology* (Last 1995). For protective interventions the main relative measure of impact is the protective efficacy, which is based on the relative risk or relative rate (both are abbreviated RR). The protective efficacy is calculated as $(1 - RR) \times (100)$. Since the RR is based on a ratio between the incidence rates in the intervention and control groups (I_e/I_o), it is independent of the initial risk of dying and it has no units.

By contrast, the absolute risk reduction (sometimes also called the attributable risk, despite the potential for confusion with similar epidemiological terms relating to relative measures of impact) is given by the risk difference (I_e-I_o). It has the same units as the incidence rates used for its calculation (in this case deaths per 1000 children-years). The risk difference indicates directly how many children's deaths could be avoided through the use of ITNs (in this case per 1000 children-years). The risk difference is dependent both on the relative risk reduction and on the initial baseline mortality rate. For example in Ghana, the 18% reduction in child mortality from a baseline rate of 34.2 deaths per 1000 per year leads to less averted deaths (5.9 per 1000 per year) than in Burkina Faso with a reduction of 14% on a baseline mortality rate of 48.7 deaths per 1000 per year (6.9 per 1000 per year).

Confidence intervals for the protective efficacies were adjusted for clustering as described in Nevill *et al.* (1996) and Habluetzel *et al.* (1997). Unfortunately this could not be done for the confidence intervals of the risk difference because the

data to do so were not available. For the latter, the confidence intervals are therefore too narrow and this explains why for Burkina Faso the confidence interval overlaps zero (no impact) for the protective efficacy (– 8–30%) but not for the absolute risk difference (2.0–11.8 deaths averted per 1000 child-years).

Testing for trend in protective efficacies according to transmission intensity was done with an unweighted regression of the natural logarithm of protective efficacies on the EIR, using EpiInfo version 6.2 (USD Inc., Stone Mountain GA, USA). The trend of the risk differences was calculated with an unweighted regression of their natural logarithms on the EIR, also using EpiInfo.

Results

Protective efficacies ranged from a reduction of 29% in overall mortality in Kenya to a reduction of 14% in Burkina Faso (Table 1). In the latter country the result did not quite reach significance at the 5% level (95% confidence limit: -8–30%; $P = 0.13$) but it was largely consistent with the result in neighbouring Ghana (18% reduction, 95% confidence limit: 1–30%; $P = 0.04$). The trend for protective efficacies to decrease with increasing EIR is apparent, especially if one assumes that the estimate for the Gambian trial is likely to be an underestimate of the potential impact, as suggested by the very much higher results from the earlier Gambian trial (Alonso *et al.* 1991) and by the authors themselves (D'Alessandro *et al.* 1995). A formal testing of that trend was obtained with a linear regression analysis of the ln (RR) on the EIR: $r2 = 0.99$, $F = 245$ on 1,2 DF, $P = 0.003$.

For the four TDR trials the risk differences ranged from 3.8 to 6.9 averted deaths per 1000 protected children per year. The higher risk differences were rather found at the higher end of the transmission spectrum. There was no evidence of trend when regressing the ln (RD) on the EIR: $r2 = 0.58$, $F = 2.8$ on 1,2 DF, $P = 0.2$. Thus, using the risk difference as measure of impact suggests that ITNs seem to work as well in areas of high endemicity as in areas of lower endemicity – a different conclusion from the comparison of the protective efficacies.

Discussion

Both absolute measure of impact (risk difference) and relative measures of impact (protective efficacy) are important for public health assessment. The decision to invest or not in an ITN programme is complex, and malaria-affected countries will have to make that decision by taking into account their specific health problems, infrastructure and economic situation. Among other assessments, comparing the cost-

effectiveness of different child survival interventions will be fundamental to reach fair and rational decisions. In this context the risk differences measured above provide directly the effectiveness component for the cost-effectiveness calculations.

However, with absolute measures of impact the generalization of the results needs to be considered carefully because they are dependent on the level of overall child mortality, which in turn is the result of many factors (among which malaria transmission is only one). Access to prompt and adequate curative care for example is another major determinant. It is interesting to note that the three sites with similarly poor access to modern health care (Gambia, Ghana, Burkina Faso) show very similar risk differences, while in the one site where access to effective care is much better (Kenya) the risk difference was lowest (mainly as a result of the lower background mortality level).

To some extent protective efficacies allow the extrapolation of trial results to other areas with a similar transmission situation. If the baseline mortality rate is known, the expected incidence rate after intervention can be calculated with the help of the RR and the rate difference is then easily obtained. Such an approach has already been used in an initial cost-effectiveness calculation based on the Gambian data (Evans *et al.* 1997). That study pointed out that ITNs could compete with childhood vaccination in terms of cost-effectiveness (around $20 per prevented disability-adjusted life-years).

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