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Malaria epidemiology and economics: the effect of delayed immune acquisition on the cost-effectiveness of insecticide-treated bednets

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An understanding of the epidemiology of a disease is central in evaluating the health impact and cost-effectiveness of control interventions. The epidemiology of life-threatening malaria is receiving renewed interest, with concerns that the implementation of preventive measures such as insecticide-treated bednets (ITNs) while protecting young children might in fact increase the risks of mortality and morbidity in older ages by delaying the acquisition of functional immunity. This paper aims to illustrate how a combined approach of epidemiology and economics can be used to (i) explore the long-term impact of changes in epidemiological profiles, and (ii) identify those variables that are critical in determining whether an intervention will be an efficient use of resources. The key parameters for determining effectiveness are the protective efficacy of ITNs (reduction in all-cause mortality), the malaria attributable mortality and the increased malaria-specific mortality risk due to delays in the acquisition of functional immunity. In particular, the analysis demonstrates that delayed immune acquisition is not a problem *per se*, but that the critical issue is whether it occurs immediately following the implementation of an ITN programme or whether it builds up slowly over time. In the 'worst case' scenario where ITNs immediately increase malaria-specific mortality due to reduced immunity, the intervention might actually cost lives. In other words, it might be better to not use ITNs. On the other hand, if reduced immunity takes two years to develop, ITNs would still fall into the category of excellent value for money compared to other health interventions, saving a year of life (YLL) at a cost of between US$25–30. These types of calculations are important in identifying the parameters which field researchers should be seeking to measure to address the important question of the net impact of delaying the acquisition of immunity through preventive control measures.

Keywords: malaria; bednets; control; epidemiology; mortality; cost-effectiveness

1. INTRODUCTION

Modelling the effectiveness or impact of an intervention requires consideration of the epidemiology of the disease in question. This is especially true in the case of *Plasmodium falciparum* malaria, which demonstrates a wide spectrum of epidemiological patterns under different endemic conditions. For instance, under conditions of high and intense transmission, disease burden is concentrated amongst children aged less than 24 months, whereas under conditions of low to moderate transmission the disease risk is spread more evenly through childhood (Snow *et al.* 1997). These differences in age-specific disease profiles, and the inferences for the acquisition of functional immunity, have raised concerns of the long-term effects of control measures in high transmission areas which aim to reduce parasite exposure.

One such preventive measure, which has recently received a great deal of interest, is insecticide-treated bednets (ITNs). Four large-scale randomized controlled trials in malaria-endemic areas in Africa have demonstrated an impact of ITNs of between 17 and 33% on all-cause mortality in children under five (D'Alessandro *et al.* 1995; Binka *et al.* 1996; Nevill *et al.* 1996; Habluetzel *et al.* 1997), and a Cochrane review meta-analysis of these trials has estimated an average proportional reduction in all-cause mortality of 0.18 (Lengeler 1998). These field trials, however, only measured the short-term impact on all-cause mortality, since they have been evaluated only over a maximum of two years, and it remains unclear what the impact of reduced parasite exposure will be on the long-term patterns of mortality and morbidity. In addition, the cost-effectiveness analyses that have shown ITNs to be a relatively good public health buy, with costs per disability-adjusted life year (DALY) or discounted

healthy life year (DHLY) gained of between US$7.90–73.50 (Binka *et al*. 1997; Picard *et al*. 1993; Evans *et al*. 1997), have considered only short-term efficacy in their calculations or assumed that short-term efficacy is maintained over the life of the intervention.

Although there does seem to be a consensus that the implementation of ITNs in high transmission areas may shift the risk of clinical disease to older children due to delayed acquisition of functional immunity (Menendez *et al*. 1997; Snow *et al*. 1997; Snow & Marsh 1998), the resulting impact on intervention effectiveness is the subject of much debate. Some authors suggest that a reduction in transmission could, in the long term, result in subsequent increased mortality (Snow *et al*. 1997), others that the overall gain may remain unchanged (Trape & Rogier 1996), or that reducing exposure will probably always be beneficial because of the indirect impacts of malaria on mortality (Molineaux 1997).

Analyses of the long-term impact of delayed immune acquisition is hampered by the lack of empirical data, and until the effects of the ITN trials are monitored over longer time periods, this will remain the case. In the meantime, it is critical to begin to examine what level and timing of delayed immune acquisition would reduce the effectiveness of ITNs to such an extent that governments would be advised to reconsider their use. The aim of this paper is to illustrate the importance of combining the disciplines of epidemiology, demography and economics into such questions by exploring the possible effects of increased malaria-specific mortality risks, due to delayed immune acquisition, on the effectiveness and cost-effectiveness of ITNs implemented in high transmission areas.

2. METHODS

(a) *Basic framework*

The analysis uses a similar approach to Evans *et al.* (1997) by evaluating the impact of intervention on a cohort of 10 000 newborns. The cohort is followed from birth to age 85 and the impact of intervention is assessed by comparing the number of survivors at each age, with and without the intervention.

In the absence of intervention, the number of survivors at each age is assumed to experience standard West African death rates with a female life expectancy of 50 years (United Nations 1991). Standard life tables are usually presented in an abridged form with the age-specific probabilities of dying (${}_nq_x$ values, the proportion of persons in the cohort alive at the beginning of an indicated age interval (x) who will die before reaching the end of that interval ($x+n$)) presented for age classes zero years (${}_1q_0$), one to four years (${}_4q_1$) and thereafter groupings of five years (${}_5q_x$) until age 80 years (${}_5q_{75}$). Single-year probabilities of dying were estimated from this abridged data using a computer package MortPak-Lite (United Nations 1988), which uses a formula for the age-curve of mortality (Heligman & Pollard 1980). The cohort analysis uses these single-year probabilities of dying (q_x) (figure 1) to calculate the number of survivors at each age x.

In the presence of ITN intervention, the number of survivors at each age is also modified by the protective efficacy of impregnated nets (e, the proportional reduction in all-cause mortality), the malaria-specific 'shifted' mortality risk arising from reduced functional immunity (p) and the proportion of deaths attributable to malaria (z). The shifted mortality risk is age-dependent and applied to ages 1–9. The efficacy of the intervention is applied to those ages that receive the intervention, and is assumed to be constant for those ages. The age-groups experiencing protective efficacy, and likewise the years of impregnated net protection required, will depend on the age-group targeted for the intervention. Two scenarios are considered:

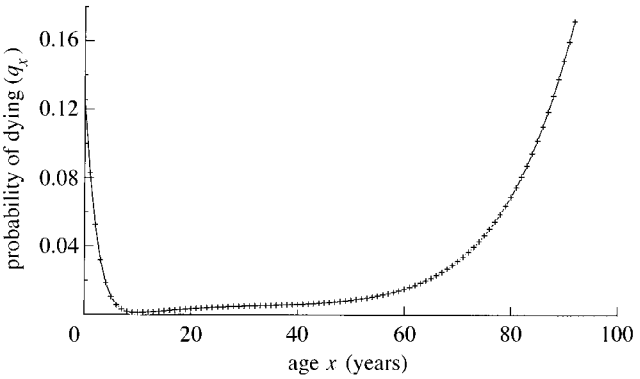

Figure 1. The probability of dying (q_x) by age (x) assuming a United Nations West African female model life table with a life expectancy of 50 years.

(i) the intervention is delivered up to the tenth birthday (target age-group is 0–9-year-olds);
(ii) The intervention is delivered up to the fifth birthday (target age-group is 0–4-year-olds).

(b) *Effectiveness*

Effectiveness is defined as the discounted years of life lost (YLLs) averted by the intervention (Murray & Lopez 1996). In this analysis, no disability and no age-weights are included. The effectiveness is assessed simply as the difference between the number of individuals surviving at each year in the cohort with the intervention (D) as compared to those without the intervention (C), discounted at 3%, and then summed over the lifetime of the cohort to give the total discounted YLLs. A discount rate of 3% is applied to both costs and effectiveness (World Bank 1993). This reflects the fact that society prefers benefits sooner rather than later, and prefers to pay costs later rather than sooner (Drummond *et al.* 1997).

It is assumed that the effective coverage of the programme is 65%, consistent with the 100% coverage achieved in the trials where all children were provided with free nets, and the observation that approximately 65% of them used the nets correctly (Binka *et al*. 1996; Nevill *et al.* 1996). Based on the Cochrane review meta-analysis of the ITN trials the proportional reduction in all-cause mortality (efficacy, e) is assumed to be 0.18 (Lengeler 1998).

(i) *Cohort size each year without intervention*

In the absence of intervention, the number in the cohort C at age $x=0$ is 10 000, and for each age $x+1$ following is

$$C_{x+1} = C_x - (C_x \cdot q_x),$$

where q_x is the probability of dying at each age x.

(ii) *Cohort size each year with intervention*

With the intervention, the number in the cohort D at age $x=0$ is 10 000, and for each age $x+1$ following is

$$D_{x+1} = D_x - ((D_x \cdot (q_x + (q_x \cdot p_x \cdot z)) \cdot (1 - e)),$$

where e is the reduction in all-cause mortality in the ages targeted by the intervention (e.g. 0.18 for 0–9- or 0–4-year-olds,

else zero), p_x is the malaria-specific 'shifted' mortality risk resulting from reduced parasite exposure in ages x (where $x=1$–9) and z is the proportion of deaths attributable to malaria. When p_x is zero, there is no shifted mortality risk from delayed functional immunity.

(iii) *Malaria-specific shifted mortality*

The malaria-specific shifted mortality risk (p_x) is based on a comparison of the rates of severe disease in 1–9-year-olds under different transmission settings. The incidence of hospitalization with potentially life-threatening malaria were recorded from four communities in sub-Saharan Africa: two exposed to intense transmission (cross-sectional *Plasmodium falciparum* rates amongst children aged 0–9 in excess of 70%) and two exposed to low-to-moderate transmission (infection risks between 30 and 40%) (Snow *et al.* 1997). The age-specific incidence of severe morbidity were computed for these two transmission settings and are shown in figure 2*a*. The increased risk of disease at age x is calculated as a simple ratio of rates under the assumption that reducing parasite exposure by preventive control efforts would in the long-term transform the patterns of severe morbidity from that in a high transmission area to that of a low-to-moderate transmission area (see figure 2*b*). In this analysis, it is assumed that this shifted risk of disease would apply equally to mortality, such that

$$p_x = -(1 - (M_x/H_x)),$$

where M_x is the average disease rate per 1000 in moderate transmission areas, and H_x is the average disease rate per 1000 in high transmission areas, at each age x (where $x=1$–9). The upper and lower 95% confidence intervals for this shifted mortality risk at each age x were calculated as according to Miettinen (Kirkwood 1988):

$$95\%\text{CIs} = -(1 - (M_x/H_x)^{(1\pm 1.96/\chi)})$$

The shifted mortality risk is malaria-specific, and assumed to apply immediately (i.e. at age 1) in the base case.

(iv) *Malaria-attributable mortality*

The proportion of deaths attributable to malaria in 1–4-year-olds is assumed to be 0.34, an estimate based on empirical data from a number of studies over the last 15 years in sub-Saharan Africa using verbal autopsies (table 1). Since empirical data from verbal autopsies suggests that the malaria attributable mortality in infants (0–1-year-olds) tends to be lower than that in 1–4-year-olds (e.g. Greenwood *et al.* 1987; Delacollette *et al.* 1989; Alonso *et al.* 1992; Jaffar *et al.* 1997), the data presented from each study site in table 1 are selected to exclude 0–1-year-olds where possible. In the absence of comparative empirical data in older children (5–9-year-olds), the proportion of deaths attributable to malaria is assumed to be equivalent to that in 1–4-year-olds.

(v) *Discounted YLLs averted*

The discounted years of life saved (YLLs averted) by the intervention is simply the difference between the number of survivors at each age multiplied by the discount factor and summed over the lifetime of the cohort:

$$\sum_{x=0}^{x=n} (D_x - C_x)(1/(1+r)^x),$$

where r is the discount rate (0.03) and n is the maximum age.

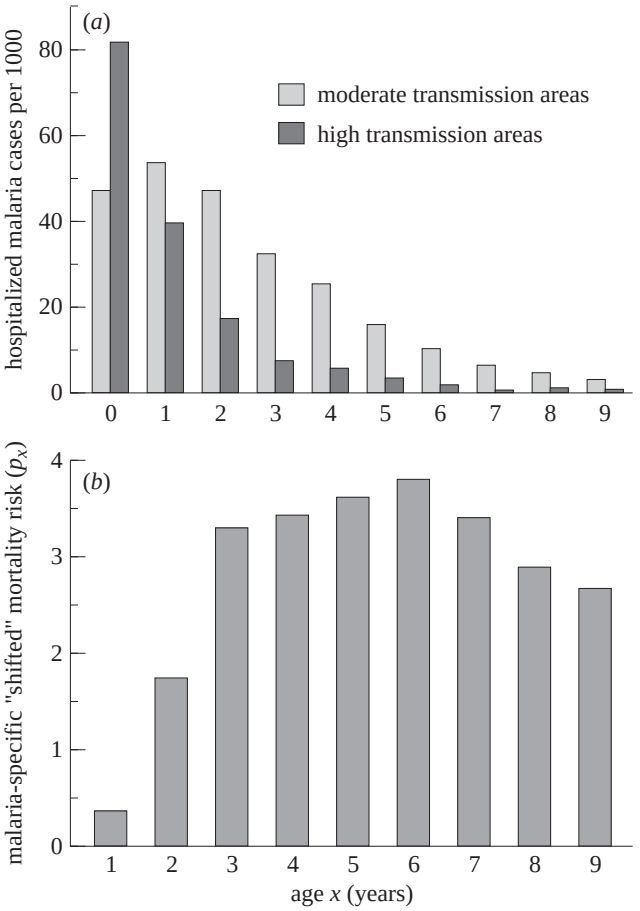

Figure 2. (*a*) The incidence of severe hospitalized malaria by age for moderate and high transmission areas. The moderate transmission areas are Sukuta (The Gambia) and Kilifi North (Kenya), and the high transmission areas, Saiya and Kilifi South, both in Kenya (Snow *et al.* 1997). (*b*) The malaria-specific 'shifted' mortality risks by age. Based on a comparison of empirical data on the age-specific risks of hospitalized malaria in moderate and high transmission areas. Note: the risk for age 7 was not consistent with other ages, so the average of age 6 and 8 was taken.

(c) *Cost analysis*

The annual cost per targeted child for delivering an impregnated bednet is based on an analysis by Paul Coleman, Catherine Goodman and Anne Mills (personal communication). They defined ranges for each costing parameter from a review of ITN studies, and calculated a mean annual cost per child under five years of US$8.06 if all nets are re-impregnated. This cost estimate was based on a mean number of nets per child of 2.96.

The total cost of the intervention will be dependent on the age-groups targeted, and therefore the number of nets and years of re-impregnation required. The general formula for calculating the total cost of the intervention is

$$\sum_{x=0}^{x=i} (v \cdot D_x \cdot (1/(1+r)^x),$$

where v is the annual cost of an impregnated ITN at each age x from birth ($x=0$) up until age i, where $i=9$ or 4 depending on the target age-group. The annual cost (v) includes the annualized capital cost of the nets and their delivery, plus the yearly cost of re-impregnation.

Table 1. *The proportion of deaths attributable to malaria in children under five years of age in various study sites in sub-Saharan Africa*

study site	survey date	age-group (months)	total number of deaths	number of malaria deaths	proportion of deaths attributable to malaria	source
Ghana[a]	1993–95	6–59	451	163	0.36	Binka *et al.* (1996)
Gambia[b]	1988	6–59	178	57	0.32	Alonso *et al.* (1992)
Lake Kivu, Zaire[c]	1986–87	12–59	191	26	0.14	Delacollette *et al.* (1989)
Burundi[b]	1990–91	12–59	72	24	0.33	Delacollette & Barutwanayo (1993)
Gambia[c]	1982–83	12–59	81	20	0.25	Greenwood *et al.* (1987)
Gambia[c]	1989–93	12–59	1464	637	0.44	Jaffar *et al.* (1997)
Gambia[a]	1992–93	12–35	104	38	0.37	D'Alessandro *et al.* (1995)
Benin[c]	1989	0–35	29	9	0.31	Velema *et al.* (1991)
Ivory Coast[c]	1984	0–30	103	21	0.20	Diplo *et al.* (1990)
Bagomoyo, Tanzania[c]	1986–87	0–59	610	124	0.20	Mtango *et al.* (1992)
Bagomoyo, Tanzania[c]	1992–94	0–59	118	63	0.53	Premji *et al.* (1997)
Muheza, Tanzania[c]	1992–93	0–59	83	30	0.36	Salum *et al.* (1994)
Kilifi, Kenya[b,c]	1991–93	1–59	321	98	0.31	Snow *et al.* (unpublished data)

[a]Control clusters; [b]pre-intervention; [c]demographic surveillance.

Table 2. *Parameter values for the base case and the sensitivity analysis*

parameter	base case	sensitivity analysis			source
annual cost of re-impregnated bednet per target child	US$8.06 (assumes 2.96 nets per child)	US$2.72 (assumes 1 net per child)			P. Coleman, C. Goodman and A. Mills (personal communication)
proportional reduction in all-cause mortality (efficacy, e)	0.18	0.29 (upper value of range)			Lengeler (1998)
malaria attributable mortality (z)	0.34	0.14 (lower value of range)			present study
malaria-specific shifted mortality risk (p_x)		(a)	(b)	(c)	present study
$x=1$	0.36	0.18	0	0	
2	1.74	1.30	0.36	0	
3	3.30	2.36	1.74	0.36	
4	3.44	2.34	3.30	1.74	
5	3.62	2.23	3.44	3.30	
6	3.80	2.03	3.62	3.44	
7	3.40	1.50	3.80	3.62	
8	2.89	0.96	3.40	3.80	
9	2.66	0.64	2.89	3.40	

(a) Immediate low risk (lower 95% CIs of base case estimates); (b) one-year time delay of base case estimates; (c) two-year time delay of base case estimates.

(d) *Sensitivity analysis*

Sensitivity analysis is a critical component of any cost-effectiveness analysis, since there are always parameter values which are uncertain or vary under different settings. The parameter values used in the base case to assess effectiveness reflect the 'worst case' scenario for ITN intervention in a high transmission area, and the sensitivity analysis investigates the impact given more favourable conditions. The parameter values used in the base case are given in table 2, alongside those explored in the sensitivity analysis.

(i) *Number of nets per child*

Many workers believe that it is necessary to distribute more than one net per child, to ensure that nets are not diverted for use by other family members, leaving the target group unprotected. The annual cost per child of administering an impregnated net of US$8.06 used in the base case assumed 2.96 nets per child. This assumption is likely to underestimate the cost-effectiveness of ITNs since the impact of providing impregnated nets to other family members is not considered. The effects of decreasing the number of nets per child to one (equivalent to reducing the annual cost per child to US$2.72) is investigated.

(ii) *Reduction in all-cause mortality (efficacy)*

In the base case, an efficacy (e) of 0.18 was assumed for all ages targeted with an impregnated bednet (Lengeler 1998). The sensitivity of the results to an increase in e to 0.29 (the upper value of the range of efficacies from the randomized trials standardized for target group) was investigated.

(iii) *Malaria-attributable mortality*

Although the estimate of malaria-attributable mortality used in the base case (0.34) is formulated from empirical data (table 1), there was variability between the individual study sites (ranging from 0.14 to 0.53). The sensitivity of the results to a decrease in malaria attributable mortality to 0.14 in 1–9-year-olds is explored.

(iv) *Malaria-specific shifted mortality risk*

The shifted mortality risk arising from a delay in the development of functional immunity is the parameter for which there is the greatest uncertainty. The base case values were computed by comparing the rates of hospitalized malaria in high transmission areas with those in moderate transmission areas, and were assumed to occur as soon as the intervention is implemented ('immediate high mortality risk'). These base case mortality risks suggest that in some age-groups intervention could result in a 300–400% increase in the rate of malaria-specific mortality. This is likely to represent the 'worst case' scenario, and two further scenarios were investigated as a form of sensitivity analysis (table 2).

(i) Mortality risks based on the lower 95% CIs for the estimates used in the base case applied at age 1 ('immediate low mortality risk').
(ii) The introduction of a time delay before the onset of the increased mortality risk ('delayed mortality risk'). The assumption is that the mortality risk occurs only up until a maximum age of 9, but that the first age at which this mortality risk is apparent is deferred from age 1 to age 2 or age 3 (corresponding to time delays of one and two years, respectively).

(e) *Optimization analysis*

An optimization analysis is also undertaken to determine the parameter values of efficacy (e) and malaria-attributable mortality (z) at which the cost per YLL averted is $\leqslant$US$25 (a level considered to be a highly attractive buy (Ad Hoc Committee on Health Research & Development 1996)).

3. RESULTS

(a) *Effectiveness*

In this analysis, the effectiveness of ITN intervention will depend on the reduction in all-cause mortality (efficacy), the age-group which receive this protection (0–9- or 0–4-year-olds), the timing and extent of the malaria-specific mortality risk from reducing the force of infection, and the proportion of mortality attributable to malaria.

In the base case, the proportional reduction in all-cause mortality (efficacy) in the target group is 0.18 and the proportion of malaria attributable mortality in 1–9-year-olds is 0.34 (table 2). The effectiveness of ITN intervention is assessed by comparing the number of survivors with and without the intervention over each year of the cohort's lifetime. Figure 3 illustrates the number of 'extra' survivors with intervention (i.e. number in cohort with intervention (D) minus the number in cohort without intervention (C)) by age, given variations in the timing and extent of the shifted mortality risk. If there is no shifted mortality risk, then intervention results in more survivors than no intervention at all years during the cohort's lifetime. Intervention is targeted at birth through to age 4 or 9. During these ages, there is an increase in the number of extra survivors, reaching a peak at ages 5 and 10, respectively (determined by the age-group targeted), after which the number of extra survivors at each age remains high with only a slight decline throughout the rest of the cohort's lifetime.

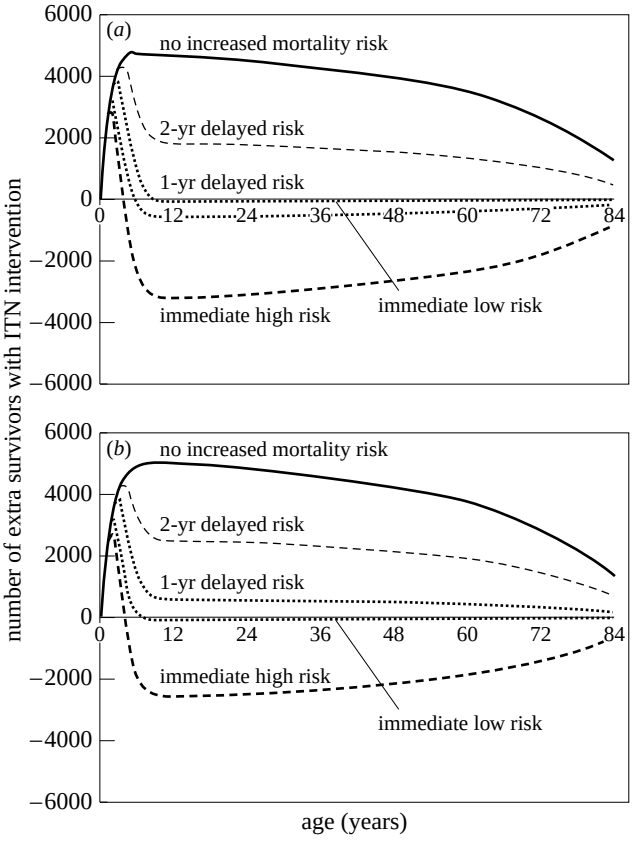

Figure 3. The extra number of survivors at each age of the birth cohort for ITN intervention targeted at (a) 0–4-year-olds and (b) 0–9-year-olds. The solid line represents no increased mortality risk, whereas the dashed lines represent a number of scenarios varying in the extent and timing of this risk. The parameter values follow the base case (see table 2).

The introduction of a shifted mortality risk can change this pattern dramatically. Taking the base case scenario (immediate high risk applied at age 1), although there is an increase in the number of extra survivors in the first few years of life, the peak occurs earlier (age 2 for both target groups), declines rapidly until age 9 (the last age-group experiencing the increased mortality) and then plateaus. Most importantly, after age 4 the number of extra survivors is negative, i.e. the intervention results in less survivors than no intervention. If the extent of the mortality risk is reduced (immediate low risk applied at age 1), a similar pattern is observed, though the level at which the curve plateaus is higher, i.e. although intervention can result in less survivors than no intervention, the numbers are markedly lower. Introducing a time delay in the onset of the mortality risk defers the age at which the number of extra survivors starts to decline, but more importantly reduces the severity of this descent. As a result, the introduction of a time delay can prevent the

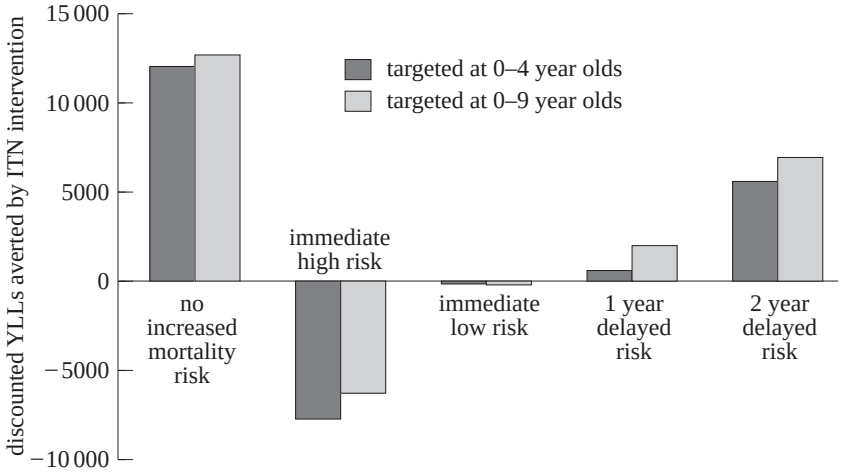

Figure 4. The discounted YLLs averted by ITN intervention considering a range of scenarios for malaria-specific 'shifted' mortality risk. The parameter values follow the base case (see table 2).

Table 3. *The cost-effectiveness (cost per YLL averted) of ITN intervention targeted at 0–4 and 0–9-year-olds at different parameter values for efficacy (e) and malaria attributable mortality (z)*

	$e = 0.18$ and $z = 0.34$				$e = 0.29$ and $z = 0.14$			
	US$8.06[a]		US$2.72		US$8.06		US$2.72	
	0–4-year-olds[b]	0–9-year-olds	0–4-year-olds	0–9-year-olds	0–4-year-olds	0–9-year-olds	0–4-year-olds	0–9-year-olds
no increased mortality risk	27.35[c]	45.41	9.23	15.32	17.09	28.58	5.77	9.64
immediate high risk	—[d]	—	—	—	28.00	42.98	9.45	14.5
immediate low risk	—	—	—	—	22.99	36.74	7.76	12.4
delayed high risk (one year)	630.02	288.54	212.61	97.37	22.25	35.16	7.51	11.86
delayed high risk (two years)	61.21	83.65	20.66	28.23	19.85	31.83	6.70	10.74

[a]Annual unit cost of an ITN per target child; [b]age-group targeted; [c]cost per YLL averted (US$); [d]negative YLLs.

increased mortality risk from resulting in fewer survivors than no intervention.

The effectiveness of the intervention (YLLs averted) is calculated as the sum of these extra survivors at each age, discounted at 3%. Figure 4 presents the effectiveness (discounted YLLs averted) for each of the scenarios explored in figure 3. In the 'best case' scenario, where ITNs do not result in any increased mortality risk due to delayed immunity, ITN intervention would save over 12 000 discounted YLLs over the lifetime of the cohort of 10 000 newborns. A high, but delayed mortality risk will also save YLLs, though the absolute numbers are lower and vary with the length of the time delay. For instance, a one-year time delay would result in 4–15% of the YLLs averted by the 'best case' scenario, while a two-year time delay would result in approximately half. At the other extreme, an immediate high risk of mortality due to delayed immunity (base case) will result in negative YLLs (worse than a 'do-nothing' approach).

In all cases, targeting 0–9-year-olds saves more YLLs than targeting 0–4-year-olds. However, targeting a wider age-group will also increase the costs of the intervention, as will any variations in the number of survivors within the target age-group.

(b) *Cost-effectiveness analysis*

Table 3 presents the cost-effectiveness ratios (costs per YLL averted) for the different variants of 'shifted' mortality risk from delayed immunity acquisition. The results are shown separately for ITN intervention targeted at 0–4 and 0–9-year-olds. It has been suggested that any control programme which costs less than US$25–30 per DALY averted is 'very attractive' and that interventions costing up to US$150 per DALY are 'attractive' buys even to poor countries (Ad Hoc Committee on Health Research & Development 1996). Assuming the base case parameters (table 2), the 'best case' scenario of no increased mortality risk is very cost-effective, while a two-year delay in the onset of this risk is still attractive ($<$ US$90 per YLL averted) (table 3). Clearly the quicker the mortality risk develops, the less cost-effective will be the intervention, with the base case assumption of immediate mortality risk showing that intervention would actually lose more years of life than it saves.

(i) *Variations in efficacy and malaria attributable mortality*

The above results are based on an efficacy (e) of 0.18 and a malaria attributable mortality (z) of 0.34. Both these parameters were derived from empirical data, but are likely to vary in different endemic settings. The results are highly sensitive to such variations. Although the baseline assumptions suggest that ITNs would cost more lives than they saved, these results can easily be reversed by changing the assumptions about e and z. For example, using the upper value of e (0.29) and the lower value for z (0.14) from table 2 (the sensitivity analysis parameters) would produce positive lives saved and result in attractive cost-effectiveness ratios of less than US$45 per YLL for any of the increased mortality risk scenarios investigated (table 3). Indeed, targeting 0–4-year-olds under these assumptions would indicate that ITNs would be 'highly attractive' even given the 'worse case' scenario for increased mortality risk (table 3).

This type of investigation allows the analyst to explore the threshold parameter values for efficacy and malaria attributable mortality at which intervention would be highly attractive (i.e. cost less than US$25 per YLL averted). For instance, given an efficacy of 0.18 for ITNs targeted at 0–4-year-olds, and an annual unit cost of US$2.72, the malaria-attributable mortality could not exceed 0.127 for the 'worst case' scenario of increased mortality risk to achieve this cost-effectiveness target. The converse is that a malaria attributable mortality of 0.34 would require the efficacy of ITNs to be no lower than 0.167 for a mortality risk delayed for two years, increasing to 0.329 if the mortality was immediate. Figure 5 expands on this type of analysis by presenting the combinations of efficacy and malaria attributable mortality which achieve a range of cost-effectiveness targets ($<$US$25, 25–149 and $>$150 per YLL averted). It is assumed that ITNs are targeted at 0–4-year-olds and the annual unit cost is US$2.72 (one net per child). The 'worst case' scenario for 'shifted' mortality risk (immediate high risk) is presented in figure 5*a*, alongside a risk delayed for two years (figure 5*b*). The white squares represent combinations of efficacy and attributable mortality which would result in negative YLLs, i.e. intervention would be worse than a 'do-nothing' approach. As expected, a high malaria attributable mortality and low efficacy can result in negative YLLs, with the range of parameter values being wider for a shifted mortality which occurs immediately, than for one which is delayed for two years. In a similar way, the range of parameter values required to achieve a cost per YLL averted of $<$US$25 is more restricted for the immediate shifted mortality risk. However, even if ITN efficacy is low (e.g. 15% reduction in all-cause mortality), then an intervention which would result in an immediate increased mortality risk in 1–9-year-olds would still be an attractive public health buy, as long as the percentage of deaths attributable to malaria was less than 15% (increasing to 45% if this risk was delayed for two years, i.e. occurred at ages 3–9 years). If there was no increased mortality risk, only the value of efficacy is important, as effectiveness is now independent of the malaria attributable mortality. Under these conditions, as long as the efficacy is greater than 0.066 (given a unit cost of US$2.72 and intervention targeted at 0–4-year-olds), then intervention will be highly attractive ($<$US$25 per YLL averted).

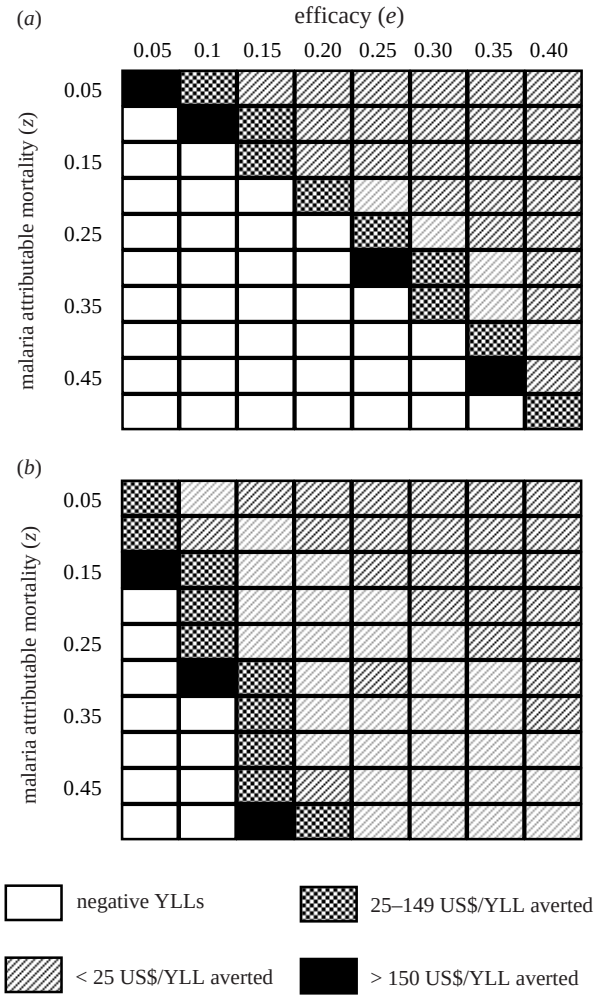

Figure 5. The combinations of efficacy (e) and malaria attributable mortality (z) which satisfy a given cost-effectiveness target given a 'shifted' mortality risk which is (*a*) immediate and (*b*) delayed by two years. Intervention is targeted at 0–4-year-olds, and assumes an annual unit cost of US$2.72 per child targeted.

4. DISCUSSION

This paper considers the impact of introducing ITNs under conditions of intense malaria transmission where functional immunity is acquired early in childhood. Under the assumption that sustained reductions in parasite exposure leads to a change in the speed at which immunity to the fatal consequences of infection occurs, a function of 'shifted' mortality risk was derived from empirical data on life-threatening disease. Incorporating this mortality risk into a cost-effectiveness framework, the impact of ITNs under various scenarios were explored. The analysis suggests that it is not possible to be confident that ITNs would be an effective or a cost-effective intervention in the presence of shifted mortality risks due to delayed acquisition of functional immunity. Both effectiveness and cost-effectiveness depend most critically on the speed at which these mortality risks develop, as well

as on the proportion of deaths that are attributable to malaria and the efficacy of ITNs.

At one extreme, if ITNs do not transfer mortality risks from younger to older children, they would be extremely cost-effective, with costs per YLL averted in the order of US$25–30. However, in the presence of delayed immunity acquisition the timing of the shifted mortality risks is critical. An immediate risk could result in the anomalous situation of ITNs costing more lives than they save, whereas a time delay of two years would save a significant number of lives on balance, and would be cost-effective for most assumptions about the other parameters. The analysis suggests the question of the timing of any delayed immunity acquisition is as important as the question of its magnitude.

These results require some qualifications, since although the parameter values for ITN efficacy, malaria-attributable mortality and shifted mortality risk were based either directly or indirectly on empirical observations, a number of assumptions were made.

First, the estimates of ITN efficacy were based on the proportional reduction in all-cause mortality in children under five (Lengeler 1998). In the absence of empirical data on the effect in older children, these estimates were extrapolated to ages 5–9. In a similar manner, the estimates of the malaria attributable mortality were formulated from data in children under five years old, and then extrapolated to 5–9-year-olds. Clearly variation in the efficacy or malaria attributable mortality in 5–9-year-olds would affect the cost-effectiveness of ITNs, the relative effect being dependent on the rate of all-cause mortality in these age-groups. However, since all-cause mortality rates in 5–9-year-olds are markedly lower than those in under-fives (figure 1), then changes in these parameter values in older children are likely to have less effect than comparable changes in younger children. The efficacy estimates for ITNs were also related to conditions of relatively high coverage and compliance. ITNs implemented as part of a control programme, rather than a field trial, are likely to result in significantly lower levels of coverage and compliance. This will reduce the effectiveness of the intervention, but the relationship between compliance and health impact, both at an individual level and in terms of reduced transmission, are uncertain (Lengeler & Snow 1996). Finally, the extent of the shifted mortality risk was based on a comparison of hospitalized malaria cases, and it is not known whether these morbidity ratios would equally apply to mortality.

The assumptions outlined above reflect the paucity of reliable field data with which to support evaluations into the impact and cost-effectiveness of control interventions. Clearly more empirical data is required on the epidemiology of malaria under different levels of transmission, and in the presence of interventions which reduce parasite exposure. However, although more accurate data may change the conditions under which the various scenarios for shifted mortality risk become cost-effective, it would not change the overall conclusion that it is the timing of the delayed immune acquisition that is absolutely critical.

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