IMPLICATIONS OF THE WESTERN KENYA PERMETHRIN-TREATED BED NET STUDY FOR POLICY, PROGRAM IMPLEMENTATION, AND FUTURE RESEARCH

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Abstract. The fifth, and probably last, large-scale, group-randomized, controlled trial of insecticide (permethrin)-treated bed nets (ITNs) showed that ITNs are efficacious in reducing all-cause post-neonatal mortality in an area of intense, perennial malaria transmission. The trial helped to define pregnant women and infants as target groups for this intervention in high transmission settings. High population coverage with ITNs in both target and non-target groups may be critical to enhance health and survival in pregnant women and infants. The proportion of households with ITNs (coverage), the proportion of individuals properly deploying ITNs each night (adherence), and the proportion of nets properly treated with insecticide (treatment) are the three key determinants of effectiveness of large-scale ITN programs. These three simple outcomes should serve as the basis for program objectives and monitoring and evaluation efforts. Coverage effects and economic analysis support the proposition that ITNs may be viewed as a public good, worthy of public support. Research should continue to improve the intervention tools (the net, the insecticide, and methods for durable treatment and re-treatment) and their deployment.

INTRODUCTION

The rationale for the study described in this supplement was a simple question: will use of insecticide (permethrin)-treated bed nets (ITNs) reduce child mortality and morbidity in an area of intense, perennial malaria transmission in Africa? Although the question was straightforward, the project design was ambitious and multidisciplinary in scope.1 In consequence, the study has implications beyond providing evidence on the efficacy of ITNs in an area of Africa with a particular level and pattern of malaria transmission. In this concluding paper, we outline our view of the implications of our most important results for policy, program implementation, and future research. Key results and implications generated from the study are summarized in Tables 1 and 2.

MATERIALS AND METHODS

Our study followed four previous randomized controlled mortality studies of ITNs and curtains conducted in areas with either low to intermediate malaria transmission, or high but markedly seasonal malaria transmission.2−5 The primary purpose of our study was to fill the remaining gap in knowledge and to determine whether ITNs were equally effective in areas with intense perennial malaria transmission, or whether there exists an upper limit in malaria transmission intensity above which ITNs are ineffective. Although ITNs are directed at malaria-transmitting mosquitoes, the rationale underlying this saturation-effect hypothesis stems from a decades-old immunologic idea: when transmission is high and continuous, the immune system’s response and associated rates of morbidity and mortality plateau, implying that mere reduction in transmission may have little or no effect on human health.6,7 Our results refute this idea, at least for infants followed for two years: an imperfect intervention such as ITNs sufficiently reduces malaria transmission to lower by approximately one-fourth the burden of post-neonatal infant mortality in this area of intense malaria transmission.8 Reduced malaria exposure during infancy did not result, with continued ITN use, in increased malaria morbidity in one-year old children.9 Furthermore, our immunologic studies suggest that reduced malaria exposure due to the use of ITNs do not inhibit maintenance of the predominant antibody effector mechanism in children less than three years of age.10 Thus, this intervention, if properly implemented, could be effective anywhere in Africa with high levels of sustained malaria transmission. In our study, we inferred from reductions in numbers of infective indoor-resting mosquitoes that malaria transmission was reduced by approximately 90%;11 force of infection in infants was reduced by about 74%.9 By implication, any intervention that reduces malaria transmission by this amount, whether indoor residual spray, source reduction, or other more speculative interventions (transgenic mosquitoes or transmission blocking vaccines), would have similar efficacy. In this regard, it worth noting that a non-randomized indoor residual spray program conducted near our study site 25 years ago resulted in a 40% reduction in infant mortality.12

Insecticide-treated bed nets were shown to have clear and profound effects on morbidity in young children. Episodes of clinical malaria and severe malarial anemia were all substantially reduced in infants and in children 1−3 years of age.9,13 Growth and weight gain were improved in infants.13 Maternal and placental malaria and maternal anemia in pregnant women (for the first four pregnancies) were reduced, resulting in reduced risk of low birth weight of newborns.14 Although some effect on malarial anemia was seen in schoolgirls (12−13 years old),15 other effects in primary schoolchildren were less dramatic, with a small effect of ITNs on body composition (percent body fat and lean body mass) seen in children 5−12 years old, but no effect on standard anthropometric parameters.16

Our age-stratified analysis of the impact of ITNs on child mortality in those less than five years old showed that the greatest impact, both in terms of relative efficacy (protective efficacy expressed as %) and particularly in terms of absolute
Targeting of infants and pregnant women does not necessarily imply, however, that ITNs should be distributed solely to areas that have ITNs, the greater the benefit to neighboring households without nets. If high coverage is essential for ITNs to attain their greatest impact, then all members of a population should use ITNs to maximize benefit for target groups. The intensity of the community effect is also likely to vary with the absolute distance between houses, but has been observed in sufficiently diverse settings to support the hypothesis that the anthropophilic malaria vectors of Africa are susceptible to this phenomenon.

The importance of insecticide in augmenting protective effects of bed nets has been inferred from comparison of ITN studies using either untreated bed nets or no bed nets as controls. Our results extend this finding by showing that delayed re-treatment of nets leads to diminution of efficacy on both mosquito populations and child mortality. Since the impact of ITNs on mosquitoes extend beyond the borders of the intervention area, it is likely that population-wide effects of ITNs on the vector population are augmented by specific effects of insecticide. Furthermore, since proper adherence (daily deployment of nets in terms of hanging and use) was needed for maximal impact on indoor resting densities of mosquitoes, it is likely that proper adherence, which clearly is essential to the individual protective effect of ITNs, also contributes to the community effect of ITNs by maximizing contact between host-seeking mosquitoes and insecticide-treated fabric and minimizing contact with potentially infective hosts.

Thus, for nets to be maximally effective, our data show that coverage should be high, that nets should be retreated promptly, and that individuals should properly deploy their nets each night. Because simple, clear, and correct messages are not always provided, there is a need to reorient our thinking, regarding population-level versus individual (household)-level effects, also emerged from our analysis of the impact of ITNs on household expenditures. We anticipated that ITNs would markedly reduce household expenditures on malaria treatment, and found that they did in relative terms, but that this only resulted in minor actual savings. The reason for this is simple: in this impoverished area, little money is spent on health care so little opportunity for savings exists. In contrast, from a population-level perspective, ITNs will be cost-effective as a community-wide intervention. Part of this cost-effectiveness derives from the reduction by more than one-fourth of the number of

<table>
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<td>90% reduction in malaria vector population; force of infection in infants reduced by 74%.</td>
<td>9,11</td>
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<td>23% reduction in all-cause mortality in infants (excluding neonates).</td>
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<td>No evidence for compromised immunologic antibody response in children less than five years of age.</td>
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<tr>
<td>Clear beneficial effects on malaria specific morbidity (clinical malaria, malarial anemia) and growth in infants and 1–3-year-old children. Reduction in exposure to malaria in infancy does not, with continued bed net use, result in increased malaria morbidity in one-year-old children.</td>
<td>9,13</td>
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<td>Clear reduction in visits of sick children to health facilities associated with ITN use with concomitant reduction in quantities of antimalarial drugs prescribed.</td>
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<td>Clear benefits associated with pregnancy, including reduced maternal and placental malaria, maternal anemia, and low birth weight (for the first four pregnancies).</td>
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<td>Beneficial effects of ITNs spill over into areas adjacent to villages with ITNs; magnitude of this community effect is similar to that observed within ITN villages and dependent upon coverage (the proportion of houses in a given area with ITNs).</td>
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<td>Proper net deployment (adherence) dependent upon complex social and environmental factors; lack of adherence reduces impact upon entomologic indices, particularly for <em>Anopheles gambiae</em>.</td>
<td>11,33,43</td>
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<td>Lack of prompt net re-treatment reduced impact on both entomologic indices and child mortality.</td>
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<td>Marginal economic cost savings to households using ITNs observed in comparison to households lacking ITNs as household expenditures on health care for young children is low in this poor rural setting, leaving little opportunity for household-level, ITN-induced direct savings. However, ITNs were highly cost-effective at the population level.</td>
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Recent arguments that untreated nets may be cost-effective fail to account for coverage effects. The intent of early studies of partial coverage on mosquito populations was to test the hypothesis that individuals not using ITNs might be harmed if neighbors use ITNs, but found this not to be the case. Indeed, our analysis was able to show that community level effects are important in the context of a large-scale efficacy trial; this was possible due to improved mapping and statistical techniques, coupled with a large sample size. In fact, no published data are available that compare the efficacy of sparsely distributed nets, either treated or untreated, to effects observed in areas with high coverage. If individual and community-level effects are additive, our results imply that community-level effects will predominate.

Reorientation of our thinking, regarding population-level versus individual (household)-level effects, also emerged from our analysis of the impact of ITNs on household expenditures. We anticipated that ITNs would markedly reduce household expenditures on malaria treatment, and found that they did in relative terms, but that this only resulted in minor actual savings. The reason for this is simple: in this impoverished area, little money is spent on health care so little opportunity for savings exists. In contrast, from a population-level perspective, ITNs will be cost-effective as a community-wide intervention. Part of this cost-effectiveness derives from the reduction by more than one-fourth of the number of
FUTURE RESEARCH

We believe that this will likely be the last of the series of large-scale, group-randomized, controlled mortality trials of ITNs in malaria-endemic regions of sub-Saharan Africa be-

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<td>ITNs are efficacious in areas with intense, perennial malaria transmission in reducing infant mortality.</td>
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<td>Reduction of malaria transmission, by any means, is beneficial even when the starting point is high transmission.</td>
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<td>In areas of intense transmission, groups that will benefit most from the intervention are infants; newborns will benefit further if their mothers are exposed to ITN use during pregnancy.</td>
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<td>Target groups in areas of intense malaria transmission may therefore be viewed as infants and pregnant women.</td>
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<td>ITN use may reduce drug pressure on parasite populations</td>
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<td>ITN intervention is most effective when coverage and adherence are high, and nets are effectively treated with insecticide.</td>
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<td>If individual barrier protective effects of ITNs and population-wide community effects of ITNs (coverage-dependent) are additive in their impact on morbidity and mortality, sparsely distributed ITNs will have considerably less impact.</td>
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visits of sick children to health facilities serving the area where the intervention was in place, with a concomitant savings in drug treatments provided. Fewer treatments provided imply reduced selective drug pressure for antimalarials prescribed, and possible slower evolution of antimalarial drug resistance. Whether effects of reduced drug pressure will outweigh putative effects of possible reduction of multiplicity of infection on evolution of drug resistance is unknown.

The economic and epidemiologic analysis reported here lead to some clear-cut, if perhaps unwelcome, conclusions. For ITNs to work optimally, three outcomes must be maximized in the scale-up from efficacy to effectiveness: adherence, insecticide treatment/re-treatment, and coverage. Maximization of adherence will not be simple: the daily task of ITN storage at dawn and rehanging at dusk in these small houses is onerous for some caregivers. A related behavioral message, that ITN users should re-treat their nets with insecticide, has been the focus of most educational efforts to date, with limited success, at least in contexts where users are asked to pay for net re-treatment. Fortunately, wash-durable (long-lasting) nets may obviate the need for periodic net re-treatment. As the technology for wash-durable nets matures, the focus of educational programs should shift from net re-treatment to augmenting adherence. The final parameter to be maximized, coverage, is arguably both the most important as well as the most problematic. Present efforts focus on sale of ITNs to individual users. Two general rationales for this approach exist. The first is practical: distribution mechanisms that place the cost burden upon the individual user may be viewed as the only feasible mechanism through which ITNs can be distributed. The second rationale is based upon the assumption that the beneficial effect of this intervention is primarily at the individual level, and that therefore individuals should pay for it. We believe that the latter rationale may be false. It is likely, although not proven, that much of the benefit associated with ITN use results from reductions in the population of sporozoite-carrying mosquitoes associated with high levels of coverage within the community. Since the people who are most affected by malaria have competing priorities for their little money, selling ITNs individually will indeed be difficult. High coverage within the community, and high effectiveness, may not be attained using this route. High coverage can be ensured by subsidizing ITNs where the level of subsidy (up to 100%) is determined by the amount necessary to achieve the required coverage.

So who pays for the nets, if community coverage becomes a top program objective? There is an increasing awareness in rich countries of the health problems of Africa. The malaria research and control community can play a critical role in communicating the message that malaria control is possible now, with the tools we have at hand (with ITNs being, at present, one of the best single interventions we have), and that the benefits of malaria control in terms of human lives and economic output will be substantial. Malaria control in Africa, if presented in this light, becomes not merely a good thing to do for humanitarian reasons, but a good investment.

What health sector mechanisms now exist that can be used to move ITNs into as many houses as possible? Two existing mechanism routinely achieve high population coverage: antenatal clinics and national Expanded Program on Immunization (EPI) systems. Antenatal clinics are supported by a supply infrastructure and thus represent a system pre-adapted to receive and distribute items such as ITNs. In most African countries, the proportion of pregnant women seeking antenatal care is more than 75% (and this figure might increase if ITNs became part of the services offered) and in Kenya, national data suggest that 93% of pregnant women attend antenatal care. Whether effects of reduced drug pressure will outweigh putative effects of possible reduction of multiplicity of infection on evolution of drug resistance is unknown.

In western Kenya, the yearly proportion of houses with at least one resident pregnant woman is approximately 14%; the average life of an ITN in our study area was approximately three years, although many nets can last longer if properly maintained. Thus, the household coverage that could be achieved over a three-year period by distribution solely through antenatal clinics, assuming at least 75% (or 92% for Kenya) make use of antenatal programs is 0.14 × 0.75 (or 0.93) × 3 = 31% (or 39% for Kenya). Routine EPI services coupled with measles catch-up campaigns have the potential to attain coverage in young children as high as 90%. Thus, integration of ITN distribution with antenatal clinic and EPI systems could rapidly achieve household coverage rates approaching or exceeding the 60% target coverage suggested in the Abuja RBM Summit. Additional benefits could be gained by delivering ITNs in child clinics and other community programs that may engage non-target (adults and older children) populations. This presents an opportunity for those who formulate and implement health policy to engage other programs that might reach these groups, for example, schools or agricultural outreach programs.

>TABLE 2

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cause no additional studies of this type and magnitude will be required for this intervention. Resolution of remaining scientific issues related to this intervention will require different methodologies, and, with few exceptions, different scales of inference, ranging from molecular to programmatic.

Relationships among the development of immunity to malaria, age-related development of the human immune system, and intensity and pattern of malaria transmission remain obscure. Although our results indicate no reduction in the ability of the immune system to mount antibody responses to certain antigens, and no evidence that a marked exposure reduction in infants, with continued ITN use, results in increased morbidity in one-year old children, it is by no means clear what this implies for long-term reduction in morbidity and mortality. Therefore, monitoring of age-specific morbidity and mortality in populations subjected to effective long-term malaria transmission reduction remains a high priority for research. The scale of these studies will be similar to those used for this and other ITN trials. The impact of four-years of ITN use in western Kenya is currently being investigated.

Many biologic (or epidemiologic) and operational issues remain. Uncertainties regarding the relative strength of individual and community-wide protective effects of ITNs will require inference which takes into account coverage in both target and non-target populations. If ITNs primarily act as lethal mosquito traps, it may be feasible to further increase the effectiveness of this intervention by using insecticides with minimal repellent effect.

The observation that reduction of malaria transmission is beneficial under conditions of intense, perennial transmission should reinvigorate interest into other means of reducing mosquito populations. Two possible future methods, transgenically modified mosquitoes and transmission-blocking vaccines, are now the subject of intensive laboratory research, but revitalization of some older methods of transmission reduction, such as source reduction and indoor residual spraying, is in order. In particular, development of successful source reduction methods for the African continent will require sustained attention and inventive approaches from entomologists and program officials alike.

The insecticide is a key contributor to the success of this intervention. Continued attention to understanding the molecular details of the mechanisms of resistance is of practical value both for development of more effective surveillance tools for insecticide resistance and for development of new insecticides for bed net treatment. Similarly, continued work on development of bed nets that are long-lasting in two ways are needed: the materials used should be cheap and robust, and the insecticide treatment should endure over long periods and many net washings. The more long-lasting bed nets are in both of these senses, the higher will be both coverage and the proportion of bed nets with effective insecticide treatment.

As the development, testing, and eventual production of high-quality, low-cost, wash-durable bed nets not requiring insecticide retreatment bear fruit, the focus of present behavioral research on stimulating net retreatment will become less warranted, allowing a shift in focus to devising ways to ensure adherence to proper ITN use.

At the programmatic level, the relationship of ITNs to other interventions requires clarification. Will high population coverage with ITNs alter the need for or frequency of intermittent preventative treatment in pregnant women and children? Or will these interventions act synergistically, implying that both programs should proceed? Will the reduced frequency of malaria episodes and clinic visits be borne out in program practice? Will ITN use reduce antimalarial drug use and decrease drug pressure and the concomitant rate of development of antimalarial drug resistance? Can we find additional means of further reducing malaria transmission that adds to the observed benefit of ITNs? Can we effectively deploy a full package of antimalarial strategies, including prompt effective treatment of malaria illness and appropriate and timely use of antimalarial drugs for prevention of malaria in target populations, and achieve the needed high coverage and proper use of ITNs?

CONCLUSION

Insecticide-treated bed nets do not constitute a stand-alone solution to the problem of malaria in Africa; however, their remarkable impact on malaria transmission reduction and lives saved suggest that they should be a key part of the health program of every malaria-endemic African country (with the exception of those with an effective indoor residual spray program). Communities protected with ITNs still have children affected by and dying of malaria. As Hackett and others noted 66 years ago, malaria transmission “has never been able to resist any long-continued sabotage.” Thus, for malaria control “persistance is more important than perfection.” In the arsenal of weapons currently available for malaria control in Africa, ITNs are one of the most feasible we have. They are broadly acceptable to many cultures, effective in even the most difficult areas where African malaria holds sway, and are both inexpensive and cost-effective. We should deploy these devices now, while recognizing that their effects may be strongest at the community level. We should seek the highest possible household coverage rates, with concomitant focus on regular and correct deployment coupled with proper insecticide treatment. ITNs are, like vaccines, an intervention most efficiently deployed as a public health good.

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REFERENCES


‘Take your sick children to the clinic promptly so that they can be diagnosed and treated properly’.