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THE EFFICACY OF PERMETHRIN-TREATED BED NETS ON CHILD MORTALITY AND MORBIDITY IN WESTERN KENYA II. STUDY DESIGN AND METHODS

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Abstract. This paper describes the study design and methods used in a large community-based, group-randomized, controlled trial of permethrin-treated bed nets (ITNs) in an area with intense, perennial malaria transmission in western Kenya conducted between 1996 and 1999. A multi-disciplinary framework was used to explore the efficacy of ITNs in the reduction of all-cause mortality in children less than five years old, the clinical, entomologic, immunologic, and economic impact of ITNs, the social and behavioral determinants of ITN use, and the use of a geographic information system to allow for spatial analyses of these outcomes. Methodologic difficulties encountered in such large-scale field trials are discussed.

INTRODUCTION

Previous randomized controlled trials showed that permethrin-treated materials were effective in reducing child mortality,[1–4] but none were conducted in an area of intense and perennial malaria transmission.[5] A field site with these malaria transmission characteristics was established in western Kenya with the primary objective to test the efficacy of insecticide (permethrin)-treated bed nets (ITNs) in reducing all cause mortality in children 1–59 months of age.[6] Secondary objectives were to estimate the effect of the intervention on all-cause and malaria-specific morbidity,[7,8] immunologic parameters in pre-school age children,[9] malaria and its adverse consequences in pregnant women and their infants,[10–12] densities of malaria-transmitting mosquitoes,[13] and social and economic factors associated with ITN use.[14,15] Spatial analysis was used to evaluate the public health impact of potential area-wide reductions in mosquito abundance and of partial coverage of ITNs in the community.[16–18] A multi-disciplinary approach was used to capture a range of possible effects on child survival and health, and the other parameters of interest. Surveillance methods conformed to standards set by the World Health Organization in previous multi-center trials of insecticide-treated materials (World Health Organization, 1991, *Guidelines for the Development of Protocols for Studies to Evaluate the Impact of Insecticide-Impregnated Bednets on Child Mortality*. Report of a Meeting, London School of Hygiene and Tropical Medicine, 1991). Some difficulty was encountered in determining the exact methods used in the previous trials due to a scarcity in the reporting of detailed methods. To facilitate comparison of findings between sites, and to assist others embarking upon similar large-scale multi-disciplinary trials, we present a detailed overview of the study design and methods used in the ITN trial in western Kenya. Additional details are provided in the accompanying papers in this Supplement.

MATERIALS AND METHODS

Study design. The study design was consistent with the previous randomized controlled ITN trials: a group-randomization was used, with village as the cluster unit of allocation.

Sample size. When the study was designed in 1995, mortality in children less than five years old was reported to be 35/1,000/year,[19] and mortality in children 1–59 months old estimated by retrospective methods was 30/1,000/year (Koumans E, unpublished data). According to government figures, approximately 16.7% of the proposed population of 60,000, or 10,027 children were estimated to be 1–59 months of age.[20] Under these conditions, the study was estimated to have just over 90% power to detect at least a 30% reduction in all-cause mortality in children 1–59 months of age from 30 to 21/1,000/year, assuming a cumulative loss-to follow-up during the two year intervention period of 15%, a Type I error probability of 5% (two-sided test), a 1:1 ratio of intervention to control, and a design effect of 20%. (The design effect is the proportion by which the sample size needs to be increased to allow for correlation among observations taken from the same village, compared to a study randomized by individual.) After the study started in 1997, final results were reported from the World Health Organization–sponsored randomized trial in Burkina Faso, indicating that treated curtains had an efficacy of 14%.[4] This trial had previously shown an efficacy approximating 30% in the first year.[4] This result, when considered with the protective efficacy of 18% found in the Ghana trial, intimated that the efficacy of ITNs in areas of intense but strongly seasonal malaria transmission may be substantially less than in areas of lower transmission. Although our trial was underway, these reported results prompted us to increase our sample size to include a total population of 125,000 people by 1998. This increase gave the study power to detect differences in all cause mortality smaller than 20%. Meanwhile, data from our project collected from 1996 onwards showed that although the proportion of children 1–59 months of age was only 14.8% (i.e., lower than the government census estimate of 16.7%), all-cause mortality of children 1–59 months of age was higher than first estimated, approximating 50/1,000/year in the first year of the trial for both arms of the study combined. Under these conditions, with a sample size of 125,000 (18,500 children 1–59 months of age), the study was estimated to have 90% power to detect a 17.5% difference in mortality in children 1–59 months of age, given a study period of two years in each site, loss to follow-up of 5% per year, a design effect of 20%, and a ratio of intervention-to-control of 1.

Impact of human immunodeficiency virus (HIV) on the power of the study. When designing the study, the extent to which effects of HIV on child mortality would alter its power was unknown. The seroprevalence of HIV among pregnant women was estimated to be 18% between 1992 and 1996 (Kenya Medical Research Institute/Centers for Disease Control and Prevention, unpublished data). Based on these figures, approximately 20% of all deaths in children less than five years of age were estimated to be related to acquired immunodeficiency syndrome (AIDS), assuming that 40% of children born to HIV-infected mothers would be infected with HIV, and that 75% of them would have died by the age of five years.[21] However, it was unknown to what extent deaths due to HIV/AIDS would increase the overall mortality rate in children less than five years old without affecting the malaria attributable deaths, or to what extent HIV/AIDS-related deaths replaced deaths due to other causes, including malaria. For example, some children who otherwise would have died of severe malaria at the age of 6–12 months may die of AIDS in the first few months of life instead, or HIV-infected children protected from malaria by ITNs who survive infancy may die of AIDS at a later age. We concluded that HIV/AIDS would probably result in a mixture of additional deaths and replacement deaths, but quantifying these effects to estimate their influence on the power of the trial was not possible.

Randomization procedure. Intervention villages were assigned by public lottery, in which village representatives chose a sealed envelope from a basket containing hand written tickets (Round 1 = intervention, or villages to receive ITNs at the beginning of the trial; Round 2 = control, or villages to receive ITNs at the end of the project). Lotteries were conducted in the context of a public celebration launching the project in Asembo in August 1996, and in Gem in August and November 1997. National and local officials, community leaders, and village representatives were invited to witness the lottery procedure while enjoying a day of sports competition, participatory educational theatre, songs by traditional birth attendants (TBAs), and refreshments. Forty of 79 villages in Asembo and 71 of 142 villages in Gem were designated as intervention villages; remaining villages were controls.

Bed net distribution and coverage. The distribution of ITNs took place in Asembo and Gem in the fourth quarters of 1996 and 1997, respectively. Prior to distribution, village TBAs measured each sleeping space to determine the correct size (family, double, single) and number of ITNs for each house. A total of 45,667 polyester, 100-denier, 156-mesh bed nets, pre-treated with the target dose of 0.5 g of permethrin/m^2 of netting (Siamdutch Mosquito Netting Co., Bangkok, Thailand), were distributed to the intervention village population (61,000 at baseline), achieving an initial coverage ratio of 1.34 persons per ITN. Families signed a consent form documenting the number of ITNs received, agreement of their participation, and acknowledgment that the ITNs remained the property of the project until the end of the project, when ownership would pass to the study participants. Information leaflets on ITN care in Dholuo and English were distributed along with the ITNs. A demonstration house exhibiting ITNs hung over beds and mats was set up at each village distribution point, enabling participants to view and discuss ITN hanging. Nails and twine needed to hang nets were distributed. ITNs were issued to homes of families not attending distribution meetings through house-to-house visits.

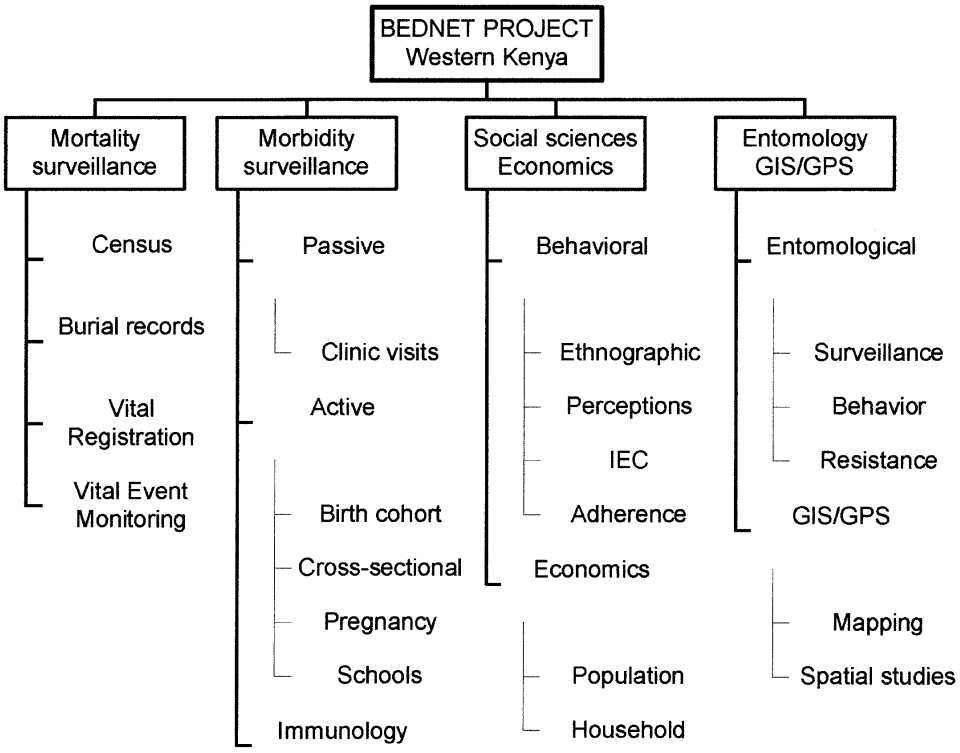

FIGURE 1. Overview of scientific disciplines within the insecticide-treated bed net project in western Kenya. GIS/GPS = geographic information system/global positioning system; IEC = information, education, and communication. Resistance refers to insecticide resistance.

Following distribution, spot-checks were made to assess immediate ITN coverage in a random sample of 1,104 houses in 10 randomly selected villages in Asembo. Half of the houses surveyed had either not hung their ITNs correctly or had not removed them from their bags. A house-to-house campaign was carried out in intervention villages throughout December 1996 to show how ITNs should be hung and used. Formal start of the intervention was thus considered January 1, 1997. A qualitative study was conducted to determine factors affecting the inadequate early response to ITNs,[22] followed by quarterly monitoring of coverage and adherence throughout the study.[14] To conclude the study, 50,974 nets were issued to participants in control villages in Asembo and Gem in the first quarters of 1999 and 2000, respectively, resulting in the distribution of a total of 96,641 bed nets during the study.

Bed net treatment. Study bed nets were pretreated by the manufacturer. Biannual re-treatment to the target dose of 0.5 g of permethrin/m^2 of netting was scheduled during the two-year intervention. Permethrin in the form of Peripel® 55% emulsifiable concentrate (AgrEvo, Berlin, Germany) was distributed to staff trained in proper handling and methods for dilution. Teams consisting of 3–4 staff members visited every compound, where residents had been notified by TBAs to wash all ITNs in preparation for re-treatment. Based upon the number and size of ITNs, an appropriate dilution of permethrin was prepared. Bed nets were dipped individually in a socially acceptable order,[22] wrung out, then dried in the shade before rehanging. The specific timing of re-treatment was determined by monitoring studies of the persistence of permethrin residues in the bed nets. At distribution and biannually thereafter, *Anopheles gambiae* mosquitoes from a laboratory colony were used to bioassay bed nets for persistence of permethrin residues. Ten samples of netting attached to nets in 20 homes were analyzed by high-performance liquid chromatography biannually to quantify the decrease in actual amounts of permethrin residue.

The various disciplines in which sub-studies were conducted are shown in Figure 1. A detailed account of methods

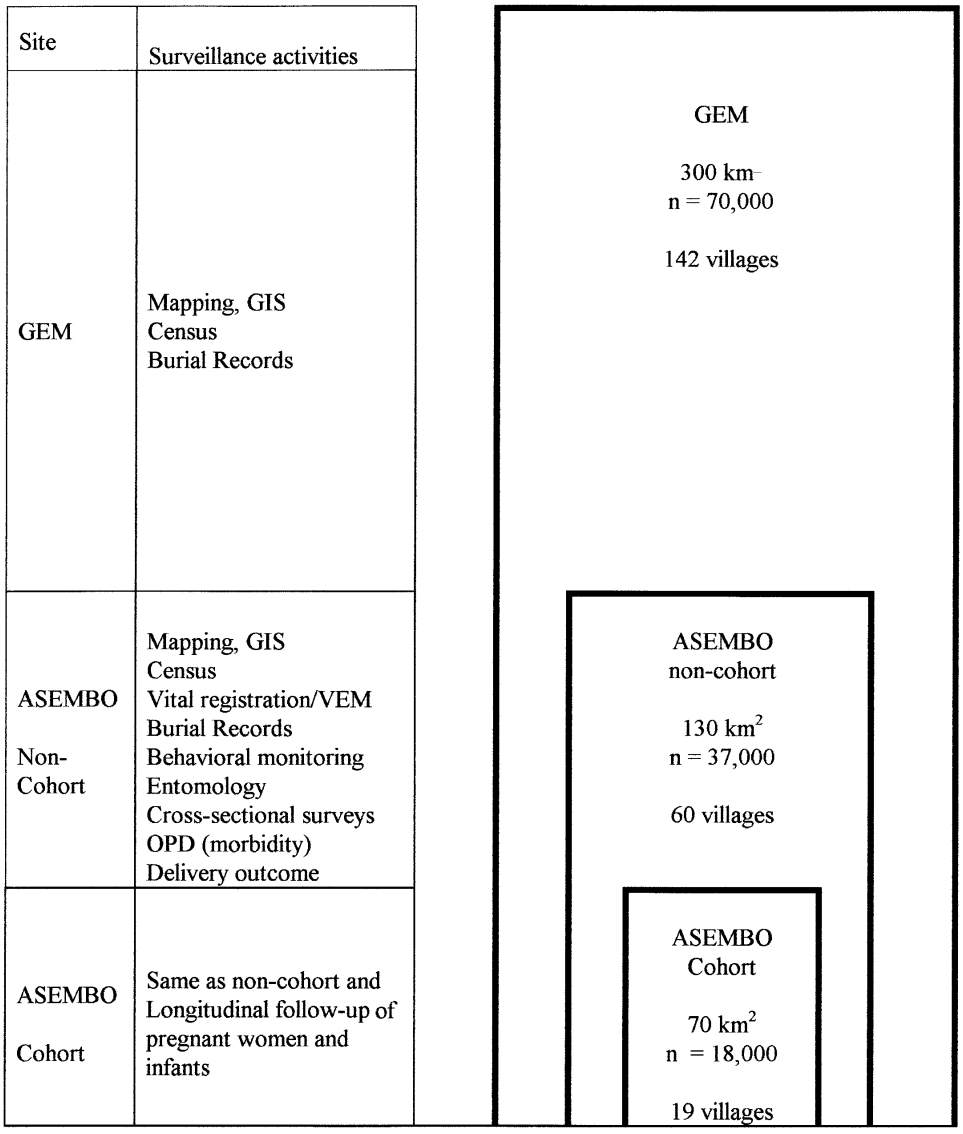

FIGURE 2. Schematic diagram of the demographic and health surveillance activities performed during the insecticide-treated bed net project, by location, in western Kenya. GIS = geographic information system; VEM = vital event monitoring; OPD = outpatient department.

for each sub-study is reported in the respective papers. Surveillance methods conformed to guidelines set by the World Health Organization for previous ITN trials. A demographic and health surveillance site (DSS) was established in the 79 villages in Asembo in 1996 (population = 55,000). The DSS monitored deaths, births, migration, and trends in child morbidity. Periodic data were gathered on coverage and adherence with ITN use,[14] entomologic indices,[13] perceptions of disease and treatment-seeking behavior,[23] and costs associated with disease at the level of both household,[15] clinic, and community[17] (Figures 2 and 3).

DISCUSSION

A randomized controlled trial provides the best test of the impact of an intervention. Differences in ITN efficacy in the

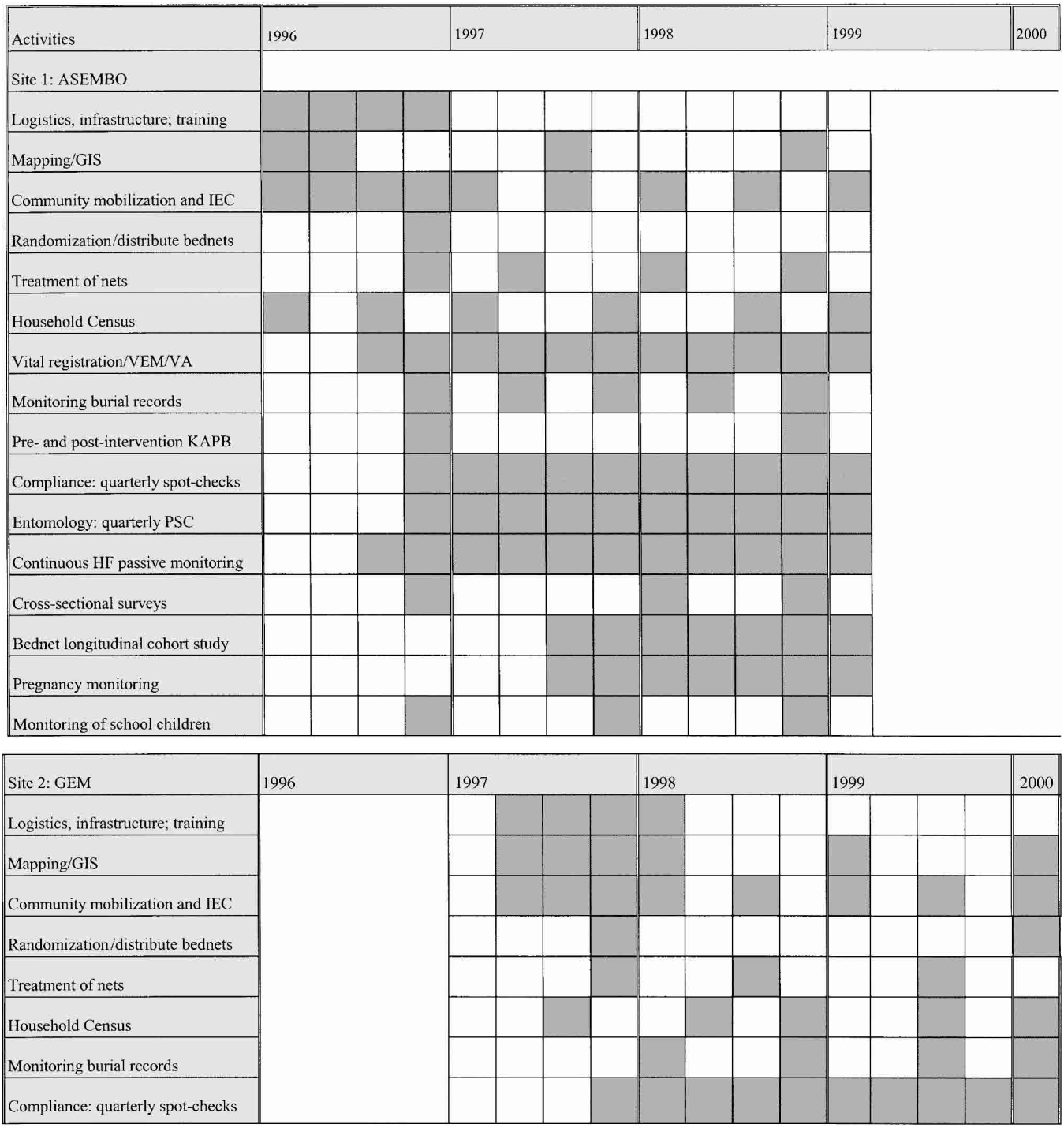

FIGURE 3. Time frame of field activities undertaken during the insecticide-treated bed net project, by location, in western Kenya. GIS = geographic information system; IEC = information, education, and communication; VEM/VA = vital event monitoring/verbal autopsy; KAPB = knowledge, attitudes, and practices, and beliefs survey; PSC = pyrethrum spray collection; HF = health facility.

four previous group randomized controlled trials were believed to be due to differences in malaria transmission intensity and pattern, which prompted implementation of the trial reported here in an area of perennial high transmission.[5] However, other important differences in the conduct and analysis of these four trials are apparent. Mortality analysis was limited to one year for The Gambia study, while others considered two years of data (with a marked reduction in efficacy observed in the second year in Burkina Faso).[1–4] The Burkina Faso study assessed efficacy of permethrin-treated curtains,[4] while other sites evaluated permethrin-treated bed nets.[1–3] Bed net coverage varied two-fold between coastal Kenya (1.4 persons per net)[3] and Ghana (2.8 persons per net).[2] The time during pregnancy when bed nets were introduced differed, as did parity of recipients.[24–26] We have provided a detailed description of our methods to allow easier comparison of our study in western Kenya with previously published trials. This will enable more informed evaluation of the contribution of methodologic differences as opposed to other factors in comparing our results to those from other trials. The detailed description of methods given for the ongoing ITN social-marketing program in Tanzania serves a similar purpose.[27,28]

In addition to measuring effects on child mortality, our trial measured effects on a broad range of morbidity indicators, entomologic outcomes, socioeconomic factors, and collected basic meteorologic data. These interdisciplinary efforts not only allow assessment of consistency of effects, but also allow a better understanding of the mechanisms through which ITNs work (e.g., the role of a community-wide or mass effect), determination of the target groups that are likely to benefit most, and assessment of determinants of ITN efficacy and community adherence.

This study was conducted in the context of a high prevalence of HIV in the antenatal population and presumably in young infants. We estimated that roughly one-fifth of all children less than five years of age deaths were likely HIV-related at the beginning of the trial based on HIV prevalence data among pregnant women in this area.[21] We anticipated that HIV/AIDS would probably result in a mixture of additional deaths and replacement deaths, but its precise effect on the power of the study was impossible to predict at the time the study was designed. Thus, while the mortality data generated from the DSS during the trial revealed a higher mortality rate in children less than five years of age than estimated retrospectively prior to the trial, doubling the study population in response to results from Burkina Faso may also have helped compensate for possible loss of statistical power due to an increasing number deaths due to HIV/AIDS.

Measurement of the impact of interventions, particularly on child survival at the periphery of the health care system, is difficult. The use of a DSS for routine reporting of deaths exceeds the health budget of most countries in sub-Saharan Africa. For programs, different methodologies are required for measuring the effectiveness of ITNs over extensive periods.[29,30] This study provided the opportunity to compare morbidity and mortality data generated by the DSS with that collected simultaneously in the same area through government health systems and routine civil registration of child deaths.[31] Thus, in addition to assessing the impact of ITNs on childhood morbidity and mortality, this study allowed us to evaluate the use of routinely collected health statistics for assessing the impact of this population based intervention against malaria.

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