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Child mortality in a West African population protected with insecticide-treated curtains for a period of up to 6 years
D.A. Diallo, 1 S.N. Cousens, 2 N. Cuzin-Ouattara, 3 I. Nebié, 4 E. Ilboudo-Sanogo, 5 & F. Esposito 6

Objectives To determine the impact of insecticide-treated curtains (ITC) on all-cause child mortality (6–59 months) over a period of six years. To determine whether initial reductions in child mortality following the implementation of ITC are sustained over the longer term or whether “delayed” mortality occurs.

Methods A rural population of ca 100 000 living in an area with high, seasonal Plasmodium falciparum transmission was studied in Burkina Faso. Annual censuses were conducted from 1993 to 2000 to measure child mortality. ITC to cover doors, windows, and eaves were provided to half the population in 1994 with the remainder receiving ITC in 1996. Curtains were re-treated or, if necessary, replaced annually.

Findings Over six years of implementation of ITC, no evidence of the shift in child mortality from younger to older children was observed. Estimates of the reduction in child mortality associated with ITC ranged from 19% to 24%.

Conclusions In our population there was no evidence to suggest that initial reduction in child mortality associated with the introduction of insecticide-treated materials was subsequently compromised by a shift in child mortality to older-aged children. Estimates of the impact of ITC on child mortality in this population range from 19% to 24%.

Keywords Malaria/epidemiology/mortality; Bedding and linens/utilization/statistics; Child, Preschool; Infant mortality; Plasmodium falciparum/immunology; Malaria, Falciparum/prevention and control/transmission; Anopheles; Mosquito control; Permethrin; Remission induction; Age factors; Regression analysis; Incidence; Survival rate; Randomized controlled trials; Burkina Faso/epidemiology (source: MeSH, NLM).

Mots clés Paludisme/épidémiologie/mortalité; Literie et linge/utilisation/statistique; Enfant âge pré-scolaire; Mortalité nourrisson; Plasmodium falciparum/immunologie; Paludisme plasmodium falciparum/prévention et contrôle/transmission; Anophèles; Lutte contre moustique; Perméthrine; Traitement induction rémission; Facteur âge; Analyse régression; Incidence; Taux survie; Essai clinique randomisé; Burkina Faso/épidémiologie (source: MeSH, INSERM).

Palabras clave Paludismo/epidemiología/mortalidad; Ropa de cama y ropa blanca/utilización/estadística; Infante; Mortalidad infantil; Plasmodium falciparum/inmunología; Paludismo plasmodium falciparum/prevención y control/transmisión; Anopheles; Control de mosquitos; Permethrina; Inducción de remisión; Factores de edad; Análisis de regresión; Incidencia; Tasa de supervivencia; Ensayos controlados aleatorios; Burkina Faso/epidemiología (fuente: DeCS, BIREME).

Introduction

Large trials of insecticide-treated netting (ITN), conducted over 2-year periods in various epidemiological settings across Africa, have reported 15–33% reductions in all-cause child mortality (1–4). An outstanding concern regarding the translation of these findings into a policy of large-scale implementation of ITN in malaria-endemic areas has been the extent to which this impact on child mortality is sustainable over longer periods of time (5–7). It has been hypothesized that reducing malaria transmission levels might slow the development of clinical immunity leading to a shift in child mortality to older ages (“delayed mortality”), with
little or no long-term survival gain. Support for this hypothesis has been largely derived from ecological comparisons of the age distribution and clinical patterns of severe malaria as well as malaria-specific mortality rates between areas with different levels of malaria transmission across Africa (5, 6). This hypothesis triggered a fierce debate within the scientific community, since the interpretation of such comparisons is fraught with difficulty (8–11).

It would be unethical to perform controlled trials in which part of the study population does not receive ITN for many years. Thus, to address whether ITN has a long-term impact on child mortality, it is necessary to use other, less well-controlled, approaches. We report observational data on all-cause child mortality in communities in Burkina Faso which have used insecticide-treated curtains (ITC) for up to six years following a randomized, controlled trial of ITC conducted between 1993 and 1996.

Methods

Study area
The study was carried out in a rural setting, in Oubritenga Province, Burkina Faso, West Africa. Malaria transmission is stable but markedly seasonal, peaking in the rainy season (June–October) with only low levels of transmission occurring in the dry season. The annual rainfalls recorded in the study area in the years 1993–99 were 662, 860, 609, 637, 642, 831, and 772 mm, respectively. The main malaria vector is *Anopheles gambiae* s.s., with *Anopheles arabiensis* and *Anopheles funestus* contributing to a lesser extent (12–14). The average entomological inoculation rate (EIR) prior to intervention was estimated to be 300–500 infective bites/person/year (15). *Plasmodium falciparum* is responsible for more than 95% of malaria infections in children.

A district hospital and 10 dispensaries provide health care to the communities in the study area.

Study population
The study area was first censused in 1993, when a population of 88,087 inhabitants living in 158 villages was enrolled in the study. Most of the study population (>95%) belongs to the Mossi ethnic group and lives by subsistence farming. The population migration rate has been estimated at about 2.5% per year (4).

Study design
The initial study was designed as a randomized, controlled trial of the impact of ITC on all-cause child mortality. After the census in 1993, the 158 villages in the study area were grouped into 16 geographical clusters. Clusters were paired according to their baseline mortality rates, population size, and ecological features. In each pair, one cluster was randomly selected to receive the intervention in June–July 1994. The eight remaining clusters acted as control areas, receiving the intervention in June–July 1996. The intervention was maintained and mortality measured across the whole study area until May 2000.

Demographic surveillance
Details of the methods used to measure child mortality have been published elsewhere (16). In brief, annual censuses have been performed since 1993. At each census after the first, pre-printed “rollcalls” have been used to register births, deaths, and migrations occurring since the previous census. Pregnancies were also recorded when identified. During the census in 1999 all married women aged less than 45 years who had not reported a birth in the past 2.5 years were revisited to check that no early child deaths had been missed. This exercise identified only two children who had been born and died previously without being recorded. The last census was carried out in May 2000.

The intervention: treatment and utilization of curtains
Doors, windows, and eaves were covered with mosquito netting (Polyester, 100 denier, Siamdutch Co., Thailand), dipped in permethrin (Imperator 50 EC, ZENEECA/ICI, UK). Netting, insecticide, and other materials were provided to the communities free of charge. Dipping of the netting was performed to achieve a target dose of 1 g of permethrin/m². After the first treatment in June–July 1994, re-treatment was performed in November–December 1994. From June–July 1995 onwards, only one round of re-treatment was performed each year. At each re-treatment, damaged curtains (10–30% each year) were replaced with new ones. Monitoring of the efficacy of impregnated netting in killing mosquitoes was assessed every six months using WHO’s standard bioassay. Except for the first year, the average killing efficacy of the netting exceeded 90% at each survey.

Curtain utilization
To monitor utilization of the curtains, cross-sectional surveys were performed every year during the peak malaria transmission season. Randomly selected compounds were visited between 19:00 and 21:00 to check the position of door curtains to determine whether they were hanging down and covering the opening or tied/held back in some way.

Community and institutional approval
The initial trial and the present study protocol were presented to the Ministry of Health and local authorities in Burkina Faso in 1992 and 1996. Approval was received from the local ethics committee. Before the trial began in 1993, and the follow-on study in 1996, meetings were held with the population to explain the purpose of the research, what was involved, and to seek informed consent.

Statistical methods
All-cause mortality rates were calculated as the number of child deaths aged 6–59 months per 1000 child years at risk. Point estimates of the mortality rate ratio (RR), comparing the original intervention areas with the original control areas for each 2-year period since mid-1994, were obtained using Poisson regression, adjusting for age and sex. The 95% confidence intervals (CI) were calculated using the Huber–White sandwich estimator to take account of the cluster randomization (17). To estimate the impact of ITC over the entire period of the study, we fitted a Cox regression model with calendar time as the underlying timescale and with the presence/absence of ITC, age and sex of the child, and cluster as terms in the model. To explore whether there was evidence of delayed mortality, we investigated whether the association between ITC and child mortality varied over time among older children. Kaplan–Meier survival curves for the cohorts of children born and living before the installation of ITC and for children born and living after the installation of curtains were also constructed and compared. Using Poisson regression, we compared the distributions of ages at death among children dying before the implementation of ITC and among children dying during the 6th year after ITC implementation. All analyses were performed using Stata version 7.0 software (http://www.stata.com).
Results

From July 1993 to May 2000, around 48,000 children contributed to the analysis of mortality during the age range of principal interest, 6–59 months. Of these, around 25,000 were born within the study area during the study period. Over the entire period, including 1-year pre-intervention, a total of 107,312 child-years at risk and 3,497 deaths accrued in the age range 6–59 months. In the original intervention areas there was evidence that curtain utilization declined over time with 78%, 69%, 62%, 57%, 42%, and 43% of houses visited to check on curtain utilization having door curtains hanging down correctly during the surveys held from 1994 to 1999, respectively ($P < 0.01$).

A similar pattern was observed in the former control group, the proportions of correctly hanging curtains being 66%, 53%, 48%, and 48% from 1996 to 1999, respectively ($P < 0.01$).

Child mortality rates

In the pre-intervention period, mortality rates were similar in intervention and control areas (45.3 versus 44.3/1000 child-year respectively; $P = 0.95$) (Table 1). Over the two years of follow-up during which the control group was maintained (1994–96), mortality was 19% lower in the intervention areas (RR = 0.81; 95% CI = 0.62, 1.08; $P = 0.15$). This estimate differs slightly from that previously presented ($P < 0.01$) due to additional follow-up accrued in the 2nd year since that publication. When account is taken of the mortality observed in the year preceding the intervention, ITC are estimated to be associated with a 20% reduction in mortality (95% CI = 3%, 34%; $P = 0.02$).

In the first two years during which the whole population was protected with ITC (mid-1996 to mid-1998), mortality rates were similar in the former intervention and control areas (RR 1.01, Table 2), and much lower than in the year prior to the installation of ITC (23.8/1000 versus 44.8/1000) (Tables 1 and 2). In the next 2 years (1998–2000), mortality rates were higher than in the period 1996–98 (Table 2), although they remained lower than in the baseline year (1993–94). This increase was more marked in the former intervention areas than in the former control areas in this period (mortality RR = 1.19; 95% CI = 0.90, 1.57; $P = 0.20$). During this period all children in both groups had lived for at least 2 years under ITC protection.

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<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>6–11</td>
<td>108.1 (99)</td>
<td>102.0 (90)</td>
</tr>
<tr>
<td>12–23</td>
<td>63.3 (111)</td>
<td>51.2 (84)</td>
</tr>
<tr>
<td>24–35</td>
<td>39.6 (66)</td>
<td>46.7 (73)</td>
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<tr>
<td>36–47</td>
<td>25.3 (41)</td>
<td>32.8 (52)</td>
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<tr>
<td>48–59</td>
<td>14.8 (23)</td>
<td>14.0 (22)</td>
</tr>
<tr>
<td>6–59</td>
<td>45.3 (340)</td>
<td>44.3 (321)</td>
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</table>

Mortality RR, \(a\) intervention areas versus control areas (95% CI): \(b\) 1.01 (0.75, 1.35) \(c\) 0.81 (0.62, 1.08)

\(a\) Figures in parentheses are the numbers of deaths unless otherwise indicated.

\(b\) RR = rate ratio.

\(c\) Estimated by Poisson regression controlling for age and sex: 95% confidence interval (CI) obtained using robust standard errors to take account of the cluster randomization.

The mortality RR in children aged 6–23 months (all protected since birth) was 1.21 (95% CI = 0.92, 1.60; $P = 0.17$), while the mortality RR in children aged 24–59 months was 1.16 (95% CI = 0.83, 1.60; $P = 0.39$).

We fitted Cox regression models with calendar time as the underlying timescale, to control for annual and seasonal variations in mortality, to data for the whole period 1993–2000, and included terms for the intervention, the age and sex of each child, and the randomization cluster to which they belonged. We first fitted a model that assumed that the impact of ITC on mortality was constant across all ages in the range 6–59 months and did not vary with the duration of the implementation of ITC. The estimated mortality RR associated with ITC use in this model was 0.76 (95% CI = 0.66, 0.87; $P = 0.0001$) (Table 3, Model 0). We then investigated whether there was evidence that the impact of ITC varied with the age of the child, regardless of the duration of implementation of ITC. There was some evidence to suggest that the relative impact of ITC may be greater in children aged two years and above than in children aged less than two years ($P = 0.03$) (Table 3, Model 1). The ITC mortality RR was 0.80 in younger children compared with 0.69 in older children. To look for evidence of delayed mortality we then fitted a model in which the ITC mortality RR in children aged two years and above was allowed to vary according to the duration of ITC implementation. If delayed mortality had occurred one might expect to observe the ITC mortality RR moving closer to 1 (and possibly exceeding 1) as the duration of ITC implementation increased. There was no evidence of such a phenomenon ($P = 0.92$) (Table 3, Model 2), with very similar mortality RR estimates obtained for the first 2 years of ITC implementation (0.69), for the 3rd and 4th years of implementation (0.67) and for the 5th and 6th years of implementation (0.69).

Child survival

We compared the survival experience of those children who had been born and lived all their lives under ITC protection (a protected cohort of 21,255 children, of whom 1,324 had reached their 5th birthday by the end of follow-up, 44,247 child years at risk, 2,673 deaths) with that of children living in the study area before the intervention was implemented (an unprotected cohort of 27,587 children, 35,828 child years at risk).
Insecticide-treated curtains and child mortality, Burkina Faso
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Risk, 2120 deaths). Fig. 1 shows the Kaplan–Meier survival curves for these two cohorts. If delayed mortality had occurred one might expect the two survival curves to move closer to one another over time or even cross. There is no suggestion of this in Fig. 1. Estimated survival from birth to five years of age was 83% for the protected cohort and 76% for the unprotected cohort. Estimated survival from six months to five years of age was 88% for the protected cohort and 83% for the unprotected cohort.

Age at death
If delayed mortality does occur we would expect to see an increase in the proportion of child deaths that occur at older ages (or an increase in the mean age at which children die). We compared the distribution of ages at death among children dying before the introduction of ITC with that of children born and living in the former intervention areas in the period 1999–2000 (when all children aged 0–5 years would have been protected by ITC since birth). The age distribution of deaths among children aged 6–59 months is shown in Table 1. There was some evidence of a difference in the age patterns of deaths in the two periods (likelihood ratio test; \( P = 0.01 \)). However, rather than a shift in deaths from younger to older ages among children protected by ITC, there were relatively fewer older deaths among children protected by ITC (Table 1).}

Discussion
In our study ITC were implemented over a 6-year period, in a rural setting in West Africa characterized by high and markedly seasonal malaria transmission. We wished to assess the impact of ITC over this longer time period and, in particular, to address the question of whether the initial reductions in child mortality, observed in several randomized, controlled trials over 2-year periods, are preserved over the longer period of 6 years.

Is there any evidence in our study to suggest that initial reductions in childhood mortality following the introduction of ITC were subsequently compromised by the phenomenon of “delayed mortality”? A rise in mortality in the last two years of the study (1998–2000), with mortality apparently higher (though not statistically significantly so) in the former intervention than control areas (RR = 1.19), may appear to be such evidence. However, the mortality RR for this period was higher (1.21) in children aged 6–23 months than in older children (RR = 1.16). We can state with confidence that this higher mortality in the former intervention areas among children aged 6–23 months cannot be due to delayed mortality since children in both groups had lived since birth under ITC protection. The higher mortality in older children could be due to the same cause as that responsible for higher mortality in younger children, possible causes including chance but not delayed mortality.
We do not know the explanation for the generally increased mortality in 1998–2000 or for the apparently higher mortality in the former intervention areas during this period. No epidemics of measles, meningitis, or other infectious diseases were identified in the area during this period and a similar pattern was not observed in children aged 5–9 years (data not shown). Mortality in the period 1998–2000 was highest during the rainy seasons of those years when malaria transmission peaks (data not shown). ITC utilization, as measured by the proportion of houses with curtains correctly placed in the evening, declined over the years. However, this decline began well before the period 1998–2000 and a similar pattern was not observed in children aged 5–9 years (data not shown). Mortality in 1998–2000 or for the apparently higher mortality in those years when malaria transmission peaks (data not shown).

The absence of any convincing evidence of vector control measures have been implemented over a period of six years or more. The absence of any convincing evidence of “delayed mortality” in our study is consistent with data from Sri Lanka where nationwide insecticide (dichlorodiphenyl-trichloroethane (DDT)) spraying of houses was implemented over a period of almost 10 years. By 1953, the all-cause mortality rate had fallen to about half that observed in 1945, just prior to the start of spraying (19, 20). In the absence of any concurrent control data from Sri Lanka, the attribution of this decline to the

Table 4. Distribution of ages at death among children living and dying before the introduction of ITC and among children living since birth and dying under ITC

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<tr>
<td></td>
<td>Observed number of child deaths</td>
<td>Expected number of deaths</td>
</tr>
<tr>
<td>6–11 months</td>
<td>376 (30)</td>
<td>376.3</td>
</tr>
<tr>
<td>12–23 months</td>
<td>368 (30)</td>
<td>386.7</td>
</tr>
<tr>
<td>24–35 months</td>
<td>243 (20)</td>
<td>239.1</td>
</tr>
<tr>
<td>36–59 months</td>
<td>259 (21)</td>
<td>243.9</td>
</tr>
<tr>
<td>Total</td>
<td>1246 (100)</td>
<td>1246</td>
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</table>

* Expected numbers of deaths calculated assuming identical age-specific mortality patterns in the two periods and based on the available child-time at risk.

We therefore have no evidence that malaria transmission during this period was higher than in the preceding 2-year period. We cannot, however, rule out that our entomological work failed to detect a small rise in the average EIR resulting in some increased mortality due to malaria. Using a Cox regression model we found no evidence that the impact of ITC in children aged two years or more declined, compared with that in younger children, with the duration of ITC implementation.

If delayed mortality had occurred to an important extent we should have observed a shift in the distribution of ages at death with a higher proportion of deaths occurring in older children after the introduction of ITC than before. Table 4 provides no indication of such a shift. Based on the age distribution of deaths before the introduction of ITC, a 20% reduction in child deaths restricted to the age range 6–23 months would need to be followed by something approximating a 30% increase in deaths in the age range 24–59 months for the initial benefit of ITC to be lost entirely. Such a change would increase the mean age of deaths from around 1.9 to 2.2 years (scenario A). If ITC reduced deaths in the age range 6–35 months by 20%, this would have to be offset by an increase of 75% in deaths among children aged 36–59 months for all benefit to be lost by age five years. This change would result in an increase in the mean death age to about 2.3 years (scenario B). In the absence of any confounding effect masking delayed mortality, we estimate that our study had around 85% power to detect the degree of shift outlined in scenario A and around 99% power to detect the degree of shift outlined in scenario B.

A major limitation of our study is the lack of a fully concurrent comparison group over the full period of our study. If there was an underlying decline in mortality over the period of the study, then we may have overestimated the impact of ITC, particularly in our analysis of child survival (Fig. 1). Data from the recent Demographic and Health Survey conducted in Burkina Faso in 1998–99 do not suggest that child mortality in the country as a whole has declined substantially in the recent past (18). Indeed, it is stated that “over the last 15 years mortality among children aged less than five years does not appear to have declined”. Our Cox regression analyses are conditional on the underlying baseline mortality rate and thus control for temporal changes in mortality to some extent.

There are few data on mortality rates from other areas where vector control measures have been implemented over a period of six years or more. The absence of any convincing evidence of “delayed mortality” in our study is consistent with data from Sri Lanka where nationwide insecticide (dichlorodiphenyl-trichloroethane (DDT)) spraying of houses was implemented over a period of almost 10 years. By 1953, the all-cause mortality rate had fallen to about half that observed in 1945, just prior to the start of spraying (19, 20). In the absence of any concurrent control data from Sri Lanka, the attribution of this decline to the
spraying programme has been hotly debated since it coincided with improvements in clinical services and socioeconomic development (19–25). The extent to which these data from Sri Lanka, where indoor spraying with DDT was performed and where *P. vivax* is more important than in Africa, provide reassurance to ITN programmes in Africa is limited.

A review of 20 national vector control programmes that were active in the 1950s in South America and Asia, and which aimed to eliminate malaria through widespread insecticide-spraying, reports sustained reductions in malaria mortality over periods of up to 13 years (26). However, the magnitude of these reductions appeared to be similar in countries with and without effective programmes and, in the absence of concurrent control data, one can only speculate as to the extent to which these declines are attributable to the vector control programmes. Again, the relevance of these findings to programmes in Africa is debatable.

In summary, we have followed for up to six years a population of children living in an area with previously high levels of malaria transmission, where transmission levels have been reduced substantially by the use of ITC. Using Cox regression with the full dataset we obtained a point estimate for the mortality RR associated with ITC of 0.76 (P = 0.0001). An analysis restricted to only the fully-randomized component of the data produced a point estimate of 0.81. Over the period of our study we found no evidence of a shift over time in mortality from younger to older children, which might have indicated that the effect of ITC was to delay rather than prevent child mortality.

**Acknowledgements**

We thank the population of the study villages for their cooperation, the Burkina Faso Ministry of Health, the Director of Health of the Oubritenga Province and the staff of CNRFP for their assistance in the implementation of the study. We are grateful to Dr Christian Lengeler, Dr Annette Habluetzel, Pr Mario Coluzzi, and Dr Vincenzo Racalbuto for their support. This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the European Commission (INCO-DC, Directorate General XII), the Danish Agency for International Development, and the Ministry for University and Scientific Research of Italy.

It formed part of a programme of activities run by CNRFP, under the bilateral cooperation agreement between Burkina Faso and the Italian Direzione Generale per la Cooperazione allo Sviluppo, Ministry of Foreign Affairs. We also thank the anonymous referees who reviewed this paper and made many constructive suggestions.

**Conflicts of interest:** none declared.

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**Résumé**

Mortalité de l’enfant dans une population d’Afrique de l’Ouest ayant utilisé pendant une période maximale de 6 ans des rideaux imprégnés d’insecticide

**Objectifs**

Déterminer l’effet des rideaux imprégnés d’insecticide sur la mortalité de l’enfant (6 à 59 mois), toutes causes confondues, pendant 6 ans. Déterminer si les baisses initiales constatées lors de la mise en place de ces rideaux sont durables et si la mortalité n’est pas « reportée ».

**Méthodes**


**Résultats**

Au cours des 6 ans de l’opération, on n’a pas constaté de report de la mortalité sur les enfants plus âgés. On estime que les rideaux ont permis de diminuer globalement la mortalité de l’enfant de 19 à 24%.

**Conclusion**

Les auteurs estiment que, dans la population étudiée, rien ne permet de penser que la baisse initiale de la mortalité de l’enfant liée à l’introduction des rideaux imprégnés d’insecticide a été suivie d’une augmentation de la mortalité chez les enfants plus âgés. On estime que les rideaux imprégnés d’insecticide ont permis de faire baisser la mortalité de l’enfant dans cette population de 19 à 24%.

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**Resumen**

Mortalidad en la niñez en una población de África occidental protegida con cortinas tratadas con insecticida durante un período de hasta seis años

**Objetivo**

Determinar el impacto de las cortinas tratadas con insecticida (CTI) en la mortalidad en la niñez (6-59 meses) durante seis años. Determinar si las reducciones iniciales de la mortalidad en la niñez observadas tras implantar las CTI se mantienen a largo plazo o si, por el contrario, se produce una mortalidad “retardada”.

**Métodos**

Se estudió en Burkina Faso una población rural de 100 000 habitantes que vivía en una zona con alta transmisión estacional por *Plasmodium falciparum*. Se llevaron a cabo censos anuales entre 1993 y 2000 para medir la mortalidad en la niñez. En 1994 se proporcionó CTI a la mitad de la población para que cubriese puertas, ventanas y aleros, y el resto de la población recibió las CTI en 1996. Las cortinas eran tratadas de nuevo, o reemplazadas si hacía falta, cada año.

**Resultados**

A lo largo de los seis años de implantación de CTI, no se ha observado ningún indicio de desplazamiento de la mortalidad de los niños más jóvenes a los niños mayores. La reducción de la mortalidad en la niñez asociada a las CTI se estimó en un 19%–24%.

**Conclusion**

En la población estudiada no se observó ningún indicio de que la reducción inicial de la mortalidad en la niñez asociada a la introducción de material tratado con insecticida se viera contrarrestada luego por un desplazamiento de la mortalidad a los niños de más edad. El impacto de las CTI en la mortalidad en la niñez en esta población se sitúa en el margen de 19% a 24%.
References


