Vector control complements mass drug administration against bancroftian filariasis in Tirukoilur, India

IP Sunish,⁎ R Rajendran,⁎ TR Mani,⁎ A Munirathinam,⁎ AP Dash⁎ & BK Tyagi⁎

Objective To determine the role of vector control in further decreasing the transmission of bancroftian filariasis achieved by mass drug administration and the long-term impact on filariometric indices.

Methods Three rounds of annual mass drug administration, with diethylcarbamazine and ivermectin, were complemented by vector control (mainly using polystyrene beads) in villages of Tirukoilur, south India, during 1995–99. Subsequently, drug administration is being carried out with diethylcarbamazine and albendazole or diethylcarbamazine alone. We evaluated the impact of mass drug administration used alone or in conjunction with vector control (from 1995 to 2005) on vector transmission indices (such as transmission intensity index, monthly biting rate, monthly transmission potential and annual transmission potential). We analysed data on filarial infection in the community to estimate the prevalence of microfilaraemia and antigenaemia using χ² analysis and Fisher’s exact test.

Findings Vector density greatly decreased in villages where vector control was used as an adjunct to mass drug administration and almost no infective mosquitoes were found in the small numbers still remaining. Filarial antigenaemia was low and continued to decrease significantly in the age group 15–25 years in villages receiving mass drug administration with vector control in contrast to villages receiving only mass drug administration.

Conclusion The gains of mass drug administration were sustained only with the integration of vector control measures. We advocate the incorporation of vector control in the Global Programme to Eliminate Lymphatic Filariasis as it can potentially decrease the time required for eliminating lymphatic filariasis.

Introduction Lymphatic filariasis is a major cause of acute and chronic morbidity among humans in tropical and subtropical areas of Asia, Africa, the western Pacific and some parts of the Americas. Of the estimated 128 million cases of lymphatic filariasis, 91% are caused by Wuchereria bancrofti.1 The Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched in 2000 based on the principles of interruption of transmission, and alleviation and prevention of disability due to lymphatic filariasis.2 Currently, the GPELF depends largely on mass drug administration (MDA) to interrupt the transmission of W. bancrofti. This strategy is based on the evidence that single annual doses of antifilarial drugs (diethylcarbamazine (DEC) with or without ivermectin (IVR) or albendazole (ALB)) can suppress microfilaraemia for prolonged periods, and the cumulative effect is expected to lead towards the elimination of lymphatic filariasis.3,4 Globally, the majority of W. bancrofti is transmitted by Culex quinquefasciatus, which typically breeds in stagnant and organically polluted water.5 It seems unlikely that MDA would be sufficient for sustained interruption of transmission in areas of Culex transmission of lymphatic filariasis, due to their high vectorial efficiency.6 Therefore, vector control would be an important supplement to sustain the interruption of transmission in some epidemiological settings.7 In Makunduchi, Zanzibar, the Culex mosquito population decreased by about 98% after applying expanded polystyrene (EPS) beads to all the wet pit latrines, without any change in a nearby untreated community.8 One round of MDA with DEC resulted in decreasing the proportion of mosquitoes with third-stage larvae (L₃) causing an overall 99.7% decrease in the number of infective bites per year in the treated area. In this area, microfilaraemia also remained low for 10 years, whereas in another Zanzibari community where only one round of MDA was given, microfilaraemia reemerged after five years.

In the present study, we aimed to determine the role of vector control (with EPS beads in soakage pits and larvivorous fishes in unused wells) when used as adjunct to MDA given annually (not just for one year, as in United Republic of Tanzania) in reinforcing the effects of annual MDA on antigenaemia and microfilaraemia.

Methods

Study area The study area was located in the filaria endemic villages of Tirukoilur (latitude: 11°57'00’; longitude: 79°12’00’’) of Villupuram district, Tamil Nadu state, south India, 40–80 km inland from Pondicherry on the east coast (Fig. 1). Most of the annual rainfall (mean = 1125 mm) occurs during the north-east monsoon months of October–December. Agriculture is the predominant occupation of the study population with

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Ref. No. 06-029389

(Submitted: 10 January 2006 – Final revised version received: 25 September 2006 – Accepted: 12 October 2006)
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Fig. 1. Map of the study area showing six filarial endemic villages of Tirukoilur, India

- Vanapuram
- Edaiyur
- Ariyur
- Pavandhur
- Mandagapadi
- Rishivandhiyam

- MDA alone
- MDA + vector control
- PHC

the majority being landless labourers depending on agriculture and livestock husbandry for their survival. The population depends mainly on primary health centres for health care.

Study design

We have been conducting lymphatic filariasis control studies in nine villages of south India from 1995 to 1999 and in six villages since 2000.\(^5,10\) The nine villages were randomly allocated to three groups; one group of three villages received MDA (DEC + IVR) in 1995 and 1996; a second group of three villages received a combined approach of MDA (DEC + IVR) with vector control in 1995 and 1996; and a third group of three villages was the placebo group until 1999, for comparison. In 1999, as the placebo group also received antifilarial drugs, we confined our analyses to six villages — those receiving MDA only versus those receiving MDA with vector control. From 2001, these six villages were included in the GPELF programme with the community carrying out vector control activities in villages receiving MDA with vector control (Fig. 2). The institutional ethical committee has approved this study.

Intervention strategies

Mass drug administration

We conducted three rounds of MDA with DEC + IVR in all the six villages during 1995–99. Of the total residents eligible for treatment more than 90% took the drugs. We carried out MDA through door-to-door visits. The Government of Tamil Nadu included these villages in the GPELF in 2001 using DEC alone in one village and DEC + ALB in the other two (Fig. 2). In villages receiving MDA with vector control, one village received DEC + ALB while two villages received DEC alone.

Vector control activities

In urban areas of India Culex breeds heavily in blocked drains. But in rural areas, where our study was carried out, the soakage pits in the backyard of each household rendered an environment suitable for breeding of the vector. Unused wells were the other primary breeding habitats in this area. We undertook vector control operations in all three villages by modifying all the soakage pits and subsequently applying EPS beads @ 350–400 g/m² water surface area between 1995 and 1999.\(^10\) We carried out the cleaning of soakage pits, bead expansion and application with active involvement of the community. During the initial period, we introduced larvivorous fishes in the unused wells. We monitored the vector breeding habitats until October 1997, after which the community assumed responsibility for it.

Monitoring and evaluation

Vector transmission parameters

We monitored the vectors every month in the six villages by collecting adult Culex quinquefasciatus “resting” in 16 houses between 09:00 and 11:00 hours, spending 15 minutes in each house. We also collected mosquitoes “landing” on human volunteers from 18:00 to 06:00 hours, from one village in each intervention strategy, i.e. MDA alone and MDA with vector control, every month. After the MDA in 2001, landing collections were made every quarter. Mosquitoes from the resting and landing collections were identified in the laboratory and we dissected all female mosquitoes to determine the parity and filarial infection status. We calculated infection rates by including all mosquitoes found to have microfilariae and/or other filarial larval stages. Infectivity rates were based on mosquitoes with third-stage larvae (L₃).
We observed the antigenaemia and who were screened for microfilaraemia. (ICT) kit, from the same individuals on a immunochromatographic card test estimated from 100 µl of blood placed larial antigen) prevalence (AGP) was also the 1999 survey, the antigenaemia (filaria endemic mosquitoes.

**Filarial infection in the community**

We measured the microfilaraemia status in the community in 1994 (pre-treatment), in 1997 (one year after two annual MDAs) and in 1999 (before the 1999 MDA). We used the conventional finger prick–thick smear method for determining microfilaraemia by collecting 20 µl of blood placed 21:00 and 00:00 hours from 10% of the randomly selected population. During the 1999 survey, the antigenaemia (filarial antigen) prevalence (AGP) was also estimated from 100 µl of blood placed on an immunochromatographic card test (ICT) kit, from the same individuals who were screened for microfilaraemia. We observed the antigenaemia and microfilaraemia status in subsequent parasitological surveys (2001–04) where only age groups 2–5 years and 15–25 years were screened. While the 2001 survey was carried out before MDA in 2001, in subsequent years the surveys were carried out one year after each MDA.

**Data analyses**

We analysed the data on filarial infection obtained from humans as well as mosquito vectors until 2005. We tested the significance of the prevalence of microfilaraemia and antigenaemia in the two treatment arms (before and after MDA) using χ² analysis and Fisher’s exact test. Geometric mean intensities of microfilaraemia were calculated as antilog [Σ log (x+1)/n] –1, with ‘x’ being the number of microfilarae/20 µl of blood and ‘n’ the number of individuals examined, including microfilaraemia-negative individuals. We attached binomial confidential intervals to the proportions of the vector infection and infectivity rates.

**Findings**

**Vector transmission parameters**

We found a drastic decrease in the vector density in villages receiving MDA with vector control (Table 1 and Table 2) and this was sustained throughout the study period.

Considerable numbers of filarial larvae (including L₃ stages) were found in the mosquitoes caught in the villages receiving MDA alone. Very few (Table 1) or no (Table 2) filarial larvae were found in villages receiving MDA with vector control but very few mosquitoes were available for dissection here. The very low or zero infection and infectivity rate had a wide 95% confidence limit and did not differ significantly from those in villages receiving MDA alone.

**Filarial infection status Microfilaraemia**

We observed that the prevalence and intensities of microfilaraemia decreased sharply (in the survey during 1997) in villages receiving both MDA alone and MDA with vector control (88% to 92%), after two MDAs using DEC + IVR (carried out in 1995 and 1996) (Table 3). In the subsequent survey in 1999 (without any MDAs in between) the microfilarial prevalence and intensities resurged in villages receiving MDA alone but did not do so in villages receiving MDA with vector control.

We found microfilaraemia in two age groups during 1999–2002 and
2003–04 (Table 4). The observed microfilaraemia prevalences continued to be lower among villages receiving MDA with vector control than among villages receiving MDA alone, but the differences were either not significant or of only borderline significance.

**Antigenaemia**

We found statistically comparable estimates of AGP in 1999 for villages receiving MDA alone and those receiving MDA with vector control — 16.75% and 14.41% ($\chi^2 = 1.14; P = 0.2855$), respectively. The AGP among children 2–5 years old was low (5.33%) in villages receiving MDA with vector control as compared to villages receiving MDA only (7.32%), but the difference was not statistically significant on Fisher’s exact test ($P > 0.05$). Similarly, the AGP in the age group 15–25 years were not significantly different between the two treatment arms during 1999.

Antigenaemia rates for 1999–2002 and 2003–04 (Table 5) were significantly less among villages receiving MDA with vector control than for villages receiving MDA alone for the age group 2–5 years. We found a definite impact of vector control on the age group 15–25 years among villages receiving MDA with vector control, whereas there was no significant impact relating to age group 15–25 years among villages receiving MDA only. Villages receiving MDA with vector control did show a highly significant decrease in antigenaemia rates between the periods 1999–2002 and 2003–04.

**Discussion**

We provide strong evidence of the benefit of integrating vector control with MDA (Table 1, Table 2, Table 3 and Table 5). Culicines exhibit the phenomenon of limitation or negative density-dependence, in which the parasite yield ($L_3$) increases when the number of ingested microfilariae is low. These vectors are capable of picking up microfilariae and developing $L_3$ larvae after feeding on very low-level microfilaraemia carriers. In areas where limitation occurs, eradication of filariasis is hard to achieve. Although intensive MDA using DEC (and some vector control) has been carried out in Polynesia for more than 50 years, elimination was not attained on any of the islands where *W. bancrofti* was transmitted by *Aedes*

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**Table 1. Entomological parameters estimated from the indoor resting Culex quinquefasciatus, Tirukoilur, India**

<table>
<thead>
<tr>
<th>Treatment in village</th>
<th>Period</th>
<th>Mosquitoes caught per worker hour</th>
<th>Number dissected</th>
<th>Number infected (%) with 95% CI</th>
<th>Number infective (%) with 95% CI</th>
<th>Mean number of third-stage larvae ($L_3$)</th>
<th>Transmission intensity index*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass drug administration (MDA) alone</td>
<td>July 1999–March 2002</td>
<td>23.70</td>
<td>2108</td>
<td>44 (2.09)*</td>
<td>9 (0.43)*</td>
<td>3.44</td>
<td>0.3486</td>
</tr>
<tr>
<td></td>
<td>April 2002–August 2005</td>
<td>39.15</td>
<td>3073</td>
<td>43 (1.40)*</td>
<td>6 (0.20)*</td>
<td>4.33</td>
<td>0.3312</td>
</tr>
<tr>
<td>MDA with vector control</td>
<td>July 1999–March 2002</td>
<td>1.49</td>
<td>373</td>
<td>6 (1.61)*</td>
<td>2 (0.54)*</td>
<td>1.00</td>
<td>0.0080</td>
</tr>
<tr>
<td></td>
<td>April 2002–August 2005</td>
<td>0.83</td>
<td>354</td>
<td>3 (0.85)*</td>
<td>0 (0)*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* 95% binomial confidence interval.
* Transmission intensity index = mosquitoes caught per man hour x proportion infective x mean $L_3$.

**Table 2. Entomological parameters estimated from the indoor landing Culex quinquefasciatus, Tirukoilur, south India**

<table>
<thead>
<tr>
<th>Treatment in villages</th>
<th>Period</th>
<th>Mosquitoes caught per worker hour</th>
<th>Number dissected</th>
<th>Number infected (%) with 95% CI</th>
<th>Number infective (%) with 95% CI</th>
<th>Mean number of third-stage larvae ($L_3$)</th>
<th>Mean annual biting rate</th>
<th>Mean annual infective biting rate</th>
<th>Mean annual transmission potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass drug administration (MDA) alone</td>
<td>July 1999–March 2002</td>
<td>14.44</td>
<td>4678</td>
<td>64 (1.37)*</td>
<td>7 (0.15)*</td>
<td>4.14</td>
<td>54.309</td>
<td>159.70</td>
<td>326.98</td>
</tr>
<tr>
<td></td>
<td>April 2002–August 2005</td>
<td>4.16</td>
<td>549</td>
<td>9 (1.64)*</td>
<td>1 (0.18)*</td>
<td>15.00</td>
<td>17.661</td>
<td>30.42</td>
<td>456.25</td>
</tr>
<tr>
<td>MDA with vector control</td>
<td>July 1999–March 2002</td>
<td>0.17</td>
<td>66</td>
<td>0 (0)*</td>
<td>0 (0)*</td>
<td>0</td>
<td>1833</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>April 2002–August 2005</td>
<td>0.32</td>
<td>66</td>
<td>0 (0)*</td>
<td>0 (0)*</td>
<td>0</td>
<td>2008</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* 95% binomial confidence interval.
* No significant difference among % infected (based on $\chi^2$ or Fisher’s exact test).
* No significant difference among % infective (based on $\chi^2$ or Fisher’s exact test).
polynesiensis.\textsuperscript{17} Prevalence decreased in a few years from 30–35% to 3–6%, and then was maintained at this level for several decades. A test of interruption of MDA in one of the islands resulted in filariasis prevalence returning to initial levels within five years. We found that it was advantageous to use polystyrene bead treatment (Table 1 and Table 2) to maximize the chances of success in decreasing vector density. The much lower mosquito densities in villages receiving MDA with vector control confirm that transmission was very low there. The zero values calculated for TII and ATP in 2002–05 in three villages are very encouraging but we cannot assert that there was absolutely no transmission in these villages.

Microfilaraemia

We did not observe a significant short-term decrease in microfilaraemia when vector control was used as an adjunct to MDA (Table 3 and Table 4). While we found evidence that on stopping MDA resurgence occurred (Table 3), we believe that this could be prevented if the vector population is suppressed by using polystyrene beads, similar to the experience reported from Zanzibar.\textsuperscript{18}

Antigenaemia

Estimation of antigenaemia prevalence is becoming increasingly important to evaluate the impact of filarial control programmes, especially when microfilaraemia decreases to near zero in specific age groups, as in French Polynesia.\textsuperscript{19} Antigenaemia positivity was reported to be low in villages where the ATP was also low.\textsuperscript{20} A greater proportion of antigenaemia-positive children (91%) from villages receiving MDA with vector control were amicrofilaraemic and expected to have lower antigen levels compared to antigenaemia-positive and microfilaraemia-positive children,\textsuperscript{21,22} highlighting the role of vector control in restricting worm burden.

We observed a significant benefit of vector control when used as an adjunct to MDA in decreasing antigenaemia levels among young children (age group 2–5 years). There was no apparent decrease in antigenaemia from MDA alone among young adults (age group 15–25 years), but a very significant decrease when vector control was used as adjunct to MDA (Table 5).

Role of vector control in filariasis elimination

We found that annual MDAs alone decreased the filarial infection load in the community if there were no lapses. However, residual microfilaraemia of 0.4% and antigenaemia positivity of 4.6% were observed even after 36 years of filariasis control in French Polynesia.\textsuperscript{19} MDA with "DEC drug combination" was found to be more effective than DEC alone in decreasing filarial infection variables.\textsuperscript{23,24} Vector control was found to be important during any lapse in the MDA programme.\textsuperscript{5,18} The importance of vector control methods has been emphasized, as they play a key role in the prevention of disease transmission.\textsuperscript{25} In China, the campaign against lymphatic filariasis turned successful when vector control was integrated with other intervention measures, such as DEC administration (selective and mass treatment, and as fortified salt), resulting in the interruption of filarial transmission without any resurgence.\textsuperscript{26,27} In Brazil,\textsuperscript{26,28} Zanzibar\textsuperscript{4-18} and India,\textsuperscript{10} the impact of MDA in combination with vector control has been extensively studied. The usefulness of polystyrene

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### Table 3. Microfilaraemia status before and after two rounds of mass drug administration (diethylcarbamazine and ivermectin) alone or combined with vector control, Tirukoilur, India

<table>
<thead>
<tr>
<th>Treatment in villages</th>
<th>1997 &amp; 1999 % decrease (b)</th>
<th>1997 &amp; 1999 % decrease (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-mass drug (MDA) (1994)</td>
<td>Post-MDA</td>
<td>Pre-MDA</td>
</tr>
<tr>
<td>MDA alone</td>
<td>15.19 (724)</td>
<td>1.81 (609)</td>
</tr>
<tr>
<td>MDA with vector control</td>
<td>15.09 (795)</td>
<td>1.24 (645)</td>
</tr>
</tbody>
</table>

\(a\) After two rounds of MDA (in 1995 and 1996). \(b\) Decrease with respect to pre-MDA. \(c\) No MDAs during 1997 and 1998. \(d\) \(P<0.05.\)

### Table 4. Microfilaraemia prevalences in two age groups in villages that received mass drug administration alone or combined with vector control, Tirukoilur, India

<table>
<thead>
<tr>
<th>Treatment in villages</th>
<th>Age group</th>
<th>1999–2002</th>
<th>2003–04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass drug administration (MDA) alone</td>
<td>2–5</td>
<td>0.9\textsuperscript{d} (333)</td>
<td>0.85\textsuperscript{d} (353)</td>
</tr>
<tr>
<td>MDA with vector control</td>
<td>0\textsuperscript{d} (379)</td>
<td>0\textsuperscript{d} (327)</td>
<td></td>
</tr>
<tr>
<td>MDA alone</td>
<td>15–25</td>
<td>4.2\textsuperscript{d} (334)</td>
<td>3.3\textsuperscript{d} (608)</td>
</tr>
<tr>
<td>MDA with vector control</td>
<td>1.5\textsuperscript{d} (395)</td>
<td>1.8\textsuperscript{d} (621)</td>
<td></td>
</tr>
</tbody>
</table>

\(a, b, c, d\) Data sharing the same superscript letter do not differ statistically significantly (based on \(\chi^2\) or Fisher’s exact test).
La lutte antivectorielle complète le traitement médicamenteux de masse contre la filariose à W. bancrofti à Tirukoilur (Inde)

Objectif Déterminer le rôle de la lutte antivectorielle dans l’abaissement des niveaux de transmission de la filariose à W. bancrofti déjà obtenu grâce au traitement médicamenteux de masse et son effet à long terme sur les indices filariométriques. 


Résultats La densité vectorielle a sensiblement diminué dans les villages où des mesures de lutte antivectorielle complétaient le traitement médicamenteux de masse et chez les rares moustiques qui subsistaient, l’infestation avait presque entièrement disparu. L’antigénémie filarienne était faible et elle a continué à diminuer considérablement parmi la tranche d’âge 15-25 ans dans les villages bénéficiant à la fois du traitement et de la lutte antivectorielle par rapport aux villages qui ne bénéficiaient que du traitement. 

Conclusion Les avantages du traitement médicamenteux de masse n’ont pu être durablement maintenus qu’en intégrant des mesures de lutte antivectorielle. Il est donc conseillé d’incorporer des telles mesures au Programme mondial d’élimination de la filariose lymphatique car elles offrent un moyen susceptible de réduire le délai d’élimination.

Acknowledgements We wish to thank the director general of the Indian Council of Medical Research, New Delhi, India, for providing research facilities. We are grateful to the director of the Tamil Nadu Public Health Department and his staff for their cooperation in the field study. We thank the staff of the Centre for Research in Medical Entomology at Madurai and its Field Station at Tirukoilur for their excellent cooperation in carrying out this study. We also thank R Balasubramanian, Assistant Programme, Statistics, at the Centre for Research in Medical Entomology for his help in the data analyses and the medical officers for their clinical expertise during the MDA programme. We are grateful to the panchayat presidents and the villagers in the study communities for their active cooperation in conducting the field trials. We appreciate the excellent help, particularly related to word processing, rendered by A Venkatesh of the Centre for Research in Medical Entomology, Madurai.

Funding: This investigation received partial financial support from WHO/TDR (grant ID No.940340) and WHO/CTD/FIL (ID No.990574), Geneva.

Competing interests: none declared.
La lucha antivectorial como complemento de la administración masiva de medicamentos contra la filariasis de Bancroft en Tirukoilur, India

Objetivo Determinar la contribución de la lucha antivectorial a la reducción de la transmisión de la filariasis de Bancroft lograda mediante la administración masiva de medicamentos y su impacto a largo plazo en los índices filariométricos.

Métodos Se procedió a complementar tres rondas de administración anual masiva de diethylcarbamazine e ivermectina con medidas de lucha antivectorial (principalmente microesferas de poliestireno) en aldeas de Tirukoilur, en el sur de la India, durante 1995-1999. Posteriormente ha proseguido la administración de medicamentos, utilizando conjuntamente diethylcarbamazine y albendazol, o bien sólo diethylcarbamazine. Evaluamos el impacto de la administración masiva de medicamentos por separado o unida a medidas de lucha antivectorial (entre 1995 y 2005) en los índices de transmisión vectorial (como el índice de transmisión de masa, la tasa de picaduras al mes, el potencial de transmisión mensual y el potencial de transmisión anual). A partir de los datos sobre la infección filaria en la comunidad se estimó la prevalencia de microfiaremia y antigenemia usando la prueba de ji cuadrado y la prueba exacta de Fisher.

Resultados La densidad de vectores disminuyó considerablemente en las aldeas donde se recurrió a medidas de lucha antivectorial como complemento de la administración masiva de medicamentos, y entre los escasos mosquitos supervivientes apenas se hallaron ejemplares infecciosos. La antigenemia filaria fue baja y siguió disminuyendo de forma significativa en el grupo de edad de 15 a 25 años en las aldeas donde la administración masiva de medicamentos se combinó con la lucha antivectorial, a diferencia de las aldeas en que sólo se hizo lo primero.

Conclusión Los beneficios conseguidos mediante la administración masiva de medicamentos sólo pudieron mantenerse integrando un componente de control de los vectores. Preconizamos la incorporación de la lucha antivectorial en el Programa Mundial de Eliminación de la Filariasis Linfática, pues ello permitiría reducir el tiempo requerido para eliminar esa enfermedad.

Referencias
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