Overview of integrated vector management (IVM), summary of previous dengue vector control trials in Cambodia

John Hustedt
## Vector control tools tested in Cambodia

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Temephos (Abate)
Abate distribution and dengue control in rural Cambodia

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Received 29 June 2006; received in revised form 20 December 2006; accepted 9 January 2007
Available online 16 January 2007
Temephos (Abate)

Background

• Abate distribution has been conducted yearly since mid 1990s, with financial support for the larvicide and health education materials provided by the Cambodian Ministry of Health, World Health Organization (WHO), the International Red Cross, and the World Bank.

• The Ministry of Health spends around US$1 million per annum to purchase 200 metric tonnes of Abate.

• In 2002, WHO and the World Bank also provided US$ 150,000 and 250,000, respectively, to meet the operational costs of distribution, such as transportation, per diem for distributors and the cost of packaging Abate into small plastic bags.

• In 2003, Abate was distributed to select areas in 15 out of 22 dengue endemic provinces in the country, based on the prevalence of the disease identified by monthly surveillance reports.
Temephos (Abate)

Challenges

- Coverage varied significantly, based on the commitment of distributors.
- Difficulties in measuring the container capacity correctly and incorrect quantities of Abate being placed in containers.
- Where Abate was introduced with minimal health education, some householders refused to accept it, or removed the bag of Abate from their water containers.
- Limited understanding of the duration of its effectiveness as a larvicide and less understanding and adherence to other control activities.
- Water jars were positive with larvae in both rainy and dry seasons, although Abate was applied only in the rainy season.
- Development of insecticide resistance
Temephos (Abate)

Conclusions

• Control strategies emphasizing the use of Abate should be reconsidered.

• In total, almost US$ 1.4 million is currently expended on the distribution of Abate, which could be redirected, at least in part, for other preventive activities such as the production of appropriate, effective and sustained health education and promotion as a health centre outreach activity.
Mesocyclops
Mesocyclops

• Following the success of *Mesocyclops* (a genus of copepod crustaceans) programs in locally eliminating *Aedes* mosquitoes in Vietnam, the Cambodian NDCP implemented a two-year *Mesocyclops* project in Kratie province.

• *Mesocyclops* from the local water sources had various parasites, and colonising them parasite-free requires special training beyond what is possible in most rural Cambodian villages.

• People did not accept *Mesocyclops* to the same extent as other interventions that were provided by the NDCP such as temephos.
Mesocyclops

Larval Density Per House After Mesocyclops Introduction in Kratie, June 2003-September 2004

- June 2003
- September 2003
- January 2004
- April 2004
- June 2004
- September 2004

Pilot Areas
Control Areas

Larvae Per House

Jun 2003: 100
Sept 2003: 50
Jan 2004: 250
Apr 2004: 150
Jun 2004: 300
Sep 2004: 180
Insecticide Treated Jar Covers
The effect of long-lasting insecticidal water container covers on field populations of *Aedes aegypti* (L.) mosquitoes in Cambodia

Chang Moh Seng\(^1\), To Setha\(^2\), Joshua Nealon\(^1\), Ngan Chantha\(^2\), Doung Socheat\(^2\), and Michael B. Nathan\(^3\)

\(^1\)World Health Organization Cambodia. #177-179, Pasteur Street (51), Phnom Penh, Cambodia
\(^2\)National Centre of Parasitology, Entomology and Malaria Control, Ministry of Health, Phnom Penh, Cambodia
\(^3\)Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Received 2 April 2008; Accepted 31 July 2008
Insecticide Treated Jar Covers (Seng et al. 2008)

- Despite correct high utilization rates (88%), cost of $1.20 is prohibitive to most rural Cambodians
- Container cover not 100% insect-proof due to incorrect closure allowing mosquito entry and exit
- Harsh outdoor tropical environment degrade fabric & netting of water jar covers; more improvements are needed
- Potential insecticide resistance development → safe alternatives to pyrethroids
- What is the strategy for the “last mile”?
Insecticide Treated Jar Covers (Seng et al. 2008)

Figure 1. Mean number of indoor resting female *Ae. aegypti* per house in the intervention and control areas.

Figure 2: Mean *Aedes* pupae per house
Guppy Fish
Guppy Fish  (Seng et al. 2008)

- One year after project commencement, 56.9% of eligible containers contained guppies and there was a 79.0% reduction in *Aedes* infestation in the intervention community compared with the control.
- Smaller or discarded containers unsuitable for guppy distribution in the intervention area also had 51% less infestation than those in the control area, suggesting a “community-wide” protective effect.

Table 4. The house, container, and Breteau indices of the intervention and control areas of this study one year after project implementation. “n” refers to either number of houses (a) or number of containers (b). “No. positive” refers to the number of houses (c) or containers (d).

<table>
<thead>
<tr>
<th>Area</th>
<th>House Index</th>
<th>Container Index</th>
<th>Breteau Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n^a</td>
<td>No. positive^c</td>
<td>Index</td>
</tr>
<tr>
<td>Intervention</td>
<td>249</td>
<td>112</td>
<td>45.0</td>
</tr>
<tr>
<td>Control</td>
<td>65</td>
<td>61</td>
<td>93.8</td>
</tr>
</tbody>
</table>
Guppy Fish  (WHO, 2013)

• The project resulted in a decline in the number of mosquito larvae present in three key water containers (jars, cement tanks, and drums).
• Scale-up of the low-cost intervention *is recommended in Cambodia and Lao*
• Accepted well by community
Bacillus Thuringiensis Israelensis (Bti)
Efficacy of Bacillus thuringiensis israelensis, VectoBac® WG and DT, Formulations Against Dengue Mosquito Vectors in Cement Potable Water Jars in Cambodia

To Setha, Ngan Chantha and Doung Socheat

National Malaria Center (CNM), Center for Entomology, Parasitology and Malaria Control, Phnom Penh, Cambodia
**Bti** (Setha et al, 2007)

- The VectoBac treatments significantly reduced the pupae numbers for a minimum of 3 months in the river water and 2.5 months in the well water.
- In the rain water, the pupae densities in the VectoBac WG® and DT® treated jars were not significantly different from the untreated jars.
- It was also observed that VectoBac WG® and DT® were target specific, without any adverse effects on aquatic predatory insects common in well and rain water.
**Bti** (Setha et al, 2007)

Table 2
Mean number of pupae collected from cement jars per week from 12 June to 6 September 2004 and successfully emerged into *Ae. aegypti* adults.

<table>
<thead>
<tr>
<th>Water type</th>
<th>Treatment</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; month post-treatment</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; month post-treatment</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; month post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$\chi \pm SE$ (p value)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$\chi \pm SE$ (p value)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>$\chi \pm SE$ (p value)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>River water</td>
<td>VectoBac WG</td>
<td>2.0 ± 1.41 (p=0.023)</td>
<td>1.25 ± 0.95 (p=0.066)</td>
<td>1.75 ± 1.75 (p=0.008)</td>
</tr>
<tr>
<td></td>
<td>VectoBac DT</td>
<td>2.5 ± 2.50 (p=0.025)</td>
<td>2.25 ± 1.65 (p=0.072)</td>
<td>1.75 ± 0.25 (p=0.008)</td>
</tr>
<tr>
<td></td>
<td>UTC</td>
<td>45.50 ± 14.22</td>
<td>39.75 ± 17.14</td>
<td>56.75 ± 13.98</td>
</tr>
<tr>
<td>Well water</td>
<td>VectoBac WG</td>
<td>5.5 ± 5.17 (p=0.082)</td>
<td>0.5 ± 0.29 (p=0.013)</td>
<td>9.0 ± 2.86 (p=0.396)</td>
</tr>
<tr>
<td></td>
<td>VectoBac DT</td>
<td>4.25 ± 4.25 (p=0.069)</td>
<td>5.00 ± 3.72 (p=0.051)</td>
<td>3.50 ± 1.94 (p=0.242)</td>
</tr>
<tr>
<td></td>
<td>UTC</td>
<td>37.75 ± 14.56</td>
<td>23.25 ± 6.50</td>
<td>22.50 ± 14.51</td>
</tr>
<tr>
<td>Rain water</td>
<td>VectoBac WG</td>
<td>21.50 ± 19.84 (p=0.377)</td>
<td>6.25 ± 5.60 (p=0.626)</td>
<td>29.5 ± 29.5 (p=0.715)</td>
</tr>
<tr>
<td></td>
<td>VectoBac DT</td>
<td>11.50 ± 7.24 (p=0.23)</td>
<td>1.50 ± 1.50 (p=0.095)</td>
<td>9.0 ± 8.03 (p=0.213)</td>
</tr>
<tr>
<td></td>
<td>UTC</td>
<td>61.00 ± 36.35</td>
<td>9.75 ± 3.88 (p=0.095)</td>
<td>44.00 ± 23.82</td>
</tr>
</tbody>
</table>

<sup>a</sup> *T*-test was done to determine the significant difference between the respective populations in treated and untreated jars with each Bti formulation.
Bti (Setha et al. 2016)


To Setha†*, Ngan Chantha††*, Seleena Benjamin‡*, Doung Socheat‡‡

1 National Center for Parasitology, Entomology and Malaria Control, Ministry of Health, Phnom Penh, Cambodia, 2 Public Health, Valient BioSciences Corporation, Kuala Lumpur, Malaysia
**Bti** (Setha et al. 2016)

- Good supporting evidence that larviciding with Bti strain AM65-52 by a single dose of 8g per 1000 L in all in-use containers significantly suppresses *Aedes aegypti* pupae production and adult mosquitoes for a continuous 13 weeks in the peak rainfall and vector season.
Bti Treatment
July 25--29

Ae aegypti pupae and adult numbers per household

Pre Treatment → Post Treatment (weeks)
Pyriproxyfen
Pyriproxyfen  (Seng et al, 2008)

SIX MONTHS OF *Aedes aegypti* CONTROL WITH A NOVEL CONTROLLED-RELEASE FORMULATION OF PYRIPROXYFEN IN DOMESTIC WATER STORAGE CONTAINERS IN CAMBODIA

Chang Moh Seng¹, To Setha², Joshua Nealon¹, Duong Socheat² and Michael B Nathan³

¹World Health Organization, Phnom Penh; ²Center of Parasitology, Entomology and Malaria Control, Ministry of Health, Phnom Penh, Cambodia; ³Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
Pyriproxyfen (Seng et al, 2008)

- This single treatment provided control of Ae. aegypti in water jars for the length of the main dengue transmission season in Cambodia that normally extends from May to November.
- The device floated on top of water and was easily scooped up by households.
- No alteration of taste or other undesirable effects of the treatment were reported by householders.

| Table 1 |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Inhibition of emergence (IE) of adult Aedes aegypti in domestic water storage jars. Phum Thmei, Cambodia, April-December, 2005. |
| Weeks after treatment with pyriproxyfen\(^a\) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | Total |
|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| **Treated jars** | **0** | **100** | **99** | **99** | **96** | **96** | **95** | **95** | **95** | **94** | **94** | **94** | **94** | **93** | **92** | **92** | **0** | **0** | **0** | **92** |
| No. of water jars | **100** | **99** | **99** | **96** | **96** | **95** | **95** | **95** | **94** | **94** | **94** | **94** | **94** | **93** | **92** | **92** | **0** | **0** | **0** | **92** |
| No. of pupae collected | **291** | **414** | **225** | **654** | **337** | **555** | **219** | **763** | **722** | **364** | **499** | **376** | **250** | **124** | **246** | **299** | **7** | **138** | **6,553** |
| No. of viable adults emerged | **291** | **1** | **0** | **5** | **1** | **0** | **0** | **2** | **13** | **11** | **13** | **48** | **0** | **22** | **14** | **30** | **0** | **27** | **488** |
| Inhibition of emergence (%) | **0.0** | **99.8** | **100.0** | **99.2** | **99.7** | **100.0** | **99.7** | **98.2** | **97.0** | **97.4** | **87.2** | **100.0** | **82.3** | **94.3** | **90.0** | **87.0** | **80.4** | **92.6** |
| **Control jars** | **0** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** |
| No. of water jars | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** | **25** |
| No. of pupae collected | **51** | **206** | **36** | **129** | **47** | **137** | **53** | **135** | **225** | **231** | **18** | **86** | **36** | **35** | **149** | **86** | **9** | **47** | **1,746** |
| No. of viable adults emerged | **50** | **199** | **36** | **126** | **46** | **135** | **53** | **132** | **223** | **231** | **18** | **83** | **35** | **35** | **146** | **85** | **9** | **47** | **1,719** |
| Inhibition of emergence (%) | **2** | **3.4** | **0** | **2.3** | **2.1** | **1.5** | **0** | **2.2** | **0.8** | **0** | **0** | **3.5** | **3.5** | **0** | **2** | **1.1** | **0** | **0** | **1.5** |

\(^a\)Week 0 was a pre-treatment assessment.
Thermal Fogging

- No published data on efficacy or susceptibility of mosquitoes
- Impact on mosquito susceptibility from use by public and private sectors
## Vector control tools tested in Cambodia

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Discussion

- Reduction in vectors, but increase in cases?
- Improved surveillance (majority non-severe cases)
- Decreased Immunity and increase in average age of clinical cases
- Possible need for genetically modified/Wolbacia infected mosquitoes or vaccine for elimination

Source: Egger et al. 2008
CONSISTENT EFFICACY PROFILE OF CYD 14 & CYD 15 IN SUBJECTS 9–16 YEARS OF AGE DURING ACTIVE PHASE

Key Efficacy Results
25-month active phase*  Pooled efficacy analyses‡1

**Reduction in symptomatic dengue**

- 65.6% (95% CI: 60.7–69.9)

**Reduction in hospitalized dengue**

- 80.8% (95% CI: 70.1–87.7)

**Reduction in severe dengue†**

- 92.9% (95% CI: 76.1–97.9)

*Data come from the 2 pivotal, phase III, large-scale efficacy trials CYD14 and CYD15, which were designed to fully assess efficacy; postdose 1; †Full Analysis Set for Efficacy (FASE): all subjects who received at least one injection. *dengue hemorrhagic fever, World Health Organization 1997 criteria. CI=confidence interval; DENV=dengue virus.

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- Reduction in hospitalized dengue: 80.8% (95% CI: 70.1–87.7)
- Reduction in severe dengue†: 92.9% (95% CI: 76.1–97.9)

For each serotype:
- DENV-1: 58.4% (95% CI: 47.7–66.9)
- DENV-2: 47.1% (95% CI: 31.3–59.2)
- DENV-3: 73.6% (95% CI: 64.4–80.4)
- DENV-4: 83.2% (95% CI: 76.2–88.2)

By dengue serostatus:
- Seropositive: 81.9% (95% CI: 67.2–90.0)
- Seronegative: 52.5% (95% CI: 5.9–76.1)

*Data come from the 2 pivotal, phase III, large-scale efficacy trials CYD14 and CYD15, which were designed to fully assess efficacy; postdose 1; ‡Full Analysis Set for Efficacy (FASE): all subjects who received at least one injection. †dengue hemorrhagic fever, World Health Organization 1997 criteria. CI=confidence interval; DENV=dengue virus.

Clinical trials identified serostatus-specific efficacy. WHO recommends vaccine use in areas of high endemicity

“Prior infection, as measured by seroprevalence, should be approximately 70% or greater... to maximize public health impact and cost-effectiveness”

“Vaccination of populations with seroprevalence between 50% and 70% is acceptable”

“The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination”
Wolbachia Infected Mosquitoes
Wolbachia Infected Mosquitoes

**How Wolbachia Spreads...**
- Infected female + infected male → Eggs → Infected mosquitoes
- Infected female + uninfected male → Eggs → Infected mosquitoes
- Uninfected female + infected male → Eggs → Unhatched eggs

**...and Stops Dengue**
- Uninfected female → Bites human infected with dengue virus → Dengue virus replicates in mosquito
- Infected female → Dengue spreads via bite → Dengue virus does not replicate → Dengue does not spread
Genetically modified mosquitoes

Source: Scientific American, 2014
Discussion

Waiting for perfect interventions such as new vaccines or genetically modified/wolbachia infected mosquitoes and abandoning traditional vector control tools is not best practice. Even with the introduction of new methods traditional tools can provide value:

• Effective environmental sanitation encouraged in COMBI activities can reduce incidence of enteric diseases, vector borne diseases and create healthier environments.

• Effective larval control can reduce mosquito populations impacting vector borne diseases for which we don’t yet have effective vaccines (e.g. Zika, chikungunya) or are not targeted by modified mosquitoes.

• Community engagement strategies can help encourage uptake of any additional measures that may come in the future
Thank you