Role of research in malaria control in India

Malaria in Southeast Asia: Perspectives, progress and partnerships

7th November 2012

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National Institute of Malaria Research

- Established in 1977
  - to conduct basic, applied and operational field research
  - To support NVBDCP & to develop trained manpower in the country
- Human resource
  - Scientists: 56
  - Ph. D Students: 35
NIMR-Field Units

- Urban Malaria Paradigm
  - Chennai (T.N.)
  - Panjim (Goa)

- Rural Malaria Paradigm
  - Nadiad (Gujarat)
  - Bangalore (Karnataka)
  - Ranchi (Jharkhand)
  - Raipur (Chhattisgarh)

- Tribal Malaria Paradigm
  - Rourkela (Orissa)
  - Jabalpur (M.P.)
  - Guwahati (Assam)

- Industrial Malaria Paradigm
  - Hardwar (Uttrakhand)
Existing Strategy of Malaria Control in India

**Diagnosis**
- Microscopy
- RDT

**Treatment**
- National Drug Policy

**Vector Control**
- Larval Control
- IRS
- ITN
Research contributing to malaria control

Therapeutic efficacy studies
- Changes in drug policy

Clinical development of antimalarials
- Registration of new antimalarials

Pharmacovigilance of antimalarials
- Ensuring safety of antimalarials

Studying treatment practices
- Ban on artemisinin monotherapy

Evaluation of RDTs
- Marketing permission for RDTs
- RDTs in National Programme

QA of RDTs
- Improvement in diagnosis

Evaluation of non invasive methods

Monitoring insecticide resistance
- Guiding insecticide policy

Evaluation of insecticides/ LLINs/ vector control tools
- New molecules/ tools for vector control

Effective Treatment

Quality Diagnosis

Improved Vector Control

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Evolution of present drug policy

CQ resistance

- P. falciparum
- P. vivax

1st drug policy

Risk areas introduced

AS+SP 2nd line

Universal ACT

Malaria incidence (per 1000)

Chloroquine resistance in India

Districts with CQ treatment failure ≥10% (red) in any trial between 1978 and 2007 and Pf endemic areas (pink)

Lancet Infectious Diseases 2011, 11, 54-67
Molecular genotyping for CQ resistance in Indian field Isolates

- Analysis of pfcrt mutations & haplotypes from low & high endemic areas
- High endemic regions- Higher diversity in respect of pfcrt haplotype-SVMNT (S.Am), CVIET (SEA), CVMNK (wild)
- Low endemic regions- SVMNT only
- Threonine at codon76 (76T) was prevalent in both chloroquine responders and non responders
- Lysine at codon76 (K76) was observed only in clinical responders (10%) and never in non-responders
- High prevalence of mutant alleles and haplotypes among the isolates of different regions reflect the presence of resistant strains in the country

Therapeutic efficacy of antimalarials
(guiding the national drug policy)

- Therapeutic efficacy studies provided evidence to switchover to ACT for Pf malaria
  - Shah et al, Lancet Infect Dis; 2011;11: 57-64

- Developed national network of sentinel sites for monitoring antimalarial drug resistance

- Efficacy of AS+SP in Pf: 94 – 100% (n=2053)
- 2012: 21% PCR corrected failures in Mizoram
- Efficacy of CQ in Pv: 100% (n=413)

Valecha et al, Acta Tropica 2009 Jul;111(1):21-8,
Shah et al, Lancet Infect Dis; 2011;11: 57-64
Molecular analysis of dhfr and Pfcrt (Therapeutic efficacy studies)

- dhfr: Increasing trend of point mutation
- dhps: wild in 2009; in 2010-3% mutations
- Widespread Pfcrt mutation
Chloroquine efficacy in *P. vivax*

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Trans Royal Soc Trop Med Hyg 2006; 100: 831-837
Annals Trop Med Parasitol 2008; 102: 1-10

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Malaria treatment: Clinical development of new antimalarials

- **Phase I**
  - Artesunate + Curcumin

- **Phase II**
  - ACT in pregnancy
  - Arterolane + Piperaquine

- **Phase III**
  - Dihydroartemisinin + Piperaquine
  - Pyronaridine + Artesunate

- **Phase III Completed**
  - Artesunate + Amodiaquine
  - Artesunate + mefloquine
  - Arterolane + Piperaquine

- **Registered**

- ACT becomes first line treatment for *P. falciparum*
- Phase III studies with different FDCs
New drug/vaccine target(s) in *P. vivax* and *P. falciparum*

- Two genomic regions containing genes for drug/vaccine candidates identified by population genomic studies
- Cysteine proteases (falcipains): Ionic and hydrophobic interactions are crucial for the activation of major cysteine proteases, falcipain-2 and falcipain-3 of *P. falciparum*
- Computer aided designing of new drug compounds by modification of known aspartic protease inhibitor pharmacophores to fit in Plasmepsin4 structures.

Structural view of falcipain-2: Salt bridge and hydrophobic interactions (see inset) are crucial for activation.
Malaria in pregnancy: Prevention and treatment

- Study to assess effective and safe treatment for falciparum malaria in pregnancy initiated
  - 2 arms: AS+SP and AS+MQ
  - Cohort of more than 4000 pregnant women being followed
  - 169 patients enrolled

- Study to assess effective and safe interventions for preventing malaria in pregnancy
  - Intermittent screening and treatment
  - 700 pregnant women enrolled in cohort

Future activities
- To develop most appropriate strategy for prevention and treatment of malaria in pregnancy

Training of ANMs
Arterolane+Piperaquiene combination for uncomplicated 
*P. falciparum* malaria

Arterolane:
Synthetic trioxolane
No supply constraint
Rapid clearance of parasitaemia
Similar mechanism of action as artemisinin

Arterolane +piperaquiene combination:
- Phase II: 240 patients in India, Tanzania, Thailand
- Phase III adult-FDC tablets: 327 patients in Bangladesh, India Thailand
- Safe and effective
- PCR corrected cure rate: 100%
- Registered for marketing

Valecha et al, Clin Infect Dis. 2012 Sep 1; 55: 663
## Pharmacovigilance of antimalarials

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Drug</th>
<th>Adverse Event</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quinine n=7</td>
<td>Gastritis</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Itching</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Chloroquine + Primaquine n=1379</td>
<td>Loss of appetite</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Giddiness</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain in abdomen</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Artesunate + Doxycycline n=13</td>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Artesunate + Sulphadoxine-Pyrimethamine n=2604</td>
<td>Headache</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jaundice</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomatitis</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastritis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>82</strong></td>
</tr>
</tbody>
</table>
Ban on AS Monotherapy in India

1. No new license should be granted for the said formulations.
2. Manufacturing licenses granted earlier should be withdrawn by March 2009.
3. The formulations should be phased out from the market by July 2009.
## Evaluation of Diagnostic Kits by NIMR

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Sensitivity/Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ParaSight F</td>
<td>Becton Dickinson, U.S.A.</td>
<td>93/92.4</td>
</tr>
<tr>
<td>ICTPf/Pv</td>
<td>-do-</td>
<td>96.0/93.1(Pf)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75.5/99.0(Pv)</td>
</tr>
<tr>
<td>Rapid Test Malaria</td>
<td>Quoram Diagnostics, Canada</td>
<td>100/98.3</td>
</tr>
<tr>
<td>Pf Check-1</td>
<td>Veda Lab., France</td>
<td>87.7/98.9</td>
</tr>
<tr>
<td>Determine Malaria Pf</td>
<td>Dainabot Co., Japan</td>
<td>96.5/87.2</td>
</tr>
<tr>
<td>ACCU Stat Malaria</td>
<td>Millennium Bio-Technology Inc</td>
<td>86.9/90.3</td>
</tr>
<tr>
<td>Paracheck</td>
<td>Orchid Biomed.Systems(Goa)</td>
<td>95.8/85.7</td>
</tr>
<tr>
<td>OptiMAL</td>
<td>DiaMed, Switzerland</td>
<td>92.2/99.3(Pf)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>94.5/98.2(Pv)</td>
</tr>
<tr>
<td>Parascreen</td>
<td>Zephyr Biomedicals</td>
<td>—</td>
</tr>
<tr>
<td>Parahit</td>
<td>Premier Medical Corporation Ltd., Mumbai, India</td>
<td>96/95</td>
</tr>
<tr>
<td>First Response combo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>malaria Ag card</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quality Assurance of Malaria Rapid Diagnostic Tests

- Mechanism for quality assurance of malaria RDTs used in NVBDCP established
- Quality Control panels (2000 parasite/µl and 200 parasite/µl) prepared.
- Pre-dispatch QC: 50 batches tested
- Panel detection score: 91.7%; Specificity: 100%

Picking up RDTs for QA from different levels
Genetic polymorphism in Pfhrp2 and Pfhrp3 (n=140)

- Pfhrp2 fragments: size from 669 bp to 1000 bp
- Pfhrp3 varied from 477 bp to 832 bp
- RDT detection limit of isolates varied from 31 to 1000
- RDTs could detect 68.3% of *P. falciparum* isolates at densities ≤ 200 /µl.

- Relation between type 2 (AHHAHHAAD) and 7 (AHHAAD) repeats and RDT performance
- We also reported Indian *P. falciparum* field isolates lacking these genes
- Variation in Pfhrp2 and Pfhrp3 as well as deletion of these genes may lead to false negative results in RDTs
Improving Malaria Diagnosis

- Evaluation of RDTs
- Evaluation of non-invasive methods for malaria diagnosis using saliva
  - multiplex PCR based assay
  - LAMP
- Immunodiagnostic reagent for the detection of *P. vivax*
  - Patent filed: Ref: IP01699/RT (No. 1606/DEL/2008)

Reactivity of Monoclonal Antibody with *P. vivax* in IFA
Table: Indian malaria vectors: distribution, influence, and contribution

<table>
<thead>
<tr>
<th>Species</th>
<th>Distribution</th>
<th>Behavior</th>
<th>Control Option</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culicifacies</td>
<td>Wide spread (Plains)</td>
<td>Endo-phagic/ philic</td>
<td>IRS/ ITNs/LNs</td>
<td>Wide spread resistance to insecticides (DDT/MLN)</td>
</tr>
<tr>
<td>Fluviatilis</td>
<td>Wide spread (forest and foot hills)</td>
<td>Endo-phagic/ philic/Exo-philic</td>
<td>IRS/ ITNs/LNs</td>
<td>Susceptible to insecticides</td>
</tr>
<tr>
<td>Stephensi</td>
<td>Localized &amp; urban settings</td>
<td>Type form -Endo-phagic/ philic Mysorensis- endo-phagic/ philic</td>
<td>Larvicides and personal protections</td>
<td>No reports of resistance that can effect the interventions</td>
</tr>
<tr>
<td>Minimus</td>
<td>Wide spread NE and forested areas</td>
<td>Endo-phagic/ philic</td>
<td>IRS/ ITNs/LNs</td>
<td>No reports of resistance</td>
</tr>
<tr>
<td>Sundaicus</td>
<td>Only in A &amp; N. islands</td>
<td>Endo-phagic/ philic</td>
<td>IRS/ ITNs/LNs</td>
<td>No reports of resistance that can effect the interventions</td>
</tr>
<tr>
<td>Dirus</td>
<td>Localized in NE</td>
<td>Exo-phagic/ philic</td>
<td>--</td>
<td>Personal protection is an option</td>
</tr>
</tbody>
</table>

No. of anopheline species - ~ 60
No. of vectors - 9 (primary 6)
Geographical distribution of insecticide resistance/susceptibility status in *An. culicifacies* in India (based on available data 1995 – 2012)

(Compilation based on published and unpublished reports that needs further confirmation)

Other vector species are mostly susceptible to the insecticides used in vector control
- *An. fluviatilis* - sporadic reports of resistance, but not of serious operational concern
- *An. stephensi* - urban vector - reported resistance to DDT and malathion but larvicides are used for its control to which it is susceptible
Knockdown resistance (kdr) in malaria vectors

An. culicifacies complex

- Knockdown resistance (kdr) is one of the resistance mechanism against DDT/pyrethroids
  - An. culicifacies: Identified three kdr mutations—L1014F and L1014S & V1010L(novel)
  - An. stephensi: identified two mutations—L1014F and L1014S & V1010L(novel)

An. stephensi

- Developed PCR-based assays for detection of kdr resistance in An. culicifacies and An. stephensi

PCR assays developed for kdr detection
Chronology: insecticide introduction and resistance development

- Resistance to DDT 1950's
- Resistance to MLN 1973
- Resistance to HCH 1962
- Resistance to DM 2001 & localized spread
- Banned - Toxicity & safety issues
- DDT & still in use
- Malathion
- Pyrethroids
- ITNs
- LLINs

21st century
Mid 1990s
1969-70
1958-60
1950's
New Tools for Vector Control

INSECTICIDES TESTED

• Indoor Residual Spraying
  - Deltamethrin *
  - Bifenthrin
  - Chlorpyriphos methyl
  - Bendiocarb
  - Lambda cyhalothrin *
  - Fipronil

• Insecticide treated mosquito nets
  - Deltamethrin *
  - Cyfluthrin *
  - Lambda cyhalothrin *
  - Alpha-cypermethrin
  - Bifenthrin

*Registered and are being used by NVBDCP

• LLINs/LMs
  - Olyset#
  - Permanet #
  - Interceptor#
  - K-O-Tab 1,2,3 (kit)
  - ZeroFly

#Specifications approved for use in programme

LARVICIDES TESTED

• Pirimiphos methyl (Chemical)
• Bti aqueous suspension (Biopesticide)
• Bti tablets (Biopesticide)
• Insect growth regulators
• Neem formulation (Plant based)
• Attracticide (Oviposition pheromone)

BIOLOGICAL CONTROL

• Aphanius dispar

PHYSICAL BARRIERS (Larvicidal)

• Mono molecular film
• EPS beads

Interventions under consideration for trials

• Chlorfenapyr
• Combinations nets: Olyset plus, Permanet 3.0
Other operational research projects
Health Impact Assessment of Indira Sagar Dam and Sardar Sarovar Project Areas in Madhya Pradesh

Interventions suggested by NIMR
- De-weeding in canals
- Use of plastic sheets in canal
- Fogging in power house
- Leveling of river-bed pools by filling
- Construction of mosquito proof house
- IEC activities

<table>
<thead>
<tr>
<th>Year</th>
<th>Pf</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>52</td>
<td>100</td>
</tr>
<tr>
<td>2005</td>
<td>83</td>
<td>299</td>
</tr>
<tr>
<td>2006</td>
<td>32</td>
<td>153</td>
</tr>
<tr>
<td>2007</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>2008</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>2009</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>2010</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

No. of Cases

% Positivity of *Ae. aegypti* in Narmada Nagar (2004-2010)
Malaria Burden Estimation

- Morbidity Estimation
  - NVBDCP Data
  - NFHS 1 & 2
  - NSSO 2004
- Mortality Estimates MCCCD Data
- New methodology for morbidity estimation proposed.

**NIMR Morbidity Estimation Model**

\[ EMC = Pop. \times FR \times SPR \]

- **EMC**: Estimated Malaria Cases
- **FR**: Fever Rate
- **SPR**: Slide Positive Rate

Kumar et al., 2010. Lancet 377; 991-992
Valecha et al., 2010. Lancet. 377:992-993;
Kumar et al., 2012. Acta Tropica 121: 256-266
Sixty eight most malaria affected districts from 11 states of India were identified by NVBDCP to prioritize the villages for focus intervention.

- Village wise GIS mapping has been carried out for 27 problematic districts identified by NVBDCP.
- Decision support for NVBDCP to develop focused intervention for malaria control.
**Other Vector Borne Diseases**

- Aedes breeding surveys to support control of dengue and chikungunya
- Areas at risk of chikungunya/dengue identified using GIS
- Evaluation of attracticide for surveillance and control of Aedes
- Sentinel site for dengue and chikungunya testing
- Epidemic thresholds for dengue outbreaks determined (WHO project)
  - C-SUM +1.96SD and Mean +2SD were found useful for early detection of outbreaks in July month.
Impact of Climate Change on malaria

- Using PRECIS model, projection of transmission Windows of malaria by 2030 with emphasis on Himalayan, northeastern, coastal and western Ghats.
- Opening of a new such as in NE-states is projected.
Thank you