MALARIA: PAST, PRESENT, AND FUTURE



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Overview

- Malaria 101: Early history, biology, and epidemiology
- The first push for malaria eradication (1950–1970)
- Worsening of malaria control (1990s)
- New focus and scale-up success (2000–2010)
 - Is eradication possible now?



History: Major Scientific Milestones



Charles Alphonse Laveran Demonstrated parasites in patient's blood, 1880 Ronald Ross Discovered *Anopheles* mosquito as vector, 1897 Giovanni Batista Grassi Demonstrated life cycle from mosquito to man, 1898–1899



Malaria Biology: The Human Malaria Parasites

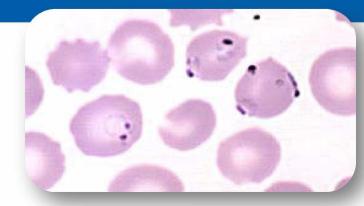
Intra-erythrocytic protozoan

Human malaria: 4 major species

- Plasmodium falciparum
- Plasmodium vivax
- Plasmodium ovale
- ≽ Plasmodium malariae

🖵 P. falciparum

- Potentially fatal severe disease
 - Red blood cell destruction → severe anemia
 - Sequestration in cerebral vessels →coma
- Multi-drug resistant







Malaria Biology: Vectors of Human Malaria

- >400 species of Anopheles mosquitoes found worldwide; ~50 transmit malaria
- Each species occupies distinct ecological niche
- Major African vectors tend to bite indoors and at night
- Biting and resting behavior affect transmission potential and control





Malaria Global Burden, 2008

~250 million clinical cases per year; 80% in Africa

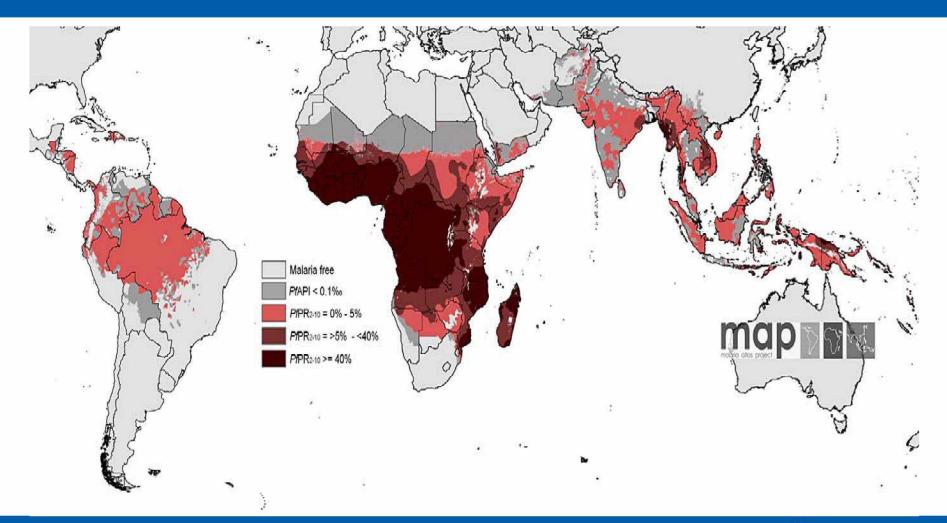
- > Children aged <5 years and pregnant women most affected
- >800,000 deaths per year; >90% in Africa
- Disability from severe forms of the disease
- Annual economic burden

> GDP \rightarrow 1.3% loss





Prevalence of *P. falciparum* Malaria in Children Aged 2–10 Years



Hay et al, PLoS Med 2009



Events Leading up to the Global Malaria Eradication Program

- Early successes in mosquito control (Panama Canal)
- Effective interventions, chloroquine and DDT, became available after WWII
- Availability of good diagnosis with microscopy
- 8th World Health Assembly launches Global Eradication Campaign (1955)



Eradication Strategies 1950–1970

Magic bullet": DDT indoor residual spray (IRS)

Assumptions

- People stay indoors at night
- Anopheles mosquito bites at night, rests indoors on house walls, and receives a toxic dose of DDT

Other major activities

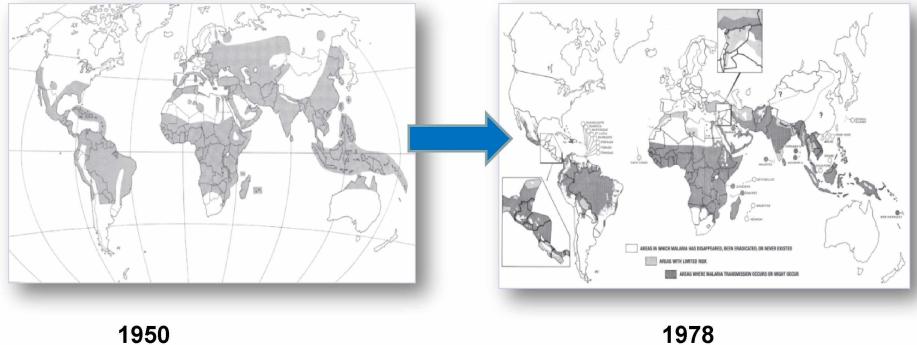
- Antimalarial drug treatment: Patients, occasionally as mass treatment
- Surveillance to detect and eliminate any reservoirs





Eradication Successes

Malaria was eliminated in 37 countries during 1950–1978



1950



What Were the Problems?

Technical	Insecticide and drug resistance
Logistics	Supply chain failures Poor delivery of IRS
Strategic	Rigidity Lack of research Africa not included
Financial	Funds diverted elsewhere
Sociocultural	Lack of community buy-in and participation Decreasing acceptance of IRS



IRS, Indoor residual spraying

Consequent Change in Strategy (1970s)

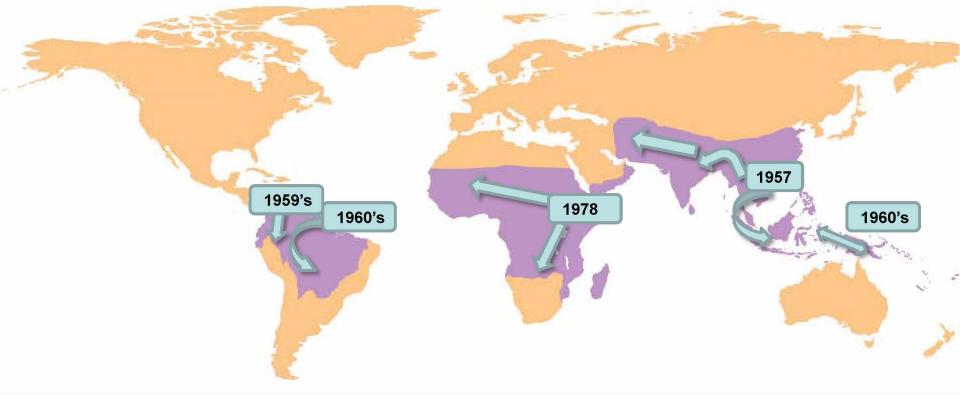
22nd World Health Assembly (1969)

- "Suspended" eradication campaign
- Goal became control to "Minimize the health damage by malaria"
 - Less ambitious
 - Strategy adapted to local context
- Shift from prevention with insecticides/DDT to antimalarial treatment
- Integrate activities into primary health care



Worsening of Malaria Control (1990s)

Decreased funding Intensification and spread of chloroquine resistance





Renewed Optimism in the New Millennium

- New partnerships
- New funding
- New political leadership in endemic countries
- New tools (drugs, bed nets)





A COMMITMENT TO MALARIA CONTROL AND PREVENTION: THE FIRST STEPS TOWARDS ELIMINATION



John R. MacArthur, MD, MPH Chief, Program Implementation Unit Division of Parasitic Diseases and Malaria Center for Global Health Centers for Disease Control and Prevention



Overview

Roll Back Malaria and U.N. Millennium Development Goals

President's Malaria Initiative (PMI)

- PMI under two presidents
- Goals, targets, and funding
- Focused interventions
- CDC's role in PMI: Strategic information

Results achieved

Significant reductions in malaria transmission



Roll Back Malaria (RBM)

🖵 Global partnership

- Launched in 1998
- > WHO, UNICEF, UNDP, World Bank

Global framework

- Coordination of activities
- Mobilization of resources
- Establishment of technical working groups
- Establishment of subregional networks

Global Malaria Action Plan

- Launched September 25, 2008, by RBM partnership
- Scaling up for impact
- Sustaining control over time





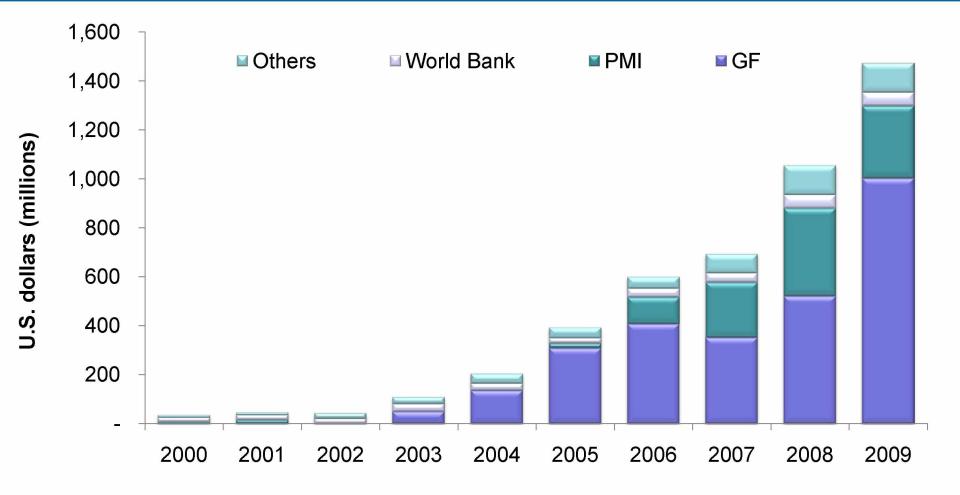
United Nations Millennium Development Goals (MDG) www.un.org/millenniumgoals

- Goal 4: Reduce child mortality
- Goal 5: Improve maternal health
- Goal 6: Combat HIV/AIDS, malaria, and other diseases
 - Target 6c: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases
 - Incidence and death rates associated with malaria
 - Children under 5 sleeping under insecticide-treated bednets
 - Children under 5 with fever who are treated with appropriate antimalarial drugs



A Gateway to the UN System's Work on the MDGs

International Financial Disbursements to Malaria Endemic



Source: Malaria funding and resource utilization: the first decade of Roll Back Malaria. http://www.rbm.who.int/ProgressImpactSeries/docs/RBMMalariaFinancingReport-en.pdf PMI, President's Malaria Initiative GF, Global Fund



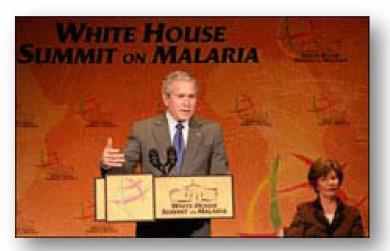
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President's Malaria Initiative (PMI)

On June 30, 2005, President Bush announced a new initiative to rapidly scale up malaria control interventions in high-burden countries in Africa

5-year and \$1.2B investment

Challenged other donors to increase their funding



PMI is led by USAID and co-implemented with CDC

Source: S. Craighead/White House (12/14/06)





PMI Goal and Targets

Goal: Reduce malaria-related mortality by 50% in 15 selected countries

Targets: Achieve 85% coverage of vulnerable groups with 4 key interventions (~270 million residents)





PMI Interv

Artemisinin-based combination therapies (ACTs)



Indoor residual spraying (IRS) (where appropriate)



ventions

Insecticide-treated bed nets (ITNs)



Intermittent preventive treatment in pregnancy (IPTp)







PMI Funding Levels and Coverage

Year	Funding Level	No. Countries Covered
2006	\$30 M	3
2007	\$135 M	7
2008	\$300 M	15
2009	\$300 M	15
2010	\$500 M	15
TOTAL	\$1,265 M	



PMI and the Global Health Initiative (GHI)

- President Obama signals support for global health including malaria (September 2008)
- The White House launches Global Health Initiative
 - U.S. Government will invest \$63 billion over 6 years

PMI is now a major component of GHI

"We will not be successful in our efforts to end deaths from AIDS, malaria, and tuberculosis unless we do more to improve health systems around the world, focus our efforts on child and maternal health, and ensure that best practices drive the funding for these programs."

-President Barack Obama, May 5, 2009



CDC's Mandate in PMI: Strategic Information

U.S. Congress (through the Lantos-Hyde Act, 2008) charged CDC to take a leading role in strategic information

- Monitoring and evaluation
- Surveillance
- > Operations research

An Act

To authorize appropriations for fiscal years 2009 through 2013 to provide assistance to foreign countries to combat HIV/AIDS, tuberculosis, and malaria, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

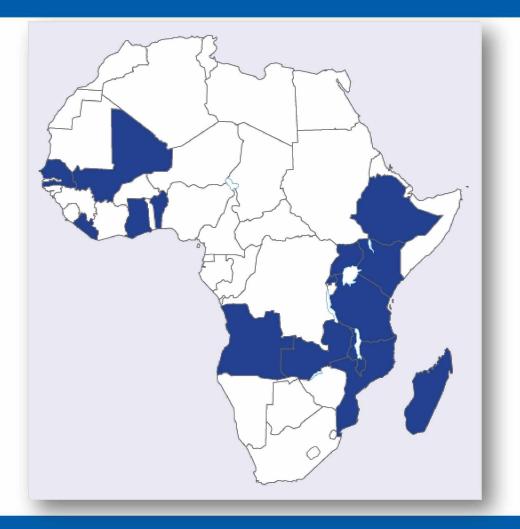
SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008".

CDC is advising the U.S. Malaria Coordinator on priorities for these activities and being a key implementer



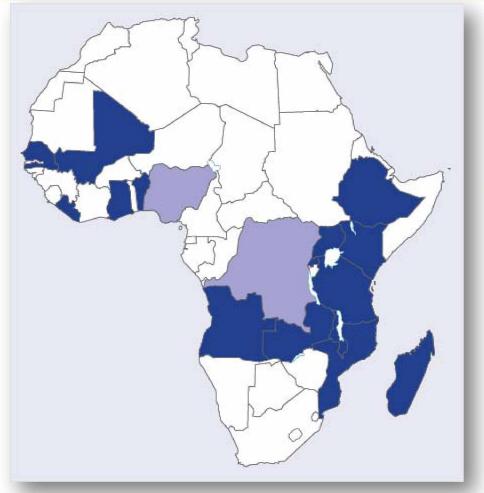
PMI Focus: 15 African Countries



Angola **Benin Ethiopia** Ghana Kenya Liberia Madagascar Malawi Mali Mozambique Rwanda Senegal Tanzania Uganda Zambia



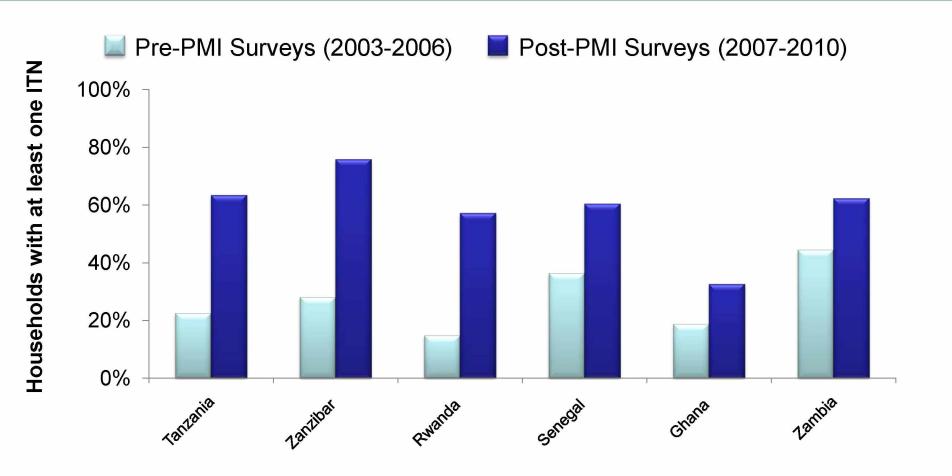
PMI Focus: Additional African Countries



Nigeria and the Democratic Republic of Congo account for the 23% of the world's burden of the falciparum malaria



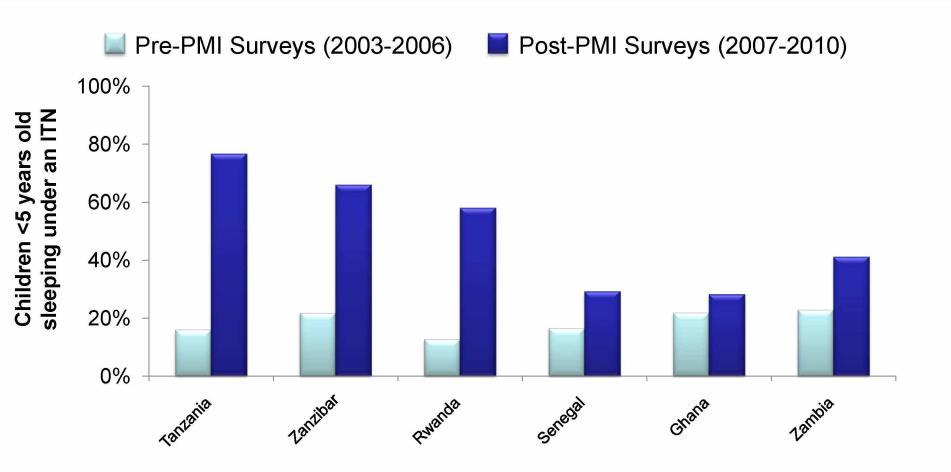
Proportion of Households with at Least 1 Insecticide-Treated Bed Net (ITN) from 2 Survey Points





Data source: Demographic Health Survey, http://www.measuredhs.coom

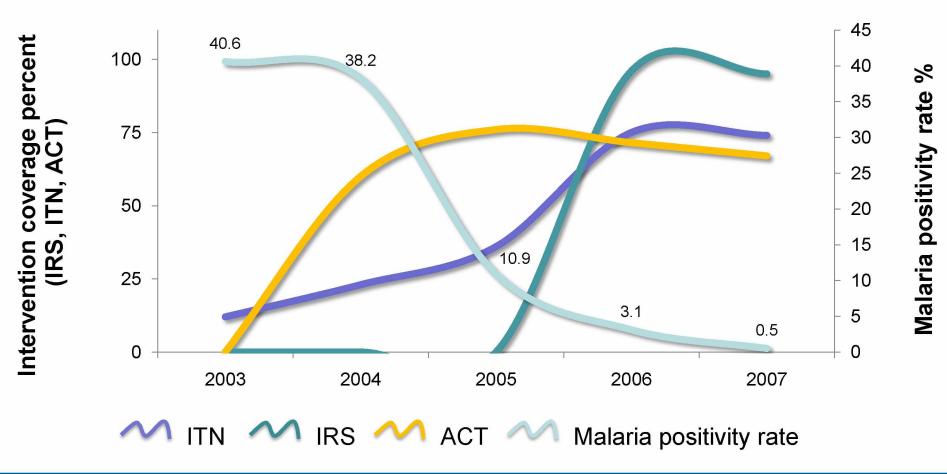
Proportion of Children Aged <5 Years Who Slept Under an ITN the Previous Night

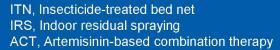




Data source: Demographic Health Survey, http://www.measuredhs.coom

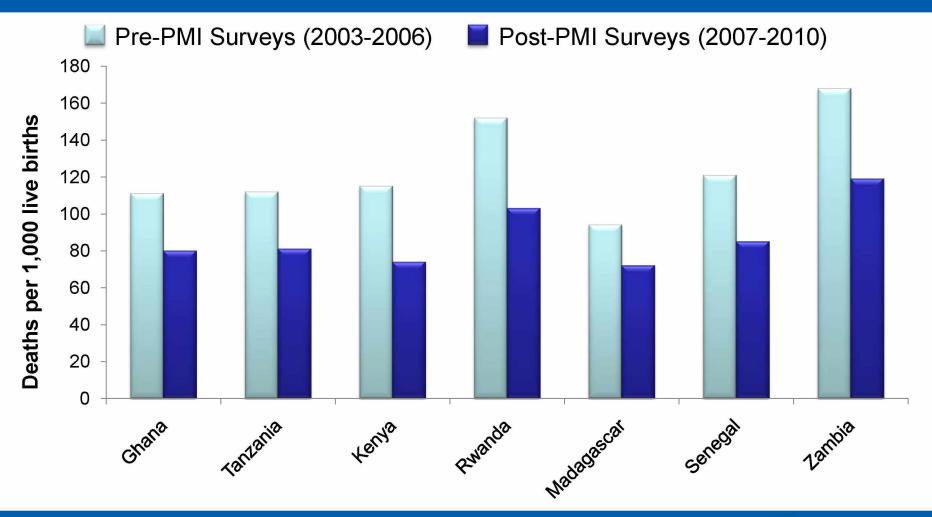
Zanzibar: Intervention Coverage and Malaria control







Declines in All-Cause Mortality in Children Aged <5 Years, 7 PMI Countries, 2003–2010





Data source: Demographic Health Survey, http://www.measuredhs.coom

Resistance – A Lurking Threat

Emergence of insecticide resistance in Africa

DDT, pyrethroids

Emergence of artemisinin resistance in Southeast Asia

> Thai-Cambodia border

TREPAR-988; No. of Pages 8 ARTICLE IN PRESS	The NEW ENGLAND JOURNAL of MEDICINE
Pyrethroid resistance in African	ORIGINAL ARTICLE
anopheline mosquitoes: what are the implications for malaria control?	Artemisinin Resistance in Plasmodium falciparum Malaria
Hilary Ranson ¹ , Raphael N'Guessan ^{2,5} , Jonathan Lines ³ , Nicolas Moiroux ^{4,5} , Zinga Nkuni ³ and Vincent Corbel ^{4,5} ¹ Vector Group, Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, UK, L3 50A ² London School of Hygiene and Tropical Medicine, Keppel Street, London, UK, WC1E 7HT, UK ³ Global Malaria Programme (GMP), World Health Organization, 1211 Geneva 27, Switzerland ⁴ Institut de Recherche pour le Développement (IRD), RU016 « Caractérisation et Contrôle des Populations de Vecteurs », 01 BP 4414, Cotonou, Benin ⁵ Centre de Recherche Entomologique de Cotonou (CREC), Laboratoire National, Ministère de la Santé, Cotonou 06 BP 2604, Benin	 Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D., Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hanpithakpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharath Lim, M.D., Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D., Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S.



DDT, Dichlorodiphenyltrichloroethane

Summary: Results Achieved

Significant reductions in all-cause mortality

Fanzania	19%
Madagascar	22%
Ghana	28%
Zambia	29%
Senegal	30%
Rwanda	32%
Kenya	36%

Massive scale-up of control interventions has been followed by substantial decreases in all-cause mortality in children aged <5 years</p>

Initiative-wide impact assessment is under way



CDC's SCIENTIFIC EVIDENCE BASE FOR SCALE-UP AND POSITIONING FOR MALARIA ELIMINATION



S. Patrick Kachur, MD, MPH Chief, Strategic and Applied Sciences Unit Division of Parasitic Diseases and Malaria Center for Global Health Centers for Disease Control and Prevention



Overview

Scientific evidence: Basis for current interventions
 Global Malaria Eradication Research Agenda
 CDC operational research priorities, 2010





1. Scientific Evidence: Basis for Current Malaria Interventions

Artemisinin-based combination therapies (ACTs)



Insecticide-treated bed nets (ITNs)



Indoor residual spraying (IRS) (where appropriate)



Intermittent preventive treatment in pregnancy (IPTp)





Efficacy of ITNs on All-Cause Child Mortality from 4 Randomized Controlled Trials in Africa

Study or subgroup	Treated nets	Control	log [Relative rate]	Relative rate	Relative rate
	Ν	Ν	(SE)	IV,Fixed,95% CI	IV,Fixed,95% CI
I Controls with no nets					
Kenya (Nevill)	11596	11439	-0.3425 (0.157)		0.71 [0.52, 0.97]
Ghana (Binka)	18457	18054	-0.1985 (0.093)		0.82 [0.68, 0.98]
Burkina Faso (Habluetzel)	14773	4 8	-0.1508 (0.1139)		0.86 [0.69, 1.08]
Kenya (Phillips-Howard)	17833	18099	-0.1744 (0.058)		0.84 [0.75, 0.94]
Subtotal (95% CI)				•	0.83 [0.76, 0.90]

17% protective efficacy against child mortality before age of 5 years Could save 5.5 lives for every 1,000 children protected

ITN, Insecticide-treated bed net C Lengeler. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database of Systematic Reviews 2004, Issue 2.



Additional Lessons from the KEMRI/CDC ITN Trial and Follow-up Studies

People without nets experienced the same benefit if they lived within 300 meters of net users – reduction in

- Parasite infection (odds ratio=0.59)
- Malaria illness (odds ratio=0.52)
- Anemia (odds ratio=0.53)
- Child mortality (hazard ratio=0.72)

Am. J. Trop. Med. Hyg., 68(Suppl 4), 2003, pp. 121–127 Copyright © 2003 by The American Society of Tropical Medicine and Hygiene

COMMUNITY-WIDE EFFECTS OF PERMETHRIN-TREATED BED NETS ON CHILD MORTALITY AND MALARIA MORBIDITY IN WESTERN KENYA

WILLIAM A. HAWLEY, PENELOPE A. PHILLIPS-HOWARD, FEIKO O. TER KUILE, DIANNE J. TERLOUW, JOHN M. VULULE, MAURICE OMBOK, BERNARD L. NAHLEN, JOHN E. GIMNIG, SIMON K. KARIUKI, MARGARETTE S. KOLCZAK, AND ALLEN W. HIGHTOWER

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Abstract. Spatial analyses of the effect of insecticide (permethrin)-treated bed nets (ITNs) on nearby households both with and without ITNs was performed in the context of a large-scale, group-randomized, controlled mortality trial in Asembo, western Kenya. Results illustrate a protective effect of ITNs on compounds lacking ITNs located within 300 meters of compounds with ITNs for child mortality, moderate anemia, high-density parasitemia, and hemoglobin levels. This community effect on nearby compounds without nets is approximately as strong as the effect observed within villages with ITNs. This implies that in areas with intense malaria transmission with high ITN coverage, the primary effect of insecticide-treated nets is via area-wide effects on the mosquito population and not, as commonly supposed, by simple imposition of a physical barrier protecting individuals from biting. The strength of the community effect decoverage with treated nets is essential.



Additional Lessons from the KEMRI/CDC ITN Trial and Follow-up Studies

Survival benefit lasted beyond 6 years

Mortality rates

- Infants: 113/1,000
- Children 1–5 years old: 28/1,000



Sustainability of Reductions in Malaria Transmission and Infant Mortality in Western Kenya With Use of Insecticide-Treated Bednets 4 to 6 Years of Follow-up

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Jo	hn M. Vulule, PhD
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Ui th m ta	ations Development Program, the nited Nations Children's Fund, and e World Bank, aims to halve malariz ortality by 2010 through implemen- tion of 4 key technical strategies: in cticide-treated bednets, improved casa

See also Patient Page.

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Ity and mortality in short-term trials, but this impact may not be sustainable. Previous investigators have suggested that bednet use might paradoxically increase mortality in older children through delayed acquisition of immunity to malaria. **Objectives** To determine whether adherence to and public health benefits of insecticide-treated bednets can be sustained over time and whether bednet use during infancy increases all-cause mortality rates in older children in an area of intense peren-

Context Insecticide-treated bednets reduce malaria transmission and child morbid-

nial malaria transmission. Design and Setting A community randomized controlled trial in western Kenya (phase 1: January 1997 to February 2000) followed by continued surveillance of adherence, entomologic parameters, morbidity indicators, and all-cause mortality (phase 2: April 1999 to February 2002), and extended democraphic monitoring (January to December 2002).

Participants A total of 130000 residents of 221 villages in Asembo and Gem were randomized to receive insecticide-treated bednets at the start of phase 1 (111 villages) or phase 2 (110 villages).

Main Outcome Measures Proportion of children younger than 5 years using insecticide-treated bednets, mean number of Anopheles mosquitoes per house, and allcause mortality rates.

Results Adherence to bednet use in children younger than 5 years increased from 65.9% /AMA. 2004;291:2571:2580 www.jama.com

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CDC/Kenya, Kenya Medical Research Institute, Nairobi (Dr Adazu). Drs ter Kulle and Terlouw are now with Liverpool School of Tropical Medicine, Liverpool, England. Dr Nahlen is now with Roll Back Malaría, World Health Organization, Geneva, Switzerland.

Corresponding Author: Kim A. Lindblade, PhD, Division of Parasilic Diseases, Centers for Disease Control and Prevention, 4770 Buford Hwy, MS F-22, At-Lanta, CA 30333 (kindblade@kislan.mimcom.net).

(Reprinted) JAMA, June 2, 2004-Vol 291, No. 21 2571

KEMRI, Kenya Medical Research Institute ITN, Insecticide-treated bed net Lindblade et al. Sustainability of reductions in malaria transmission and infant mortality in western Kenya with use of insecticide-treated bed nets: 4-6 years of follow-up. JAMA 2004;291(21):2571-80.



Additional Lessons from the KEMRI/ CDC ITN Trial and Follow-up Studies

Providing nets to 65% of older children and adults would protect even children without nets



Adam Nadel, Freelance

OPEN O ACCESS Freely available online

Preventing Childhood Malaria in Africa by Protecting Adults from Mosquitoes with Insecticide-Treated Nets

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PLOS MEDICINE

Policy Impact of the KEMRI/ CDC ITN Trial and Follow-up Studies

Established the evidence-base for widespread scale-up and universal coverage

FROM EXIDENCE TO POLICY



Continued progress in scale-up and elimination will require improved tools for malaria control and surveillance

Scale-up: Aims to reduce morbidity and mortality
 Elimination: Aims to reduce transmission
 Basic reproduction number <1.0



2. Global Malaria Eradication Research Agenda

New tools and systems to accommodate

- Drugs
- Vaccines
- Diagnostics
- Insecticides
- Strategies to manage resistance to antimalarial drugs and insecticides for public health
 - Combination treatments
 - Combined delivery systems
 - Rotational or mosaic deployment



Global Malaria Eradication Research Agenda

Alternative vector interventions



- ITNs and spraying work against mosquitoes indoors
- Some mosquitoes feed and rest outdoors
 - Larviciding
 - Spatial repellants, baited traps

Drug interventions for reducing transmission

- Mass screen and treatment
- Transmission-blocking agents

Surveillance: Detecting and responding to local transmission



3. CDC Operational Research Priorities in 2010

From Scale-up To Elimination

Optimize current malaria control interventions

Establish role for new and revisited interventions

- Research and development
- Clinical and field trials of new interventions
- Integration with other initiatives



Research and Development: Field-Ready, High-Sensitivity Test for Malaria

WHO now calls for universal access to malaria diagnosis and treatment for every case of suspected malaria

Diagnostic confirmation

- Minimize the overuse of treatments
- Improves detection and treatment of other causes of illness
- Forms the basis of a reliable system for monitoring malaria and malaria control



Light microscopy



Rapid antigen detection



Research and Development: Field-Ready, High-Sensitivity Test for Malaria

- As endemic countries approach elimination, highly sensitive tests become more critical
- Current diagnostic formats will improve management of malaria illness
- Elimination may rest on molecular assays
 - > Available only in reference laboratories far from remote areas



Molecular assays



Research and Development: Field-Ready, High-Sensitivity Test for Malaria

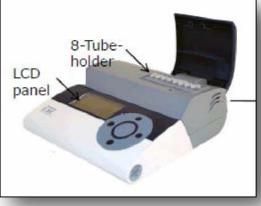
CDC and University of Georgia

Novel system for molecular diagnosis

Real-time fluorescence loop-mediated amplification: Real LAMP

- Detection of malaria parasites at very low numbers
- Without access to reference laboratory staffing and equipment
- Validation of the first generation prototype on specimens from Tanzania completed

Real-LAMP





Clinical and Field Trials of New Interventions

Phase III malaria vaccine trial in Kenya

- First candidate vaccine to reach this stage of development
- One of 11 sites in 9 countries
- Could reduce clinical malaria by up to 35%, severe malaria by 49%



PL Alonso, *et al.* (2004). Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial. *Lancet* 364(9443):1411-20.



Clinical and Field Trials of New Interventions

When will we have a vaccine that can eliminate malaria?

- Current vaccine within 18–24 months
- Will reduce illness burden, not transmission
- Hundreds of other candidates in development
- Millennia of co-evolution confound development





Clinical and Field Trials of New Interventions

Combined impact of ITNs with indoor residual spraying

- > Western Kenya (2008–2010)
- Northern Ghana (starting 2011)

Combined impact of ITNs with insecticide-treated durable wall liners

Lakeside Malawi (starting 2011)







Integration Opportunities

From Scale-up To Elimination

- Community-based control/ elimination
- Integrated case management interventions
- Integrated vector control
- Integrated surveillance, monitoring and evaluation





From Scale-Up to Elimination: the Role of Partnership

Creative partnerships within the U.S. government

- Within Department of Health and Human Services
- With U.S. government partners

Partnerships beyond our system



