

MALARIA

What's New?

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- **2016 Annual Scientific Meeting**
- **Wyndham Grand Orlando Resort**
- **Bonnet Creek-Orlando, FL.**

African Proverb

- **“If you think you are too small to make a difference, you have not spent a night with a mosquito.”**

- Malaria 102

Just in Case You Missed or forgot Malaria 101

- Malaria is a disease caused by infection with a protozoan of the Plasmodium genus, transmitted to humans by the bite of a female Anopheles mosquito

More Malaria 101

- *Plasmodium falciparum* infection is the major cause of mortality

More Malaria 101

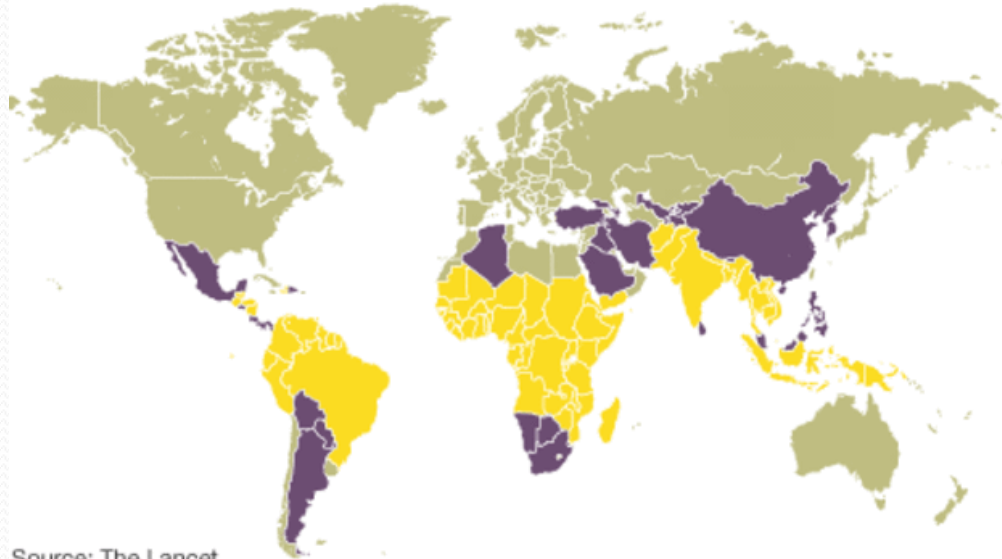
- Pregnant women and young children are the most likely to die from this disease

More Malaria 101

- Malaria kills by causing profound anemia and by interfering with microcirculation causing organ dysfunction, especially in the CNS.

Malaria around the world

■ Malaria free ■ Eliminating malaria ■ Controlling malaria



Source: The Lancet

- 
- **Now, back to Malaria 102**

MALARIA:PERHAPS THE MOST COMMON INFECTION WORLDWIDE

- **3.2 Billion people are at risk of acquiring malaria worldwide ⁽¹⁾**

● (1)WHO fact sheet updated Jan 2016

PERHAPS THE MOST COMMON INFECTION WORLDWIDE

- **350-500 million new malaria infections per year (2004) ⁽¹⁾**

(1) World Malaria Report 2005 (WHO/UNICEF/RollBack Malaria)

Malaria

Cause of 1-3 million deaths per year (2004)

(1),(2)

-
-
-

(1) World Malaria Report 2005 (WHO/UNICEF/RollBack Malaria)

(2) Global malaria mortality between 1980 and 2010: a systematic analysis.

Murray CJ et al. Lancet. 2012 Feb;379(9814):413-31.

Malaria

- Way too big a problem so not worth putting resources into.
- After all, you can't eliminate malaria from a huge country or area,



RIGHT?

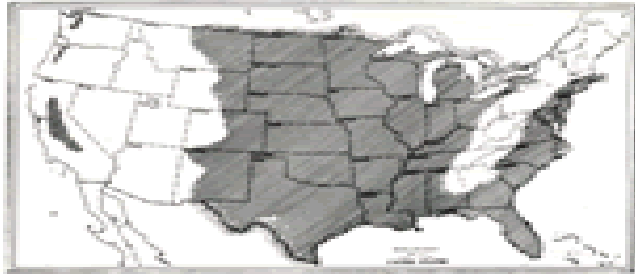


- **WRONG!**

USA Malaria

US Army Medical Department

**MALARIOUS AREA OF THE UNITED STATES
1882**



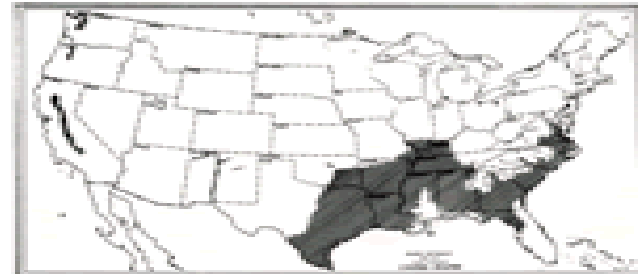
**MALARIOUS AREA OF THE UNITED STATES
1932**



**MALARIOUS AREA OF THE UNITED STATES
1912**



**MALARIOUS AREA OF THE UNITED STATES
1934-5**



Malaria

- But that was a long time ago...
- And in the US
- What about now? And the world?

Malaria Incidence 2015

- **214 million new cases of malaria in 2015**
 - VS
- **(300-500 million new cases in 2004)**

WHO fact sheet updated Jan 2016

Malaria Mortality 2015:

- 438,000 deaths (range 236,000-635,000) in 2015. ⁽¹⁾
 - vs
 - 1-3 million in 2004 ^{(2), (3)}

(1) WHO fact sheet updated Jan 2016

(2) World Malaria Report 2005 (WHO/UNICEF/RollBack Malaria)

(3) Global malaria mortality between 1980 and 2010: a systematic analysis. Murray CJ et al. Lancet. 2012 Feb;379(9814):413-31.

MALARIA

- **3.2 Billion at risk of infection:**
- **That's almost half the world's population**

- 
- **214 million new cases of malaria in 2015:**
 - **That was the entire US population in 1974**

- 
- **438,000 malaria deaths in 2015:**
 - **That's a little more than the entire population of Miami, FL**

Malaria Progress

- Since 2000, there has been a significant increase in the number of countries that have moved towards malaria **elimination**.

Malaria Progress

- Of the 106 countries with ongoing malaria transmission in 2000:
- **57** achieved reductions in new malaria cases of at least **75%** by 2015.
- **18** countries reduced their malaria cases by **50-75%** in the same period. ⁽¹⁾

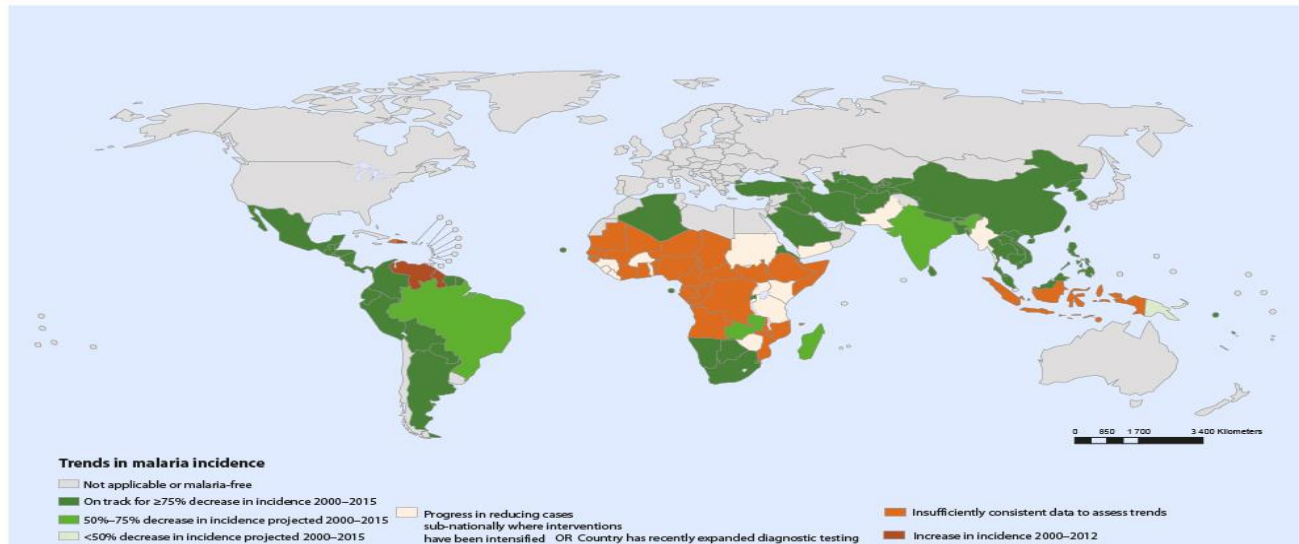
⁽¹⁾ WHO fact sheet updated Jan 2016

Malaria Progress

- In 2014, **17** countries with a history of endemic malaria in 2000 reported fewer than 1000 cases of malaria.
- That same year, **16** similar countries reported **NO** indigenous cases of the disease: Argentina, Armenia, Azerbaijan, Costa Rica, Iraq, Georgia, Kyrgyzstan, Morocco, Oman, Paraguay, Sri Lanka, Tajikistan, Turkey, Turkmenistan, United Arab Emirates and Uzbekistan. ⁽¹⁾

⁽¹⁾ WHO fact sheet updated Jan 2016

Trends in reported malaria incidence, 2000–2012



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
World Malaria Report 2013
Map Production: Global Malaria Programme
World Health Organization



World Health Organization
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Africa and Malaria

- Most of the malaria in the world occurs in Sub-Saharan Africa.
- In 2015, **88%** of malaria cases and **90%** of malaria deaths occurred here. ⁽¹⁾

⁽¹⁾ WHO fact sheet updated Jan 2016

Progress in Africa

- From 2000-2015, expansion of malaria interventions helped reduce malaria incidence by
- **37% globally**
- **42% in Africa** ⁽¹⁾

(1) WHO Fact Sheet: World Malaria Report 2015

Progress in Africa

- During the same period, malaria mortality rates decreased by an estimated

60% worldwide

66% in Africa ⁽¹⁾

Progress in Africa

- During the same period the under-5 age group (greatest risk of death along with pregnant women), mortality rates declined by:
 - **65% globally**
 - **71% in Africa** ⁽¹⁾

(1) WHO Malaria Fact sheet Updated January 2016

Progress in Africa

- These reductions in malaria have occurred despite a **43% increase** in the African population living in malaria transmission areas. ⁽¹⁾

• ⁽¹⁾ Fact sheet on the World Malaria Report 2014

Malaria

- How was this reduction accomplished?
- 1) **Improvements in Education/Access**
- 2) **Improved Dx (Rapid Diagnostic Testing=RDT)**
- 3) **New Therapies**
- 4) **New/Enhanced Preventive Measures (vector control is the mainstay of prevention/reduction of malaria transmission)**
- 5) **Possibly Due to Differences in How the Disease is Diagnosed (RDT availability)= not a real reduction.**

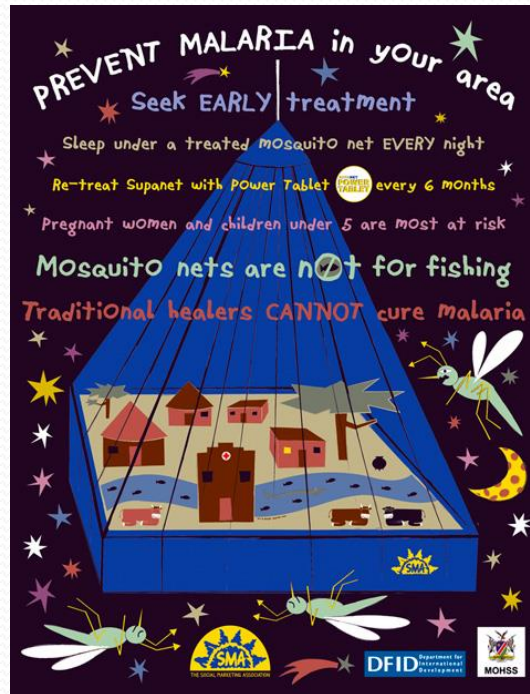
Education

- What's new?
- More \$ Available
- Better infrastructure/logistical support to provide education

Education



Education



Improved Access

Basic elements of malaria control:

- 1) Early detection and
- 2) Prompt Rx of malaria cases,

Especially in areas where health care facilities are inadequate. ⁽¹⁾

⁽¹⁾ Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. *Malaria Journal*, 2008 May 7;7:5. doi: 10.1186/1475-2875-7-75. Das et al.

Improved Access/Community Health Workers (CHWs)

- So why not set up a system of community health workers, i.e., village volunteers with no prior formal medical training who are:
- 1) Given a simple algorithm to help decide if a patient might have malaria,
- 2) Taught how to use an RDT for diagnosis
- 3) Taught how to prescribe the appropriate anti-malaria medication

CHWs, One Example in India

- Volunteers from villages were selected for distribution of chloroquine
- All volunteer services were free and voluntary in nature.
- Chloroquine was provided without charge to all fever cases ⁽¹⁾
- ⁽¹⁾Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. Malaria Journal, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.

CHW study

- **411 village volunteer CHWs in**
- **378 villages in the experimental community**
- **with a population of 125,439.**

CHW study

- Impact of CHWs evaluated based on the changes observed in **fever days** and **fever incidence**, among other things. ⁽¹⁾
- ⁽¹⁾ Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. Malaria Journal, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.

CHW study

- **Comparison between 1st, 2nd and 3rd year of operation in the experimental villages and between the experimental and control villages**

(1)

- (1) Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. Malaria Journal, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.

CHW study

- **RESULTS:**
- They treated **88,575 fever cases** with a **mean annual incidence of 331.8 cases per 1,000 people** during the 3 year study period. ⁽¹⁾

- ⁽¹⁾ Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. Malaria Journal, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.

CHW study

- **75% decline in mortality** due to malaria in the experimental villages in the adult age group
- whereas there was an increasing trend in control villages. ⁽¹⁾

• ⁽¹⁾ Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. *Malaria Journal*, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.

CHW study

- Avg morbid days due to fever decreased to 1.6 from 5.9 in the experimental villages while it remained at 5.0 in the control villages. ⁽¹⁾

- (1) Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. Malaria Journal, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.

CHW study

- **There was a significant reduction, ($p < 0.05$) in annual fever incidence in the experimental villages when compared to control villages. ⁽¹⁾**
- **(1) Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. Malaria Journal, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.**

CHW study/Conclusion

- **The study demonstrated that a passive chloroquine distribution system operated by village volunteers in tribal areas is feasible and effective in reducing malaria-related morbidity and mortality. ⁽¹⁾**

- (1) Impact of community-based presumptive chloroquine treatment of fever cases on malaria morbidity and mortality in a tribal area in Orissa State, India. Malaria Journal, 2008 May ;7:75. doi: 10.1186/1475-2875-7-75, Das et al.

Improved Access/Cellphone Study

- The recent introduction of mobile phones into the rural Bandarban district of Bangladesh provided a resource to improve case detection and treatment of patients with malaria. (1)

(1) **Mobile phones improve case detection and management of malaria in rural Bangladesh**, Malar J. 2013; 12: 48.

(2) Published online 2013 Feb 4. doi: 10.1186/1475-2875-12-48, PMCID: PMC3585886, Chai S Prue et al

Improved Access/Cellphone Study

- During studies to define the epidemiology of malaria in villages in SE Bangladesh, this project recorded **986 mobile phone calls** from families because of illness suspected to be malaria between **June 2010 - June 2012**.

Cell Phone Study/Results

- Based on phone calls, field workers visited the homes with ill persons, and collected blood samples for malaria on **1,046 people**.

Cell Phone Study/Results

- 265 (25%) of the patients tested were **positive for malaria.**

Cell Phone Study/Results

Of the 509 symptomatic malaria cases diagnosed during this study period, (52%) were detected because of an initial mobile phone call.

Cell Phone Study/Conclusion

- **Mobile phone technology --an efficient and effective method for rapid detection/Rx patients with malaria in this remote area.**

Cell Phone Study/Conclusion

- This technology, when combined with local knowledge and field support, may be applicable to other hard-to-reach areas to improve malaria control.

- 
- What's new in Dx?

Rapid Diagnostic Testing (RDT)

- Introduced widely in the past decade,
- Swiftly distinguishes between malarial and non-malarial fevers, enabling timely/ appropriate Rx. ⁽¹⁾

• ⁽¹⁾ WHO Fact Sheet: World Malaria Report 2015

RDT

- Access to rapid diagnostic tests (RDTs) has been increasing around the world.

RDT in Africa

- In **2005**:
- **36%** of suspected African malaria cases were tested with RDT
- In **2014**:
- **65%** of suspected cases were tested with RDT. ⁽¹⁾

● ⁽¹⁾ WHO Fact Sheet: World Malaria Report

RDT

- Sales of RDTs reported by manufacturers rose from fewer than **50** million globally in **2008** - **314** million in **2014**. ⁽¹⁾

RDT

- WHO recommends diagnostic testing for all people with suspected malaria ***before*** treatment is administered.

RDT

- This has not been the standard of care in the past in many countries and there is still resistance to this at a local level.

Bias

- Do WHO numbers reflect change in what's called “malaria” by shifting from clinical grounds to RDT methods?
- Don't know, but this could certainly reduce the numbers of “malaria” cases reported.

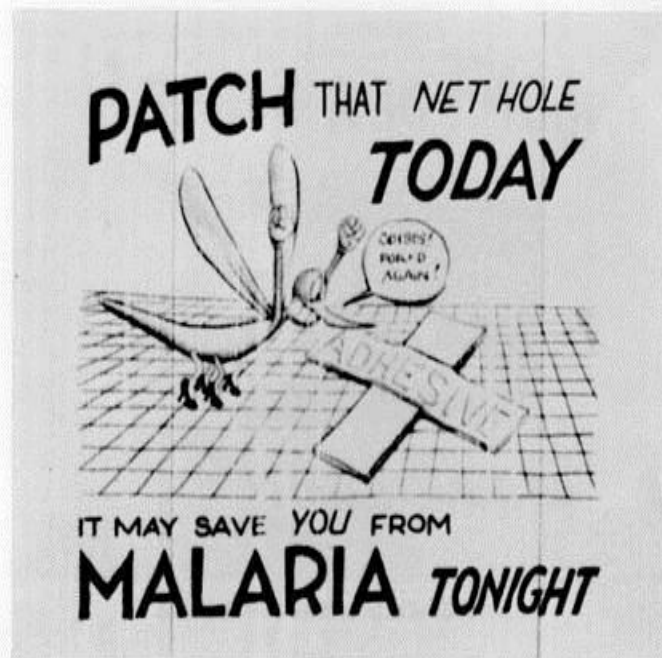


FIGURE 62.—Cartoon, "Patch That Net Hole Today."



Artesunate Containing Treatment (ACT)

What's new in Rx?

Artesunate

- Semi-synthetic derivative of artemisinin also called **qinghaosu**
- Derived from the sweet wormwood plant, *Artemisia annua*.

Artemisinin

- Medicinal value of this plant known to the Chinese for at least 2,000 years.

Artemisinin

- The earliest record dates back to 200 BC, in the “**Fifty-two Prescriptions**” unearthed from the Mawangdui Han Dynasty tombs.



Artemisinin

- In 1596, LI Shizen recommended tea made from *qinghao* to Rx malaria symptoms in his “Compendium of Materia Medica.”

Artemisinin

- The compound artemisinin itself was discovered by **Tu Youyou**, a Chinese scientist
- She was awarded half of the 2015 Nobel Prize in Medicine for her discovery

T



**HE MOSQUITO IS LITTLE
BUT
HAS BUGS IN HER SPITTLE .
REPELLENT AND SPRAY
*WILL KEEP HER AWAY!***



REPELLENT AND SPRAY ARE TRADE NAMES

U.S. GOVERNMENT PRINTING OFFICE : 1945-O-443218

NAVJED 351

Brief Aside

- Who won the 1902 Nobel Prize for Physiology or Medicine discovering that the Anopheles mosquito transmits malaria?
- Hint: This question is targeted only at the US trained doctors in the room because I'll bet those of you who trained in a Indian/Pakistani/British based system all know the answer.

- 
- Second Hint:
 - Not Walter Reed

SIR RONALD ROSS





Artesunate vs Quinine

- Artesunate prevented more deaths from severe malaria than quinine in 2 large multicentre randomized controlled trials from Africa and Asia. ^{(1), (2)}
- 1) Dondorp AL; et al. (2010). "Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open label randomized trial. *The Lancet* **376** (9753): 1647–1657.
- 2) South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) (2005). "Artesunate versus quinine for treatment of severe falciparum malaria: a randomized trial. *The Lancet* **366** (9487): 717–725.

Artesunate vs Quinine (AQUAMAT Study)

- **Artesunate vs quinine**
- **Treatment of severe falciparum malaria**
- **African children**
- **Open-label, randomised trial ⁽¹⁾**

- Lancet Vol. 376, No.9753, p1647-1657, 13 November 2010, Dondorp AM, et al.

AQUAMAT Study

- 5425 children were enrolled;
- 2712 artesunate group
- 2713 quinine group

Mortality AQUAMAT Study

230 (8.5%) patients assigned to artesunate Rx **died**

297 (10.9%) assigned to quinine Rx **died**

relative reduction 22.5%, 95% (CI 8.1–36.9; $p=0.0022$).

Non Lethal Malaria Complications AQUAMAT Study

1) **Coma**

3.5% artesunate group

vs

5.1% quinine group

- **Sz**

- 8.3% artesunate group

- vs

- 10.1% quinine group

- Both findings were statistically significant

AQUAMAT Study Side Effects

- Post-Rx hypoglycemia (a major quinine side effect that can kill patients) less frequent in patients on
- artesunate 1.8%
- vs
- quinine 2.8%

AQUAMAT

- In this study Artesunate was well tolerated, with no serious drug-related adverse effects. ⁽¹⁾

(1) Lancet Vol. 376, No.9753, p1647-1657, 13 November 2010, Dondorp AM, et al.

Artesunate

- Meta-analysis of all trials artesunate vs quinine, shows that **artesunate is better** than quinine at reducing mortality in African children with severe malaria. ⁽¹⁾
- And strongly suggests that **parenteral artesunate should replace quinine** as Rx of choice for severe falciparum malaria worldwide.

- (1) Sinclair, D; Donegan, S; Isba, R; Lalloo, DG (Jun 13, 2012). "Artesunate versus quinine for treating severe malaria.". *The Cochrane database of systematic reviews*

Artesunate Side Effects

- A) Most common side effect: **decreased reticulocyte count**.
(Not usually clinically relevant)
- B) **Delayed hemolysis** (occurs around 2 wks post Rx) has been observed in patients treated with artesunate for severe malaria.
- Not clear if hemolysis due to artesunate, or to the malaria itself^{(1), (2)}

¹⁾ Rolling T, Agbenyega T, Issifou S; et al. (2013). "Delayed hemolysis after treatment with parenteral artesunate in African children with severe malaria—a double-center prospective study." *J Infect Dis* **209** (12): 1921–8.

²⁾ Clark RL (2013). "Hypothesized cause of delayed hemolysis associated with intravenous artesunate." *Med Hypotheses* **82** (2): 167–70

Artesunate Side Effects

- Despite this, studies overall have showed that **artesunate was generally safe and well-tolerated.** ⁽¹⁾

● ¹⁾ World Health Organization. "Guidelines for the treatment of malaria; Second edition 2010"

Artesunate

- Therefore, WHO currently recommends IM/IV artesunate as the first line treatment for severe malaria.

Radical cure is then affected with a full course of an effective oral antimalarial.⁽¹⁾

- ¹⁾ World Health Organization. "Guidelines for the treatment of malaria; Second edition 2010"

Artesunate

- Does this include pregnancy?

Artesunate and Pregnancy

- OK in 2nd and 3rd trimesters
- 1st trimester not as clear ⁽¹⁾

• 1) WHO (2007). Assessment of the safety of artemisinin compounds in pregnancy. World Health Organization, Geneva.

Artesunate and Pregnancy - 1st Trimester

- Embryotoxicity in animal models (long bone defects and VSDs in rats and monkeys).
- However, observational evidence 123 human 1st trimester pregnancies:
- **No evidence of damage to the fetus.** ⁽¹⁾

- ¹⁾ Clark RL (2009). "Embryotoxicity of the artemisinin antimalarials and potential consequences for use in women in the first trimester.". *Reprod Toxicol* **28** (3): 285–96.

Is There an Oral Form of Artesunate?

- Yes

PO Artesunate

- For Rx of less severe forms of malaria when can be given po,
- BUT
- should always be taken with 2nd antimalarial, e.g., mefloquine or amiodiquine, to avoid development of resistance. ⁽¹⁾

• 1) World Health Organization. "Guidelines for the treatment of malaria; Second edition 2010"

Artesunate Resistance

- In recent years, parasite resistance to artemisinin has been detected in
- Cambodia, Laos, Myanmar, Thailand and Vietnam.
- Studies have confirmed that artemisinin resistance has emerged independently in many areas of this subregion. ⁽¹⁾

• ⁽¹⁾ WHO Malaria Fact sheet Updated January 2016

Artesunate Resistance

- Most patients are cured S/P Rx with an ACT if no resistance to the partner drug.
- However, in parts of Cambodia/Thailand, *P. falciparum* resistance to both artemisinin and partner drugs (multi-drug resistance) has developed ⁽¹⁾

• ⁽¹⁾WHO Malaria Fact sheet Updated January 2016



Prevention Measures

Prevention Measures

- 1) **ITN's** (Insecticide Treated Nets)/**LLIN's** (Long Lasting Insecticide Impregnated Nets)
- 2) **IRS** (Indoor Residual Spraying)
- 3) **Sterile Male Mosquitoes**
- 4) **Malaria Resistant Mosquitoes**
- 5) **Intermittent Malaria Prophylaxis**
- 6) **Malaria Vaccine**
- 7) **Education**
- 8) **Stagnant Water Removal**
- 9) **Larval Control**
- 10) **Laser Shoot Down**

INSECTICIDE TREATED NETS (ITN'S)

- Developed in 1980's
- Nets are dip-treated using synthetic pyrethroid insecticide (deltamethrin or permethrin, e.g.) –
- **-doubles protection** when compared to non-treated net by killing and repelling mosquitoes.

INSECTICIDE TREATED NETS (ITN'S)

- In a Cochrane Review ITNs were found to reduce the incidence of uncomplicated malarial episodes
- by **50%** compared to **no nets**, and

by **39%** compared to **untreated nets** ⁽¹⁾

- (1) Lengeler C. (2004) Insecticide-treated bed nets and curtains for preventing malaria. *The Cochrane Database of Systematic Reviews*. Issue 2.

ITN Progress

- **ITNs reduce malaria mortality rates by an estimated 55% in children under 5 years old in sub-Saharan Africa.** ⁽¹⁾

(1) WHO World Malaria Report 2015

ITN Progress

- There is a significant public health impact due to reduction in malaria deaths,
- **AND** also due to reductions in child deaths from other causes that associated with/exacerbated by, malaria
- (e.g. acute respiratory infection, low birth weight and malnutrition) ⁽¹⁾

(1) WHO World Malaria Report 2015

ITN ISSUES

- Experience has shown that possession and appropriate use of ITNs do not automatically go hand-in hand due to poor education and or cultural/economic issues.

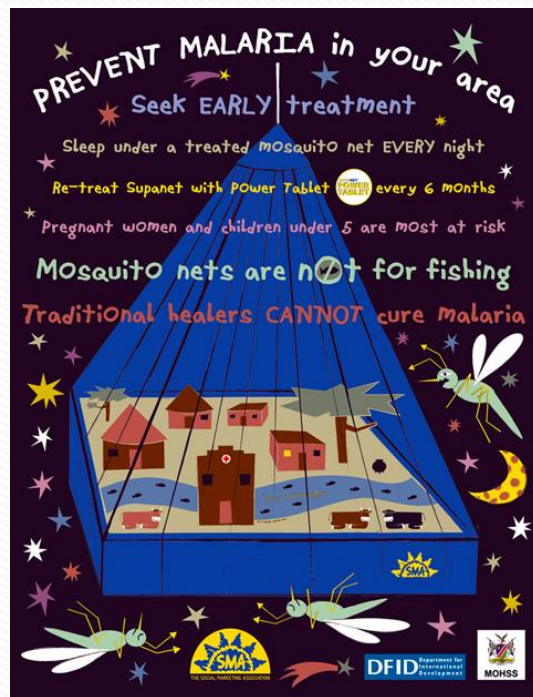
ITN ISSUES

- Many people who received the ITNs:
- 1) **Didn't sleep under them,**
- 2) **Re-sold them,**
- 3) **Reduced their efficacy through inappropriate washing practices, or**
- 4) **Failed to replace them when damaged or torn.** ⁽¹⁾

• ⁽¹⁾ "Insecticide Treated Mosquito Nets: a [WHO] position statement October 2009

ITN ISSUES

- For example, in one study in Niger, West Africa, **as few as 33%** of available mosquito nets in mosquito net owning households were used the night prior to survey⁽¹⁾
- (1) Thwing J, Hochberg N, Vanden Eng J, Issifi S, Eliades MJ, Minkoulou E, Wolkon A, Gado H, Ibrahim O, Newman RD, Lama M. Insecticide-treated net ownership and usage in Niger after a nationwide integrated campaign. Trop Med Int Health. 2008;13:827–834.



Remember

- The nets are not for sale
- You should not be asked to pay any money to get your net during the campaign period
- All you have to do is present your net card
- Sleep under your net to protect yourself and your family
- Do not sell your nets
- Government and Roll Back Malaria partners have provided the nets free of charge to protect you from malaria.



Get 2 Free Nets



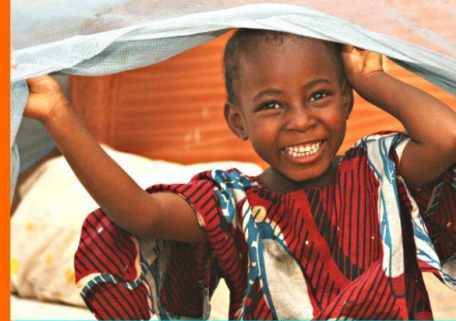
When everybody uses the net,
everybody benefits

For more information, contact:

Primary Health Care Department
Kano State Ministry of Health



Long Lasting Net Campaign in Kano State



Get
your

Free
Nets



ITN ISSUES

- Unfortunately, **standard ITNs** also must be replaced or re-treated with insecticide **after 6 washes**

Therefore, ITN's are **not seen as a convenient, effective long-term** solution to the malaria problem.⁽¹⁾

•

•

(1) "Insecticide Treated Mosquito Nets: a [WHO]position statement October 2009

Long-Lasting Insecticidal Mosquito Nets (LLIN's)

- As a result, the mosquito netting and pesticide industries developed so-called long-lasting insecticidal mosquito nets, which also use pyrethroid insecticides.

3 types of LLINs

-
- 1) polyester netting--has insecticide bound to external surface of the netting fiber using a resin;
- 2) polyethylene -- has insecticide incorporated into the fiber and
- 3) polypropylene --has insecticide incorporated into the fiber.
- All types can be washed at least 20 times, but physical durability will vary.

ITN PROGRESS

Despite the issues, the proportion of the population sleeping under an ITN has increased markedly in sub-Saharan Africa, from **< 2% in 2000** to an estimated **46% in 2014** ⁽¹⁾

•
⁽¹⁾ WHO World Malaria Report 2015

Insecticide Resistance

- Pyrethroids are the only class of insecticides currently recommended for ITNs or LLINs. ⁽¹⁾

- ⁽¹⁾WHO **Malaria** Fact sheet Updated January 2016

Insecticide Resistance

- 1) In recent years, mosquito resistance to pyrethroids has emerged in many countries.
-
- 2) Fortunately, resistance is only rarely associated with decreased LLIN efficacy, which continue to provide a substantial level of protection in most settings. ⁽¹⁾

• ⁽¹⁾WHO Malaria Fact sheet Updated January 2016

Insecticide Resistance

- 1) However, malaria-endemic areas of sub-Saharan Africa and India with high levels of malaria transmission have had widespread reports of insecticide resistance.
- 2) The use of 2 different insecticides in a mosquito net offers an opportunity to mitigate the risk of the development and spread of insecticide resistance; developing these new nets is a priority.
- 3) Several promising insecticides are in the pipeline. ⁽¹⁾

• ⁽¹⁾WHO Malaria Fact sheet Updated January 2016

Don't strip tease
for Anopheles



The anopheles mosquito
is a carrier of

MALARIA

KEEP COVERED

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With this film, you can see how the Anopheles mosquito carries the malaria parasite. It shows you how to protect yourself from malaria by using mosquito nets, screens, and coils. It also shows you how to recognize the symptoms of malaria and how to get medical help if you are sick.

Indoor Residual Spraying (IRS)

IRS

- IRS involves coating walls/other surfaces of houses with a residual insecticide. ⁽¹⁾

⁽¹⁾ CDC Malaria Fact Sheet

IRS

- Effective for 3–6 months, depending on the insecticide formulation used and the type of surface on which it is sprayed.
- In some settings, multiple spray rounds are needed to protect the population for the entire malaria season. ⁽¹⁾

• ⁽¹⁾WHO Malaria Fact sheet Updated January 2016

IRS

- Doesn't directly prevent people from being bitten by mosquitoes.
- Usually kills mosquitoes after they have fed if they come to rest on the sprayed surface.
- Prevents transmission of infection to other persons. ⁽¹⁾

IRS

- To be effective, IRS must be applied to a very high proportion of households in an area (usually >80%) ⁽¹⁾

●
⁽¹⁾ CDC Malaria Fact Sheet

IRS

- In 2014, 116 million people globally were protected by indoor residual spraying (IRS), including 55 million people in Africa. ⁽¹⁾

• ⁽¹⁾ Fact Sheet: World Malaria Report 2015



IRS

About 6% of the population at risk of malaria in Africa live in households that are protected by IRS. ⁽¹⁾

(1) Fact Sheet: World Malaria Report 2015

Does IRS Work?

- Scientific evidence of IRS efficacy in reducing or interrupting malaria transmission in different epidemiological settings has been available since the 1940s and 1950s.
- Numerous studies have shown that IRS has substantially reduced infant and child mortality.
- This evidence formed the rationale for introduction of IRS as a primary intervention for malaria control and eradication. ⁽¹⁾

• ⁽¹⁾ WHO: Global Malaria Programme, Indoor Residual Spraying 2006

Does IRS Work?

- Evidence over several decades has confirmed the effectiveness of IRS in reducing levels of infection and incidence of malaria.
- For example, malaria incidence was reduced by 90% or more in major areas of tropical Asia during an eradication program via a combination of IRS and other measures. ⁽¹⁾

• ⁽¹⁾ WHO: Global Malaria Programme, Indoor Residual Spraying 2006

Bridges to Malawi

- WHAT WE DO
 - 1) **IRS** (indoor residual spraying)
 - 2) **Annual Medical Mission Trip**
 - 3) **Acquisition/Provision** of desperately needed **medical supplies/equipment/medication** in support of 2 hospitals and a community outreach organization
 - 4) **4TH year medical school elective**
 - 5) **Annual Local High School Contest**; winner travels to Malawi with medical team
 - 6) **Microcredit Bank**
 - 7) **Food Donation**
 - 8) **Telemedicine Project**
 - 9) **Goat “Pass-On” Project**

Bridges to Malawi

- We couldn't bear to watch any more children die from malaria in the hospital, so, working with our Malawian NGO partner K2 TASO, we began a campaign in August 2014 to wipe out the Anopheles mosquitoes in the area where we work, using the long lasting insecticide alpha cypermethrin designated by the WHO for this purpose

Indoor residual spraying



PHOTO 4: A

the houses in Makanda villages. This is indeed a battle which K2 TA
happening with support from Bridges to Malawi.

Does IRS Work?

- In Makanda, the first village we sprayed, the malaria rate was reduced from 16% (Jan-May 2014) to 2.9% (Sept 2014-Feb 2015), based on RDT positive tests, which were done only on patients who were sufficiently sick to warrant a test.

Does IRS Work?

- When we visited the village in March 2015, the chief thanked us by saying, “There are no more mosquitoes in our village... all of us feel better, even those who didn’t think they were sick. Our pregnant women and children aren’t getting sick with malaria and dying...we are spending more time in the fields and growing more crops because we all have more energy and feel healthier.”

Does IRS Work?

- Not only did we reduce the incidence of malaria with IRS but we also had improved the overall economic well-being of the village

BTM

- We are currently protecting approximately 5200 people in 4 villages by IRS with similar results

Bridges to Malawi

This year (2016) we hope to expand to 7-8 more villages and protect 20,000 people over 2 years working with local/International Rotary at a cost of approximately \$2.66 per person for two sprayings per year.

BTM

- In fact, it is our hope that our project will act as a pilot to encourage Rotary International to “adopt” the elimination of malaria by IRS (and/or other means) as their next great public health measure (their last was/is polio).

WHO and IRS

- WHO's Global Malaria Programme recommends the following 3 primary interventions that must be scaled up in countries to effectively respond to malaria:
 - A) Dx of malaria cases and Rx with effective medicines;
 - B) Distribution of insecticide-treated nets (ITNs/LLIN's) to achieve full coverage of populations at risk of malaria
 - C) Indoor residual spraying (IRS) as a major means of malaria vector control to reduce and eliminate malaria transmission including, where indicated, the use of DDT. ⁽¹⁾
- (1) WHO: Global Malaria Programme, Indoor Residual Spraying 2006

IRS ISSUES

- 1) Insecticide resistance develops
- 2) Requires money/infrastructure/organization
- 3) Human toxicity
- 4) Environmental toxicity

Insecticide Resistance

- IRS will only be effective if the target vectors are susceptible to the insecticide in use.
- The development of resistance to insecticides constitutes a major threat to the chemical control of malaria vectors. ⁽¹⁾
-
- (1) WHO: Global Malaria Programme, Indoor Residual Spraying 2006

Insecticide Resistance

- In the past, countries deploying IRS have often been forced to switch to alternative and more expensive insecticides on account of the development of vector resistance.
- In general, outside Africa, insecticide resistance in malaria vectors has not, so far, been a major impediment to insecticide-based interventions. ⁽¹⁾

- (1) WHO: Global Malaria Programme, Indoor Residual Spraying 2006

Insecticide Resistance

- However, in Africa, the potential threat of resistance to insecticides appears to be significant.
- Resistance to DDT and pyrethroids in major malaria vectors has been found throughout West and Central Africa, in some areas at a high level, as well as in several parts of Eastern and Southern Africa.
- Selection of resistance in most malaria vectors is thought largely due to past/present use of insecticides in agriculture. ⁽¹⁾
- ⁽¹⁾ WHO: Global Malaria Programme, Indoor Residual Spraying 2006

Insecticide Resistance

- A comprehensive assessment of resistance at the local level must be carried out before planning any IRS program, especially in West and Central Africa.
- The possibility of insecticide resistance calls for the careful monitoring of the susceptibility of malaria vectors to insecticides throughout the world, and the sound management of resistance. ⁽¹⁾

• ⁽¹⁾ WHO: Global Malaria Programme, Indoor Residual Spraying 2006

Insecticide Safety

- Another major consideration when selecting an insecticide is safety. ⁽¹⁾

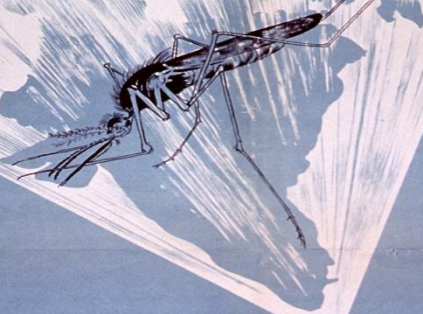
- ⁽¹⁾ WHO: Global Malaria Programme, Indoor Residual Spraying 2006

Insecticide Safety

- Insecticides recommended by WHO are deemed safe for public health use as long as they are used correctly.
- Concerns over DDT safety, a persistent organic pollutant, have been comprehensively addressed in the Stockholm Convention on Persistent Organic Pollutants (POPs) which bans its use except for public health purposes.
- Thus, DDT can be used for IRS where indicated, provided that stringent measures are taken to avoid misuse and leakage outside public health ⁽¹⁾

- (1) WHO: Global Malaria Programme, Indoor Residual Spraying 2006

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मलेरिया मिटाइये



ERADICATE **MALARIA**
BY SPRAYING



MALARIA ERADICATION PROGRAMME INDIA

POSTER IS PROVIDED BY CENTRAL HEALTH EDUCATION COUNCIL, DIRECTORATE GENERAL OF HEALTH SERVICES, MINISTRY OF HEALTH,
GOVERNMENT OF INDIA, NEW DELHI.

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Intermittent Malaria Prophylaxis

Intermittent Preventive Treatment of Malaria in Pregnancy (Pit)

- Definition:
- Full therapeutic course of antimalarial medicine given to pregnant women at routine prenatal visits, regardless of whether the recipient is infected with malaria. ⁽¹⁾

● ⁽¹⁾ WHO Intermittent preventive treatment in pregnancy (Pit) Fact Sheet Feb 2015

Pit

- Pit reduces:
- 1) **Maternal Malaria Episodes,**
- 2) **Maternal and Fetal anemia,**
- 3) **Placental Parasitemia,**
- 4) **Low Birth Weight, and**
- 5) **Neonatal Mortality** ⁽¹⁾

Pit

- WHO recommends Pit:
- A) Using sulfadoxine-pyrimethamine (IPTp-SP) in all areas with moderate-high malaria transmission in Africa
- B) Given to all pregnant women at each of the 4 scheduled antenatal care visits after the 1st trimester. ⁽¹⁾

Pit ? Resistance

- **Pit** works even in areas where quintuple mutations linked to SP resistance are prevalent in *P. falciparum*. ⁽¹⁾

● ⁽¹⁾WHO Intermittent preventive treatment in pregnancy (Pit) Fact Sheet Feb 2015

Pit Problems

- **1) Resistance Concerns**
- **2) Implementation difficulties**
 - a) Money
 - b) education
 - c) access/logistics ⁽¹⁾

• ⁽¹⁾WHO Intermittent preventive treatment in pregnancy (Pit) Fact Sheet Feb 2015

Pit

- In Africa, the proportion of women receiving **Pit** has been increasing over time, but levels remain below national targets.
- In 2014, an estimated 15 million/28 million pregnant women at risk of malaria didn't receive any Pit. ⁽¹⁾

(1) WHO fact sheet

Pit Problems

- Not due to low levels of antenatal clinic attendance.
- May be due to uncertainty among health workers/patients about SP administration for Pit. ⁽¹⁾
-

• ⁽¹⁾WHO Intermittent preventive treatment in pregnancy (Pit) Fact Sheet Feb 2015

Pit

- Simplified **Pit** messages and health worker training have been shown to improve Pit coverage. ⁽¹⁾

- ⁽¹⁾WHO Intermittent preventive treatment in pregnancy (Pit) Fact Sheet Feb 2015

Intermittent Preventive Treatment in Infants

Intermittent preventive treatment in infants (ITPi)

- Definition:
- Full therapeutic course of antimalarial medicine delivered to infants through routine immunization services, regardless of whether the child is infected with malaria. ⁽¹⁾

IPTi

- WHO recommends IPTi
- with sulfadoxine-pyrimethamine (IPTi-SP)
- in areas with moderate-high malaria transmission in sub-Saharan Africa
- that have less than 50% prevalence of pfdhps 540 mutation in the *P. falciparum* parasite. ⁽¹⁾

(1) WHO Fact Sheet **Intermittent preventive treatment in infants (IPTi)** Feb 2015

IPTi

- IPTi reduces clinical malaria, anemia and severe malaria in the 1st year of life. ⁽¹⁾

⁽¹⁾WHO Fact Sheet **Intermittent preventive treatment in infants (IPTi)** Feb 2015

ITPi

- Rx is given 3 times during the 1st year of life:
- A) 10 weeks,
- B) 14 weeks, and
- C) 9 months of age,
corresponding to the routine childhood vaccination schedule.

ITPi

- Administration is safe, simple, cost-effective and well accepted by health workers and communities.
- No negative effect on the protective efficacy of routine childhood vaccines. ⁽¹⁾

• ⁽¹⁾WHO Fact Sheet **Intermittent preventive treatment in infants (IPTi)** Feb 2015

ITPi

- Among the approximately 840 million persons at risk of malaria in sub-Saharan Africa, a large proportion of the 28 million infants born each year could benefit from ITPi. ⁽¹⁾

• ⁽¹⁾WHO Fact Sheet **Intermittent preventive treatment in infants (IPTi)** Feb 2015

ITPi

- Full implementation is not happening because of:
- A) Insufficient Funding
- B) Logistical Difficulties



**DON'T GO TO BED WITH
A MALARIA MOSQUITO**

★ SLEEP UNDER A NET! ★ KEEP IT
REPAIRED! ★ TUCK IT IN! ★

BE SURE NO MOSQUITO IS INSIDE
WAITING FOR YOU

FIGHT THE *PERIL* BEHIND THE LINES

STERILE MALE MOSQUITOES

Sterile Insect Technique (SIT)

1) Species-specific , environmentally nonpolluting method of insect control. ⁽¹⁾

⁽¹⁾ Vector Borne Zoonotic Dis. 2010 Apr; 10(3): 295–311 **Sterile-Insect Methods for Control of Mosquito-Borne Diseases: An Analysis**; Alphey et al,

SIT

Relies on the release of large numbers of sterile insects ⁽¹⁾

- ⁽¹⁾ Vector Borne Zoonotic Dis. 2010 Apr; 10(3): 295–311 **Sterile-Insect Methods for Control of Mosquito-Borne Diseases: An Analysis**; Alphey et al,

SIT

- Mating of released sterile males with native females leads to decrease in the females' reproductive potential ⁽¹⁾

- ⁽¹⁾ Vector Borne Zoonotic Dis. 2010 Apr; 10(3): 295–311 **Sterile-Insect Methods for Control of Mosquito-Borne Diseases: An Analysis**; Alphey et al,

SIT

If enough males are released over a sufficient period of time, leads to the local elimination or suppression of the pest population. ⁽¹⁾

(1) Vector Borne Zoonotic Dis. 2010 Apr; 10(3): 295–311 **Sterile-Insect Methods for Control of Mosquito-Borne Diseases: An Analysis**; Alphey et al,



SIT

“Mosquito Birth Control”

SIT

- Field trials in the 1970s and 1980s demonstrated that SIT could be made to work in mosquitoes, even with the technology then available, BUT not pursued due to cost/logistics ⁽¹⁾
- (1) Lofgren, CS et al. Release of chemosterilized males for the control of *Anopheles albimanus* in El Salvador. III. Field methods and population control. *Am J Trop Med Hyg.* 1974;23:288–297.

SIT

- Interest in SIT has re-emerged recently, driven by the availability of new technologies that have the potential to provide significant cost-effectiveness improvements for SIT, as well as by recognition of the limitations of current vector control strategies.
- (And this is pre-Zika!)

SIT Problems

- 1) Application to large areas needs to be ongoing for a long time, otherwise migration of wild insects from outside the control area could repopulate.
- 2) Irradiation can weaken the mosquito giving wild males a survival advantage
- 3) Cost of producing such a large number of sterile insects is often prohibitive in poorer countries.

SIT Environmental Problems

- Of course, there are lots of problems with using a system that could decimate an entire species--many other creatures, bats, e.g., rely on mosquitoes for food, and so wide-scale eradication of mosquitoes isn't generally seen as a viable strategy.



FIGURE 11.—Antimalaria poster.

MALARIA RESISTANT MOSQUITOES

Malaria Resistant Mosquitoes

- The use of genetically modified mosquitoes refractory to *Plasmodium* transmission is a potential strategy for controlling vector-borne diseases.

Malaria Resistant Mosquitoes

- In 2013 Smith et al reported the creation of a transgenic line of *Anopheles stephensi*, a natural vector of *Plasmodium falciparum*, which secretes a catalytically inactive phospholipase A₂ (mPLA₂) into the midgut lumen that ***interferes with Plasmodium ookinete invasion.*** ⁽¹⁾

- ⁽¹⁾ PLOS One. 2013; 8(10): e76097. Published online 2013 Oct 1. Transgenic Mosquitoes Expressing a Phospholipase A₂ Gene Have a Fitness Advantage When Fed *Plasmodium falciparum*-Infected Blood; Smith RC, et al.

Malaria Resistant Mosquitoes

- Their experiments show that this transgenic line expressing mPLA₂ ***significantly impairs the development of human malaria parasites in the mosquito*** ⁽¹⁾

- ⁽¹⁾ PLOS One. 2013; 8(10): e76097. Published online 2013 Oct 1. **Transgenic Mosquitoes Expressing a Phospholipase A₂ Gene Have a Fitness Advantage When Fed *Plasmodium falciparum*-Infected Blood**; Smith RC, et al.

Malaria Resistant Mosquitoes

- Marelli et al also found that, when fed on malaria-infected blood, mosquitoes from their new transgenic line had a ***survival advantage*** over non-transgenic mosquitoes.
- Consistent with these observations, cage experiments with mixed populations of transgenic and non-transgenic mosquitoes showed that the percentage of transgenic mosquitoes increases when maintained on *Plasmodium*-infected blood. ⁽¹⁾

- (1) Transgenic malaria-resistant mosquitoes have a fitness advantage when feeding on *Plasmodium*-infected blood
- Marrelli M, et al
-

Malaria Resistant Mosquitoes

- In 2015, Gantz and Bier described a technique for creating mutations that invade the genome and ***transmit themselves across to the next generation with near 100% success***, defying the classic laws of Mendelian genetics. ⁽¹⁾

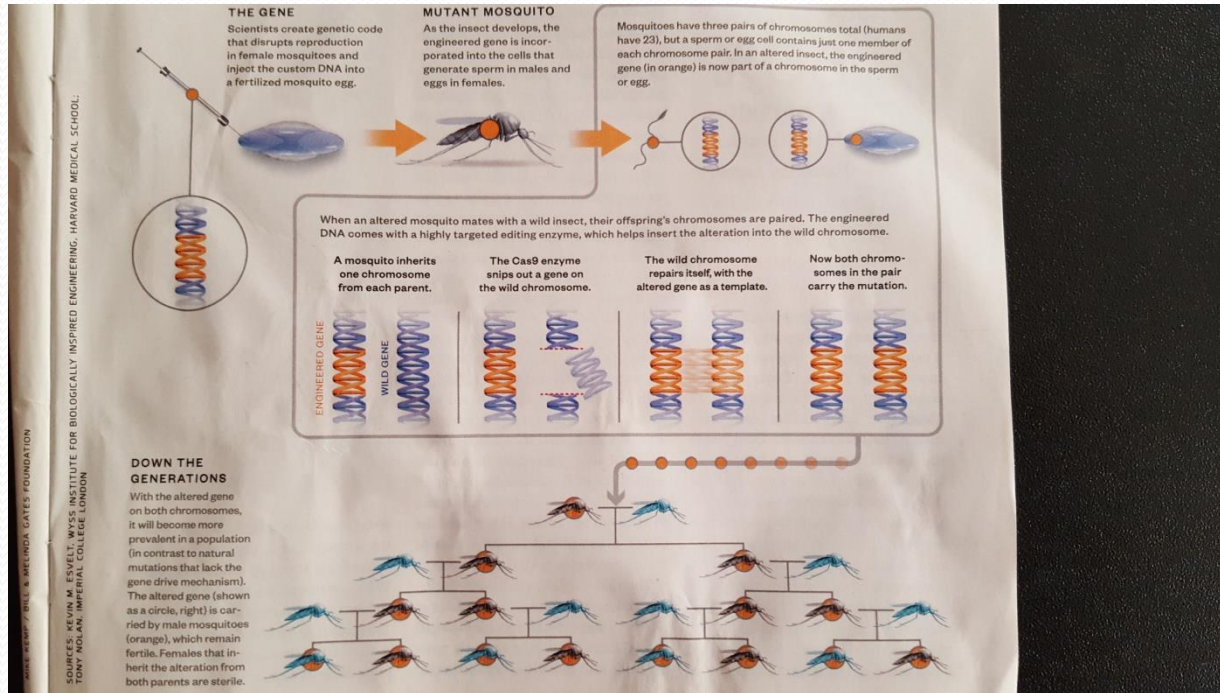
- ⁽¹⁾ Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Asian malaria vector *Anopheles stephensi* Proceedings of the National Academy of Sciences, vol. 112 no. 49, Valentino M. Gantz, et al, E6736–E6743

Malaria Resistant Mosquitoes

- This generates inheritance in such a way as to spread a gene rapidly through a population, or even an entire species. ⁽¹⁾

- ⁽¹⁾ Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Asian malaria vector *Anopheles stephensi* Proceedings of the National Academy of Sciences, vol. 112 no. 49, Valentino M. Gantz, et al, E6736–E6743

From June 2016 Smithsonian Magazine (Kevin M. Esvelt, Wyss Institute for Biologically Inspired Engineering, Harvard Medical School, Tony Nolan, Imperial College, London)



Malaria Resistant Mosquitoes

- At this level of efficiency, a single mosquito equipped with a parasite-transmission blocking gene could in theory ***spread malaria resistance through an entire breeding population in a single season.***
- A collaboration is under way, based on this study, to do just that.

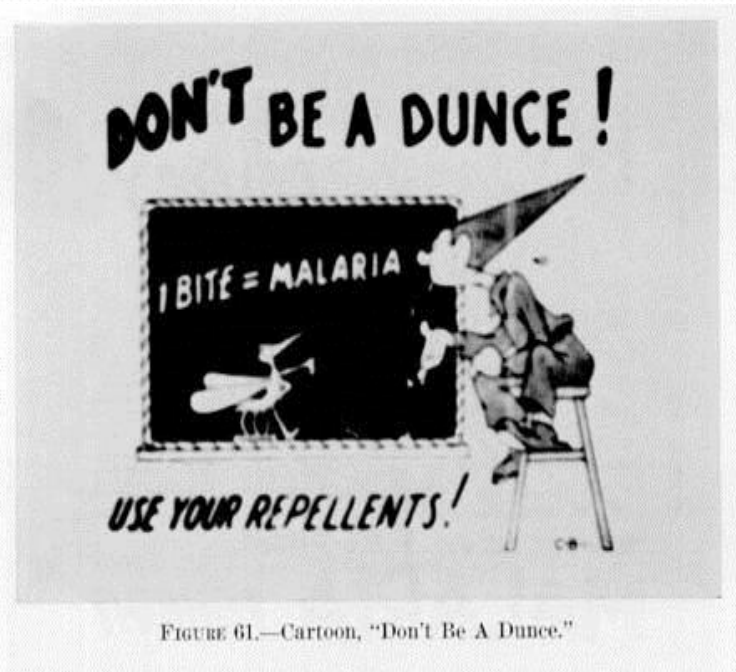


FIGURE 61.—Cartoon, "Don't Be A Dunce."

Malaria Vaccine

Malaria Vaccine

- More than 30 *P. falciparum* malaria vaccine candidates in the pipeline

RTS,S/AS01 Malaria Vaccine

- Thus far, **only one**, the RTS,S/AS01 vaccine has completed Phase 3 evaluation and received a positive regulatory assessment. ⁽¹⁾
-

RTS,S/AS01 Malaria Vaccine

Only effective against *Plasmodium falciparum* ^(1,2)

- (1) Malaria vaccine: WHO position paper – January 2016
- (2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

-

RTS,S/AS01 Malaria Vaccine

2 Groups Studied

- A) Infants 6 weeks old at time of 1st dose
- B) Young Children 5-17 months

RTS,S/AS01 Malaria Vaccine Phase 3 Trial

- A) > **15,000 infants/young children** in 7 sub-Saharan African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania).
- B) Trial sites in these countries represented a range of malaria transmission settings (low, medium and high) in order to determine the vaccine's efficacy in these different settings. ^(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

(2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine Trial

- 2 Target Age Groups in Trial.
- A) **Infants** received the malaria vaccine together with routine childhood vaccines at **6, 10, and 14 weeks of age** as well as at **20 months**. (mean follow-up 38 months)
- B) Other group: **Young children who got their 1st dose of vaccine between 5 - 17 months of age** followed by additional doses every month x 2 (3 dose total) and then a 4th dose 20 months later. (mean follow-up 48 months). ^(1,2)

1) Malaria vaccine: WHO position paper – January 2016

(2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine Trial

- **3 vs 4 doses** of vaccine was also studied ^(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

(2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine Trial Results

- **4 doses of vaccine are necessary**
- **First 3 doses every month and a 4th dose 20 months later.**
(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

(2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

•

RTS,S/AS01 Malaria Vaccine Trial Infants

-
- **27% efficacy** against clinical malaria in the group that received **4 doses** of vaccine
- **18% efficacy** against clinical malaria in the group that **didn't receive the 4th dose** of vaccine.
- In these infants, **no significant efficacy** was noted against **severe malaria, with or without 4TH dose.** ^(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

- (2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine Trial (Children aged 5-17 months)

- No protection against severe malaria occurred overall **UNLESS** a 4th dose of vaccine was given...
- **BECAUSE** any malaria prevented in the first 20 months occurred later.
- These results highlight the **importance of a 4TH dose** with this vaccine, as **efficacy is short-lived.** ^(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

- (2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine Trial (Children aged 5-17 months)

4 Dose Group

-
- A) **Vaccine efficacy** against **clinical** malaria was **39%**
-
- B) With 4 dose schedule, overall efficacy against **severe** malaria was **31.5%**, with reductions in:
 - 1) Severe anemia, 2) Malaria hospitalizations and 3) All-cause hospitalizations also seen. ^(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

- (2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine Trial Results

1774 cases of clinical malaria averted per 1000 children in the 4 dose group

- **983 cases of clinical malaria averted per 1000 young infants in the 4 dose group.⁽¹⁾**

- (1) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership

RTS,S/AS01 Malaria Vaccine Trial Adverse Effects

- **Febrile Sz's**

- **Children in the older age group, had increased risk febrile Sz's (2.5/1000 doses) within 7 days after any of the vaccine doses.**
- **Among infants, excess risk (2.2/1000 doses) only apparent after 4TH dose.**
- **No long-lasting sequelae due to any of the febrile Sz's.**^(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

(2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine Trial **Adverse Effects**

- **Older age group only:**
- A) Increased number of meningitis cases (22 children overall, 11 in the 4 dose group, 10 in the only 3 dose group, and **one in the control group**).

B) Significance of these findings in relation to the vaccination is unclear. ^(1,2)

(1) Malaria vaccine: WHO position paper – January 2016

- (2) Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet. 2015 Jul 4;386(9988):31-45; RTS,S Clinical Trials Partnership.

RTS,S/AS01 Malaria Vaccine

- Where Do Things Stand?
- Not Ready for Prime Time ⁽¹⁾

(1) Malaria vaccine: WHO position paper – January 2016

RTS,S/AS01 Malaria Vaccine

- Uncertainties:
- How long does the protection last?
- Is there a good enough healthcare infrastructure to enable 4 vaccine doses to be given at the appropriate times to the target population?
- WHO therefore recommends further evaluation of RTS,S/ASo1 via a series of pilot implementations ⁽¹⁾

Fighting Malaria: The Future is About Money

- International and domestic funding for malaria control and elimination totalled \$ **2.7 billion** in 2013.
- This is **3 fold** increase since 2005, but is still significantly below the \$ **5.1 billion** that is required to achieve global targets for malaria control and elimination.

- 
- Lasers to shoot mosquitoes from the sky?
 - <https://www.youtube.com/watch?v=OM6E3f2lT14>

