Applying public health science in the quest for malaria elimination

Manuel Hetzel & Christian Lengeler
Swiss Tropical and Public Health Institute
In 2019

✓ 229 million cases per year (vs ca 500 million in 2000)
✓ 409,000 deaths, mainly African children (vs >1 million in 2000)
✓ 1 Billion individuals living in areas at risk of malaria

WHO - World Malaria Report 2020
Malaria in the World around 1900 (Celli 1913)
Malaria was transmitted in Switzerland before 1896

Seeland ca. 1880 und 2021

Grenzacher Fluh / Basel ca. 1750 und 2021
Malaria, as many other similar diseases, is not a "Tropical Disease". It is a disease of poverty, which nowadays has a strong concentration in tropical areas.

Other examples are:
- Comon worms (*Ascaris sp.*, *Hookworms*, *Schistosoma sp.*, etc.)
- Cholera
- Tuberculosis
- Typhus
- Amoebas
- Etc.
Funding for malaria control 2000 – 2019: 6x increase
Trends in infections and deaths 2000 – to-date

Average infection rates in children 2-10 years

Bhatt et al. 2015 Nature

Cumulative number of cases and deaths averted globally, 2000-2019

WHO: World Malaria Report 2020
The malaria life cycle

Parasite
*Plasmodium falciparum,*
*P. vivax,* *P. ovale,*
*P. malariae,* *P. knowlesi*

Mosquito (vector)
Night-biting
*Anopheles* spp.

Human (host)

Photo credit: National Geographic
The malaria life cycle

1. Mosquito infected with *Plasmodium* parasite

2. *Plasmodium* parasites multiply in mosquito

3. Human infected during bite of infectious *Anopheles* mosquito

4. *Plasmodium* parasites multiply first in liver, then in red blood cells
Malaria control: prevention & treatment
(Simplified)

Vector control
- Mosquito nets
- Insecticide spraying
- Repellents
- Environmental management
- Genetically modified mosquitoes

Health systems
- Access to diagnosis & treatment
- Surveillance-response

Drugs in humans
- Treatment of infection
- Chemoprophylaxis
- Chemoprevention

Vaccine (RTS,S)

Cycle in mosquito

Cycle in human

• Education
• Behaviour change

Human genetic resistance

Swiss TPH
Challenges to malaria control & elimination

• Drug resistance
• *P. vivax* hypnozoites
• Diagnostic sensitivity

• Insecticide resistance
• Biting behaviour (plasticity)

• Human behaviour
• Diagnostic sensitivity
• Socio-economic situation

• Health system & policies
• Infrastructure & access
• Quality of care
• Health data

Photo credit: National Geographic
From research to implementation: vector control in Tanzania

KINET project 1996-2000
15 Publications
5 PhDs

Effect of large-scale social marketing of insecticide-treated nets on child survival in rural Tanzania

Joanna R M Armstrong Schellenberg, Salim Abdulla, Rose Nathan, Oscar Mukasa, Tanya J Marchant, Nassor Kikumbih, Adiel K Mushiri, Haji Mponda, Happiness Minja, Hassan Mshinda, Marcel Tanner, Christian Lengeler

Summary
Background Insecticide-treated nets have proven efficacy as a malaria control tool in Africa. However, the transition from research to implementation can be challenging.

Introduction Malaria remains the greatest threat to survival for young African children, causing at least 750,000 deaths each year. In endemic areas, people of all ages have regular contact with infected mosquitoes.

Usefulness of a dispensary-based case-control study for assessing morbidity impact of a treated net programme

S Abdulla, JRM Armstrong Schellenberg, O Mukasa, and C Lengeler

Introducing insecticide-treated nets in the Kilombero Valley, Tanzania: the relevance of local knowledge and practice for an Information, Education and Communication (IEC) campaign

Happiness Minja, Joanna A. Schellenberg, Oscar Mukasa, Rose Nathan, Salim Abdulla, Haji Mponda, Marcel Tanner, Christian Lengeler, and Brigit Obrist

1 Ifakara Health Research and Development Centre, Ifakara, Tanzania
2 Swiss Tropical Institute, Basel, Switzerland
3 Institute of Anthropology, University of Basel, Basel, Switzerland
NATNETS consist(ed)s of four main components:

1. An ITN coordination cell within the NMCP - Supported by the Swiss Agency for Development and Cooperation & Swiss TPH  \[2002\text{-}\text{present}\]

2. A strategic social marketing programme to support the commercial ITN sector - SMARTNET (DfID/RNE, implemented by Population Services International) \[2002\text{-}2007\]

3. A subsidy scheme targeting pregnant women and infants with vouchers (price reduction around $ 4.50) \[2004\text{-}2014\]

4. Mass distribution of free nets to all U5 and to the rest of the population \[2009\text{-}2011, 2015\text{-}2016, 2020\text{-}2021\]

On the KINET evidence base, a National Strategic Plan was produced in August 2000 and discussed among all stakeholders. This plan was approved by the MoH as the national policy in December 2000, creating the national ITN initiative (NATNETS).
To-date, nearly 100 million treated nets have been distributed in Tanzania (2.5 billion globally)
Mean $PfPR_{2-10}$ 1990 – 2017 per district

Improvement of 43% (from 100 to 57 per 1000) in U5 mortality; 70,000 less deaths per year
Drug resistance

- Parasites have become resistant to many “traditional” antimalarial drugs (e.g. chloroquine, sulfadoxine-pyrimethamine)
- Artemisinin-based combination therapies are currently the most efficacious treatment (e.g. artemether-lumefantrine)

Fake drugs

- 1 in 10 medicines administered in low- and middle-income countries are thought to be substandard or falsified.


https://fightthefakes.org/
Resolving the lack of incentives for investing in new antimalarials: Product Development Partnerships (PDPs)
Remote rural environment, high malaria transmission

Children < 5 years with severe fever

Community health worker

Pre-referral rectal artesunate and referral

Step 1: Administer rectal artesunate

Step 2: Refer

After receiving rectal artesunate suppository the child must be referred immediately to the nearest hospital or health care facility where the full required treatment for severe malaria can be provided.

Referral health facility, treatment of severe malaria
From research to implementation: case management

Observational research to measure effectiveness of rectal artesunate in DR Congo, Nigeria, Uganda (CARAMAL Project)

- Health Provider Survey
- Household Survey
- Patient Surveillance System (PSS)
- Drug resistance

12,000 children <5 years of age
Rectal artesunate is just one ‘piece in the puzzle’:  
- Children >3 years often received only 1 instead of 2 rectal capsules  
- Children treated with rectal artesunate are less likely to go to a hospital  
- Children referred to a hospital are usually treated with injectable artesunate but often do not receive a full course of oral artemisinin combination therapy  
- 13% of children were sick 28 days after initial treatment  
- RAS had no effect in Nigeria, where case fatality was highest

Can rectal artesunate reduce case fatality “in the real world”?

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CARAMAL Scientific Report, April 2021
From research to implementation: surveillance-response

Malaria control & elimination activities must be based on data

“…transformation of malaria surveillance into a core intervention in all malaria-endemic countries and in those countries that have eliminated malaria but remain susceptible to re-establishment of transmission.”

• Passive case detection
• Active case detection
• Reactive case detection
From research to implementation: surveillance-response

Re-active case detection (RCD) of malaria in Zanzibar (Tanzania)
Find and eliminate undetected infections in the community

System effectiveness of RCD depends on:
• Treatment seeking
• Notification
• Follow-up
• Diagnostic sensitivity
• Treatment adherence
• Drug efficacy

From research to implementation: surveillance-response

- Not infected
- Infected asymptomatic subpatent
- Infected asymptomatic detectable
- Infected symptomatic

Attend HF (passive)
**From research to implementation: surveillance-response**

**RDT sensitivity: 34%**

- **Parasites per microliter blood**
- **Rapid diagnostic test (RDT) result**
- **Positive**
- **Negative**
- **RDT detection limit**

**Current System Effectiveness: 3.2%**
(qPCR detected infections cleared by the current reactive case detection system)

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<th>Scenario</th>
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<th>S with h=20</th>
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<tbody>
<tr>
<td>RCD with RDT</td>
<td>3.2 (2.1-4.5)</td>
<td>8.1 (5.9-10.5)</td>
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<tr>
<td>rfMDA</td>
<td>10.8 (8.1-13.8)</td>
<td>34.4 (30.3-38.4)</td>
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RCD = Reactive Case Detection; rfMDA = reactive focal Mass Drug Administration; RDT = rapid diagnostic test


Logan Stuck, PhD Thesis, Tulane University, 2019
Manuscript in preparation
Cost-effectiveness calculation

- Total costs of reactive case and **reactive focal Mass Drug Administration** (rfMDA) are comparable
- A much larger number of infections can be treated at a similar total cost by switching from reactive case detection (RCD) to rfMDA

➔ Pilot implementation of rfMDA by the Zanzibar Malaria Elimination Programme

Stuck, Fakih, Yukich, Hetzel et al. manuscript in preparation
From research to implementation: surveillance-response

**Minimal essential data**

- Which information is required for decision-making?
- Avoid excessive collection of data that is not used!

*Minimal essential data*

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**From research to implementation: surveillance-response**

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[Graph showing number of form fields by year]

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Bringing it all together at country level: Epidemiological stratification of malaria risk + modelling the best combination of interventions

Empowering people to develop and implement strategies

Public Health Science for malaria elimination

- Parasitology
- Genetics
- Entomology
- Immunology
- Epidemiology
- Medical anthropology
- Demography
- Cell biology
- Biostatistics
- Health systems research
- Health economics

Understanding of parasite, mosquito, human
Development of interventions
Strengthening of systems that deliver interventions
Accurate and timely real-world data
Empowering people to develop and implement strategies

Photo credit: National Geographic
Thank you for your attention

Manuel Hetzel
manuel.hetzel@swisstph.ch

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