River blindness – the keys to control

A unique feature of onchocerciasis control has been the central role of research in helping to optimize and innovate control actions

Janis K Lazdins-Helds, MD, PhD
ONCHOCERCIASIS The Disease

- Caused by a parasitic worm *O. volvulus*
- Transmitted from person to person by a blackfly
- The worm (MACROFILARIA) lives 14 years in the human body, producing millions of microscopic parasites (MICROFILARIA)
ONCHOCERCIASIS The Disease

The microfilaria cause:

- unbearable itching
- disfiguring skin disease
- blindness
ONCHOCERCIASIS

- **120 million people at risk**
- **Disease is endemic in 30 African countries and 6 in the Americas**
- **18 million people are infected**
- **6.5 million suffer from severe itching or dermatitis and 270 000 are blind**
- **ivermectin (Mectizan®) is the only therapy**
GEOGRAPHICAL DISTRIBUTION OF ONCHOCERCIASIS IN THE WORLD
Phase 1: Vector Control based on aerial insecticide spraying

The programme was supported by research on:

- Entomological research identifying different vector species and determining their role in transmission of different *Onchocerca* species

- Research and development of new larvicides

- Continuous evaluation of larval susceptibility to available larvicides

- Monitoring of the environmental impact of larvicide operations.
Development of PCR technology to distinguish infected black flies with human or animal parasites. This helped larviciding where needed, cutting costs and environmental impact.

— APOC/OCP Lab (now Multidisease Surveillance Centre) Ouagadougou, BF
Research on mathematical modeling... a tool for advocacy

Predicted and observed trend in the prevalence of microfiladermia

Villages in the Central OCP Area with a pre-control CMFL > 30 mf/snipe

- Observed:
- Predicted for:
  - CMFL=90
  - CMFL=30

Years of vector control

Prevalence of microfiladermia in adults (as percentage)
Phase 2: Chemotherapy based control

Ivermectin (Mectizan®)

1987 "Given free for as long as needed to as many as need"
However, this came to be reality because research...


SKIN-SNIPS FROM TAMALE

In the vanguard of onchocerciasis chemotherapy work

The Onchocerciasis Chemotherapeutic Research Centre in northern Ghana is leading the field testing of potential drugs for the treatment of oncho. The man in charge, Dr Awadzi (right) has developed it almost single-handedly.

Dr Kwablah Awadzi is a rare jewel. Capable of commanding a senior post in most international research for water. Also, being on the fourth floor means we have to carry all the water we need up the stairs to our laboratories and offices. We do now have our own generator, so at last our electricity problems are solved!

We are looking at the possibility of setting up our own little reservoir downstairs and getting a pump that will lift the water up to the fourth floor for distribution to the laboratories and wards from there. The water would have to be delivered by tanker. Whatever, these are problems that are surmountable. . . but they do consume an, furazolidine, mebendazole, levamisole, flubendazole, ivermectin, and the Chlo Geigy compounds.

A major problem with onchocerciasis is the kill of microfilariae following chemotherapy, is initially much more painful than the itching experienced by the patient prior to presentation.

We have now assembled data on 1300 onchocerciasis patients. Nowhere else in the world has such a large patient base — and some of our trials

Decade of achievement

Dr Adetokunbo Lucas summarises the scientific progress made by Dr Awadzi and his team.

IN 1975, Dr Kwablah Awadzi became the Director of the Onchocerciasis Chemotherapy Research Centre (OCRC) at Tamale, Ghana, and thus began a decade of solid achievements in clinical and pharmacological research on old and new drugs for the treatment of onchocerciasis. Occupying a wing of the Tamale Northern Regional Hospital, the OCRC pro-
Ivermectin (Mectizan®)

Single treatment per year kill 95% of the microscopic worms in the body with negligible side effects.

However, it does not kill the adult worm

It must be given for the life of the adult worm (14 years) or as long as transmission is ongoing
Search for a macrofilaricidal drugs high priority for the onchocerciasis control programmes

• Drug discovery
  – Screening facilities: in vitro and in vivo (Gerbils, Dogs, Cows)
  – Chemical leads from academia and pharma partners
  – Discovery of Molecular targets (genomic information)
    – New concepts: Wobachia

• Drug evaluation
  – Pharmacology
  – Drug combinations
  – Evaluation of new drug candidates
Dr. Awadzi still leading OCRC (now in Hohoe, Ghana)
Moxidectin (a potential macrofilaricidal)
Development Plan and Status

Consultation with EU Regulators

Phase 2 study

Consultation with EMEA

Phase 3 study

Healthy Volunteers
- Food Effect
- Milk Excretion
- Drug interaction

Pediatric study

Formulation and manufacturing site qualification

WHO Expert Committee recommendation

IVM ------- Mox 1 ------- Mox 2-------

Submission to endemic countries

EMEA Scientific Opinion

Implementation into control programmes

Submission for MoH permit to conduct study

2006 2008 2010 2014

UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

World Health Organization

13 May 2009 J. Lazdins
Moxidectin Phase 3 Clinical Trial Sites

Rethy, Ituri Nord, DRC
Butembo, Kivu Nord, DRC

Bolahun, North West
Liberia

Hohoe, Upper Volta Region, Ghana

Butembo, DRC

Dr. Eric Kanza & Dr. Didier Bakajika

July 2008

Subject Accommodation

Dr. Hayford Howard

Dr. Kwablah Awadzi
Dr. Nicolas Opoku

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New generation of onchocerciasis clinical researchers in DRC and Liberia
In addition...

Disease control strategies based on ivermectin brought new challenges and concerns to the control programs that required research.
Research on mathematical modeling... a tool for advocacy

Fig. 4. The predicted epidemiological impact of 25 years of annual large scale ivermectin treatment.
Research that established a new paradigm on how to reach the population:
Community-Directed Treatment

- Community collects ivermectin (Mectizan®) from the nearest health facility
- Community decides how and when to distribute ivermectin (Mectizan®)
- Community collectively selects distributors
- Health Services/NGDOs train and monitor ComDT activities
- ComDT empowers local communities
Overcome an obstacle for control: loiasis

Severe/fatal reactions in people that receive (Mectizan®) and have high intensity of Loa loa infection

- TDR researched and developed simple rapid assessment method based on history of 'eye worm'

Figure 11  Eye worm: adult Loa loa migrating under the conjunctiva. Source: TDR Image Library.

Research to Policy

- Mectizan Expert Committee concluded that RAPLOA was valid for use in all African countries
- Modified treatment policy and guidelines
  - treatment strategies with intensified monitoring in areas where according to RAPLOA the risk of SAEs is high
Need for a diagnostic tool to assess epidemiological situation, specially impact of ivermectin treatment programs

- Currently skin snipping (not amenable for large scale epidemiological use)

- Immunodiagnostics: OV-16 alone or in cocktail

- DEC Patch test: Onchocerciasis diagnosis using transdermal delivery of a drug (DEC) that kills the microfilaria and produces a local reaction

  - Pioneered and optimized for field use by OCP scientists
"OCP" PATCH PREPARED, APPLIED AND READ ON THE FIELD

-20% DEC solution in Nivea milk
THE WAY OF THE FUTURE:
OPTIMIZING A "LOCAL PRODUCT" THROUGH APPLICATION OF TRANSDERMAL DRUG DELIVERY TECHNOLOGY

Step 1:
Development of patch prototypes by LTS (Lohmann Therapie-Systeme)

Step 2:
Proof-of-concept study of patch prototype (OCRC Hohoe, Ghana, K. Awadzi)

Step 3:
Testing as epidemiological tool in low prevalence areas (Senegal, L. Diawara; Mali, M.O. Traore,)

[LTS patch reaction at 24hr Subject No. 10]
The threat of ivermectin resistance

A survey in 1997 in the Lower Black Volta and Pru River basins (Ghana) revealed individuals with persistent, significant microfilaridermia after multiple ivermectin treatments.

Clinical Research that APOC/OCP and TDR sponsored


Microfilaria is killed as expected, however, adult female fertility does not seem affected after multiple treatments as expected.
Molecular Research that APOC/OCP and TDR sponsored

- W. Grant & R. Prichard observed genetic differences among parasites from individuals that had not been exposed to ivermectin and those that had multiple exposures.
  - SNP’s of the loci c777.2, 783, 787, 188001, 2206001, 146005, 1328001
  - beta-tubulin gene, ABC transporter (OvPLP-p-glycoprotein) and dyf-8 (amphid structural protein).

APOC and TDR will promote (technology transfer and capacity building) and support African research centres for parasitology material collection & storage their molecular and parasitological evaluation and development of molecular tools to do so.
ComDT network offers a key entry point for many health interventions

- Lymphatic Filariasis Treatment
- Vitamin A Distribution
- Schistosomiasis Treatment
- Guinea Worm Intervention
- Immunizations (polio, measles, others)
- Eye Care (cataract identification, primary eye care)
- Malaria Bed Net Distribution
- HIV/AIDS and Reproductive Health
Integrated Community-directed Interventions

A Multi-Country Study
## Study Design

### Complexity of individual interventions

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Interventions delivered through the CDI process</th>
<th>Comparison District</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CDI District 1</td>
<td>CDI District 2</td>
</tr>
<tr>
<td>Year 1</td>
<td>CDTi + Vit. A</td>
<td>CDTi + ITN</td>
</tr>
<tr>
<td>Year 2</td>
<td>CDTi + Vit. A</td>
<td>CDTi + ITN</td>
</tr>
<tr>
<td>Year 3</td>
<td>CDTi + Vit A + ITN + DOTS + HMM</td>
<td>Ti + ITN + Vit A + DOTS + HMM</td>
</tr>
</tbody>
</table>

Traditional delivery of the 5 interventions

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3 Countries - 7 Study Sites - 35 Health Districts - 2.4 Million People
Integrated community directed interventions study

- Integrated community directed interventions study influencing
  - policy and practice in Africa, especially APOC countries
  - primary healthcare perspectives
  - concept of implementation research
The Classical Model of R&D / Disease Control Interaction

- Clear boundaries between research and disease control

Area of R&D responsibility

Area of disease control responsibility

What are the consequences of this "clear cut" separation

- Research is promoted by ministries of science & technology, education, economic development, etc
- Disease control activities by ministries of Health
- The priorities and sustainability of funding decisions are not necessarily driven by same criteria
- Delay in translating innovation into impact
Model embraced and advocated by the African Onchocerciasis control programs

- New Basic Knowledge
- New and Improved Tools
- New and Improved Methods
- New and Improved Strategies

Science & technology opportunities (*push*)

Disease control needs (*pull*)

academia - industry - disease control
Thanks

lazdinsj@who.int
Vitamin A coverage

P<0.001

% of children that received Vitamin A

Comparison districts: 81
Vitamin A through CDI for 1 year: 89
Vitamin A through CDI for 2 years: 90

Target
Households with at least 1 ITN

<table>
<thead>
<tr>
<th></th>
<th>% of households having at least 1 ITN</th>
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<tbody>
<tr>
<td>Comparison districts</td>
<td>31</td>
</tr>
<tr>
<td>ITN through CDI for 1 year</td>
<td>52</td>
</tr>
<tr>
<td>ITN through CDI for 2 years</td>
<td>57</td>
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</tbody>
</table>

RBM target

P < 0.001
Children sleeping under ITN

% of households having at least 1 ITN

Comparison districts

ITN through CDI for 1 year

ITN through CDI for 2 years

RBM target

P<0.001

16

36

33
Pregnant women sleeping under ITN

% of households having at least 1 ITN

- Comparison districts: 33%
- ITN through CDI for 1 year: 57%
- ITN through CDI for 2 years: 49%

RBM target

P = 0.014

13 May 2009
J. Lazdins
Appropriate treatment of children with fever

<table>
<thead>
<tr>
<th></th>
<th>Comparison districts</th>
<th>HMM through CDI for 1 year</th>
<th>HMM through CDI for 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>% children with fever who received appropriate treatment</td>
<td>28.6</td>
<td>54.9</td>
<td>69.4</td>
</tr>
</tbody>
</table>

P<0.001

RBM target
Ivermectin Treatment Coverage

Comparison districts

CDI districts

Treated with ivermectin (%)

63.8

73.7

P<0.001

APOC target