Module 6. Monitoring and Evaluation (M&E)

Session 5. Monitoring Drug Efficacy
Overview

1) Current situation on NTD drug resistance:
   • Accelerating work in NTDs and lessons from livestock.
   • Reports of reduced efficacy in NTDs: evidence to date.
   • Causes of reduced efficacy other than drug resistance.

2) What NTD Programme Managers need to do:
   • Predicted and observed reduction in prevalence of NTD.
   • Algorithm and referral process.
   • Monitoring drug efficacy (WHO recommendations).
Report on 5th Meeting of the Global Working Group on Monitoring of NTD drug efficacy

18 February 2014
In the last two decades: availability of effective, safe, single dose and relatively cheap drugs.

1990: 16 out of 19 helminth infections could be cured with the administration of ALB, PZQ and IVM.

2000: rational use and careful choice of drugs increases long-term efficacy, sustainability, and benefit from treatment.
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Uniting to Combat Neglected Tropical Diseases
Ending the Neglect and Reaching 2020 Goals

Accelerating Work to Combat NTDs
Accelerating Work to Combat NTDs

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The Challenge for the Worms

About 70 million PSAC and 220 million SAC were de-wormed in 2013, mainly using BZ drugs.

1 billion treatments with ALB and IVM were delivered for the elimination of LF since 2000.

1.2 billion tablets of IVM were distributed since the beginning of the oncho programme.

54th World Health Assembly - June 2000, resolution WHA 54.19:
To regularly treat 75% of SAC at risk of morbidity for STH and schisto by 2020.
Are you aware of the problem of drug resistance?

For which parasite/drug?
Lessons from Livestock

• In the last 40 years, frequent large-scale treatment of sheep and other domestic animals with anthelminthic drugs has led to the development of high levels of DR.

• In sheep nematodes MDR (Benzimidazole (BZs), levamisole (LEV), pyrantel and/or IVM) is widespread.

• In horses, strongyles, BZ, and LEV resistance are a serious problem.

• In cattle some parasites are developing resistance to ML, BZ, and other classes.
Drug Resistance

Genetically transmitted loss of sensitivity for a drug in a parasite population previously sensitive to the appropriate dose.
Reports of Reduced Efficacy/Resistance to Anthelmintics
Currently there is no conclusive data demonstrating that DR is widespread in human STH and only a limited number of studies (less than 10!!) have been performed.
Resistance in Schistosomiasis?

• Oxamniquine resistance reported from several countries in Latin America.
• Reduced efficacy of PZQ from N. Senegal, Egypt, Kenya has been reported; selection of resistance isolates in the lab.
• No sign of resistance in public health use of PZQ which is still an excellent drug but...
  – To have a single drug available for a disease affecting 200 M people is a dangerous situation.
  – Not knowing the mechanism of action of PZQ hinders progress.
  – New antischistosomal drugs are needed for the above and because PZQ is far from being an ideal (it is ineffective against immature worms).
Resistance in LF and Oncho?

- No sign of reduced efficacy of IVM + ALB or DEC + ALB for treatment of LF.
- Reduced efficacy of IVM against Oncho has been reported from some sites in Ghana* after several rounds of MDA, but it is probably due to low compliance.

* Osey-Atweneboana et al., Lancet 2007
• No evidence to date of reduced efficacy of azithromycin for trachoma.
• However, nasopharyngeal pneumococcal and resistance to macrolides was significantly higher in communities randomized to intensive azithromycin treatment given in mass distributions for trachoma control.

* Scalet AH et al. Plos Medicine, 2010, 7(12), epub100o377
Is reduced efficacy always due to drug resistance (confounding factors)?
Reduced Efficacy

- **Drug-patient interaction**
  - Poor drug quality
  - Reduced absorption and bioavailability
  - Poor patient/community compliance
- **Host-parasite relationship**
  - Pre-treatment intensity of infection
  - Density dependent female fecundity
  - Heavy transmission of infections (presence of immature worms)
- **Diagnostic method used**
  - Timing of parasitological examination after treatment
  - Lack of standardised technique
- **Tolerance** (genetic variations between parasites strains leading to poor drug susceptibility)
- **Drug resistance**
Risk of Drug Resistance in Human Helminth Control
How is the Risk from Livestock Applicable to Human Helminths?

- Mass treatment (all animal treated in herds).
- Very frequent treatment (2-4/year).
- Underdosing or treatment with only partially-effective drugs.
- Compliance (DOTS?).
- Drug quality (use of generic, sometime sub-standard product).
- Use of single drugs.
Which are the scenario most at risk for drug resistance in NTDs?
Scenarios at Risk for Increasing DR?

- Community MDA with ALB and/or IVM for elimination of LF or for control/elimination of Oncho.
- More frequent MDA when schistosomiasis/onchocerciasis is target for elimination to aim at the highest coverage.
- Reliance on a single class of drugs.
- Repeated use of same drug in the same target group.
- Using generic products of not proven quality.
WHO Efficacy Monitoring Recommendations in NTD Control Programmes

Which is the alarm bell?
Predicted Trend in Prevalence After Ivermectin Treatment

(Onchosim simulations for annual treatment at 70% coverage)
Predicted and Observed Trend in Prevalence After Ivermectin Treatment

(Results of epidemiological surveys in 2009-2011)
Observed vs. Predicted Prevalence Using Transition Probabilities for Schistosomiasis

Reduction in overall prevalence obs vs predicted

- Observed
- Predicted

Prevalence

Baseline 1 year 2 years 3 years 4 years 5 years

Treatment Round
STH Model

Aims:
• Allowing testing different approaches on national data and facilitate decision making.
• Acting as “alarm bell” in case of poor programme performances.

Status:
• 3 modules developed.
• Beta version under test (data from BF and Uganda).

Next steps:
• Publication of the performances.
• WHO WEB site
• Development of SCH version (in collaboration with SCI, following up on SCHISTOSIM model).
• Combination with mapping.
If prevalence is not declining as expected in your NTD programme, how would you respond?
Algorithm and Referral Process for Monitoring DR in Endemic Areas

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## Work Plan – Drug Efficacy Monitoring System

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>District</strong></td>
<td><strong>National sentinel sites</strong></td>
<td><strong>Reference lab</strong></td>
</tr>
</tbody>
</table>
| Data show lower than expected reduction in prevalence/Intensity | Check other factors for low efficacy (compliance, drug quality)  
Second level test  
Collection of isolates | Molecular tests – genetic polymorphism, PCR on isolates from national labs |

Data show lower than expected reduction in prevalence/Intensity

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Collection of isolates

Molecular tests – genetic polymorphism, PCR on isolates from national labs
Work Plan – Drug Efficacy Monitoring System: Actions and Responsibilities

• Phase 1
  – NTD programme managers notice that prevalence of NTD is not declining as expected.
  – NTD PM organize survey in sentinel sites and analyse data.

• Phase 2
  – If prevalence/intensity thresholds are below expectation, NTD PM alert WHO collaborating center (CC) for monitoring drug efficacy.
  – WHO CC organizes field visit to analyse confounding factors, plan further investigations, collect repositories of samples.

• Phase 3
  – Repositories of samples are sent to reference laboratory for molecular analysis and confirmation of DR.
Work Plan – Drug Efficacy Monitoring System: Thresholds for Reduced Efficacy

Albendazole
- Ascaris Egg reduction rate (ERR) > 95%
- Hookworms ERR > 90%
- Trichuris ERR > 50%

Mebendazole
- Ascaris ERR > 95%
- Hookworm ERR > 70%
- Trichuris EUR > 50%

Praziquantel
- All schistosoma ERR > 90%

Ivermectin
- For LF to be determined
- For Oncho: CMFL below Onchosim curve

DEC
- To be determined
### Drug Efficacy Monitoring for PC NTDs

<table>
<thead>
<tr>
<th>NTD</th>
<th>“Alarm Bell”</th>
<th>Where</th>
<th>When</th>
<th>Efficacy Testing</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncho</td>
<td>&lt;expected decline in prevalence based on Oncho Sim</td>
<td>Sentinel sites</td>
<td>?</td>
<td>Effect of IVM on re-population of mf in skin N=?</td>
<td>Doxycycline (DEC/ALB?)</td>
</tr>
<tr>
<td>LF</td>
<td>&lt;expected decline in prevalence?</td>
<td>Sentinel sites</td>
<td>After 3 or 5 MDAs</td>
<td>Effect of drug on clearance of mf N=?</td>
<td>Doxycycline ALB (# days?)</td>
</tr>
<tr>
<td>STH</td>
<td>&lt;expected decline in prevalence/intensity from baseline</td>
<td>Sentinel schools</td>
<td>After 3 or 5 MDAs</td>
<td>Effect of drug on egg count reduction (WHO SOP) N=50-75</td>
<td>Levamisole, Pyrantel,</td>
</tr>
<tr>
<td>Trachoma</td>
<td>&lt;expected decline in prevalence?</td>
<td>Population-based cluster survey</td>
<td>After 3 or 5 MDAs</td>
<td>Effect of drug on bacterial clearance as assessed by PCR N=?</td>
<td>?</td>
</tr>
</tbody>
</table>
Which is the measure you would take to minimize the risk of DR in your NTD Programme?
Measures to Minimize the Risk of DR

• Ensure quality of drugs, including proper storage.
• Promote drug combination/alternate drugs (IVM/ALB ALB/Pyrantel).
• Encourage proper dosing and compliance.
• Don’t overtreat for a long time (reduce morbidity or reach elimination in the shorter time possible).
• Establish a strong monitoring system.
• Ensure other agencies/charities are not also providing unregulated NTD drugs to communities already treated by the NTDP.
What do you think are the key messages from this session?
Key Messages

• DR is an important problem in veterinary public health and lessons learnt should be kept in mind for NTDPs.

• Despite anecdotal evidence of treatment failures, DR is not yet a problem in NTDP.

• NTDP managers are responsible for the rational use of drugs which will help prevent development of DR.

• Vigorous monitoring is crucial to detect reduced efficacy and exclude causes other than DR.

• NTDP managers should know the risk of DR exists and should take steps to delay its occurrence.