Module 5. NTD Drug Management

Session 3. PC Safety
Objectives

- Identify possible Adverse Events (AE) and Serious Adverse Events (SAE) following large scale interventions with PC medicines and classify their causes.
- Know the recommendations for co-administration of MDA drugs and their safety profile.
- Be aware of precautions when administering PC medicines to young children.
Overview

- Definitions of Adverse Event (AE) and Serious AE (SAE)
- Classification of AEs
- Review of possible AEs and SAEs following large scale interventions with PC medicines
- Drug co-administration (TDA)
- Administering PC medicines to young children (+ Case study)
- Training CDDs/Health Workers (DOT and attitudes)
Definitions of AEs and SAEs

• **AE.** Any medical incident that occurs after an intervention that is suspected to be, but it is not necessarily caused by the medicine used in the intervention.

• **SAE.** Any medical occurrence at any dose that results in: hospital admission, prolongation of existing hospital stay, persistent physical disability or incapacity, life threatening (including cancers, birth defects) or death.
Adverse Events (AEs)

- Common, expected
- Transient
- Easily Managed

Usually no reporting requirements

Serious Adverse Events (SAEs)

- Uncommon
- Prolonged hospitalization
- Death
- Disability

Reporting requirements to regulatory authorities
Classification of Adverse Events: 5 Categories

1. Adverse reaction to the medicine: ADR caused directly by the medicine(s).
2. Adverse reaction due to the destruction of parasites killed by the medicine.
3. Operational error: any errors and accidents in treatment procedures, logistic or manufacture, handling or administration.
4. Coincidental event: event unrelated to the medicines but with a temporal association with the intervention.
5. Unknown cause.
SAE and AE are the main factors (barriers) that can negatively impact MDA coverage and compliance of target communities.

Are the PC medicines safe?

How can AE and SAE affect MDA?

Are the PC medicines safe?
From your experience, has BZ (ALBENDAZOLE/MEBENDAZOLE) administration been safe?

What circumstances and/or factors may contribute to the occurrence of BZ related AEs?
### Mebendazole and Albendazole

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Exclusion Criteria</th>
<th>AE/SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB</td>
<td>One 400 mg tablet per person (200 mg for &gt;1&lt;2 years old)</td>
<td>&lt; 1 years of age</td>
<td>- Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnant women in 1\textsuperscript{st}</td>
<td>- Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>trimester</td>
<td>- With heavy intensity STH infection:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Transient abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Diarrhea</td>
</tr>
<tr>
<td>MBD</td>
<td>One 500 mg tablet per person</td>
<td>&lt;1 year of age</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnant women in 1\textsuperscript{st}</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>trimester</td>
<td></td>
</tr>
</tbody>
</table>

- BZ can be given to pregnant women in hookworm endemic areas in the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester.
- BZ can be administered to lactating women.
Summary of Benzimidazole (BZ) Safety

- Millions of BZ doses have been administered alone or in combination in MDA and side effects are rare, mild, and transient.
- BZ can be administered to school-age children by non-health personnel (teachers) after simple training.
- Care is needed when tablets are given to young children. Tablets should be crushed to avoid choking.
- BZ can be given in pregnancy except in the 1st trimester; postnatal surveillance has not shown BZ to be associated with birth defects. Postnatal surveillance should continue.
From your experience, what circumstances and/or factors may contribute to the occurrence of IVERMECTIN related AEs?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Exclusion Criteria</th>
<th>AE/SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVM</td>
<td>150-200 μg/kg using tablet pole • 1 tablet • 2 tablets • 3 tablets • 4 tablets</td>
<td>• &lt;5 years of age • Pregnant women • Severely ill • &lt;1 week postpartum mothers • IVM where Loa loa is endemic, assessed by RAPLOA is justified only when oncho prevalence is &gt;40%</td>
<td>• Most AEs are mild and last &lt;3 days • More frequent AEs are reported in naïve population after the first round of MDA: need to monitor for 36 hrs • Treatment: analgesics and antihistamines <strong>Mazzotti reaction</strong>- arising from the death of the mf: fever, pruritus, rashes, myalgia, asthenia, orthostatic hypotension, tachycardia, oedema, lymphadenopathy, GI symptoms, sore throat, cough, and headache, mild ocular irritation, somnolence, transient eosinophilia, and elevated liver enzymes</td>
</tr>
</tbody>
</table>
SAEs- Following IVM in Loa Loa Co-endemic Areas

• The most important risk is the development of an encephalopathic syndrome in people with very high levels of L. loa (incidence < 1:10,000 treatments).
• IVM is also effective against L. loa mf, the rapid killing of which is associated with this encephalopathy.
• Symptoms: confusion, lethargy, coma, urinary incontinence.
• Encephalopathy requires prompt medical and nursing care for supportive treatment and to prevent nosocomial infections.
• With competent, timely medical care, patients usually recover fully.
Module 5. NTD Drug Management
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Figure 5. Map of the predictive probability that the local prevalence of eye worm history exceeds 40%.

From Zourè et al., Plos NTDs, June 2011, 5(6) e1210
Use of IVM in Area Endemic for Loa Loa for Onchocerciasis Treatment*

- Based on risk/benefit assessment
  - Only areas **meso/hyperendemic** for oncho are associated with high morbidity (blindness, itching) then treating those communities will be beneficial

- If decision made to treat,
  - If RAPLOA (prevalence of eye worm history) <40%
    - The risk of SAEs (encephalopathy) is **low**
    - **Sensitize the communities targeted for MDA** about the **possibility** of SAEs;
    - **Train personnel involved in case identification**, referral, reporting, and general management of the SAE cases (passive surveillance)
  - If RAPLOA is ≥40%
    - The risk of SAEs (encephalopathy) is **high**
    - the above recommendations also apply
    - **in addition**, referral hospitals for SAE management should be designated and properly equipped and should have trained **medical staff** (enhanced passive surveillance).

CDTI Eligible Areas (meso/hyper-endemic areas)
MDA for LF in Loa Loa Co-endemic Areas*

Loa Loa +

If eligible for CDTI

• MDA with ALB+IVM

If NOT eligible for CDTI

• MDA with ALB only 2x/year +
• Integrated vector management

Summary of IVM Safety

- Safe drug when administered in single dose (150 mg/kg) in PC for Oncho and LF.
- Side effects are mild and transient and related to the parasite load.
- Care is needed in areas where Loa-loa is co-endemic and SAEs (encephalopathy) may occur.
  - Preventive measures: training and information of the health staff and the community for passive/active surveillance
In your experience, which are the AEs when Diethylcarbamazin (DEC) is administered as single dose in MDA campaigns?
DEC Related AEs

Mazzotti reaction: may occur a few hours after the first oral dose of DEC, generally last <3 days.
- Nausea, vomiting (if taken empty stomach), drowsiness, headache, dizziness, and sometimes attacks of bronchial asthma in asthmatic patients.
- Fever and systemic reactions are reactions to the dying mf.
- AEs are more likely to occur with heavy infections.
- DEC is NOT recommended in onchocerciasis endemic areas.

Local reactions:
- Tend to occur later in the course of treatment and last longer.
- They include lymphadenitis (string lesion), abscess, ulceration, and transient lymphoedema; funiculitis and epididymitis (acute hydrocele) may also occur in bancroftian filariasis.
DEC in Pregnancy, Children, and the Elderly

- DEC is not recommended in pregnant women.
- Since safety and efficacy of DEC has not been evaluated for young children, it is not recommended for children <2 years.
- Elderly and debilitated people (especially those with cardiac and renal failure) should be excluded from MDA.
From your experience, what circumstances and/or factors may contribute to the occurrence of PRAZIQUANTEL related AEs?
# Praziquantel

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Exclusion Criteria</th>
<th>AE/SAE</th>
</tr>
</thead>
</table>
| PZQ  | 40 mg/kg using pole 600 mg tablets  
• 1 tablet  
• 1 1/2 tablets  
• 2 tablets  
• 2 1/2 tablets  
• 3 tablets  
• 4 tablets  
• 5 tablets | <4 years of age  
Severely ill  
Ocular cysticercosis  
Pediatric solution under trial for use in children aged 2-4 years, recommendations updated in the future | Usually mild and transient:  
• Headache, dizziness, drowsiness, malaise.  
• Most common effects on the gastrointestinal tract: abdominal discomfort, colicky abdominal pain, bloody diarrhoea, nausea, and vomiting.  
Hypersensitivity reactions: fever, urticaria, pruritic skin rashes, eosinophilia, raised liver enzymes.  
Special care to patients with neurocysticercosis: CNS effects like headache, hyperthermia, seizures, and intracranial hypertension. Corticosteroids are advised in such patients |

PZQ can be given to pregnant and lactating women in endemic areas.
Rash Following PZQ Treatment

- Resolved within 24 hours
- Prescribed oral antihistamine medicine
Abdominal Pain Following PZQ Treatment

- Resolved within 24 hours
Summary PZQ Safety

- PZQ is safe and effective and has been administrated to populations in schistosomiasis endemic countries for decades.
- **PZQ should be preferably taken after food with water.**
- Extra-preventive measures should be taken during the first time large scale PC with PZQ.
- Co-administration of PZQ with ALB and IVM should follow specific guidelines.
- Pregnant and lactating women should be included in PC with PZQ but cautioned exercised in areas with high maternal mortality.
- Concurrent infection with cysticercosis and epilepsy may worsen SAEs and PZQ should not be used in patients with ocular cysticercosis or a history of seizures.
From your experience, what circumstances and/or factors may contribute to the occurrence of AZITHROMYCIN related adverse events?
## Azithromycin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Exclusion Criteria</th>
<th>AE/SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZM</td>
<td>20mg/kg using dose pole</td>
<td>250 mg tablets Pediatric Oral Suspension</td>
<td>&lt;6 months of age</td>
</tr>
</tbody>
</table>
Azithromycin in Pregnancy and in Children

• For pregnant women vulnerable to trachoma, the documented benefits of treatment outweigh the potential but undetected risks to the fetus. The implication of this policy is that ITI supported programmes have three options with respect to the treatment of pregnant women.
  – 1. Provide pregnant women with treatment by Zithromax (after the first trimester).
  – 2. Provide pregnant women with an alternative treatment, e.g. tetracycline eye ointment.
  – 3. Provide pregnant women with counseling to receive treatment as soon as possible post partum.

• Children aged 6 months to 5 years (or those weighing less than 15 kgs) should receive Zithromax POS. Children over the age of 5 years who can swallow tablets should receive Zithromax tablets. Dosages are according to height (dosing stick).
Summary AZM Safety

• AZM is safe and effective and has been administrated to millions of people in trachoma endemic areas.

• **The AEs are mainly abdominal discomfort and skin rushes, but they are self-limited.**

• AZM should be preferably taken after meal.

• Co-administration of AZM with other PC drugs is not yet recommended.

• Pregnant and lactating women can be treated with AZM after the first trimester.
Co-administration Safety: PZQ and ALB

- Million of doses have been distributed with negligible side effects (no more than PZQ alone)

Review article

Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics

A.D. Dayan *

Double-Blind Placebo-Controlled Study of Concurrent Administration of Albendazole and Praziquantel in Schoolchildren with Schistosomiasis and Geohelminths

G. R. Olds, C. King, J. Hewlett, R. Olveda, G. Wu,

* Case Western Reserve University, Cleveland, Ohio; Research Institute

The Journal of Infectious Diseases 1999;179:996-1003

Available online at www.sciencedirect.com

SCIENCE DIRECT

Acta Tropica 86 (2003) 141–159

ACTA TROPICA

www.elsevier.com/locate/actatropica
Co-administration Safety: PZQ, IVM and ALB

• Triple drug administration (TDA) has been carried out in Nigeria, Zanzibar, and Uganda.
  • **Nigeria**: TDA of 5084 people. Passive surveillance 7 D later: 1.1% mild AEs.
  • **Zanzibar**: TDA of 5000 people with active (D 7) and passive surveillance (D 1-2): about 10% mild AEs. Then 6° rounds of MDA on 700,000 people with passive surveillance: 1.4% transient AEs.
  • **Uganda**: randomised trial on 235 primary school children, TDA versus control, monitoring liver function and active surveillance. No difference in AEs.

** Khalfan, et al., *PLOS NTD*, 2008, 2, e171
Triple Drug Administration (TDA)

- Co-administration of ALB, IVM, and PZQ can be used in areas co-endemic for LF, Oncho, SCH and STH where they have already been used separately and infection intensities are low.
- If MDA has not been performed or infections intensities are high, rounds 1-2 of PZQ should be given separately (at least 1 week) from ALB and/or IVM.
- Surveillance conducted in different endemic areas may strengthen this conclusion and should be implemented where PC with individual drugs has been limited.
- Co-administration with azithromycin is not recommended although a study is underway.
Administering PC Medicines to Young Children
Case Study: UNICEF Report from Ethiopia

- 4 children died in 2006 during deworming due to swallowing problems.
- Children 18, 23, 24 and 32 months old.
- A remote area of Amhara Region, Gondar, SNNPR, and Benj Maji.
- ALB (chewable tab), 200 mg as a half tab, given by parent or HW.
- Investigated by MOH and UNICEF.
- Children crying or forced to take tablets.
- Between 1998-2003, 14 child deaths were reported in the country following Vitamin A administration.
- Cascade training and little supervision of community HWs.
## How Many Children Have a Problem Swallowing?

### Data from Rwanda and Madagascar - 2006

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>No problem recorded + those who had a problem but were still successfully treated on site</th>
<th>Crying</th>
<th>Spitting</th>
<th>Choking</th>
<th>Vomiting</th>
<th>Tablet given to mother to give at home</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>2648</td>
<td>2224 (85%)</td>
<td>187 (7%)</td>
<td>61 (2%)</td>
<td>2 (0.1%)</td>
<td>11 (0.4%)</td>
<td>406 (15%)</td>
</tr>
<tr>
<td>M</td>
<td>1160</td>
<td>1058 (91%)</td>
<td>168 (14%)</td>
<td>46 (4%)</td>
<td>14 (1%)</td>
<td>10 (1%)</td>
<td>102 (9%)</td>
</tr>
</tbody>
</table>

R= Rwanda  
M= Madagascar
Approach of CDD/Health Workers (HWs)

0.1-1% of a campaign treating millions is significant

The approach of CDDs/HWs appears to be the most important determinant affecting the number of children having problems.
• Only chewable deworming tablets should be given to children <5 years of age.
• For children <3 years of age, tablets should be broken and crushed between two spoons, then water added to help administer the tablets.
• Mother/CDD/HW and child should be relaxed, calm, friendly.
• Don’t rush.
• Never force a child to swallow.
• Alternatively a syrup preparation can be used.
• Train CDDs and HWs.
• Give by DOT.

http://www.who.int/wormcontrol/newsletter/PPC8_eng.pdf
Administering PC Medicines to Young Children

- CDD and HWs need to be aware of issues related to administering medicines to children.
- CDDs and HWs should be properly trained in directly observed treatment in MDA and how to respond if an emergency occurs.
- Communities and parents must be informed and advised to avoid the unlikely but possible risk of choking and other AE.
- When possible, the formulation should be a safe oral single dose formulation (e.g. granules, liquid etc.) to replace the tablets currently in use.
Key Issues on Training CDD/HW on PC Safety

• PC medicines used are generally safe.
• AEs occasionally and SAEs rarely occur.
• Proper preparation of communities, health workers, and CDDs is essential for continued community participation in MDA.
• Exclusion criteria MUST be understood by CDDs, HWs, and communities (social mobilization, IEC, health education).
• Resuscitation manoeuvre promptly applied if choking occurs.
• Well-trained personnel & community members can effectively handle concerns of communities and media when AEs occur.
• Continued surveillance and reporting is required.
Rash, Swelling After MDA with IVM & ALB

Investigating Stevens Johnson syndrome:

- Ulcerous lesions of mucous membranes and skin.
- Patient required hospitalization and made a full recovery.

Photo: courtesy of NTD Programme, Ghana
Rash After MDA with IVM & ALB

• Investigated, over one dermatome
• Herpes zoster
• Patient later found to be HIV+
• Coincidental event

Photo: courtesy of NTD Programme, Ghana
**Management of Side Effects of Medicines for Neglected Tropical Diseases**

**Tips for the Drug Distributors**

**Side effects** are any unwanted effects that result from taking any form of medicine. As such people who take medicines used in Mass Drug Administration (MDAs) such as Ivermectin, Albendazole, Mebendazole, Praziquantel and Azithromycin could experience some form of side effects. However, most of these side effects may occur within the first two days and are likely to disappear by the 5th to 7th day after taking the medicines. The side effects may be mild, moderate or severe in rare cases.

**Mild side effects** may cause a little discomfort and do not affect activity and require no treatment. They just require reassurance that the effects will disappear on its own.

**Moderate side effects** might result in some more discomfort and affect activity and require treatment. They often need some pain killers or antihistamines. However, it is advised that they visit the health facility.

**Severe side effects** of this treatment should be reported immediately to the hospital or health facility.

**Management**

Side effects of Ivermectin, Albendazole, Menbendazole and Praziquantel include:

- Itching
- Rash
- Headache
- Abdominal pains
- Nausea
- Vomiting
- Diarrhoea
- Swellings
- Weakness
- Drowsiness
- Sores of the skin and mouth

**Mild Side Reactions**

Reassure person and encourage Rest

**Moderate**

Reassure person, may need pain killers or Antihistamines

**Severe**

Refer person to the health facility immediately
What are the key messages from this session?
Key Messages

- AEs of PC drugs are mild and transient.
- Awareness of exclusion criteria by CDDs, HWs, and recipient communities is essential for AE/SAE prevention and management.
- MDA should be prepared with care in areas covered for the first time where heavily infected individuals and AEs more likely.
- PZQ is best taken after food and water.
- TDA (BZ+DEC+PZQ) may be possible but not in treatment naïve communities, and more evidence should be gained.
- Children should never be forced to swallow tablets.
- CDDs and HWs should be properly trained in identification and competent management/referral of AEs/SAEs.