THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH AND SOCIAL WELFARE

GUIDELINES FOR ASSURING SAFETY
OF PREVENTIVE CHEMOTHERAPY

NATIONAL PROGRAMME FOR CONTROL OF NEGLECTED TROPICAL
DISEASES (NPCNTD)

&

TANZANIA FOOD AND DRUGS AUTHORITY (TFDA)

First Edition

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<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<td>CDD</td>
<td>Community Drug Distributors</td>
</tr>
<tr>
<td>CORP</td>
<td>Community Owned Resource Personnel</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-Governmental Organization</td>
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<tr>
<td>NPCNTD</td>
<td>National Program for Control of Neglected Tropical Diseases</td>
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<tr>
<td>NTD(s)</td>
<td>Neglected Tropical Disease(S)</td>
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<tr>
<td>MDA</td>
<td>Mass Drug Administration</td>
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<tr>
<td>MSD</td>
<td>Medical Stores Department</td>
</tr>
<tr>
<td>MoHSW</td>
<td>Ministry of Health and Social Welfare</td>
</tr>
<tr>
<td>NIMR</td>
<td>National Institute for Medical Research</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>TFDA</td>
<td>Tanzania Food And Drugs Authority</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Foreword

These guidelines for assuring safety of preventive chemotherapy have been developed by the Ministry of Health and Social Welfare through the Tanzania Food and Drugs Authority (TFDA) in collaboration with National Programme for Control of Neglected Tropical Diseases (NPCNTD). The World Health Organisation (WHO) facilitated the development of the guidelines.

The guidelines provide information for safety monitoring system of medicines used for neglected tropical diseases (NTDs). It offers practical advice for establishing national mechanism for: prevention of adverse events (AEs) and serious adverse events (SAEs); the objectives of safety surveillance; reporting, investigating and responding to SAEs and a communication strategy on preventive chemotherapy safety to the public and the media.

This document is organized in three parts which includes a section on Adverse Events and Serious Adverse Events monitoring, Management of Serious Adverse Events and establishment of a Safety Surveillance Programme.

The edition will be modified whenever necessary depending on discoveries of any new potential scientific information regarding mass drug administration particularly on the interventional medicines.

The guidelines will be used as a guiding tool on assurance of safety of preventive chemotherapy by Programme Managers, Coordinators, National Preventive Chemotherapy Safety Committee, District Supervisors, Frontline health workers and Community leaders in handling safety information in preventive chemotherapy.

It is therefore anticipated that mass drug administration will be conducted while maintaining safety matters of medicines and participants as outlined in this document.

Regina L. Kikuli
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Dr. Donan Mmbando
Acting Chief Medical Officer
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Glossary

In the context of these guidelines, the following words/phrases/terms are defined as follows

*Adverse event or experience*
Any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment. The basic point here is the coincidence in time without any suspicion of a causal relationship.

*Adverse reaction*
A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man. In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).

For the purpose of this document, an adverse reaction can also be the consequence of a medicine's efficacy in killing parasites.

*Cluster*
Two or more cases of the same or similar event related in time, geography, and/or medicine administered. National programme managers should decide upon a more precise and locally meaningful definition.

*Management of adverse events following preventive chemotherapy*
A set of policies and measures aimed at ensuring preventive chemotherapy safety based on detecting, reporting, investigating, and responding to serious adverse events and clusters of adverse events, and to the concerns they generate in the affected communities.

*Preventive chemotherapy*
Regular, systematic, large-scale interventions involving the administration of one or more medicines to selected population groups with the aim of controlling NTDs such as lymphatic filariasis, onchocerciasis, schistosomiasis, trachoma, and soil-transmitted helminthiasis.

The aim, and greatest challenge challenge of preventive chemotherapy, is to extend regular drug coverage as a public health intervention to reach all individuals at risk of the morbidity caused by selected NTDs.

For the purpose of this document, preventive chemotherapy will also mean mass drug administration.

*Preventive chemotherapy safety*
The public health practices and policies dealing with the various aspects of the correct administration of medicines in large-scale preventive chemotherapy. The term encompasses the spectrum of events from proper manufacture to correct
administration. The term includes both the safety of the operational aspects of interventions as well the safety of the medicinal product itself.

**Preventive chemotherapy safety surveillance**
A system for ensuring preventive chemotherapy safety through the proper management of adverse events. Preventive chemotherapy surveillance requires ad hoc reporting pathways and response mechanisms which are not usually present in a typical pharmacovigilance system

**Safe intervention management practice**
The public health and operational practices and policies which ensure that the process of administering medicines for the control of NTDs carries the minimum of risk, regardless of the specific purpose of the intervention or the medicinal product(s) used.

**Serious adverse events**
Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/ incapacity, or is life threatening. When event has caused Cancers and congenital anomalies or birth defects should also be regarded as serious. Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious.

**Side effect**
Any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological proprieties of the drug. Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended, and that there is no overt overdose.

**Surveillance**
The systematic collection of information on disease and use of medicines in preventive chemotherapy interventions that is analysed and disseminated to enable public health decision-making, action to protect the health of populations, and to ensure the safety of preventive chemotherapy interventions.
Introduction

Neglected diseases are a group of tropical infections which are especially endemic in low-income populations in developing regions of Africa, Asia and the Americas. The impact of these diseases as a group is comparable to known diseases of public health importance such as malaria and tuberculosis. Some of these diseases have known preventive measures or acute medical treatments which are available in the developed world but which are not universally available in poorer areas.

Mass drug administration is the most commonly known method for chemoprophylaxis against neglected tropical diseases. However the intervention needs systematic monitoring as it can cause adverse reactions and events to the population.

Programme coordinators and managers may be asked questions like these:

- Have you effectively sought and found information on possible adverse drug reactions (ADR) that might occur during the intervention?
- What measures have you put in place to manage adverse events (AE) during the intervention?
- Have you prepared your staff for serious adverse events (SAE) before the start of the intervention?
- Is an effective training system in place from national to community level to cope with all levels of AE?
- How will target communities be informed that there is always a small health risk as well as a big health benefit with the use of medicines?

This document aims to help coordinators and programme managers to answer questions like these with particular emphasis on the management of SAE following preventive chemotherapy using one or more of the following medicines Albendazole, Azithromycin, Ivermectin and Praziquantel.

An expansion of preventive chemotherapy programmes will lead to more AE, including more ADR, more coincidental AE and, possibly, more operational errors. It will also lead to more SAE, which are of particular concern because they may cause unjustified opposition to preventive chemotherapy.

Management of SAE requires effective reporting and investigation. It can lead to the identification and correction of operational errors, and may help to distinguish a coincidental AE from an ADR actually caused by the medicines used.

Surveillance of AE is an effective means of monitoring preventive chemotherapy programmes safety and contributes to their credibility. It allows for proper management of SAE and avoids inappropriate responses that can create a sense of crisis.
1. ADVERSE EVENTS (AES) DUE TO MASS DRUG ADMINISTRATION (MDA)

AEs can be caused by the action of the medicine or by an operational error, or be coincidental events that are not due to the medicine(s) or the MDA activities but are just temporally associated with it.

For the purpose of this document, AEs are classified into five categories:

a. Adverse reaction to medicine: ADR caused directly by the medicine(s) used in the intervention;

b. Adverse reaction due to the destruction of parasites killed by the drug - AEs (often considered ADR) that are the consequence of the death of parasites upon the action of the medicine(s);

c. Operational error - Errors and accidents in treatment procedures, logistics, or medicine manufacturing, handling, or administration;

d. Coincidental event - Event unrelated to the medicines or preventive chemotherapy procedure but with a temporal association with the intervention;

e. Unknown cause - Cases in which the cause of an AE cannot be determined.

Table 1 presents a summary of information about the first three categories of AEs. It focuses only on selected medicines used in MDA interventions, namely: Albendazole, Azithromycin, Ivermectin, and Praziquantel.

1.1 Reactions to the drugs

As already mentioned, only very mild adverse reactions have been reported for Albendazole, Azithromycin, Ivermectin, and Praziquantel when used in single dose in MDA (preventive chemotherapy). Patients should be warned that Praziquantel may cause dizziness or drowsiness. However detailed information should be sought in the leaflets accompanying the medicinal products and TFDA.

1.2 Operational errors

Operational errors result from errors and accidents in treatment procedures, logistics, or drug manufacturing, handling (including the risk of counterfeit drugs finding their way into the legitimate distribution channels), or administration. It is very important to prevent operational errors because they may jeopardize the credibility, acceptability and benefits of preventive Chemotherapy. The identification and correction of operational errors are of great importance.

An operational error may lead to a single adverse event or to a cluster of adverse events (i.e. the same adverse event appearing several times in the course of the same intervention). Clusters of events can be associated with a particular supplier, geographical location, a single batch of medicine that has been inappropriately
manufactured or handled, or a single medicine container that has been contaminated or otherwise inappropriately handled.

An operational error
In a village of country A, 2 children choked to death on a tablet of medicine B. This event caused a strong feeling of shock and anger in the affected community and declarations against any further preventive interventions, including immunizations. After investigating the case it was found out that the village worker who had been trained for administering the drugs was sick and could not participate in administering the medicines to the children. A village resident, who had not been trained nor involved in similar activities, volunteered to administer the medicines and forced the children to swallow the tablets without any consideration to the fact that in some cases children were simply unable to do so.

To avoid operational errors the following principles should be applied:

- Medicines should be procured from suppliers holding a valid marketing authorisation issued by TFDA or prequalified through appropriate procedures.

- For donated products, NTD coordinators and TFDA should make sure batches are tested for quality assurance before approval for administration purposes.

- National programme coordinator should provide information on proper way of handling and administration of medicines. They are responsible in providing enough information on:
  - inclusion and exclusion criteria for preventive chemotherapy,
  - special care that is required for administering medicines to young children and to populations that are naive to the drug being used or are at risk of being co-infected by parasites whose destruction may lead to serious adverse events,
  - how to react to aspects of interventions that are not proceeding as originally planned,
  - how to manage expected adverse reactions.

1.3 Coincidental events

A coincidental event is an adverse event that happens during or immediately after a MDA. In certain cases such events are falsely attributed to the drug(s) used in the intervention. When treating large numbers of people, there is a fair chance that any event taking place immediately after the preventive chemotherapy intervention may be falsely considered to be 'caused' by the intervention.
In addition, MDA involve populations living in remote areas, which are frequently affected by infections and other illnesses and inadequately covered by health facilities. It is therefore possible that many events, including deaths, be falsely attributed to the medicines used in preventive chemotherapy interventions.

A coincidental event
In a little town of country C, a 10 years old boy developed serious neurological symptoms and died two days after mass administration of medicine D at the child’s school. Medicine D can cause the symptoms observed in the child. The parents and the community attributed this death to the administration of medicine D. After investigating the case it was found that the boy had had neurological symptoms on 2 occasions in the months before the mass drug administration campaign and that he was not at school the day on which medicines were administered to all children.

The actual number of coincidental deaths depends on specific local factors such as population size, population-specific mortality rate, and intervention coverage. It is important to compare expected (if such information were available) versus actual events through appropriate statistical analysis to ensure that differences, if any, are not simply the result of chance.

Often, coincidental events are clearly unrelated to the preventive MDA and should not require a thorough investigation. However, certain serious events may be blamed on the intervention by relatives or other members of the community because of the close temporal association with it, especially if the person affected was previously healthy. Investigating such cases is very important to enable programme managers/ coordinators to respond to a community’s concerns, to dissipate public fear and maintain the credibility of and confidence in preventive chemotherapy interventions.

When investigating a case it could be useful to calculate the expected rate of a specific event and to find out if the same or similar adverse event also affected, around the same time, others who are in the same age group but have not been treated with the same medicine(s).
Table 1 – Summary of Adverse events that may occur during preventive chemotherapy to control morbidity associated with NTDs

<table>
<thead>
<tr>
<th>Type of adverse reaction</th>
<th>Specific drugs</th>
<th>Clinical presentation and direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Adverse reactions to the medicine</td>
<td>Azithromycin, Albendazole, Ivermectin and Praziquantel</td>
<td>Reactions are generally mild and self-limiting, especially when used in single dose for preventive chemotherapy. However, detailed safety information can be sought in the leaflets accompanying the medicinal products, the TFDA and the manufacturer.</td>
</tr>
<tr>
<td>b) Adverse reactions due to the destruction of killed parasites</td>
<td>Ivermectin in patients with heavy Loa loa infection</td>
<td>The use of ivermectin in areas where Loa loa is endemic should be based on appropriate epidemiological assessment. Effect of ivermectin in patients with onchorcearsis and filariasis</td>
</tr>
<tr>
<td></td>
<td>Albendazole in patients with heavy Loa loa infection</td>
<td>Albendazole is not contraindicated in areas with loaiasis.</td>
</tr>
<tr>
<td></td>
<td>Praziquantel in patients with neurocysticercosis (especially those with hydrocephalus and parenchymal brain cysts)</td>
<td>Fever, meningism (headache, photophobia, neck stiffness), intracranial hypertension (occasionally fatal), seizures.</td>
</tr>
<tr>
<td></td>
<td>Albendazole in patients with neurocysticercosis</td>
<td>Same as praziquantel</td>
</tr>
<tr>
<td></td>
<td>Praziquantel in patients with ocular cysticercosis</td>
<td>Destruction of the parasite may cause severe eye damage. Praziquantel should not be used in patients with ocular cysticercosis</td>
</tr>
<tr>
<td></td>
<td>Albendazole in patients with heavy ascariasis infections</td>
<td>Worm migration to and occasional expulsion through nose or mouth.</td>
</tr>
<tr>
<td>c) Operational errors</td>
<td>Choking from large tablets and vomiting</td>
<td>Anxiety reactions (e.g. clusters of vomiting episodes), especially in children, that arise from the fear of treatment</td>
</tr>
</tbody>
</table>
As shown in the table, the information available on all these medicines indicates an excellent safety profile when used in single dose in preventive chemotherapy. Rarely, SAE, i.e. death, hospitalization, or other severe and unusual events that are thought by health workers or the public to be related to the medicines used in the preventive chemotherapy can occur and cause concerns in the affected community. Available information suggests that SAEs are invariably related to the destruction of parasites killed by the medicine. For this reason, interventions should be prepared with special care in areas that are being covered for the first time and where, therefore, it is more likely to find heavily infected individuals.

2. PRECAUTION TO ENSURE SAFE IMPLEMENTATION OF LARGE-SCALE PREVENTIVE CHEMOTHERAPY

2.1 General precaution

The following general precautionary measures are recommended to ensure safe implementation of large-scale preventive chemotherapy.

- Seriously ill individuals (people unable to engage in the normal activities of daily living without assistance) should be excluded from large-scale antihelmintic and antibiotic treatment.

- Precautions should be taken when administering drugs to pregnant women and lactating mothers; some drug combinations are contraindicated in pregnancy, and WHO guidelines should always be observed.

- The NTD Coordinator and Programme Managers must ensure that people who are about to receive medicines are adequately informed about possible ADRs and about what they should do if an AE appears. In particular, the persons who administer medicines should be adequately prepared for the exercise and capable of explaining to community members - in a language they can understand - possible ADRs and what should be done if an AE appears.

- People who have previously suffered one of the rare serious ADR in conjunction with the use of the same medicines should be excluded from large-scale antihelmintic treatment.

- Programme Managers must ensure that care and support are available for individuals who experience AEs. It is important that medical or community health personnel are available throughout the rounds of treatment.

- Any SAE should be reported following national guidelines. An example of a reporting form for SAEs is provided in Appendix A.

- Scored tablets should be broken into smaller pieces, or crushed, for administration to young children and older children should be encouraged to chew tablets of Albendazole or Mebendazole.
• Forcing very small children to swallow large tablets may cause choking or asphyxiation.

• Programme managers should try and coordinate interventions on NTDs with other initiatives that are distributing medicines or vaccines in the same areas targeting other diseases. However, when coordinated action is not possible, the fact that medicines or vaccines are being distributed by different programmes should be taken into account when investigating SAEs.

2.2 Special precautions

There are special precautions to be considered during mass drug administration in risk groups.

2.2.1 Use in pregnancy and lactating mothers

Special considerations must be made concerning women of reproductive age and pregnant women. There is no enough information on the usage of these drugs in pregnancy thus pregnant women must be informed that they have the right to refuse or delay treatment and programme managers/coordinators must ensure that treatment is subsequently available to women who choose to exercise this right. In areas where schistosomiasis and soil-transmitted helminthiasis are endemic, risk–benefit analysis have revealed that the health advantages of treating women of reproductive age and pregnant women far outweigh the risks to their health and to the health of their babies. The benefits of treating pregnant women include reduced maternal anaemia and improved infant birth weight and survival. The proven benefits of antenatal deworming in the absence of any data indicative of drug teratogenicity or embryotoxicity in humans provides compelling evidence to support the treatment with albendazole of women for soil-transmitted helminthiasis after the first trimester of pregnancy.

Available evidence also shows that women can be treated with praziquantel at any stage of pregnancy and during lactation. No increased rates of preterm delivery or abortion have been observed in pregnant women treated with praziquantel in mass drug administration intervention. Praziquantel is distributed into breast milk. Programme managers/NTD coordinators should take this into account and decide on the best advice to give breast feeding mothers in the specific context of their interventions.

Although there is no evidence that ivermectin is not safe in pregnancy, the number of studies is limited and this drug has been largely used in areas where drug safety monitoring is not fully developed. There is therefore not enough safety information regarding their use in pregnancy. For this reason, it is prudent to consider that pregnant women are not eligible for treatment with ivermectin (either alone or in combination with other drugs) in MDA against lymphatic filariasis and/or onchocerciasis. In addition, ivermectin should be given to lactating women only when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.
2.2.2 Use in Young Children

Albendazole has not been extensively studied in children under 2 years of age. WHO suggests that a reduced dose of 200 mg of albendazole in children between 12 and 24 months of age may be used in the presence of risks from adverse consequences caused by soil-transmitted helminths. Millions of children have been treated in mass deworming interventions with adverse events occurring in only up to 1% of treated children, chiefly mild gastro-intestinal symptoms.

3. APPROACH TO MANAGEMENT OF SERIOUS ADVERSE EVENTS

3.1 Communicating information of known Adverse Events and Serious Adverse Events

During preparation of MDA health care providers and community volunteers should inform the community the objectives, expected benefits as well as known AEs and SAEs that may occur during intervention. They should make sure the targeted community is well motivated especially all at-risk individuals to accept treatment.

In developing such communication it is essential to ensure that staff and communities are aware of and know how to manage possible adverse events. At the same time, the message should not scare or make them uncomfortable about the mass treatment intervention.

Possible aspects to be addressed in communicating about known AE include the following:

- Stress that events will be minor and preventive chemotherapy is highly beneficial.
- Minor reactions such as nausea, vomiting, diarrhoea or fatigue are very transient and can be managed with traditional inexpensive remedies.
- A serious event may happen at the same time or immediately after the treatment, but an event of the same kind may have already happened before the treatment was started, may happen again and should not be falsely attributed to the treatment.

Communication about SAEs should mainly target health workers and provide practical hints on where and how to refer patients to appropriate care levels.
3.2 Proper Preparation of MDA and Timely Management of SAEs

As mentioned earlier, most, if not all, SAEs associated with drugs used in MDA, occur in patients with heavy infections or co-infections and are the consequence of the destruction of parasites. For this reason, prevention of SAEs is largely dependent on proper preparation of interventions, careful application of criteria for excluding people from treatment, and prudence when expanding treatment coverage to populations never treated before.

However, SAEs will inevitably occur and it is therefore necessary to embed drug safety surveillance in MDA. This means that interventions should be designed, prepared and organized in such a way that SAEs and all AEs that worry communities are adequately investigated, lessons are learnt, and feedback is provided to the affected communities. In addition to establishing a surveillance system, it may be necessary to add specific operational procedures to preventive chemotherapy. For example, measures should be taken to ensure that, at all steps from MSD (Central storage) to the peripheral staff (community drug distributor), information that identifies the specific medicinal products is recorded, even when the drugs are not distributed in their original container (e.g. brand name, batch and any other identification number, date received, and dates used).

3.3 Treating affected patients

Symptoms of AEs and SAEs encountered in conjunction with preventive chemotherapy are not unusual or special and do not require unusual treatment. Nonetheless, preparatory work must be undertaken and guidance (and, possibly, supplies) provided to all concerned health staff and facilities to ensure proper care
for patients. Most symptoms are mild and transient and can be satisfactorily treated as per standard of care available.

4. RESPONDING TO SAEs

Response is based on four complementary approaches:

- Providing care for those affected by the AE (regardless of the fact that their illness has actually been caused by preventive chemotherapy),
- Establishing the facts,
- communicating with the affected communities as well as those that may be concerned, and
- Fixing the problem when the AE was caused by operational error.

4.1 Providing care

Health workers at all levels need to know how to recognize and treat mild AEs. National programme managers should prepare ad hoc guidance for health workers to be prepared to treat or refer affected patients, and to report SAEs.

4.2 Establishing the facts

Before responding to a reported situation it is essential to establish the facts and base any further action on solid and accurate knowledge of the situation.

4.3 Communicating with the communities

As mentioned above, when a community experiences adverse events and this generates concerns about the safety of a preventive chemotherapy intervention, it is necessary to undertake an investigation. Usually, it is not necessary to discontinue the intervention while awaiting the completion of the investigation. One of the most important aspects of communication with communities is to establish trust in preventive chemotherapy and those who manage it. Before an investigation is completed there should not be premature statements or overconfidence about risk estimates. If these are later contradicted by the results of the investigation the breakdown of trust would be very difficult to heal. Until the investigation is ongoing, it is important to admit uncertainty, investigate honestly and fully, and keep the community informed of the activities being undertaken.

In communicating with communities, it is extremely important to ensure that information is rapidly disseminated and this is best achieved through direct and privileged links with community leaders and frontline workers. These lines of communication between investigators and concerned communities must be kept throughout the investigation.

Sometimes an operational error is identified as the cause of an AE. In these cases, it is essential not to put blame on anyone and to put the stress on a) the systematic problems which have made the operational error(s) possible, and b) the steps that are being taken to correct the problems.
4.4 Messages before the investigation has come to an end

The following points should be considered when developing messages to address concerns about a medicine or treatment approach when communicating with communities and the media:

- Provide statements on the known benefits of preventive chemotherapy, the uncertainty of the causality of the adverse event(s), and the certainty of the disease in the absence of preventive treatment

- Operational errors or coincidental illness are much more likely since reports of serious adverse events caused by the medicines used in preventive treatment are very rare.

- That appropriate action is being taken to safeguard the public.

The conclusions reached by the investigators on the cause of the event(s) must be communicated to the community. At the same time, information should be provided about the steps being taken to remedy the situation and to prevent a recurrence, if such steps are needed. The following points may help developing messages after the end of the investigation/assessment:

a) If the AE has been caused by the medicine(s) (i.e. is an ADR) and appeared at the expected rate
   - the benefits of preventive chemotherapy outweigh the adverse events it causes

b) If the AE has been caused by the medicine(s) (i.e. is an ADR) and appeared at higher than expected rate
   - the problematic batches should be withdrawn from the MDA
   - Manufacturing specifications or quality control procedures should be reviewed and National Coordinator should give feedback to donors.

c) If the AE has been caused by operational error
   - the causes/source of the error should be corrected immediately (e.g. change in logistics the logistics for supplying medicines; change in procedures at treatment sites; further training of relevant staff; intensified supervision);
   - Corrective measures will be reviewed immediately to insure errors have actually been corrected.

d) If the AE is coincidental
   - There should be convincing evidence showing that the event truly was coincidental.
   - Involve key personnel such as medical personnel, community leader and security system organs reviewing investigation process and conclusions and seek their help to convince/ensure that the event truly was coincidental.
e) If the cause of the AE is unknown

- a further investigation by additional experts may be needed;
- It must be accepted that in some cases the cause-effect relationship between adverse events and medical treatment remains unclear.

4.5 Communicating with the media

The effectiveness of communication depends on audience's perception on MDA credibility. Trust and credibility are difficult to achieve; if lost, they are extremely difficult to regain. When establishing relations with the media, the key following factors that can establish and strengthen MDA credibility should be taken into account:

- Empathy and caring;
- Competence and expertise;
- Honesty and openness;
- Dedication and commitment.

Before any media contact it is vital to prepare:

- Key messages;
- Answers for the likely and awkward questions;
- Identifying which issues not to respond to (e.g. blaming an individual or speculating on the cause before the investigation is complete).

The key messages should be kept to a minimum and are likely to include some of these facts:

- Benefits of preventive chemotherapy are well proven;
- It is very risky not to carry out preventive treatment;
- Preventable neglected diseases caused millions of death and/or disability before the introduction of preventive chemotherapy, and that situation would return without continued use of preventive treatment with effective medicines;
- Medicines do cause reactions, but these are rarely serious and hardly ever cause long-term problems (if feasible, provide a list of known adverse reactions);
- Preventive chemotherapy safety is of paramount importance, and any suspicion of a problem is investigated through a well established safety surveillance system;
- The AE is currently being investigated, but the medicines' quality is guaranteed (provided this is true) and the treatment intervention must continue to keep the population safe from disease;
- Action is being taken (describe what is being done).
It is essential to present information to the media in a credible way. This entails being:

- Honest: never lie; if you do not know, say so, but promise to find out (e.g. “We don’t know at this time, but we have taken steps to answer that question”); note that a lie or cover-up can become a bigger news story than the initial event;

- Caring: create a strong, compassionate, competent image for yourself and the preventive chemotherapy programme;

- Clear: avoid jargon; use simple phrases and give examples to clarify meaning;

- Serious – jokes can be disastrous and the subject is rarely amusing anyway;

- Aware of body language: it is of critical importance in perceptions;

- Responsible: don’t be defensive, but accept responsibility appropriate to your position and avoid blaming someone else (e.g. “We will see if there is any truth in the report.”);

- Responsive: hold a daily press conference if that is what is needed to meet the needs of the public and media; regular contact helps build a trusting relationship with the media;

- Positive: reframe the situation in positive terms; use terms such as vaccine safety (which has a positive connotation) rather than adverse event

When facing a hostile interviewer, prepare these techniques:

- Block: respond to a negative question with a positive answer (e.g. when asked, “How many children have died from preventive treatment?”), answer: “Preventive chemotherapy saves lives. Since our programme began X children have been treated, and of them Y% might have died from one of these diseases. That is the context in which we must consider the tragic, but thankfully rare adverse events which follow preventive chemotherapy.”

- Bridge: having answered a difficult question, move quickly to something linked but positive;

- Correct what is wrong: immediately correct information from the interviewer that is wrong. Be assertive, not aggressive and state the facts simply, factually and in a friendly way;

- Stay cool: no matter how bad it gets, don’t get angry or defensive; stay friendly, polite and warm;
• Be assertive: means stating what you want to say in a clear way without getting aggressive; take time to think about the response and don’t be rushed or forced.

Needless to say, all those who sit in a press conference will have to be prepared to show unity of intent and approach, and this also requires previous discussion and agreement. Media conferences must be very carefully prepared or risk to do more harm than good. Preparation for a press conference includes at least the following:

• The messages to be communicated should be written down and kept under the eyes of all spokespersons;

• The spokesperson(s) (one for each participating institution/organization);

• An information kit for all reporters and other participants that includes:
  □ a press release with all the essential facts and messages;
  □ background information on the diseases targeted by the preventive chemotherapy initiative and the benefits/expected benefits of the initiative;
  □ a list of possible questions that have been or are likely to be asked by concerned members of the public, with their respective answers;
  □ agreed standardized statements to answer unexpected questions that have not been discussed among the institutions/organizations participating in the press conference.

Media interest is usually greatest at the beginning of or even before an investigation, when rather little is known. At this time rumours can spread and do much harm to the preventive chemotherapy approach. For this reason, a media conference should be organized as early as possible, even if there is very limited information to give. This will limit the circulation of rumours and build a relationship with journalists. At the end of each press conference, a further conference can be announced within a suitable number of days. Keeping regular contact with the media helps creating confidence and contributes to prevent 'scoops'.

4.5.1 Preparing a press release

When dealing with the media, it is extremely useful to prepare materials in advance. Statements for the press or press releases should include information on the following aspects:

• A description of the events and their context (e.g. an isolated event, a coincidental event, etc.) using terms and concepts that can be understood by people who are not familiar with health services or disease patterns; the language should aim at limiting the possibility of projecting the specific event onto the entire preventive chemotherapy approach;

• Whether or not the adverse event is still ongoing, i.e. new cases are still appearing;

• Actions taken or planned (depending on the stage, this may range from a plan of action to a completed investigation);
• The cause of the event (when identified with reasonable certainty);
• The corrective action that has been or will be taken.

Media are important in addressing communities' concerns about preventive chemotherapy and public health in general. Balanced reporting, where two opposing expert opinions are given, is often an essential way for reporters, who do not possess detailed critical knowledge themselves, to indicate that there may be uncertainty in a situation. Such uncertainty is common in science. In public health, decisions will often need to be made on serious matters affecting health when some uncertainty exists and such decisions are based on a balance of probabilities between a good and bad outcome; decisions may also need to be made where information is incomplete. Acknowledging uncertainty does not make an easy message, and every effort is needed to ensure that reporters and editors accurately represent the dilemma, and what is being done to resolve it (such as review at a later date, collecting better information, seeking other expert opinion).

For all the above reasons it is good to be proactive with the media, positively seek them out with good stories and make yourself known to key reporters/editors: they need good, positive stories as well as negative crises. So, communicating with the media requires some knowledge and understanding of their needs.

The response of the health system to any concern about preventive chemotherapy safety must be seen to be compassionate and, at the same time, highly professional with careful investigation of the problem. Spokespersons (and other staff even more) should avoid improvisation and casual remarks. They should always emphasize the rationale and the proven benefits of preventive chemotherapy and to avoid dwelling on negative examples. One approach is to avoid, as much as possible, to use negative terms such as 'adverse event' but rather turn phrases to use 'preventive treatment safety'.

4.5.2 Holding a media conference

Responding to public concerns includes disseminating information through mechanisms such as a media conference or a press release. They provide all journalists the same access to the information and this reduces the risk of 'exclusive' reports that tend to fall into sensationalism. Professional organizations and NGOs should join governmental institutions in press conferences to increase the credibility of messages and show their support for preventive chemotherapy and the efforts to investigate a problem

4.5.3 Fixing the underlying problem in the case of an operation error

An investigation may eventually lead to identify an operational error as the main cause of an AE. This needs to be made widely known so that others can also learn from the experience. The investigation itself may be used as a teaching resource in training investigators in the future. However, it is essential that operational errors be corrected and that a checking mechanism be implemented to ensure that they don't happen again. The media should be informed about the solution and outcome.
When the cause of an AE is an expected adverse reaction or when the investigation points to a coincidental event, the main task for programme managers is communication.

5. REPORTING SERIOUS AEs

5.1 What events should be reported?

Unless otherwise established in National Policy, only SAEs should be reported. This should include at least: any death, hospitalization, or other severe and unusual events that are thought by health workers or the public to be related to the medicines used in the preventive chemotherapy intervention and cause concerns in the affected community.

Some events, even when not serious (e.g. choking on tablets without dramatic consequences), are indicators of the quality of the intervention or of operational error, and should be reported.

Examples of serious Adverse Events include:

- Any hospitalization
- Death
- Anaphylactic Reaction
- Mazzotti Reaction (fever, urticaria, swollen and tender lymph nodes, tachycardia, hypotension, oedema, joint and abdominal pain)
- Fits, convulsion, and seizures
- Choking

People receiving preventive chemotherapy should also be given advice on effective ways to seek medical attention if a serious event occurs or mild symptoms do not disappear. It is also important for preventive chemotherapy interventions to be prepared to provide care for a coincidental illness falsely considered to be an adverse event.

Adverse events that, although not matching the criteria for serious adverse event, occur in clusters (e.g. most school-age children develop diarrhoea within 24 hours of treatment) should be reported and investigated.

5.2 Who should report?

Detection and reporting of AEs should be, primarily, the responsibility of:
- Village health workers, teachers and Community drug distributors administering medicines in preventive chemotherapy interventions;
- Frontline health workers providing clinical treatment of AEs in health facility;
- Relatives/parents who report AEs affecting members of their family;
- Researchers conducting clinical studies or operational research.
5.3 When to report?

SAEs and cases of serious community concern should be reported as soon as possible. A report should trigger an immediate decision on the need for action and investigation. In some situations and in cases with a high level of community concern, an urgent phone call to the appropriate focal point is probably the most effective way of getting the information up the safety surveillance system.

5.4 How to report?

Reports should be made on a standard Report Form (Appendixes A). A phone call to a more central office where trained staff can complete the form may be a more practical option for peripheral staff. Reporting needs to be kept simple (Appendix A) to ensure that all essential information becomes quickly available and a decision on the need for further investigation can be made.

The minimum essential information that should be obtained from w person experiencing AE or care taker includes;

- Description of the event (national programmes may develop case descriptions of the expected serious adverse events to simplify the task of peripheral staff).
- Time/date of appearance of the event and time/date of medicine(s) administration.
- Medicine(s) given (brand, batch number, original/non-original container).
- Site of treatment and name/contact of person(s) who provided treatment and
- Affected person’s identifying details (name, age, gender, contact information).

Reports concerning SAEs received at the appropriate reporting centre should also be provided to TFDA and the concerned manufacturer(s) of the medicine(s).

5.5 How to overcome under-reporting?

The following points need to be carefully considered in order to overcome under-reporting

- increasing awareness of the importance and benefits of reporting;
- ensuring proper understanding of the system for reporting and making it easy to report, especially in situations in which staff are uncertain about the relevance of an adverse event;
- emphasizing that investigations aim at finding problems and not at blaming individuals;
- involving peripheral staff in the investigation and response to an event;
- giving positive feedback for reporting.
6. INVESTIGATING REPORTED SAEs

6.1 Which reports should be investigated?

The first assessment to conduct is to determine whether or not an investigation is needed. A reported SAE must be investigated if it:

- may have been caused by operational error (e.g. choking);
- is on the national list of events that must be reported;
- is a serious event of unexplained cause;
- is causing or is likely to lead to significant community concern.

The number of adverse events normally increases with the increase in MDA coverage, so it is essential to calculate the event reporting rate on the basis of actual coverage. In the evaluation it is always the rate and not just the number of reports that needs to be taken into account. The investigator needs to determine if there is a real increase in the event rate as well as to identify the cause of the increase. For example, a change in manufacturer or batch can lead to a change in event reporting rate.

It is the role of both national and regional assessor to insure that all reports requiring investigation have been adequately investigated.

6.2 Who should investigate?

Investigations should be done by investigator who have adequate training and resources for the investigation at each major administrative unit (e.g. national, region, or district), depending on situation. Peripheral level investigators should regularly communicate with national level investigators on all AE investigations. The NTD Coordinator is a spokesman for all investigations and no one will be allowed to speak to media on investigation results unless have been permitted do so by coordinator.

6.3 When to investigate?

The urgency of the investigation will depend on the situation. The NTD Coordinator and / or national preventive chemotherapy safety committees should establish criteria that make an investigation urgent as well as deadlines for starting an investigation in relation to its urgency (e.g. Urgent investigations should commence within two working days of the decision to investigate). Once it is decided that an investigation is needed, it should be initiated as soon as possible.

6.4 How to investigate?

Serious AE should be investigated promptly and completely. The investigator will need to look directly at the event as well as gather information (see below) from the affected person (when possible), her/his relatives, health workers and supervisors, as well as community members. A detailed report of the case (Appendix A) should have been finalized as early as possible after becoming aware
of a case. Otherwise, this should be completed at the beginning of the investigation.

A summary of the case and the conclusions of the investigation should be recorded on an AE Investigation Form (Appendix B, which could become useful in other investigations and training activities. Investigations should aim to identify programme problems rather than find individuals to blame.

When an individual may have been at fault, it is more effective to concentrate on changing the operational procedures to avoid the circumstances that permit such errors than to blame or punish any individuals. Such an approach is essential to ensure that AE reports are encouraged. It is also much more likely to improve system performance.

Operational errors are often causes of serious adverse events. Therefore, the investigator should always suspect operational error as the cause and examine the evidence for any errors in the selection of people to be treated as well as in storage, handling, or administration of medicines. Attention can then focus on finding out more about the particular error and taking the necessary corrective action. Even known medicine reactions may in fact, upon investigation, turn out to be operational errors (e.g. dosage mistakes). An investigation may lead to uncover operational errors that are not the primary cause of the AE being investigated.

6.4.1 Adverse Events in a Cluster

A cluster of similar adverse events may be the consequence of operational errors or reflect unusual local circumstances. If the event also occurred in untreated people, it may be coincidental. If all cases received the same medicine brand/batch and there are no similar cases in the community, a problem with the medicine is likely. If the event is known and expected but occurs at an increased rate, an operational error or a medicine problem are possible causes.

Investigation of a cluster requires:

- Establishing a precise description of the event.
- Identifying all the people in the area who have an illness that meets that description.
- Obtaining treatment histories (when, where and which medicines were given).
- Identifying any common exposures among all the cases.
7. **OUTLINE OF AN INVESTIGATION**

An AE investigation follows standard epidemiological investigation principles. In addition, it requires investigation of the specific medicinal product(s) as well as intervention and administration techniques and procedures. The following steps outline a typical investigation:

a) Confirm the information provided in the report and add missing.

b) Check if more than one case should be included in the same investigation and gather and verify basic information on each case:

- Age, sex, place of residence.
- Family history.
- Recent clinical features (e.g. symptoms and signs, when they appeared, duration, results of laboratory and other diagnostic tests, treatment, etc.).
- Type of event (a clear description of the clinical features, date of appearance, duration, and treatment of the clinical event and any investigations done).
- History of the patient (past medical conditions, previous reactions to vaccines or medicines, allergies, pre-existing neurological disorders, medicines recently or currently taken, etc.).
- MDA (Preventive chemotherapy) history: type of medicine(s) taken, date of the last and previous (if any) doses, type of previous reaction (if any).
- In the event of death, full autopsy report (or reason why not available), toxicological screening, and pathological findings.

c) Make a direct examination of preventive treatment site:
• Storage facilities – whether dedicated storage facilities exist and how medicines are stored, what else is stored (note if similar containers are stored next to medicines containers which could be confused); which other medicines are stored in the same place;
• Whether any container is not the original or carries no readable label;
• Ask to be shown treatment procedures, medicine administration technique, how dose is calculated, how water used in administering the medicines is obtained and checked;
• Any (open) container looks particularly dirty? Physical environment compatible with administration of medicines?
• Presence and completeness of records of medicines that are received and used in treatment operations;
• Presence of up-to-date guidelines on medicines handling and treatment procedures;
• Details of staff training (when trained, for doing what, any verification of skills?);
• Number of persons to treat greater than usual?

d) Gather information on the suspected medicine and obtain a sample (preferably from and with the container of the suspected medicine):

• Brand, batch number, expiry date;
• Describe any unusual appearance (broken tablets, unusual tablet colour/shape, etc.);
• Conditions under which the medicine was shipped, its present storage condition, storage of medicine before it arrived at treatment site, where it has come from (who imported, who sent to treatment site & how).
• Prepare a list of sites that have received and used the same batch.

e) Gather information on clinical features of suspected ADR at same treatment site, at other sites and in non-treated persons:

• Who else received the same medicine (same batch) and developed illness?
• Who else received the same medicine (different batch) and developed illness?
• Did anyone untreated with the same medicine have similar illness (see detailed clinical features)? If so, did they take any other medicine(s) before and to treat the illness?
• Population treated with the same batch of medicine in the same period (number at same and at different sites);
• Non-treated population (number at same and at different sites).

f) Formulate a working hypothesis on the likely/possible cause(s) of the event.

g) Test the working hypothesis by checking that it matches on all cases and their distribution and is corroborated by laboratory testing (if applicable).

h) Conclude the investigation:

• Reach a conclusion on the cause of the AE
- Complete AE Investigation Form (Appendix B).
- Take corrective action, and recommend further action.

In general, it is necessary to compare information on cases with information on the prevalence of the same clinical manifestations before MDA and exposure to treatment among controls. Without such comparison it will be impossible to identify the cause of the AE, unless it is a case of operational error. The working hypothesis may change during the course of the investigation. The focus of the investigation should be to seek to confirm the working hypothesis. No action should be taken on the basis of the hypothesis until this is confirmed with reasonable certainty. An AE investigation form (Appendix B) should be completed only at the end of the investigation.

8. **CAUSALITY ASSESSMENT**

The investigation needs to include an assessment on the cause of the AE. Adverse reactions are rarely specific for a given medicine, diagnostic tests are usually absent and a re-challenge (i.e. giving the same medicine again to the patient who has experienced an adverse event) is rarely ethically justified, but it may sometimes happen by chance. In practice the cause of only few adverse events is ‘certain’ or ‘unlikely’; in most cases the cause can be classified as ‘possible’ or ‘probable’. No perfect system to assess causality can produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment must be dealt with.

<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain</td>
<td>Event or laboratory test abnormality, with plausible time relationship to drug intake</td>
</tr>
<tr>
<td></td>
<td>Cannot be explained by disease or other drugs</td>
</tr>
<tr>
<td></td>
<td>Response to withdrawal plausible (pharmacologically, pathologically)</td>
</tr>
<tr>
<td></td>
<td>Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)</td>
</tr>
<tr>
<td></td>
<td>Satisfactory re-challenge procedure, if necessary</td>
</tr>
<tr>
<td>Probable / Likely</td>
<td>Event or laboratory test abnormality, with reasonable time relationship to drug intake</td>
</tr>
<tr>
<td></td>
<td>Unlikely to be attributed to disease or other drugs</td>
</tr>
<tr>
<td></td>
<td>Response to withdrawal clinically reasonable</td>
</tr>
<tr>
<td></td>
<td>Re-challenge not required</td>
</tr>
<tr>
<td>Possible</td>
<td>Event or laboratory test abnormality, with reasonable time relationship to drug intake</td>
</tr>
<tr>
<td></td>
<td>Could also be explained by disease or other drugs</td>
</tr>
<tr>
<td></td>
<td>Information on drug withdrawal may be lacking or unclear</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)</td>
</tr>
</tbody>
</table>
- Disease or other drugs provide plausible explanations

### Conditional / Unclassified
- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

### Unassessable/ Unclassifiable
- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

* All points should be reasonably complied with

For AE, the first three categories (certain, probable, possible) are used for a known medicine reaction, when a previously unknown reaction seems likely (perhaps due to drug interaction) or when an operational error is suspected. Category 4 (unlikely) is when coincidental events are more likely and 5 (conditional) would be used for a situation where an investigation is not yet completed and category 6 (unassessable for AEs where insufficient evidence is provided to make an assessment.

Clinical judgement is crucial in deciding whether or not a medicine is responsible for a particular adverse reaction, but causality assessment must take a number of factors into account. These factors include: nature of the event, temporal relationship, dose relationship, de-challenge and re-challenge.

The following list of questions may help in the assessment of causality:
- What is the frequency of occurrence for this event (common/rare/not previously reported)?
- Are similar events known to occur with other disease?
- Is the event known to be related to this medicine(s)?
- Is the event explainable by the pharmacological properties of the medicine(s)?
- Is the interval between treatment and onset of the adverse event suggestive of causality?
- Has the patient had similar symptoms in the past?
- Was the patient on any concomitant or preceding drug therapy?
- Did the patient have any concomitant or preceding condition?
- Were there any other contributing factors?

The national pharmacovigilance committee and co-opted members from individual programme/ organ have the role of confirming the causality assessments of selected investigations and, where required, assisting investigators to determine causality.

**9. ESTABLISHING PREVENTIVE CHEMOTHERAPY SAFETY SURVEILLANCE**

Effective safety surveillance requires collaboration between the MoHSW (NTD programme), Ministry of Education and Vocational Training, TFDA, Regional, District, Media, NGOs, WHO, Donor Agencies, Partners and community authorities. The preventive chemotherapy safety surveillance system should build
on any existing functioning pharmacovigilance system on the basis of a mutually-
strengthening principle.

9.1 **Goal and objectives of preventive chemotherapy surveillance**

9.1.1 **Goal**

The main goal of establishing safety surveillance is early detection and appropriate and quick response to SAEs in order to mitigate their negative impact on the health of the individuals and on preventive chemotherapy interventions.

9.1.2 **Objectives**

Preventive chemotherapy surveillance has the following objectives

- Detecting, correcting and preventing operational errors.
- Identifying unusually high rates of AE with a specific medicine brand or batch.
- Ensuring that coincidental events are not falsely blamed on preventive chemotherapy interventions.
- Maintaining confidence in preventive chemotherapy interventions through proper responses to community's concerns about medicine safety while increasing awareness about drugs benefits and risks.
- Generating new data and hypothesis about adverse events.
- Support health professionals improve experience and skills.

9.2 **Differences between preventive chemotherapy safety surveillance and pharmacovigilance in general**

Large-scale preventive chemotherapy i.e. MDA implies administering medicines/drugs to healthy people for the prevention of disease and/or administering medicines for the mitigation of the effects of disease in the absence of a specific diagnosis resulting from the clinical assessment of each individual targeted by the intervention. The implementation of these large-scale interventions usually does not rely on the health system alone but involves community leaders, school teachers, NGOs and other members of the civil society that may have no formal links to or previous experience with the health care delivery system.

On the other hand, a typical pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverts effects or any drug related problem (WHO).

Experience in the peculiar settings and an operational aspect of preventive chemotherapy teaches that surveillance of AE cannot rely on reporting all adverse events to a regional/national pharmacovigilance centre. What is required is an ad hoc approach based on a clear definition of **serious adverse events** and the prompt involvement of preventive chemotherapy intervention managing staff in the investigation with the assistance, whenever feasible, of national / regional pharmacovigilance centre staff. Reporting criteria and pathways for large-scale preventive chemotherapy may not be part of the usual reporting scheme for medicines used in a typical patient-health professional interaction. The most appropriate ways to receive, investigate and respond to adverse event reports is likely to be different for large-scale preventive chemotherapy interventions. The investigation and assessment of causality requires an understanding of large-scale
preventive chemotherapy interventions, an assessment of coincidental events and crucially it should also aim to identify and correct operational errors. Finally, the implications of a serious adverse event are quite different in scale for preventive chemotherapy interventions.

9.3 Stakeholders for NTD Safety Surveillance

Safety surveillance during preventive chemotherapy of neglected tropical diseases will comprise of the following parties:

- TFDA
- National Programme Coordinator for NTD control
- Diseases Specific Programme Coordinator
- Regional level Coordinator
- District level Coordinator
- Frontline health workers

Table 4 - Roles and responsibilities of parties to be involved in safety surveillance

<table>
<thead>
<tr>
<th>PARTY</th>
<th>ROLE</th>
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<tbody>
<tr>
<td>TFDA</td>
<td>• Marketing authorization of medicines</td>
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<tr>
<td></td>
<td>• Post marketing surveillance of authorized medicines</td>
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<tr>
<td></td>
<td>• Performing or organizing laboratory tests</td>
</tr>
<tr>
<td></td>
<td>• Inspecting manufacturing, importation, storage and distribution of medicines</td>
</tr>
<tr>
<td></td>
<td>• Providing information on medicines use</td>
</tr>
<tr>
<td></td>
<td>• Overall responsibility for national medicines safety monitoring policy and activities</td>
</tr>
<tr>
<td></td>
<td>• Manages AE database for comprehensive analysis of available data</td>
</tr>
<tr>
<td>National Programme Coordinator for NTD control</td>
<td>• Responsible for preventive chemotherapy safety surveillance at national level;</td>
</tr>
<tr>
<td></td>
<td>• Reviews information on AE reports;</td>
</tr>
<tr>
<td></td>
<td>• Conducts regular analysis of AEs and feeds results back down the system;</td>
</tr>
<tr>
<td></td>
<td>• Provides support to provincial/regional investigator;</td>
</tr>
<tr>
<td></td>
<td>• Spokesperson for preventive chemotherapy safety system</td>
</tr>
<tr>
<td>National NTD preventive chemotherapy safety committee</td>
<td>• Composed of national programme manager for preventive chemotherapy interventions, TFDA and national pharmacovigilance centre, infectious disease physician, epidemiologist, and pharmacologist;</td>
</tr>
<tr>
<td></td>
<td>• Adopts policy and procedures; guidelines and standard forms for reporting and</td>
</tr>
</tbody>
</table>
investigating;
- Reviews overall pattern of reports and investigations;
- Provides causality assessment on inconclusive investigations;
- Provides system's quality supervision;

<table>
<thead>
<tr>
<th>Region level investigator</th>
<th>Assesses report, conducts investigation, forwards conclusions of investigation, reports action taken to respond or proposes action to be taken to respond</th>
</tr>
</thead>
<tbody>
<tr>
<td>District level supervisors</td>
<td>Checks that reports meet criteria, forwards checked and completed reports to investigator</td>
</tr>
</tbody>
</table>
| Frontline health workers   | • Treats affected patients (see Appendix G);
                          • Reports serious adverse events to supervisor (see overview of peripheral health worker action in diagram 4.2) |
| Community leaders          | • They should report to CDD |

9.4 The output of establishing surveillance

- It will enhance programme credibility, and can effectively provide new data on specific risks associated to medicines used under particular circumstances or in specific populations.
- A safety surveillance system is an indicator of intervention quality

9.5 Learning and training

Establishing a safety surveillance system entails training all concerned parties to enable them to know their roles, undertake appropriate action and provide the required response at all levels of the system. It is also important for key parties to learn more from each other's past experience.

National programme managers for preventive chemotherapy and pharmacovigilance centre staff need to keep up to date about the latest developments in safety monitoring as well as specific concerns regarding safety issues related to NTD control. They also need to keep abreast of scientific literature and debates in order to be aware of any allegations or concerns that may be circulating about preventive chemotherapy safety.

9.6 Steps for establishing a system

As stated above, depending on specific national circumstances, the national programme manager for NTD control should take the lead in collaborating with any existing system or establishing a surveillance system. The strategy, approach and actual achievements will depend to a large extent on the possibility, in each national situation, to count on support and cooperation from other institutions and concerned parties. The steps that need to be considered, not necessarily in the order outlined below, when developing a safety surveillance system in conjunction with preventive chemotherapy interventions can be summarized as follows:
• Seek cooperation and define the respective roles of the medicines regulatory authority and other intervening parties and agree on the objectives for the surveillance system.

• Identify the resources available and needed and obtain political commitment to implement safety surveillance.

• Appoint or designate regional/national assessors/focal points for NTD preventive chemotherapy safety.

• Establish the national NTD preventive chemotherapy safety committee.

• Develop and disseminate a list of serious events to be reported; a standard investigation procedure; and report and investigation forms

• Designate and train staff to prepare preliminary reports (peripheral health workers), complete report forms (district level) and investigate cases (province/region level).

• Inform all health workers/clinicians of the need to report serious AEs immediately, and clarify which ones should be reported

• Consider the establishment of a compensation scheme for people who suffered specified AEs.

9.7 Evaluation of the safety surveillance system

The safety surveillance system needs to be evaluated regularly to determine its effectiveness. This evaluation should be based on criteria that are already defined and the objectives decided at the time of establishing the system.

Unless local situations indicate otherwise, criteria should include:

• **Timeliness, completeness and accuracy of AE reporting** (this could be assessed by comparing reports with the treatment site's registers);

• **Timeliness and completeness of investigation** (check reports to ensure that those meeting the investigation criteria were investigated; that investigation was begun within the defined time criteria; confirm the adequacy of the investigation and the soundness of the conclusion reached, and corrective action recommended);

• **Audit of corrective action** (check that corrective action recommended has been taken and its effectiveness to prevent future programme error has been verified).

The progress of the safety surveillance system can also be monitored from an annual report which includes:
• Number of AE reports, grouped by medicine and type of adverse event;
• Causality assessment results by medicine and per number of people treated;
• rate of each adverse event by medicine and batch number nationally and by region;
• Unusual or unusually severe events or large clusters;
• Summary of other important/unusual investigations.

Making the annual report available to health workers encourages and provides positive feedback for their reporting. Publication of the data also allows international comparisons to be made.

The national preventive chemotherapy safety committee should encourage, facilitate and be actively involved in the evaluation of the system.
Bibliography


Recommendations for the treatment of Onchocerciasis with Mectizan® in areas co-endemic for Onchocerciasis and Loiasis - [http://www.who.int/apoc/publications/englishmectcloarecs-june04.pdf](http://www.who.int/apoc/publications/englishmectcloarecs-june04.pdf)


The Importance of Pharmacovigilance - *WHO*, 2002 - [http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf](http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf)


# Appendix A: Adverse Drug Reaction Reporting Form

## TANZANIA FOOD AND DRUGS AUTHORITY

**REPORT OF SUSPECTED ADVERSE REACTION TO MEDICINES OR VACCINES**

Note: Identities of reporter, patient and institution will remain confidential

### I. PARTICULARS OF PATIENT

<table>
<thead>
<tr>
<th>Patient Initials or Record No.:</th>
<th>Sex: Male ☐ Female ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>____________________________</td>
<td>Weight in kg: ______</td>
</tr>
<tr>
<td>Date of Birth (dd-mm-yyyy) or age:</td>
<td>______________________</td>
</tr>
</tbody>
</table>

### II. DETAILS OF ADVERSE REACTION

<table>
<thead>
<tr>
<th>Description of reaction:</th>
<th>Date Reaction Started ▶/₁ ₁ ₁</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date Reaction Stopped (if known) ▶/₁ ₁ ₁</td>
</tr>
<tr>
<td>Health related information: Medical history (e.g. hepatic, renal, HIV), allergies, pregnancy, smoking, alcohol use, etc. Please write any relevant medical and laboratory results including dates (if done) .................................................................................................................................................................................................</td>
<td></td>
</tr>
</tbody>
</table>

### III. DETAILS OF SUSPECTED MEDICINE/VACCINE USED

<table>
<thead>
<tr>
<th>Name of suspected medicine(s)/vaccine(s) (Specify brand name or manufacturer if known).</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Route</th>
<th>Therapy Date Start</th>
<th>Therapy Date Stop</th>
<th>Batch. No &amp; Expiry date (If known)</th>
<th>Reason for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other medicines used at the same time and or one month before (including herbal medicines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
</tbody>
</table>
### IV. MANAGEMENT OF ADVERSE REACTION

**Reaction subsided after stopping the suspected drug/reducing the dose:**
- Yes ☐
- No ☐
- Unknown ☐

**Reaction reappeared after reintroducing drug:**
- Yes ☐
- No ☐
- Not applicable ☐

**Seriousness of the Reaction (please tick all that apply):**
- ☐ Discomfort but able to work
- ☐ Caused persistent disability or incapacity
- ☐ Discomfort could not work
- ☐ Caused a congenital anomaly
- ☐ Required or prolonged hospitalization
- ☐ Patient Died
- ☐ Life threatening
- ☐ Others, please give details…………………………………………………………

**Treatment of adverse reaction**
- No ☐
- Yes (if yes please specify)………………………………………………………………

**Outcome of the reaction**
- Not yet ☐
- Recovered (Date): ___ ___
- Died (Date): ___ ___
- Unknown ☐

**Cause of death**
…………………………………………………………………………………………………………

### V. THERAPEUTIC FAILURE

PLEASE WRITE IF THE MEDICINE(S)/VACCINE(S) SHOWED LACK OF EFFICACY BELOW: (Continue at the back)

### VI. MEDICATION ERRORS AND OVERDOSAGE
An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?
Please report all undesirable patient effect suspected to be associated with drugs, cosmetics or medical devices use.

Report even if:
☐ You’re not sure that the product caused the event
☐ You don’t have all the details

When to report?
As soon as possible

Submission of follow-up reports:
Any follow-up information for an ADR that has already been reported should be submitted through the same ADR form or communicated directly.

Guide to filling the form:

How to report?
☐ Dully fill in the form as required
☐ Use a separate form for each patient
☐ Report direct to TFDA through the following addresses:

Mail: Tanzania Food and Drugs Authority,
P. O. Box 77150, Dar es Salaam

Fax: 22-2450793

Phone: 22-2450512 / 2450751

Submission of an ADR case report does not discredit the competence of the reporter.

Ref No. (for official use)
Moisten gum and fold. For maximum adhesion, press down for few seconds

--- Second Fold ---

No postage stamp required
If posted in Tanzania

BUSINESS REPLY
SERVICE LICENCE No.
BRS 01

TO: THE DIRECTOR GENERAL
TANZANIA FOOD AND DRUGS AUTHORITY
P. O. BOX 77150
DAR ES SALAAM
**Appendix B: Adverse Event Investigation Form**

This form should be filled at the end of an investigation into the cause of an AE.

<table>
<thead>
<tr>
<th>Investigation ID No:</th>
<th>Report ID No:</th>
<th>date investigation started:</th>
</tr>
</thead>
</table>

Describe AE that triggered investigation:

Diagnosis/clinical features:

Data on frequency of same/similar illness in same community: available/not available
Higher frequency in treated Vs not treated? Y/N/?
Other comments:

Treatment site investigated? Y/N/?
If yes, key findings:

Other relevant investigation findings:

<table>
<thead>
<tr>
<th>Conclusion about cause of AE</th>
<th>Describe</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Adverse reaction to the medicine</td>
<td></td>
</tr>
<tr>
<td>☐ Operational error</td>
<td></td>
</tr>
<tr>
<td>☐ Coincidental event</td>
<td></td>
</tr>
<tr>
<td>☐ Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion is: Certain  Probable  Possible
Reasons/justification for conclusion:

Corrective action taken (specify action or reasons for no action):

Further action recommended:

Investigator signature:…………………………….    Date:……………………

Investigator name and contact details:…………………………………………………………………….
Appendix C: Checklist for a Safety Surveillance System

1. Prepare

- Clarify respective roles of the national medicines regulatory authority, pharmacovigilance centre and NTD preventive chemotherapy programme, and agree on the overall goal and specific objectives for the safety surveillance system.
- Identify the resources available and needed and establish political commitment to preventive chemotherapy safety surveillance.
- Appoint or designate regional/national assessors for preventive chemotherapy safety.
- Establish national preventive chemotherapy safety committee.
- Develop and disseminate a list of events to be reported and their clinical features; a standard investigation procedure; and AE report and investigation forms.
- Designate and train staff, at appropriate levels, to make reports, complete report forms and investigate AEs.
- Inform all health workers/clinicians of the need to report immediately an AE, and which ones should be reported.
- Consider establishment of a compensation scheme for specified AEs.

2. Receive a report (appropriate-level investigator)

- Decide if the report matches the criteria for AE to be reported, and whether it needs investigating and/or advising to the public/media.
- Travel to the location of the AE, or delegate responsibility to another trained person or team to do this.
- Decide if and how to communicate with community and/or media to alleviate concern.

3. Investigate

- Ask about the patient, the event, and the medicine.
- Ask about treatment site and procedures and observe treatment staff in action (emphasizing that aim is to find system error not to blame individuals).
- Formulate a working hypothesis as to what was the cause of the AE.
- If appropriate, collect and dispatch specimens to a testing laboratory.

4. Analyse the data

- Review on-site investigation, clinical findings, and laboratory results (if any).
- Review epidemiological findings e.g. clustering of cases in time or space or by manufacturer or batch.
- Summarize findings and complete Investigation Form.

5. Take action

- Communicate with concerned staff (e.g. treatment, information).
• Communicate findings and action to the relatives, community, and media (as appropriate).
• Correct the problem (based on the cause) by improving training, supervision, and/or changing operational procedures.

Patient experiencing adverse event should be managed according to the available health facilities and any referral whenever necessary should follow the MoHSW Health referral system.
Appendix D: Summary of Product Characteristics of Selected Medicines

i. MEBENDAZOLE

Adverse Effects
Since mebendazole is poorly absorbed from the gastrointestinal tract at the usual therapeutic doses, adverse effects have generally been restricted to gastrointestinal disturbances, such as transient abdominal pain and diarrhoea, and have tended to occur in patients being treated for heavy intestinal infection. Headache and dizziness have been reported. Adverse effects have been reported more frequently with the high doses tried in echinococcosis and have included allergic reactions, raised liver enzyme values, alopecia, and bone marrow depression.

Incidence of adverse effects
In the first phase of WHO-coordinated multicentre studies on the treatment of echinococcosis (hydatid disease) involving Echinococcus granulosus or E. multilocularis, the most frequent adverse effects in the 139 patients given high-dose mebendazole, generally for 3 months, were reduced leucocyte count (25 patients), gastrointestinal symptoms (22 patients), and raised serum-transaminase values (22 patients). Other adverse effects were allergic conditions such as fever and skin reactions (4 patients), CNS symptoms including headache (6 patients), and loss of hair (7 patients). Seven patients stopped treatment because of adverse effects.

The second phase of studies compared albendazole with mebendazole in more prolonged high-dosage schedules for cystic E. granulosus infection. Adverse effects were similar to those reported with the first phase. However, in the first phase the allergic consequences of the 14 ruptured lung cysts and the 4 ruptured liver cysts that occurred with mebendazole were not reported. In the second phase, 2 patients suffered anaphylactic shock as a result of rupture of a lung cyst and a cyst in the abdominal cavity. These 2 patients were withdrawn from mebendazole treatment, as were another 4 patients as a consequence of their adverse reactions, although in 3 the withdrawal was only temporary. Although albendazole is preferred to mebendazole in the treatment of echinococcosis, if either drug is used there should be constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.

Overdosage
Respiratory arrest and tachyarrhythmia associated with continuous convulsions were reported in an 8-week-old infant following accidental poisoning with mebendazole. Treatment by exchange transfusion and anticonvulsants was successful.

Precautions
Patients receiving high doses of mebendazole, such as those with echinococcosis, should be supervised closely with blood counts and liver function being monitored; such high-dose therapy may be inappropriate in those with hepatic impairment.

**Pregnancy**
Mebendazole is teratogenic in rats and the manufacturers note that there are no adequate and well controlled studies in human pregnancy. Mebendazole is therefore usually contra-indicated during pregnancy. However, it was noted that in a survey of a limited number of pregnant women who had inadvertently taken mebendazole during the first trimester, the incidence of malformation and spontaneous abortion was no greater than that observed in the general population.

**Interactions**
**Antiepileptics**
Phenytoin or carbamazepine have been reported to lower plasma-mebendazole concentrations in patients receiving high doses for echinococcosis, presumably as a result of enzyme induction; valproate had no such effect.

**Histamine H₂-antagonists**
Plasma concentrations of mebendazole have been raised when the enzyme inhibitor cimetidine was also given, and this has resulted in the resolution of previously unresponsive hepatic hydatid cysts.

**ii. ALBENDAZOLE**

**Adverse Effects and Precautions**
Adverse effects have generally been restricted to gastrointestinal disturbances, such as transient abdominal pain and diarrhoea, and have tended to occur in patients being treated for heavy intestinal infection. Headache and dizziness have been reported. Adverse effects have been reported more frequently with the high doses tried in echinococcosis and have included allergic reactions, raised liver enzyme values, alopecia, and bone marrow depression.

Albendazole should only be used in the treatment of echinococcosis if there is constant medical supervision with regular monitoring of serum-transaminase concentrations and of leucocyte and platelet counts. Patients with liver damage should be treated with reduced doses of benzimidazole carbamates, if at all.

**Incidence of adverse effects**
Although generally well-tolerated, the following adverse reactions were reported in the first phase of WHO-coordinated studies involving 30 patients given high-dose therapy with albendazole for the treatment of cystic
echinococcosis (hydatid disease): raised serum-transaminase levels (2 patients), reduced leucocyte counts (1 patient), gastrointestinal symptoms (1 patient), allergic conditions (1 patient), and loss of hair (1 patient). Treatment was stopped in a further patient with alveolar echinococcosis because of depressed bone-marrow activity. In the second phase of these studies, of 109 patients given albendazole for cystic echinococcosis, 20 experienced adverse effects; similar findings were reported with mebendazole. The range of effects with albendazole was: elevation of transaminases (5 patients), abdominal pain and other gastrointestinal symptoms (7 patients), severe headache (4 patients), loss of hair (2 patients), leucopenia (2 patients), fever and fatigue (1 patient), thrombocytopenia (1 patient), and urticaria and itching (1 patient). Albendazole had to be withdrawn in 5 patients because of adverse effects, although in 3 the withdrawal was only temporary.

**Effects on growth**
A multiple-dose regimen of albendazole in children with asymptomatic trichuriasis has been reported to be associated with impaired growth in those with low levels of infection. However it was considered that this should not prevent the use of single doses in mass treatment programmes.

**Effects on the liver**
In a series of 40 patients given albendazole for echinococcosis, 7 developed abnormalities in liver function tests during therapy. Six had a hepatocellular type of abnormality attributable to albendazole; the seventh had cholestatic jaundice which was probably not due to albendazole.

**Pregnancy**
Albendazole is teratogenic in some animals and the manufacturers note that there are no adequate and well controlled studies in human pregnancy. Albendazole is therefore usually contra-indicated during pregnancy and the manufacturers caution against becoming pregnant while taking albendazole or within one month of completing treatment.

**Interactions**
**Anthelmintics**
The plasma concentration of albendazole sulfoxide has been increased by praziquantel, although the practical consequences of this were considered uncertain.

**Corticosteroids**
Plasma concentrations of the active metabolite of albendazole (albendazole sulfoxide) were reported to be raised by about 50% in a study in 8 patients receiving dexamethasone.
Histamine H2-antagonists
Concentrations of albendazole sulfoxide have been found to be raised in bile and hydatid cyst fluid when albendazole was given with cimetidine, which may increase effectiveness in the treatment of echinococcosis.

iii. IVERMECTIN

Adverse Effects and Precautions
The adverse effects reported with ivermectin are generally consistent with a mild Mazzotti reaction arising from its effect on the microfilariae. They include fever, pruritus, skin rashes, arthralgia, myalgia, asthenia, orthostatic hypotension, tachycardia, oedema, lymphadenopathy, gastrointestinal symptoms, sore throat, cough, and headache. The effects tend to be transient and if treatment is required they respond to analgesics and antihistamines.

Ivermectin may cause mild ocular irritation. Somnolence, transient eosinophilia, and raised liver enzyme values have also been reported. Ivermectin is not recommended during pregnancy. Mass treatment is generally withheld from pregnant women (see Pregnancy), children under 15 kg, and the seriously ill.

Incidence of adverse effects
Some studies have shown quite a high incidence of adverse effects with ivermectin and have associated the effects with the severity of infection. However, in none of these studies were the reactions considered to be life-threatening and only symptomatic treatment was required. The severity, incidence, and duration of adverse reactions were reported to be reduced after repeated annual administration. When larger groups of patients were considered in the Onchocerciasis Control Programme (OCP) in West Africa, a much lower incidence of adverse reactions was observed in patients given ivermectin for the first time and when treatment was repeated a year later that incidence was reduced even further. The results from several trials in this programme showed 93 severe reactions in 50,929 patients (1.83%), most of the reactions being orthostatic hypotension or dizziness (53). In a 3-year randomised, double-blind, controlled study of ivermectin for onchocerciasis control in 572 patients, 3-monthly treatment with the standard dose of 150 micrograms/kg was associated with a reduced risk of adverse reactions, especially oedema, pruritus, and back pain, when compared with the same dose given annually. Higher doses of 400 then 800 micrograms/kg, given either 3-monthly or annually, were associated with subjective ocular problems. Another study found 22 severe reactions in 17,877 patients treated for onchocerciasis in an area also endemic for Loa loa infection, and demonstrated a relationship to heavy L. loa microfilaraemia. The Mectizan® Expert Committee and the Technical Consultative Committee have reported the incidence of encephalopathy following ivermectin treatment of onchocerciasis in Loa loa endemic areas to be less than 1 case in 10,000 treatments and have implemented recommendations for ivermectin mass
treatment programmes of onchocerciasis in areas co-endemic for loiasis to reduce the risk of serious adverse events, especially in areas where the population is ivermectin naive.

Some supervision is considered necessary after administration of ivermectin; the OCP recommendation is for resident nurses to monitor patients for a period of 36 hours after treatment, whatever the level of endemicity. However, the incidence of adverse reactions reported after repeated doses appears to be lower than after the first dose and the need for supervision on re-treatment has been questioned.

Neurotoxicity seen in some breeds of dogs has not been reported in man in the above studies. Another potential concern was the prolongation of prothrombin times observed in 28 patients given ivermectin, but others have not confirmed this effect or observed any bleeding disorders.

Breast feeding
Mean ivermectin concentrations in the breast milk of 4 healthy women who had been given a standard dose of ivermectin were 14.13 nanograms/mL. It was felt that in view of this low concentration the precaution of excluding lactating mothers from ivermectin mass treatment programmes should be reassessed through proper research. Some authorities have recommended that ivermectin should not be given to mothers who are breast feeding until the infant is at least one week old. The American Academy of Pediatrics states that, since no adverse effects have been seen in breast-fed infants whose mothers were receiving ivermectin, it may be considered to be usually compatible with breast feeding. However, the information approved by the US FDA states that "treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn."

Pregnancy
Ivermectin is teratogenic in animals and the manufacturers note that there are no adequate and well controlled studies in human pregnancy. Ivermectin treatment is therefore usually contra-indicated during pregnancy and pregnant women should be excluded from mass treatment schedules with ivermectin. However, women not yet diagnosed as pregnant or unwilling to admit their pregnancy have been treated. An assessment of 203 pregnancy outcomes to women, who had received ivermectin during pregnancy, mostly during the first 12 weeks, found that the rates of major congenital malformation, miscarriage, and still-birth associated with ivermectin were similar to those in untreated mothers. In another study, 110 women also inadvertently given ivermectin during pregnancy experienced a similar lack of adverse effect on pregnancy outcome; it was considered that the precaution of avoiding the use of ivermectin in women notifying a pregnancy should be adequate.
iv. DIETHYLCARBAMAZINE - DEC

Adverse Effects
Adverse effects directly attributable to diethylcarbamazine include nausea and vomiting. Headache, dizziness, and drowsiness may occur.
Hypersensitivity reactions arise from the death of the microfilariae. These can be serious, especially in onchocerciasis where there may also be sight-threatening ocular toxicity; fatalities have been reported. Encephalitis may be exacerbated in patients with loiasis and fatalities have occurred.
Reactions occurring during diethylcarbamazine treatment of lymphatic filariasis are basically of 2 types: pharmacological dose-dependent responses and a response of the infected host to the destruction and death of parasites.
Reactions of the first type include weakness, dizziness, lethargy, anorexia, and nausea. They begin within 1 to 2 hours of taking diethylcarbamazine, and persist for a few hours.

Reactions of the second type are less likely to occur and are less severe in bancroftian than in brugian filariasis. They may be systemic or local, both with or without fever. Systemic reactions may occur a few hours after the first oral dose of diethylcarbamazine and generally do not last for more than 3 days. They include headache, aches in other parts of the body, joint pain, dizziness, anorexia, malaise, transient haematuria, allergic reactions, vomiting, and sometimes attacks of bronchial asthma in asthmatic patients.
Fever and systemic reactions are positively associated with microfilaraemia. Systemic reactions are reduced if diethylcarbamazine is given in spaced doses or in repeated small doses. They eventually cease spontaneously and interruption of treatment is rarely necessary; symptomatic treatment with antipyretics or analgesics may be helpful.

Local reactions tend to occur later in the course of treatment and last longer; they also disappear spontaneously and interruption of treatment is not necessary. Local reactions include lymphadenitis, abscess, ulceration, and transient lymphoedema; funiculitis and epididymitis may also occur in bancroftian filariasis.

It has been suggested that the release of interleukin-6 may be implicated in diethylcarbamazine's adverse effects in patients with lymphatic filariasis. In most patients with onchocerciasis, the microfilaricidal activity of diethylcarbamazine leads to a series of events with dermal, ocular, and systemic components, known as the Mazzotti reaction, within minutes to hours after its use.

Clinical manifestations can be severe, dangerous, and debilitating. Systemic reactions include increased itching, rash, headache, aching muscles, joint pain, painful swollen and tender lymph nodes, fever, tachycardia and hypotension,
and vertigo. Most patients experience eye discomfort in the first few hours after diethylcarbamazine treatment. Punctate keratitis can develop as can optic neuritis and visual field loss.

WHO no longer recommends the use of diethylcarbamazine in onchocerciasis as safer alternatives exist.

**Dose calculation**
Diethylcarbamazine was first used as the chloride, but is now produced as the dihydrogen citrate which contains only half its weight as base. In reporting doses it is therefore important to indicate whether they refer to a specific salt or to the base; unless otherwise stated, it can generally be assumed that the dose refers to the citrate.

**Precautions**
Treatment with diethylcarbamazine should be closely supervised since hypersensitivity reactions are common and may be severe, especially in patients with onchocerciasis or loiasis. Patients with onchocerciasis should be monitored for eye changes. (The use of diethylcarbamazine to treat onchocerciasis is no longer recommended.) In patients with heavy Loa loa infection there is a small risk of encephalopathy and diethylcarbamazine should be stopped at the first sign of cerebral involvement.

Infants, pregnant women, the elderly, and the debilitated, especially those with cardiac or renal disease, are normally excluded when diethylcarbamazine is used in mass treatment schedules.

**Pregnancy**
Pregnant women are normally excluded when diethylcarbamazine is used in mass treatment schedules.

Animal studies suggest that the uterine hypermotility induced by diethylcarbamazine is mediated via prostaglandin synthesis; this might explain the mechanism of the abortifacient action previously reported.

**Renal impairment**
Results in patients with chronic renal impairment and in healthy subjects, given a single 50-mg dose of diethylcarbamazine citrate by mouth, indicated that the plasma half-life of diethylcarbamazine is prolonged and its 24-hour urinary excretion considerably reduced in those with moderate and severe degrees of renal impairment. Mean plasma half-lives in 7 patients with severe renal impairment (creatinine clearance less than 25 mL/minute), in 5 patients with moderate renal impairment (creatinine clearance between 25 and 60 mL/minute), and in 4 healthy subjects, were 15.1, 7.7, and 2.7 hours, respectively. The patient with the longest plasma half-life of 32 hours did not have the poorest renal function, but it was considered likely that the abnormally slow elimination of diethylcarbamazine was due to the high urinary pH (7) resulting from sodium bicarbonate therapy. A further patient with a half-life longer than expected also had less acidic urine.
Adverse Effects
Adverse effects with praziquantel may be common but are usually mild and transient. Headache, diarrhoea, dizziness, drowsiness, malaise, abdominal discomfort, nausea, and vomiting have been reported most frequently. Hypersensitivity reactions such as fever, urticaria, pruritic skin rashes, and eosinophilia can occur; they may be due to death of the infecting parasites. Raised liver enzyme values have been reported rarely. Most patients with neurocysticercosis who are given praziquantel suffer CNS effects, including headache, hyperthermia, seizures, and intracranial hypertension, which are thought to result from an inflammatory response to dead and dying parasites in the CNS. Use with corticosteroids is advised in such patients.

Effects on the gastrointestinal tract
Colicky abdominal pain and bloody diarrhoea occurred in a small community in Zaire shortly after treatment for Schistosoma mansoni infection with single doses of praziquantel 40 mg/kg by mouth. A similar syndrome has been reported in some patients with Schistosoma japonicum infection given praziquantel. The abdominal pain occurring in these patients was very different from the mild abdominal discomfort much more commonly reported with praziquantel therapy.

Effects on the nervous system
Adverse nervous system effects are common in patients with neurocysticercosis given praziquantel. Neurological symptoms have also been reported with the much lower doses of praziquantel used in the treatment of taeniasis in a patient with undiagnosed neurocysticercosis.

Precautions
Praziquantel should not be used in patients with ocular cysticercosis because of the risk of severe eye damage resulting from destruction of the parasite. Patients should be warned that praziquantel may cause dizziness or drowsiness and if affected they should not drive or operate machinery during or for 24 hours after treatment.

Breast feeding
Praziquantel is distributed into breast milk and mothers should not breast feed during treatment or for 72 hours thereafter.

Pregnancy
In a review of 637 women who had received praziquantel in a mass distribution programme, 88 had received a single oral dose during pregnancy, including 37 in their first trimester. All pregnancies ended in full-term babies.
and there was no evidence of clinical abnormality. No difference was found in the rates of preterm delivery or abortion compared with a control group.

**Interactions**

**Anthelmintics**
The plasma concentration of albendazole sulfoxide has been increased by praziquantel, although the practical consequences of this are uncertain.

**Antiepileptics**
Carbamazepine and phenytoin have been reported to reduce the bioavailability of praziquantel.

**Antimalarials**
Chloroquine has been reported to reduce the bioavailability of praziquantel.

**Corticosteroids**
Some workers have proposed the use of dexamethasone to prevent the inflammatory response due to destroyed cysticerci in praziquantel treatment of cysticercosis. However, since dexamethasone roughly halves plasma concentrations of praziquantel, it has been suggested that it be reserved for the short-term treatment of praziquantel-induced intracranial hypertension.

**Histamine H₂-antagonists**
Cimetidine has been reported to increase praziquantel bioavailability.

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**vi. AZITHROMYCIN**

**Undesirable Effects**
The adverse effects reported with azithromycin are generally mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhoea, or abdominal pain.

**Special Warnings and Special Precautions for Use**

Allergic reactions: In rare cases azithromycin is reported to have caused serious allergic (rarely fatal) reactions such as angioneurotic oedema and anaphylaxis. Some of these reactions have caused recurrent symptoms and have required longer observation and treatment.

Renal failure: No studies have been conducted on patients with a creatinine clearance of <40 ml/min, and consequently caution must be exercised in the use of azithromycin for these patients.
Hepatic failure: Since azithromycin is metabolised in the liver and excreted in the bile, the medicinal product should not be given to patients suffering from severe liver disease. No studies have been conducted regarding the treatment of such patients with Azithromycin 250mg film-coated tablet.

When severe liver impairment occurs, the treatment with azithromycin should be ceased.

Ergot alkaloids and Azithromycin 250mg film-coated tablets: The concurrent use of ergot alkaloids and macrolide antibiotics has been found to accelerate the development of ergotism. The interactions between ergot alkaloids and azithromycin have not been studied. The development of ergotism is however possible, so that Azithromycin and ergot alkaloid derivatives should not be administered simultaneously.

QT prolongation
Prolonged cardiac repolarisation and QT interval have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk of cardiac effects. Therefore:

- Azithromycin 250mg film-coated tablets should not be used in patients with congenital or documented acquired QT prolongation.

- Azithromycin 250mg film-coated tablets should not be used concurrently with other active substances that prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.

- Azithromycin 250mg film-coated tablets should not be used in patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia

- Azithromycin 250mg film-coated tablets should not be used in patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

Pharyngitis/tonsillitis: Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Azithromycin is not indicated for the treatment of infected burn wounds. In case of sexually transmitted diseases a concomitant infection by *T. palladium* should be excluded.

Superinfections: Attention should be paid to possible symptoms of superinfections caused by non-sensitive causal agents such as fungi. A
superinfection may require an interruption of the azithromycin treatment and
initiation of adequate measures.

Neurological or psychiatric diseases: Azithromycin should be administered
with caution to patients suffering from neurological or psychiatric diseases.

Pseudomembranous colitis: After the use of macrolide antibiotics
pseudomembranous colitis has been reported. This diagnosis should
therefore be considered for patients who suffer from diarrhoea after start of
the treatment with azithromycin. Should pseudomembranous colitis be
induced by azithromycin, then anti-peristaltics should be contraindicated.

Long term use: There is no experience regarding the safety and efficacy of
long term use of azithromycin for the mentioned indications. In case of rapid
recurrent infections, treatment with another antibiotic should be considered.

Azithromycin tablets are not suitable for treatment of severe infections where
a high concentration of the antibiotic in the blood is rapidly needed.

Interactions with other medicinal products and other forms of interaction

Antacids: When studying the effect of simultaneously administered antacid on
the pharmacokinetics of azithromycin, no overall change has been observed
in the bioavailability, although the peak concentrations of azithromycin
measured in the plasma did fall by 30%. Antacids and azithromycin should
not be administered simultaneously.

Ergotamine: The combined use of ergotamine and Azithromycin may in theory
cause ergotism, and consequently their combined use is not recommended
(see also section 4.4).

Coumarin-like oral anticoagulants: An increased tendency towards
haemorrhaging has been reported in connection with the concurrent use of
azithromycin and warfarin or coumarin-like oral anticoagulants. Attention
should be paid to the frequency of prothrombin time monitoring.

Digoxin: In some patients certain macrolide antibiotics have been reported to
have impaired the metabolism of digoxin in the intestine. Consequently, in
the case of patients receiving Azithromycin and digoxin, the possibility of a
rise in the digoxin concentrations should be borne in mind.

Zidovudine: 1000 mg single doses and 1200 mg or 600 mg multiple doses of
azithromycin had only a slight effect upon the pharmacokinetics of
zidovudine or its glucuronide metabolite in the plasma or upon excretion in
the urine. However, the administration of azithromycin increased the
concentrations of phosphorylated zidovudine, the clinically active metabolite,
in mononuclear cells in the peripheral circulation. The clinical significance of this finding is unclear, but it may be of benefit to patients.

*Didanosine:* Daily dosages of 1200 mg azithromycin co-administered with didanosine in 6 volunteers appeared to have no effect on the pharmacokinetics of didanosine compared to placebo.

*Theophylline:* Azithromycin has not affected the pharmacokinetics of theophylline when healthy volunteers received Azithromycin and theophylline simultaneously. Theophylline levels may be increased in patients taking azithromycin.

Even though azithromycin does not appear to inhibit the enzyme CYP3A4, caution is advised when combining the medicinal product with quinidine, cyclosporine, cisapride, astemizole, terfenadine, ergot alkaloids, pimozide or other medicinal products with a narrow therapeutic index predominantly metabolised by CYP3A4.

*Cyclosporin:* Since pharmacokinetic and clinical studies on the possible combined effects of azithromycin and cyclosporin have not been carried out, the therapeutic situation should be carefully considered before these active substances are administered simultaneously. If combination treatment is considered justifiable, the cyclosporin levels should be carefully monitored and the dosage should be adjusted accordingly.

*Terfenadine:* In pharmacokinetic studies there are no reports of interactions between azithromycin and terfenadine.

There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred. Azithromycin should be administered with caution in combination with terfenadine.

*Cisapride:* Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsade de pointes.

*Astemizol, Triazolam, Midazolam, Alfentanil:* No data are available on interactions with Astemizol, Triazolam, Midazolam and Alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentation of its effect during concomitant use of the macrolide antibiotic erythromycin.