

ASSURING SAFETY OF PREVENTIVE CHEMOTHERAPY INTERVENTIONS FOR THE CONTROL OF NEGLECTED TROPICAL DISEASES

PRACTICAL ADVICE FOR NATIONAL PROGRAMME MANAGERS ON THE
PREVENTION, DETECTION AND MANAGEMENT
OF SERIOUS ADVERSE EVENTS.



**World Health
Organization**

WHO Library Cataloguing-in-Publication Data

Assuring safety of preventive chemotherapy interventions for the control of neglected tropical diseases: practical advice for national programme managers on the prevention, detection and management of serious adverse events.

1.Neglected diseases - prevention and control. 2.Endemic diseases - drug therapy. 3.Parasitic diseases - drug therapy. 4.Anti-infective agents - therapeutic use. I.World Health Organization.

ISBN 978 92 4 150219 1

(NLM classification: WC 680)

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ACKNOWLEDGEMENTS

This document is based on and should be read in conjunction with *Preventive chemotherapy in human helminthiasis : coordinated use of anthelmintic drugs in control interventions : a manual for health professionals and programme managers, WHO 2006.*

This document has largely relied on existing WHO publications from which much inspiration and materials have been derived: *Surveillance of adverse events following immunization - Field guide for managers of immunization programmes WHO/EPI/TRAM/93.02 REV.1, Immunization safety surveillance: Guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization WPRO/EPI/99.01, The safety of medicines in public health programmes: pharmacovigilance an essential tool, WHO 2006; The importance of pharmacovigilance, WHO 2002; Safety monitoring of medicinal products, WHO/UMC 2000; Expecting the Worst - Anticipating, preventing and managing medicinal product crises, WHO-UMC 2003.*

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GLOSSARY

a) Definitions adopted by the WHO Programme on International Drug Monitoring¹

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.

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).

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.

Serious adverse events can be defined as those that:

- a. are life-threatening or fatal
- b. cause or prolong hospital admission
- c. cause persistent incapacity or disability; or
- d. concern misuse or dependence.

b) Definitions adopted for and applicable to this document

Adverse event following preventive chemotherapy (AE)	A medical incident that takes place after a preventive chemotherapy intervention and is suspected to be but is not necessarily caused by the medicines used in the intervention. Some AE, after investigation, may be found to have been caused by the medicine. Such AE will also be referred to as adverse drug reactions or side effects.
Adverse experience	Synonym of adverse event
Adverse drug reaction	'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man'. In addition to that, an adverse reaction can also be the consequence of a medicine's efficacy in killing parasites. See also Adverse event following preventive chemotherapy (AE)
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.
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. Its aim, and greatest challenge, is to extend regular drug coverage as a public health intervention to reach all individuals at risk of the morbidity caused by selected NTDs.

¹ The Importance of Pharmacovigilance - WHO, 2002 - <http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf>

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 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. <i>The term includes both the safety of the operational aspects of interventions as well the safety of the medicinal product itself.</i>
Preventive chemotherapy safety surveillance	A system for ensuring preventive chemotherapy safety through the proper management of adverse events. Preventive chemotherapy surveillance requires <i>ad hoc</i> reporting pathways and response mechanisms which are not usually present in a typical pharmacovigilance system.
Safe intervention management practice	Those 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 event following preventive chemotherapy (SAE)	<p>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; Cancers and congenital anomalies or birth defects should be regarded as serious;</p> <p>Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious.</p> <p>The term “severe” is often used to describe the intensity (severity) of a medical event, as in the grading “mild”, “moderate”, and “severe”. A severe AE is not necessarily serious.</p> <p><i>from: Adverse drug reactions: definitions, diagnosis, and management I Ralph Edwards, Jeffrey K Aronson - Lancet 2000; 356: 1255–59</i></p>
Severe adverse event	<p>see Serious adverse event.</p> <p>The term “severe” is often used to describe the intensity (severity) of a medical event, as in the grading “mild”, “moderate”, and “severe”.</p>
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.

ABBREVIATIONS

AE	Adverse event following preventive chemotherapy
ADR	Adverse drug reaction
ALB	Albendazole
DEC	Diethylcarbamazine
IVR	Ivermectin
MEB	Mebendazole
MRA	Medicines regulatory authority
NGO	Non-governmental organization
NTD(s)	Neglected tropical disease(s)
PZQ	Praziquantel
SAE	Serious adverse event following preventive chemotherapy
WHO	World Health Organization

1. Purpose

Programme 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 cascade 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 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, mebendazole, azithromycin, diethylcarbamazine, 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.

The purpose of this document is to help managers establish a safety surveillance system. It offers practical advice for establishing national policies and guidelines concerning:

preventing AEs and SAEs;

the objectives of safety surveillance;

reporting, investigating, and responding to SAEs;

a communication strategy on preventive chemotherapy safety for the public and the media.

This document is organized in three parts:

- adverse events and serious adverse events: section 2;
- management of serious adverse events: sections 3 to 6;
- establishing a safety surveillance system: sections 7 and 8.

2. Adverse events following large-scale preventive chemotherapy interventions (AE)

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 preventive chemotherapy activities but are just temporally associated with it. For the purpose of this document, AEs are classified into five categories:

- a. adverse reaction to the medicine: ADR caused directly by the medicine(s) used in the intervention;
- b. adverse reaction due to the destruction of parasites killed by the medicine: 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 procedures but with a temporal association with the intervention;
- e. unknown cause: cases in which the cause of an AE cannot be determined.

Table 2 (see next page) presents summary information about the first three categories of AEs. It focuses only on selected medicines used in large-scale preventive chemotherapy interventions, namely: albendazole, mebendazole, azithromycin, diethylcarbamazine, ivermectin, and praziquantel. As shown in table 2 and annex G, 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. The following general precautionary measures are recommended to ensure safe implementation of large-scale preventive chemotherapy²:

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

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 anthelmintic 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 Annex A.

Scored tablets should be broken into smaller pieces, or crushed, for administration to young children; 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,

² Adapted from *Preventive chemotherapy in human helminthiasis : coordinated use of anthelmintic drugs in control interventions : a manual for health professionals and programme managers, WHO 2006*

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.

Table 2 - Adverse events that may occur during preventive chemotherapy to control morbidity associated with NTDs (see also Annex F and G)

a - adverse reactions to the medicine	Azithromycin	Reactions are generally mild and self-limiting, especially when used in single dose for preventive chemotherapy. However, detailed safety information is specific to each regulatory jurisdiction and should be sought in the leaflets accompanying the medicinal products, the national medicines regulatory authority, the manufacturer (who has the ultimate responsibility for product safety and quality), or WHO.
	Benzimidazoles	
	Diethylcarbamazine (DEC)	
	Ivermectin	
	Praziquantel	
b - adverse reactions due to the destruction of killed parasites	DEC in patients with heavy <i>Loa loa</i> infection	Encephalopathy (confusion, lethargy, stupor or coma). Death. DEC should not be used in areas where <i>Loa loa</i> is endemic.
	DEC in patients with onchocerciasis	Mazzotti reaction: intense itching, enlargement of lymph nodes, papular rash, fever, tachycardia, arthralgia, headache, major ocular complications (occasionally fatal). DEC should not be used in areas where <i>onchocerciasis</i> is endemic.
	Ivermectin in patients with heavy <i>Loa loa</i> infection	Same as DEC but less frequent (about 1 serious adverse event in 800,000 persons treated). The use of ivermectin in areas where <i>Loa loa</i> is endemic should be based on appropriate epidemiological assessment³.
	Albendazole in patients with heavy <i>Loa loa</i> infection	Same as DEC but much less frequent (only sporadic case reports). Albendazole is not contraindicated in areas with loiasis.
	Praziquantel in patients with neurocysticercosis (especially those with hydrocephalus and parenchymal brain cysts)	Fever, meningism (headache, photophobia, neck stiffness), intracranial hypertension (occasionally fatal), seizures.
	Albendazole in patients with neurocysticercosis	Same as praziquantel
	Praziquantel in patients with ocular cysticercosis	Destruction of the parasite may cause severe eye damage. Praziquantel should not be used in patients with ocular cysticercosis
	Albendazole in patients with heavy ascariasis infections	Worm migration to and occasional expulsion through nose or mouth.
c - operational errors	Choking on large tablets	
	Anxiety reactions (e.g. clusters of vomiting episodes), especially in children, that arise from the fear of treatment	

Further details are provided in sections 2.1 and 2.2. Information presented in Table 2 has been adapted from *Martindale: The Complete Drug Reference, 35th edition, 2008, The Pharmaceutical Press* and *Meyler's Side Effects of Drugs, 15th edition, 2006, Elsevier*, expert advice (as acknowledged at the bottom of the table), as well as direct experience and information available to staff of WHO's Department of Control of Neglected Tropical Diseases.

³ See: Recommendations for the treatment of Onchocerciasis with Mectizan® in areas co-endemic for Onchocerciasis and Loiasis - <http://www.who.int/apoc/publications/englishmectizancloarecs-june04.pdf>

2.1 Reactions to the medicines

As already mentioned, only very mild adverse reactions have been reported for albendazole, mebendazole, azithromycin, diethylcarbamazine, ivermectin, and praziquantel when used in single dose in preventive chemotherapy⁴. Patients should be warned that praziquantel may cause dizziness or drowsiness. However, detailed safety information is specific to each regulatory jurisdiction and should be sought in the leaflets accompanying the medicinal products, the national medicines regulatory authority, the manufacturer (who has the ultimate responsibility for product safety and quality). If needed, WHO is willing to assist national programme managers to obtain appropriate information on medicines safety.

Use in pregnancy

Special considerations must be made concerning women of reproductive age and pregnant women. None of the medicines considered in this manual is approved for use in pregnancy or in the first trimester of pregnancy. Women must be informed that they have the right to refuse or delay treatment if they are unsure about pregnancy, and programme managers 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 analyses 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 babies⁵. 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 or mebendazole** of women for soil-transmitted helminthiasis after the first trimester of pregnancy. Surveys on women who took mebendazole during the first trimester showed that the incidence of spontaneous abortion and malformations did not exceed that of the general population¹. A review of the risk of congenital abnormalities from benzimidazoles concluded that their use during pregnancy was not associated with an increased risk of major congenital defects; nonetheless, it is recommended that treatment should be avoided during the first trimester of pregnancy⁶. WHO recommends treatment with benzimidazoles during the second and third trimesters of pregnancy to prevent iron-deficiency anaemia leading to adverse pregnancy outcomes⁷. There is no evidence that maternal benzimidazole-based therapy presents a risk to breast-fed infants³.

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 intervention⁸. Praziquantel is distributed into breast milk. Programme managers 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 **DEC and ivermectin** are not safe in pregnancy, the number of studies is limited⁹ and these medicines have been largely used in areas where drug safety

⁴ Martindale: *The Complete Drug Reference*, 36th edition, 2009, The Pharmaceutical Press; and *Meyler's Side Effects of Drugs*, 15th edition, 2006, Elsevier

⁵ Savioli L, Crompton DWT, Neira M. Use of anthelmintic drugs during pregnancy. *American Journal of Obstetrics and Gynecology*, 2003, 188:5–6.

⁶ Urbani, C., and Albonico, M. Anthelmintic drug safety and drug administration in the control of soil-transmitted helminthiasis in community campaigns. *Acta Trop.*, **2003**, 86:215-223

⁷ World Health Organization. *Prevention and Control of Schistosomiasis and Soil-Transmitted Helminthiasis*, Report of a WHO Expert Committee. WHO Technical Report Series 912, **2002**, Geneva

⁸ Adam I, et al. Is praziquantel therapy safe during pregnancy? *Trans R Soc Trop Med Hyg* 2004; **98**: 540–3

⁹ Pacque M et al. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet*, 1990, 336:1486–1489. and Chippaux JP et al. Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1993, 87:318.

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 either DEC or ivermectin (either alone or in combination with other drugs) in preventive chemotherapy 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.

Use in Young Children

Both **albendazole** and **mebendazole** have 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 helminths¹⁰. Millions of children have been treated in mass deworming interventions with adverse events occurring in only up to 1% of treated children¹¹, chiefly mild gastro-intestinal symptoms.

Interactions

The **benzimidazoles** show no clinically relevant interactions with other medicines when used in preventive chemotherapy interventions.

Aluminium or magnesium salts can reduce the rate, but not the extent, of **azithromycin** absorption. Although there is some evidence of food-drug interaction involving azithromycin¹², recent guidance¹³ for trachoma interventions programme managers clearly states that "...recent or intended intake of alcohol, food or traditional medicine... are not contraindications to the use of azithromycin...".

2.2 Operational errors

Operational errors result from errors and accidents in treatment procedures, logistics, or medicine 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 interventions. 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.

¹⁰ Montresor, A., Awasthi, S., Crompton, D.W.T. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis *Acta Trop.*, **2003**, 86:223-232

¹¹ Urbani, C., and Albonico, M. Anthelmintic drug safety and drug administration in the control of soil-transmitted helminthiasis in community campaigns. *Acta Trop.*, **2003**, 86:215-223

Montresor, A., Awasthi, S., Crompton, D.W.T. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis *Acta Trop.*, **2003**, 86:223-232

Horton, J. Albendazole: a review of anthelmintic efficacy and safety in humans. *Parasitology*, **2000**, 121:S113-S132.

¹² Schmidt, L.E., Dalhoff, K. Food-drug interactions *Drugs* 2002, 62(10):1481-1502

¹³ Trachoma control: a guide for programme managers, WHO, London School of Hygiene & Tropical Medicine, and the International Trachoma Initiative, 2006, http://www.who.int/blindness/publications/tcm%20who_pbd_get_06_1.pdf

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 are procured from suppliers holding a valid marketing authorisation issued by TFDA (add TFDA to abbreviations list) or prequalified through appropriate national procedures,

independent quality control tests are conducted at appropriate intervals on batches before (and where applicable after) shipment to recipient countries by the appropriate entities, national programme managers and all those involved in the handling and administration of medicines receive clear and locally meaningful instructions about:

- medicines handling, storage & transportation,
- 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 medicines being used or are at risk of being coinfecting 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.

2.3 Coincidental events

A coincidental event is an adverse event that happens during or immediately after a large-scale preventive chemotherapy intervention. In certain cases such events are falsely attributed to the medicine(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. These purely temporal associations are inevitable given the large number of doses administered in a large-scale treatment intervention. In addition, large-scale interventions involve populations living in remote areas, who 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.

Coincidental adverse events may be predictable if the size of the population and the incidence of disease or death in the community are known. Knowledge, if available, of these background rates of disease and deaths allows estimation of the expected numbers of coincidental events.

For example, let's assume that one million children aged 4-15 years are treated in a mass campaign and the background mortality rate for this population is 3 per 1000 per year. Then, about 250 deaths can be expected in the month after the mass campaign and about 8 deaths on the day of medicine administration (assuming that all are treated on the same day), simply by coincidence. These deaths are chronologically associated with the mass treatment intervention, even though they are entirely unrelated to it.

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.

A number of coincidental deaths must be expected in the week and month after mass drug administration, and some of these may be wrongly associated with the medicines used in the intervention. 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 treatment intervention 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 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).

3. Approach to management of SAEs

3.1 Communicating information on known AEs and SAEs

Part of the preparation of a large-scale preventive chemotherapy intervention includes explaining objectives and expected benefits of the intervention to health-care providers or community volunteers for them to adequately inform and motivate the community and, especially, motivate all at-risk individuals to accept treatment. This social mobilization process is complex and community characteristics and responses to various types of communication and messages are different and often demand the assistance of communication experts. Investment in social mobilization strategies is critical to achieving and sustaining high coverage and achieving public health goals. This preparatory work should also include providing information about AE that are likely to occur. 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 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 (see section 3.3).

3.2 Preparing preventive chemotherapy interventions to properly and timely manage SAEs

As mentioned earlier, most, if not all, SAEs associated with medicines used in large-scale preventive chemotherapy, occur in patients with heavy infections or coinfections 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 preventive chemotherapy interventions. 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 central storage to the peripheral staff who administer medicines, information that identifies the specific medicinal products is recorded, even when medicines are not distributed in their original container (e.g. brand name, batch and any other identification number, date received, 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. National programme managers should prepare locally meaningful guidelines taking into account local information about health workers skills, health care delivery facilities, availability of medicines and other supplies.

Most symptoms are mild and transient and can be satisfactorily be treated at the drug delivery level. Annex F provides simple guidance that can be provided, after adaptation to meet local requirements,

to primary health care workers and drug distributors to assist them treating patients experiencing adverse events at the drug distribution level or referring them to the appropriate health care facility.

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 (see section 3.3 and annex F). 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. Sections 5 and 6 address this aspect.

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 ensure that information is rapidly disseminated and this is best achieved through direct and privileged links with community leaders and peripheral health 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.

The following points may help 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 (see Table 4.3).

Table 4.3 - Action taken to address AE that community leaders can verify

Stage of investigation	Action
Incident detected	Assess and investigate with appropriate degree of urgency
Investigation starts	Investigator has adequate resources Increase surveillance to identify similar cases in and out of area Define any suspect medicine
Investigator develops working hypothesis	Working hypothesis is confidential until confirmed If programme errors are working hypothesis, they are being corrected If medicine quality problem suspected, medicine batch quarantined
Investigator confirms working hypothesis	Advise community of cause, and of planned response (see below)

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 at the end of the investigation/assessment:

a) the AE has been caused by the medicine(s) (i.e. is an ADR) and appeared at the expected rate
nothing unexpected is happening, the benefits of preventive chemotherapy outweigh the adverse events it causes (see annex G).

b) the AE has been caused by the medicine(s) (i.e. is an ADR) and appeared at higher than expected rate
problematic batches are being/have been withdrawn;
manufacturing specifications or quality control procedures are being/have been changed;
new medicines are being/have been obtained from a different manufacturer.

c) the AE has been caused by operational error
the causes of the error are being/have been corrected (e.g. change in logistics for supplying medicines; change in procedures at treatment sites; further training of relevant staff; intensified supervision);
corrective measures will be reviewed in ... months time to ensure that errors have actually been corrected.

d) the AE is coincidental
Present convincing data showing that the event truly was coincidental.
Involve key persons, who enjoy community's trust, review investigation process and conclusions and seek their help to convince/ensure that the event truly was coincidental.

e) 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.

4.4 Communicating with the media

The media inform the public on any story they find that is important, interesting, entertaining and topical for their readers. They need to do this in a way which grips their audience and will lead to the sale of their media (newspapers, radio stations and television chains). They are an important player in addressing communities' concerns about preventive chemotherapy and public health in general. They will always be on the lookout for a good story. Because there is little time/space to tell their stories, reporters and editors must reduce the story to its essentials. Because of this complicated stories may be over-simplified, and also reporters may not always have the detailed knowledge in an area to grasp subtleties. This may be a cause for concern, and may be magnified if the reporter asks for expert opinion which may contradict that provided by the NTD control

programme. 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, 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. Some more detailed advice is provided in Annex D.

In certain cases, the main effect of media coverage is public concern about preventive chemotherapy. When a case arises, it is important that programme managers reach professional organizations, health professionals and field staff before the media and advise them on how to deal with public concerns and minimize potential harm to preventive chemotherapy interventions. It is also useful to seek the support of groups and individuals that have public respect and authority and get them to make public comments to endorse preventive chemotherapy and get key messages through to the communities.

It is very important to designate a spokesperson to communicate with the media. This will reduce the possibility of sending contradictory messages. The spokesperson should be prepared and provided adequate training on media relations. S/he should start acting as spokesperson and building relations with the media before any preventive chemotherapy concerns arise.

4.4.1 Understanding the media perspective

The media can be helpful in getting public health messages through. For example, they can remind the public of and get people to understand the importance of preventive chemotherapy. Certainly, the media are mainly interested in stories that will attract attention and boost their sales. One technique they use is to dramatize and personalize events: personal stories are more attention grabbing than statistics and this may be uncomfortable for health professionals

Working with the media requires establishing a good working relationship with key reporters before there is a crisis, and get them to understand the public health perspective. It is easy for media stories to create a sense of panic about events which are unrelated to the medicines used in preventive treatment or are a remediable error. In addition, the media often report numbers of events and percentages, and frequently do not put them in the right context. Needless to say, an event of unknown cause has a high potential of causing fear and to push people to find something/someone to blame for it.

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'.

4.4.2 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. 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'.

4.4.3 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.

4.5 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.**

Reports are the starting step to providing adequate response to communities' concerns, therefore they must include any deaths or serious events believed (rightly or wrongly) by the public to be caused by the medicines used in the intervention. Any event or circumstances that may jeopardize the credibility and sustainability of preventive chemotherapy interventions should be reported and properly managed. 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. Each country should decide individually which events are appropriate for inclusion in its national system. To facilitate health workers' task, national preventive chemotherapy safety committees should prepare (on the basis of national experience and published information) a list of expected serious adverse events with their detailed clinical description as outlined, as an example, in table 5.1.

Table 5.1 Examples of serious adverse events that should be reported

ADVERSE EVENTS THAT SHOULD BE REPORTED
Any hospitalization or death
Anaphylactic Reaction
Mazzotti Reaction (fever, urticaria, swollen and tender lymph nodes, tachycardia, hypotension, oedema, joint and abdominal pain)
Fits, convulsion, and seizures
Choking

In general, there is no great benefit in reporting common minor reactions such as nausea, mild abdominal pain and other self-limiting symptoms. These are expected to occur and if they were all reported, the volume of reports would overwhelm the system while contributing information of limited value. However, where national reporting guidelines exist they should be followed. It is important for those who administer the medicines to advise people treated (including parents in the case of children), at the time of treatment, that some reactions are expected and provide practical advice people can follow to manage symptoms with simple remedies. 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:

- Health and other staff administering medicines in preventive chemotherapy interventions;
- Health workers providing clinical treatment of AEs in health facilities (any kind/level);
- Relatives/parents who report AEs affecting members of their family;
- Researchers conducting clinical studies or operational research.

Health workers: When a recently treated person seeks treatment, health workers should be able to detect an AE and to determine whether it is an event requiring a report and further action. To do this, they must know what the events to be reported are and be able to prepare a report or at least send

signal up the safety surveillance system. Health workers should be able to manage mild problems and advise patients or their relatives/parents. It is not necessary to report mild reactions, unless the health worker has the perception that people's concerns are significant and may jeopardize the credibility of the preventive chemotherapy intervention.

People who are to be treated and other relevant members of the community should know what adverse events to expect after each treatment and should be urged and helped to seek medical assistance if symptoms that make them worried appear. They should understand that some symptoms actually show that the medicine is working. This knowledge may contribute to relieve anxiety about normal reactions and help people recognize more serious problems.

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.

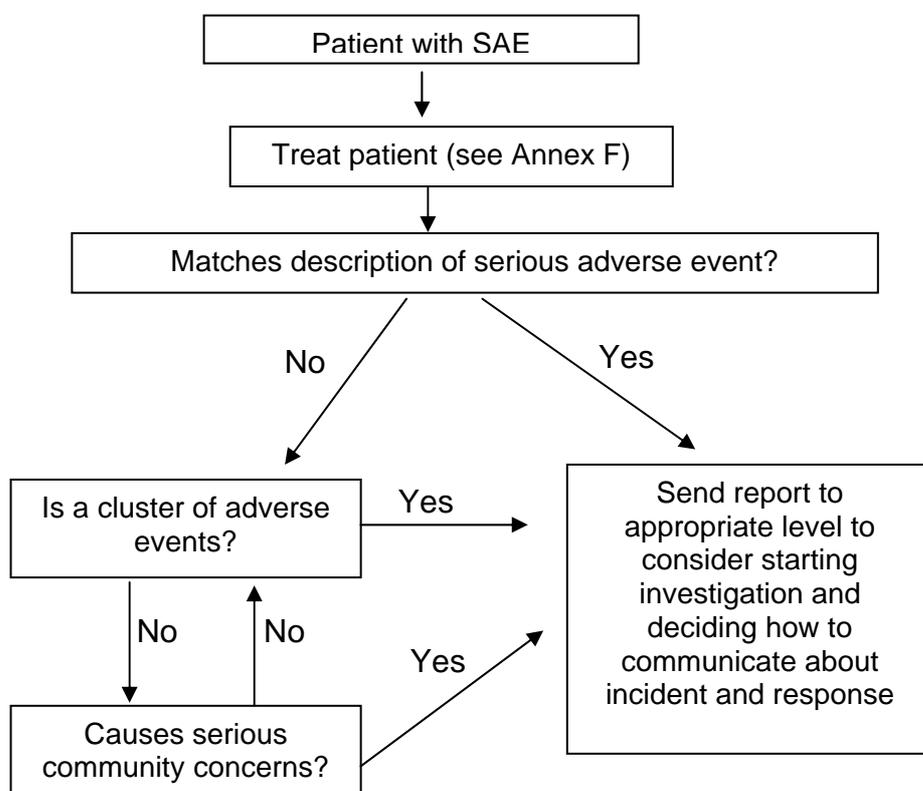


Diagram 5.3 - When peripheral health workers should report AEs

5.4 How to report?

Reports should be made on a standard Report Form (Annexes A and B). 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 (Annex A) to ensure that all essential information becomes quickly available and a decision on the need for further investigation can be made. If, for any reason, the standard report form cannot be completed, the minimum essential information that needs to be obtained at the point of contact nearest to the affected person (i.e. the person who is experiencing the adverse event being reported) is the following:

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;
affected person's identifying details (name, age, gender, contact information).

Reports concerning SAEs received at the appropriate reporting centre should also be provided to the national medicines regulatory authority and the concerned manufacturer(s) of the medicine(s). The reporting procedures are specific to each national situation and must be established by the appropriate competent authority. In the absence of such reporting procedures, preventive chemotherapy programmes should design their own mechanisms to ensure that SAEs are reported to the appropriate national health authorities and the concerned manufacturers. Where it needed, WHO can assist programme managers to design such procedures, including, where feasible, active safety surveillance.

5.5 How to overcome under-reporting?

Peripheral staff may not report AEs for one or more of the following reasons:

- not considering the event as related to the medicines used in the intervention;
- not knowing about the reporting system and process;
- procrastination, lack of interest or time, inability to find the report form or the person to contact within the safety surveillance system;
- fear that the report will lead to personal consequences;
- guilt about having caused harm and being responsible for the event;
- diffidence about reporting an event when not confident about its importance or diagnosis.

All these barriers to reporting need to be addressed in the preparation of the intervention. The following points need to be carefully considered:

- 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.

The role of peripheral staff is essential to trigger reports and to ensure the actual functioning of an adequate safety surveillance system. Peripheral health workers must be encouraged to report adverse events without fear of penalty. Reporting will enable improvement of the surveillance system and identify areas where further training or operational adaptations are necessary. It must never be the basis for blaming individuals. Positive feedback to health workers for making reports is essential. At a minimum, a personal acknowledgement to the health worker with a 'thank-you' for the report, even if the report is incomplete, should be provided. The feedback should also include the outcome of the report and involvement in the management and response to the adverse event. There must be an adequate supply of forms (and maybe postage-paid forms) to support 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. Unless national policy decides otherwise, 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 will naturally increase with increased preventive chemotherapy 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. Improved reporting can lead to more AE reports without a real increase in event rate. 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 for the national programmes to decide which level will decide which reports need to be investigated. The national preventive chemotherapy safety committee should define the type of AE that requires investigation. Regional/national assessors need to ensure that all reports requiring investigation have been adequately investigated.

6.2 Who should investigate?

Ideally, there should be an investigator with adequate training and resources for the investigation at each major administrative unit (e.g. region, or district), depending on each country's situation. In general, when embarking on an investigation, peripheral level investigators should ensure that the national level is aware and regularly updated through the investigation. A decision should be made as early as possible about who is taking up the role of spokesperson about the investigation.

6.3 When to investigate?

The urgency of the investigation will depend on the situation. National programme managers 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 (annex B) 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 (Annex C), which could become useful in other investigations and training activities. Investigations should aim to identify programme problems rather than find individuals to blame. While 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. Errors provide opportunity for learning, and creating a system that encourages hiding errors will cause more errors. 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 Investigating AE clusters

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. It is therefore important to identify if untreated people also developed similar symptoms around the same time. If all cases happen at a specific site and there are no other cases elsewhere, operational error is likely. 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.

Diagram 6.4.1 suggests a possible approach to investigating clusters of AEs.

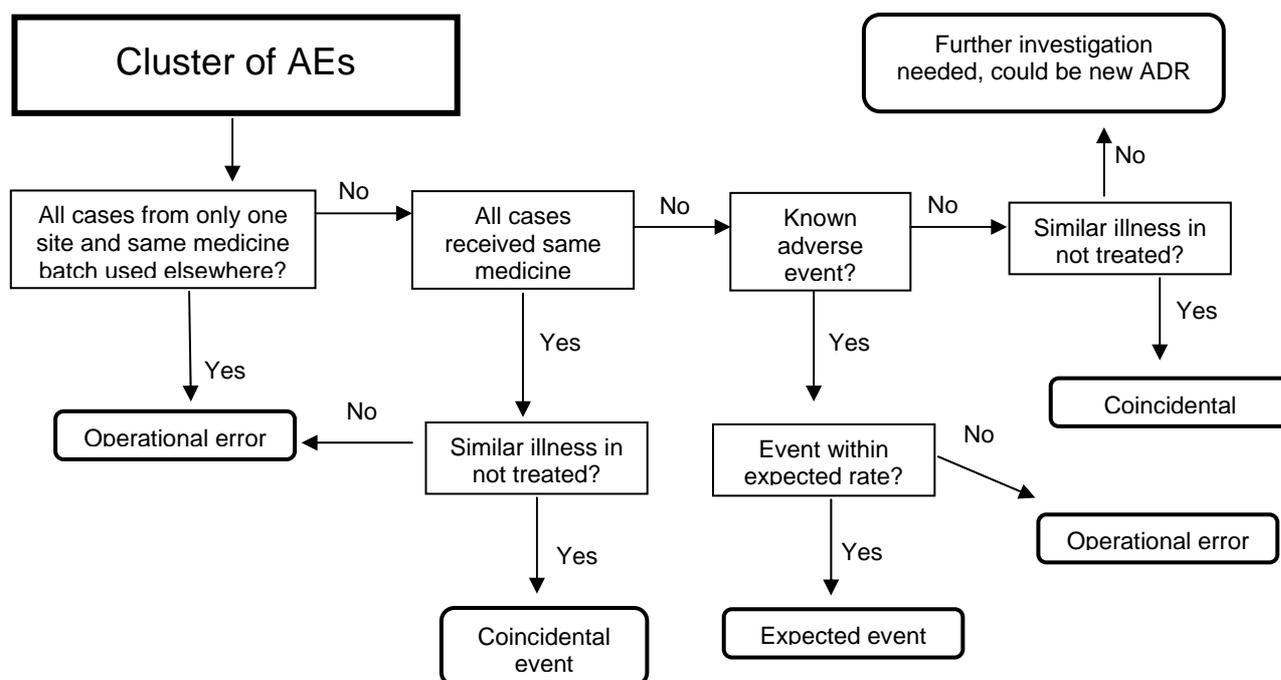


Diagram 6.4.1 - A possible approach to investigating clusters of AEs

6.5 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 information (if any).
- 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 is extremely useful and should have been included in the national guidelines on reporting or defined during a specific investigation), date of appearance, duration, and treatment of the clinical event.

History of the patient (past medical conditions, previous reactions to vaccines or medicines, allergies, pre-existing neurological disorders, medicines recently or currently taken, etc.).

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 look 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 (Annex C).

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 and exposure to treatment among controls (same population, untreated - same population, before treatment). Without such comparison it will be impossible to identify the cause of the AE, unless it is a case of operational error. Clear descriptions of the clinical features should have been included in the national guidelines on reporting or, in their absence, defined during a specific investigation. This will permit the identification of all cases in the community and find out the outcomes for all those who received the suspect medicine. A comparison of the risk of disease should be made considering those who received the medicine versus those who did not. 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 (Annex C) should be completed only at the end of the investigation.

6.6 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. WHO's Drug Monitoring Programme proposes the following approach¹⁴:

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

¹⁴ <http://www.who-umc.org/graphics/4409.pdf>

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 (i.e. recovery after medicine withdrawal and, although deliberate re-challenge is often not ethical, recurrence on re-challenge is strongly suggestive that the medicine was responsible), exclusion of confounding factors, and clinical plausibility.

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 preventive chemotherapy safety committee, if established and operational, has the role of confirming the causality assessments of selected investigations and, where required, assisting investigators to determine causality.

7. Establishing preventive chemotherapy safety surveillance

Effective safety surveillance requires collaboration between the national preventive chemotherapy programme and, when it exists, the medicines regulatory authority (MRA) and/or the national Pharmacovigilance Centre. In some countries, all or part of the activities related to pharmacovigilance are carried out by a specific organization (e.g. teaching hospital, university department), which is generally linked to the MRA. The preventive chemotherapy safety surveillance system should build on any existing functioning pharmacovigilance system on the basis of a mutually-strengthening principle. There is no pre-established model: the best surveillance system is that which achieves the highest results in terms of appropriate action in response to reports of serious AEs. A simple check-list to assist in establishing and running a safety surveillance system is provided in annex E.

7.1 Objectives

There are several possible objectives for safety surveillance in conjunction with large-scale preventive chemotherapy. These must be defined at the national level taking into account disease prevalence, treatment coverage and other local aspects. The specific objectives and their relative importance will guide in designing the surveillance system and in its implementation. It should be anticipated that objectives - and the surveillance system itself - may change over time. The most important goal of 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. A safety surveillance system is an indicator of intervention quality. 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.

Possible objectives of preventive chemotherapy safety surveillance

- 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 medicines benefits and risks;
- generating new data and hypothesis about adverse events;
- supporting health professionals to improve experience and skills in this areas;
- comparing AE rates obtained in different areas/populations.

When establishing a safety surveillance system, its objectives should be clearly stated and widely disseminated to engender the support of health workers and other concerned parties. Identifying realistic, limited, objectives is better than setting unachievable ones. One option is to have a minimum level of surveillance conducted on national level to detect operational errors with a few hospitals/facilities conducting more intensive and detailed AE surveillance. It is critical for any information obtained through safety surveillance to be immediately assessed and analysed to identify and respond to problems. Response, i.e. reacting quickly and in the correct way, is probably the most critical aspect of safety surveillance, and certainly is its most visible one.

7.2 Differences between preventive chemotherapy safety surveillance and pharmacovigilance in general

Large-scale preventive chemotherapy implies administering medicines 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 system is set up to monitor and manage adverse events that emerge in the course of a typical, often continued, patient-health professional interaction.

Experience in the peculiar settings and operational aspects 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 regional/national 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.

7.3 Roles and responsibilities for safety surveillance: involving all concerned parties

In all countries where an MRA or a national Pharmacovigilance Centre (PvC) exists, then they must be involved in preventive chemotherapy safety surveillance. The roles and responsibilities of the MRA include:

- marketing authorization of medicines;
- post-marketing surveillance of authorized medicines;
- performing or organizing laboratory testing;
- inspecting manufacturing, importation, storage and distribution sites (as applicable);
- issuing independent information on medicines.

The above responsibilities can be performed directly by the MRA or in collaboration with other institutions (e.g. teaching hospital, university department, quality control laboratory). For simplicity sake, in these notes we shall just mention MRA/PvC - letting each national situation adapt this concept to what is locally applicable. However, the MRA/PvC may have limited knowledge about large-scale preventive chemotherapy interventions. Depending on specific local circumstances, it may be essential that preventive chemotherapy programme managers take the lead in establishing and implementing an effective safety surveillance system. The system will also need to involve a number of other parties with specific roles. Table 7.3 presents just an example that needs to be adapted to suit specific national situations.

Table 7.3 - Roles and responsibilities of parties to be involved in safety surveillance

PARTY	ROLE
Medicines Regulatory Authority/National Pharmacovigilance Centre	overall responsibility for national medicines safety monitoring policy and activities manages AE database for comprehensive analysis of available data
national programme manager for NTD control	responsible for preventive chemotherapy safety at national level; reviews information on AE reports; conducts regular analysis of AEs and feeds results back down the system; provides support to provincial/regional investigator; spokesperson for preventive chemotherapy safety system
national NTD preventive chemotherapy safety committee	composed of national programme manager for preventive chemotherapy interventions, representatives MRA and national pharmacovigilance centre, infectious disease physician, epidemiologist, and pharmacologist; adopts policy and procedures; guidelines and standard forms for reporting and investigating; reviews overall pattern of reports and investigations; provides causality assessment on inconclusive investigations; provides system's quality supervision;
province/region level investigator	assesses report, conducts investigation, forwards conclusions of investigation, reports action taken to respond or proposes action to be taken to respond
peripheral/district level supervisors	checks that reports meet criteria, forwards checked and completed reports to investigator
peripheral health workers	treats affected patients (see annex F); reports serious adverse events to supervisor (see overview of peripheral health worker action in diagram 5.3)

7.4 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. WHO's NTD website (http://www.who.int/neglected_diseases/en/) provides useful resources.

7.5 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:

1. 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.
2. Identify the resources available and needed and obtain political commitment to implement safety surveillance.
3. Appoint or designate regional/national assessors/focal points for NTD preventive chemotherapy safety.
4. Establish the national NTD preventive chemotherapy safety committee.
5. Develop and disseminate a **list of serious events** to be reported; a standard **investigation procedure**; and report and investigation **forms**.
6. Designate and train staff to prepare preliminary reports (peripheral health workers), complete report forms (district level) and investigate cases (province/region level).
7. Inform all health workers/clinicians of the need to report **serious AEs** immediately, and clarify which ones should be reported.
8. Consider the establishment of a compensation scheme for people who suffered specified AEs.

8. 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.

ANNEX A - SIMPLE AE REPORT FORM¹⁵

Name	Birth date	ID Nr ¹⁶ :
Address:	Male	Female
	Reporter's name & contact:	
Treatment site:		

Medicine given (generic name)	Dose	Band & Manufacturer	Batch number

Date/time preventive treatment given	Date/time AE started	Date/time patient seen first time after AE	Date of report

Action taken to treat AE

Check box and describe as needed ¹⁷ : <input type="checkbox"/> Encephalopathy/Encephalitis <input type="checkbox"/> Mazzotti reaction <input type="checkbox"/> Severe allergic reaction <input type="checkbox"/> Other serious ¹⁸ AE (describe):	Past medical history and any other relevant information:
Currently recovered Y/N/? Hospitalized Y/N/? Died Y/N/?	

Investigator's office should complete:

Date report received:	Checked by:
Investigation needed: Y/N/?	If yes, date investigation started:
Investigator:	Investigation ID Nr:
Cause:	Degree of certainty:

¹⁵ a more detailed form should be used in conjunction with an investigation, see annex B.

¹⁶ ID Nr: unique identifier number, invented by and specific to each treatment site.

¹⁷ the list should be based on locally meaningful a table of named AE with their clinical features.

¹⁸ Serious AE = 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 concern in the community.

ANNEX B - COMPREHENSIVE AE REPORT FORM

(From: *Preventive chemotherapy in human helminthiasis : coordinated use of anthelmintic drugs in control interventions : a manual for health professionals and programme managers, WHO 2006*)

Country:		Date of report: / /			
1. Patient information					
Name (first/middle/last)			Age		Sex (M/F)
Location		District		Province/State	
2. Pre-existing conditions					
Health status before treatment with preventive chemotherapy drugs:					
<input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Unknown If "Poor", give details:					
Parasitic infections	Confirmed	Suspected	Negative	Unknown	Details
1. STH	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2. Lymphatic filariasis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
3. Onchocerciasis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4. Schistosomiasis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other parasitic infections, known or suspected:					
Malaria <input type="checkbox"/> Yes <input type="checkbox"/> No					
Loiasis <input type="checkbox"/> Yes <input type="checkbox"/> No If "Yes", mf/ml (blood): mf/ml (CSF):					
Other medications being taken (concurrently or recently):					
Is patient pregnant? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown					
3. Drugs administered					
Which of the following drugs were administered to the patient?	Dose	Brand and Manufacturer Name	Batch number	Date of treatment: (day/month/year)	
<input type="checkbox"/> albendazole					
<input type="checkbox"/> diethylcarbamazine (DEC)					
<input type="checkbox"/> ivermectin					
<input type="checkbox"/> mebendazole					
<input type="checkbox"/> praziquantel					
Source of treatment:			Patient's height (cm)	Patient's weight (kg)	
<input type="checkbox"/> Mass treatment programme <input type="checkbox"/> Clinic or physician treatment <input type="checkbox"/> Other method					

Was this a first treatment with any of the drugs selected above?

Yes No Unknown

If "Yes", which of the following drugs were first treatments?

albendazole diethylcarbamazine (DEC) ivermectin mebendazole praziquantel

If "No", explain when, and circumstances of past treatment(s) of each drug:

4. Description of the serious adverse experience (SAE)

Date of onset (day/month/year):

How long after drugs were taken?

hours OR days

Clinical signs and symptoms (please describe)

Do you think this adverse event is/was life-threatening? Yes No

Laboratory results (please provide name of test)

Dates of tests
(day/month/year)

a) **Hospitalization** Yes No

If "Yes", indicate:

1. Date of admission (day/month/year)
2. Reason(s) for admission:
3. Date of discharge (day/month/year)

b) **Drug treatments administered to treat adverse event:**

c) **Clinical course:**

(Attach any relevant reports)

5. Condition/outcome at time of last observation	
Full recovery:	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Ongoing illness:	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
If "Yes", describe current condition:	
Persistent/significant disability/incapacity:	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
If "Yes", describe:	
Death:	<input type="checkbox"/> Yes <input type="checkbox"/> No
If "Yes", indicate:	
1. Date of death (day/month/year):	
2. Cause of death:	
3. Circumstances at the time of death, in detail:	
Report any autopsy findings, including tissues taken for histopathology and any additional studies done or requested (use additional pages if necessary to complete your answers):	
6. Conclusions (to be completed by the health-care provider)	
<i>Presumptive diagnosis:</i>	
<i>Do you think the combined treatment with the drugs selected in Box 3 was a possible causative factor in this serious adverse event?</i>	
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not sure	
If "Yes", explain:	
If "No" or "Not sure", what do you believe was the cause of the experience?	
7. Source - Report prepared by:	
Name of person making the report	
Organization & Title	
Address	
Phone, mobile phone and fax numbers (<i>including country code and area code</i>)	
Signature and date	

ANNEX C - AE INVESTIGATION FORM

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

Investigation ID Nr:	Report ID Nr:	date investigation started:
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 versus not treated? Y/N/? Other comments:		
Treatment site investigated?: Y/N/? If yes, key findings:		
Other relevant investigation findings:		

Conclusion about cause of AE	Describe
Adverse reaction to the medicine Operational error Coincidental event Unknown	
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:.....

ANNEX D - COMMUNICATING WITH THE MEDIA

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

- 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 (risk of disease and complications);
- 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.

ANNEX E - 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.

ANNEX F - MANAGING PATIENTS EXPERIENCING ADVERSE EVENTS AT THE DRUG DISTRIBUTION LEVEL

Adverse event or symptom	Frequency ¹⁹	Treatment (in all cases explain to patient that adverse event is sign that medicine works and was needed)
Abdominal pain	Common	put patient at rest, protect patient from excessive temperature, noise and light
Headache, aches in other parts of the body, pain in the joints	Uncommon	paracetamol tablets; children 1-5 years: 125-250mg; children 6-12 years: 250-500mg; from 12 years old: 500mg-1g (these doses can be repeated after 4-6 hours if necessary).
Nausea, vomiting	Uncommon	traditional remedies (e.g. sour fruit juices).
Malaise (feeling unwell), feeling sleepy, tired, weak	Uncommon	put patient at rest, protect patient from excessive temperature, noise and light
Photophobia (exposure to light causes discomfort or pain to the eyes)	Uncommon	protect patient's eyes from light
Diarrhoea	Uncommon	Put patient at rest, protect patient from excessive temperature, noise and light, Make sure patient can drink water or fruit juices Watch possible signs of dehydration (thirst, dry skin, dark coloured urine, dry mouth, fatigue, weakness)..
Recrudescence of symptoms of underlying disease (e.g. blood in urine)	Uncommon	put patient at rest, protect patient from excessive temperature, noise and light
Swollen lymph nodes	Uncommon	put patient at rest, protect patient from excessive temperature, noise and light
Wheezing (whistling sound produced during breathing) in person that has no history of asthma or other respiratory disease. <i>Make sure the tablet is not choking the patient.</i>	Rare	antihistamines: chlorphenamine tablets; children 2-5 years: 1mg; children 6-12 years: 2mg; from 12 years old: 4mg (these doses can be repeated after 4-6 hours if necessary). or promethazine tablets; children 2-5 years: 5-15mg/day in 2 doses; children 6-12 years: 10-25mg/day in 2 doses; from 12 years old: 10-20mg up to 3 times a day. If symptoms are not controlled or worsen: refer patient to appropriate health facility
Allergic skin reactions (e.g. pruritus)	Rare	Antihistamines (se above)
Severe or worsening symptoms of any kind	Very rare	refer patient to appropriate health facility
Whenever applicable: warn patient not to use the same drug again		

¹⁹ *Common (frequent)* means between 1 and 10 cases per 100 treated persons - *Uncommon (infrequent)* means between 1 and 10 cases per 1000 treated persons - *Rare* means between 1 and 10 cases per 10,000 treated persons - *Very rare* means less than 1 case per 10,000 treated persons. From: *Guidelines for Preparing Core Clinical Safety Information on Drugs - Report of CIOMS Working Group III. Geneva, WHO, 1995. Page 36.*

ANNEX G - MODEL SAFETY INFORMATION SHEETS

This annex includes information that has been adapted from Sweetman S (Ed), Martindale: The complete drug reference. London: Pharmaceutical Press. Electronic version, 35th Edition, 2007. This is provided as general reference, detailed safety information is specific to each regulatory jurisdiction and should be sought in the leaflets accompanying the medicinal products, the national medicines regulatory authority, or the manufacturer (who has the ultimate responsibility for product safety and quality). Upon request, WHO is willing to assist national programme managers to obtain appropriate information on medicines safety.

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 phase²⁰ 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 studies²¹ 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 reported²² 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.

²⁰ Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64**: 383–8.

²¹ Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67**: 503–8.

²² el Kalla S, Menon NS. Mebendazole poisoning in infancy. *Ann Trop Paediatr* 1990; **10**: 313–14.

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.²³

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.²⁴

²³ Luder PJ, *et al.* Treatment of hydatid disease with high oral doses of mebendazole: long-term follow-up of plasma mebendazole levels and drug interactions. *Eur J Clin Pharmacol* 1986; **31**: 443–8.

²⁴ Bekhti A, Piroette J. Cimetidine increases serum mebendazole concentrations: implications for treatment of hepatic hydatid cysts. *Br J Clin Pharmacol* 1987; **24**: 390–2

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.²⁵

Incidence of adverse effects.

Although generally well-tolerated, the following adverse reactions were reported in the first phase of WHO-coordinated studies²⁶ 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,²⁷ 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.²⁸ However it was considered that this should not prevent the use of single doses in mass treatment programmes.²⁹

Effects on the liver.

In a series of 40 patients given albendazole for echinococcosis, 7 developed abnormalities in liver function tests during therapy.³⁰ 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.

²⁵ Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67**: 503–8.

²⁶ Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human echinococcosis. *Bull WHO* 1986; **64**: 383–8.

²⁷ Davis A, *et al.* Multicentre clinical trials of benzimidazolecarbamates in human cystic echinococcosis (phase 2). *Bull WHO* 1989; **67**: 503–8.

²⁸ Forrester JE, *et al.* Randomised trial of albendazole and pyrantel in symptomless trichuriasis in children. *Lancet* 1998; **352**: 1103–8

²⁹ Winstanley P. Albendazole for mass treatment of asymptomatic trichuris infections. *Lancet* 1998; **352**: 1080–1.

³⁰ Morris DL, Smith PG. Albendazole in hydatid disease—hepatocellular toxicity. *Trans R Soc Trop Med Hyg* 1987; **81**: 343–4.

Interactions

Anthelmintics.

The plasma concentration of albendazole sulfoxide has been increased by *praziquantel*,³¹ 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*.³²

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.³³

³¹ Homeida M, *et al.* Pharmacokinetic interaction between praziquantel and albendazole in Sudanese men. *Ann Trop Med Parasitol* 1994; **88**: 551–9.

³² Jung H, *et al.* Dexamethasone increases plasma levels of albendazole. *J Neurol* 1990; **237**: 279–80

³³ Wen H, *et al.* Initial observation on albendazole in combination with cimetidine for the treatment of human cystic echinococcosis. *Ann Trop Med Parasitol* 1994; **88**: 49–52

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.^{34,35,36} 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 was reported to be reduced after repeated annual administration.³⁷ 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 time³⁸ and when treatment was repeated a year later that incidence was reduced even further. The results from several trials in this programme³⁹ 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,⁴⁰ 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 study⁴¹ 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 treatments⁴² 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

³⁴ Kumaraswami V, *et al.* Ivermectin for the treatment of *Wuchereria bancrofti* filariasis: efficacy and adverse reactions. *JAMA* 1988; **259**: 3150–3

³⁵ Rothova A, *et al.* Side-effects of ivermectin in treatment of onchocerciasis. *Lancet* 1989; **i**: 1439–41

³⁶ Zea-Flores R, *et al.* Adverse reactions after community treatment of onchocerciasis with ivermectin in Guatemala. *Trans R Soc Trop Med Hyg* 1992; **86**: 663–6

³⁷ Burnham GM. Adverse reactions to ivermectin treatment for onchocerciasis: results of a placebo-controlled, double-blind trial in Malawi. *Trans R Soc Trop Med Hyg* 1993; **87**: 313–17

³⁸ De Sole G, *et al.* Lack of adverse reactions in ivermectin treatment of onchocerciasis. *Lancet* 1990; **335**: 1106–7

³⁹ De Sole G, *et al.* Adverse reactions after large-scale treatment of onchocerciasis with ivermectin: combined results from eight community trials. *Bull WHO* 1989; **67**: 707–19

⁴⁰ Kamgno J, *et al.* Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 2004; **98**: 496–504

⁴¹ Gardon J, *et al.* Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. *Lancet* 1997; **350**: 18–22

⁴² The Mectizan[®] Expert Committee and The Technical Consultative Committee. Recommendations for the treatment of onchocerciasis with Mectizan[®] in areas co-endemic for onchocerciasis and loiasis. 2004. Available at: [online EnglishMECTCCLoaRecs-June04.pdf](#) (accessed 20/09/05)

doses appears to be lower than after the first dose and the need for supervision on re-treatment has been questioned.⁴³

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,⁴⁴ but others have not confirmed this effect⁴⁵ or observed any bleeding disorders.⁴⁶

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.⁴⁷ 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.⁴⁸ However, the information approved by the US FDA⁴⁹ 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 assessment⁵⁰ 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;⁵¹ it was considered that the precaution of avoiding the use of ivermectin in women notifying a pregnancy should be adequate.

⁴³ Whitworth JAG, *et al.* A community trial of ivermectin for onchocerciasis in Sierra Leone: adverse reactions after the first five treatment rounds. *Trans R Soc Trop Med Hyg* 1991; **85**: 501–5

⁴⁴ Homeida MMA, *et al.* Prolongation of prothrombin time with ivermectin. *Lancet* 1988; **i**: 1346–7

⁴⁵ Richards FO, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i**: 1139–40

⁴⁶ Pacque MC, *et al.* Ivermectin and prothrombin time. *Lancet* 1989; **i**: 1140

⁴⁷ Ogbuokiri JE, *et al.* Ivermectin levels in human breast milk. *Eur J Clin Pharmacol* 1994; **46**: 89–90

⁴⁸ American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: [online](http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s0261bl.pdf) (accessed 02/06/04)

⁴⁹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s0261bl.pdf

⁵⁰ Pacqué M, *et al.* Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* 1990; **336**: 1486–9

⁵¹ Chippaux J-P, *et al.* Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg* 1993; **87**: 318

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.⁵²

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.⁵³

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.⁵⁴

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.⁵⁵

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

⁵² WHO. Lymphatic filariasis: the disease and its control: fifth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser* 821 1992

⁵³ Yazdanbakhsh M, *et al.* Serum interleukin-6 levels and adverse reactions to diethylcarbamazine in lymphatic filariasis. *J Infect Dis* 1992; **166**: 453–4

⁵⁴ WHO. WHO expert committee on onchocerciasis: third report. *WHO Tech Rep Ser* 752 1987

⁵⁵ WHO. Lymphatic filariasis: fourth report of the WHO expert committee on filariasis. *WHO Tech Rep Ser* 702 1984

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*⁵⁶ suggest that the uterine hypermotility induced by diethylcarbamazine is mediated via prostaglandin synthesis; this might explain the mechanism of the abortifacient action previously reported.⁵⁷

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.⁵⁸ 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 a less acidic urine.

⁵⁶ Joseph CA, Dixon PAF. Possible prostaglandin-mediated effect of diethylcarbamazine on rat uterine contractility. *J Pharm Pharmacol* 1984; **36**: 281–2

⁵⁷ Subbu VSV, Biswas AR. Ecbolic effect of diethyl carbamazone. *Indian J Med Res* 1971; **59**: 646–7

⁵⁸ Adjepon-Yamoah KK, *et al* The effect of renal disease on the pharmacokinetics of diethylcarbamazine in man. *Br J Clin Pharmacol* 1982; **13**: 829–34

PRAZIQUANTEL

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.⁵⁹ A similar syndrome has been reported in some patients with *Schistosoma japonicum* infection given praziquantel.⁶⁰ 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 reported⁶¹ 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.⁶²

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.⁶³

⁵⁹ Polderman AM, *et al.* Side effects of praziquantel in the treatment of *Schistosoma mansoni* in Maniema, Zaire. *Trans R Soc Trop Med Hyg* 1984; **78**: 752–4

⁶⁰ Watt G, *et al.* Bloody diarrhoea after praziquantel therapy. *Trans R Soc Trop Med Hyg* 1986; **80**: 345–6

⁶¹ Flisser A, *et al.* Neurological symptoms in occult neurocysticercosis after single taenical dose of praziquantel. *Lancet* 1993; **342**: 748

⁶² Adam I, *et al.* Is praziquantel therapy safe during pregnancy? *Trans R Soc Trop Med Hyg* 2004; **98**: 540–3

⁶³ Quinn DI, Day RO. Drug interactions of clinical importance: an updated guide. *Drug Safety* 1995; **12**: 393–452

Antimalarials

Chloroquine has been reported to reduce the bioavailability of praziquantel.⁶⁴

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,⁶⁵ 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.⁶⁶

11. Farid Z, *et al.* Unsuccessful use of praziquantel to treat acute fascioliasis in children. *J Infect Dis* 1986; **154**: 920–1.
12. Farid Z, *et al.* Treatment of acute toxæmic fascioliasis. *Trans R Soc Trop Med Hyg* 1988; **82**: 299.

⁶⁴ Masimirembwa CM, *et al.* The effect of chloroquine on the pharmacokinetics and metabolism of praziquantel in rats and in humans. *Biopharm Drug Dispos* 1994; **15**: 33–43

⁶⁵ Vazquez ML, *et al.* Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. *Neurology* 1987; **37**: 1561–2

⁶⁶ Metwally A, *et al.* Effect of cimetidine, bicarbonate and glucose on the bioavailability of different formulations of praziquantel. *Arzneimittelforschung* 1995; **45**: 516–18

Jung H, *et al.* Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. *Antimicrob Agents Chemother* 1997; **41**: 1256–9

