



A H A N D B O O K

for MANAGING ADVERSE EVENTS FOLLOWING
MASS DRUG ADMINISTRATION (AEs-f-MDA) and
S E R I O U S A D V E R S E
E V E N T S (S A E s)



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ENVISION provides assistance to national neglected tropical disease (NTD) control programs for the control and elimination of seven targeted NTDs: lymphatic filariasis, onchocerciasis, schistosomiasis, three soil-transmitted helminths (roundworm, hookworm, whipworm) and trachoma. The period of performance is September 30, 2011 through September 29, 2016.

This handbook has been designed to provide program managers with a brief, capsular set of steps to follow when required to deal with Serious Adverse Events (SAEs) – often as emergencies – and to serve as an aid to facilitate immediate and appropriate program responses.

The handbook has been created in line with suggestions from the Fifth Meeting of the Working Group on Access to Assured-Quality Essential Medicines for Neglected Tropical Diseases (WGA) WHO, Geneva, Switzerland – 26 April 2013 that resolved to “*Further encourage and support countries **to adopt and adapt existing tools and guidelines for safety monitoring** in NTD treatment & control activities through effective collaboration between national pharmacovigilance systems and NTD programmes*”. Indeed, it is derived largely from the WHO manual “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 that provides more extensive information on the detection, management, investigation and reporting of AEs and SAEs. Significant portions of the WHO Manual have been incorporated into the present handbook to ensure that standardized definitions and the recommendations made at the global level (particularly through WHO and global regulatory agencies) are accurately reflected. Additionally, documents produced by WHO for its immunization programs have also been used to develop and highlight key concepts presented in this handbook. A set of companion training materials that can be used by NTD programs for in-person and remote trainings for both program managers and health workers/community drug distributors is available separately.

The handbook was developed by the RTI-led ENVISION project in collaboration with the Task Force for Global Health, assisted by numerous concerned public health and medical professionals.

¹ World Health Organization. *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*. Geneva: WHO, 2011.

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1. BACKGROUND

1.1 Preventive Chemotherapy

Preventive Chemotherapy using Mass Drug Administration (MDA) campaigns has emerged as an important tool for the control/elimination of Neglected Tropical Diseases (NTDs). Preventive chemotherapy programs rival immunization programs in their reach and number of individuals treated. Literally, hundreds of millions of people now receive integrated preventive chemotherapy for at least one disease each year.

Although the safety of the drugs used in preventive chemotherapy programs allows them to be administered to large segments of the population by “supervised non-medical personnel”, the effective recognition and management of **adverse events following MDA (AEs-f-MDA)** – whether caused by the medicines taken, or not – should be an essential component of preventive chemotherapy program planning and implementation. As preventive chemotherapy programs scale up, more AEs-f-MDA are almost certain to be reported along with increases in the number of **serious adverse events (SAEs)** as well. Proper management of AEs-f-MDA and effective reporting and investigation of SAEs are essential and will enhance the credibility of preventive chemotherapy programs.

1.2 Purpose of the document

Two types of adverse events are recognized during MDA programs². Most AEs-f-MDA are expected, commonly seen, self-limiting and able to be treated using simple remedies. Rarely, SAEs that not only threaten the life of individuals but also the success of the program occur. Those SAEs need to be properly recognized, reported and investigated to determine their cause.

² As detailed in Section 4, SAE is a regulatory term *limited* to an adverse event (AE-f-MDA) that 1) results in death; 2) requires in-patient hospitalization; 3) results in persistent or significant disability; 4) is life-threatening; or 5) results in a congenital anomaly/birth defect.

Most MDA programs rely on health workers and volunteers to distribute drugs and report any adverse events identified. In addition they are also tasked with managing common AEs-f-MDA. Adequate preparation of the community and training of program personnel are two key determinants of success at each round of MDA. Such training should emphasize early detection to ensure a prompt response and include prevention, detection, management and reporting of AEs-f-MDA and SAEs.

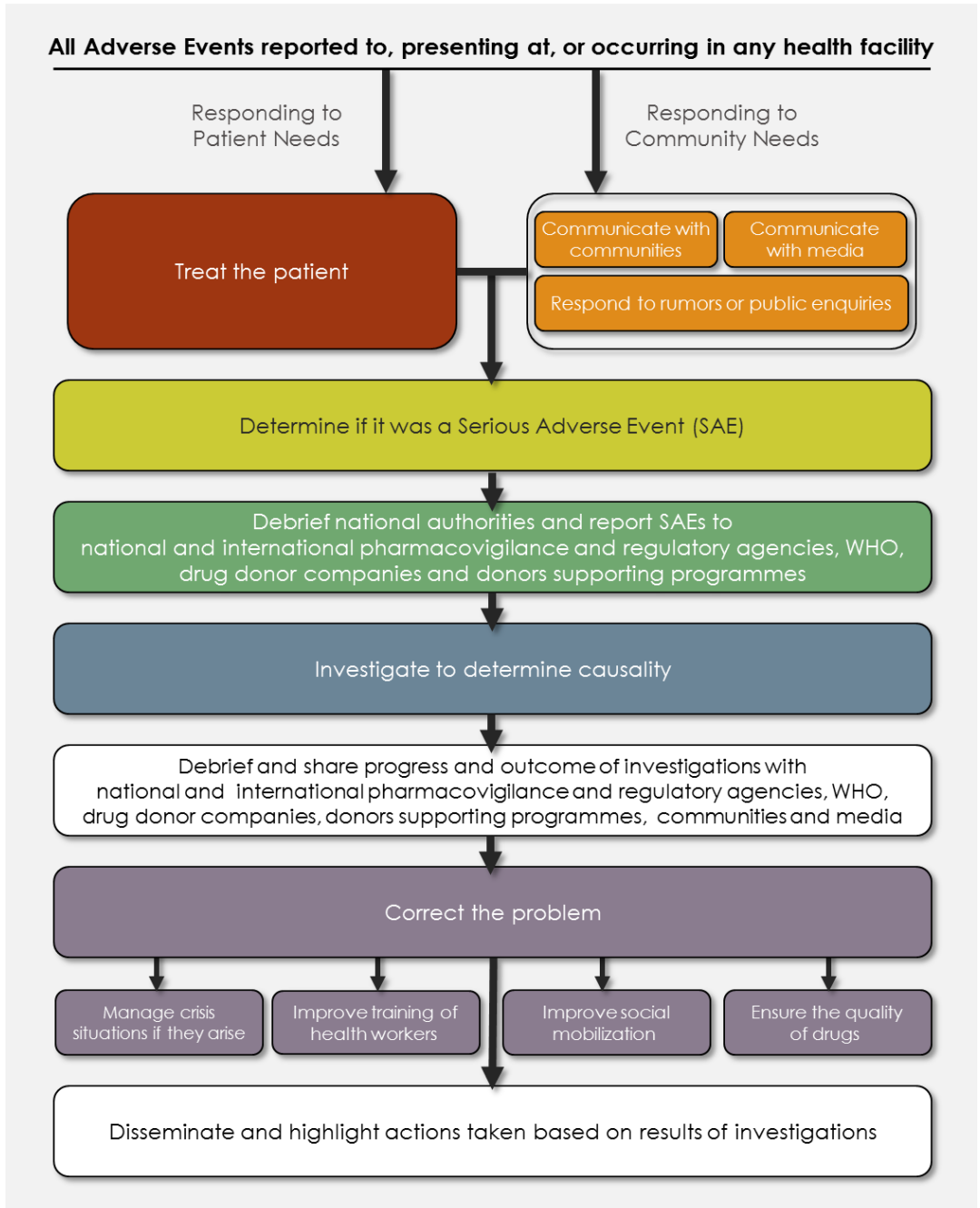
This handbook is meant to provide a user-friendly, step-by-step approach for the management of AEs-f-MDA and the reporting of SAEs by managers of preventive chemotherapy programs. It is designed to supplement the recently released, more elaborate WHO guidelines³ and draws heavily from the rich experience of immunization programs.

The overall, practical structure of the handbook is outlined on the following page in Figure 1.

³ World Health Organization. *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*. Geneva: WHO, 2011.

Figure 1

Responding to Adverse Events (AE-f-MDA and SAE)



2. RESPONDING TO PATIENT NEEDS: TREATING PATIENTS WITH AEs-f-MDA

Prompt treatment of patients is the most important step in the management of adverse events following MDAs. Besides providing medical attention it also serves as a confidence-building element of the programs, delivering appropriate care after the drug distribution has been completed.

Adverse events encountered during MDA programs are not unexpected and generally do not require complicated management. They are usually related to how heavily parasitized the community is and may be either systemic or localized. Most symptoms are mild and transient and treated using simple remedies. Sometimes these AEs-f-MDA may be *severe* in intensity, but only rarely do they progress to the category of those termed *serious* (SAEs). When the affected patient first presents with the symptoms and signs of an AE-f-MDA it is usually not possible to predict if it will be one of the rare AEs-f-MDA that will progress to an SAE. Management of all AEs-f-MDA must meet the immediate clinical needs of the patient.

2.1 Preparatory work

Plan

Preparatory activities should include planning and management of safety during MDA campaigns and adequate training of health personnel. Supplies should be provided to all concerned health staff of designated health facilities to ensure proper care for patients.

Inform communities

Communities should be informed that mild reactions are expected and can be treated using common medicines. They should, however, be encouraged to seek medical attention for any unusual and severe symptoms as soon as they occur.

Prepare rapid response medical teams

Utilize medical teams formed using available resources (doctors, nurses and auxiliary staff) and stationed at strategic places to respond to AEs-f-MDA and SAEs. Inform the community and drug administrators about the availability of such teams and their phone numbers so that they can report directly to these teams at times of emergency

2.2 Treating patients at home or at the primary health center (PHC)

Patients can be treated in the home or at the PHC.

- Obtain the clinical history including past illnesses and medications used.
- Make a rapid clinical assessment (usually by a physician, trained nurse or health worker). Record and monitor temperature, pulse rate, blood pressure and respiratory rate.

Manage common AEs-f-MDA at the drug distribution level, or the homes of patients or at the PHC:

2.2.1 Abdominal pain, vomiting and diarrhea:

- Put patient at rest, protected from excessive temperature, noise and light.
- Use traditional remedies (e.g. sour fruit juices), if available, to manage nausea and vomiting.
- Make sure patient can drink water or fruit juices.
- Watch for possible signs of dehydration such as thirst, dry skin, dark colored urine, dry mouth, fatigue, and weakness.
- Administer oral/intravenous fluid if necessary.
- Give antispasmodics and antiemetic, if necessary.

2.2.2 Fever, headache, aches in other parts of the body, pain in the joints or inflammation (usually in the inguinal area or scrotum)

- Advise the patient to rest.

- Give paracetamol tablets. The recommended doses are
 - 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)
- Apply cold compress in the affected area when there is localized inflammation.

2.2.3 Dizziness

- Advise the patient to rest.
- Check the blood pressure to rule out postural hypotension.
- Prop the head up with pillows when in bed to reduce the likelihood of orthostatic hypotension when getting up. Advise the patient to get up slowly from a sitting or lying position.

2.2.4 Malaise (feeling unwell), feeling sleepy, tired, weak

- Advise the patient to rest.
- Put patient at rest, protected from excessive temperature, noise and light.

2.2.5 Photophobia (exposure to light causes discomfort or pain to the eyes)

- Protect patient's eyes from light.

2.2.6 Urticaria, rashes, pruritus

- Assess the skin signs and symptoms. Be aware that they could be the earliest signs of conditions (e.g. Stevens Johnson Syndrome or Toxic Epidermal Necrolysis) which could be very serious and require rapid response. If Stevens Johnson Syndrome or Toxic Epidermal Necrolysis are suspected, refer patient to the nearest hospital immediately.
- Give antihistamines. The recommended doses are:
 - Chlorphenamine tablets:
 - children 2-5 years: 1mg;
 - children 6-12 years: 2mg;
 - from 12 years old: 4mg
 - (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

2.2.7 Wheezing (occurring in a person that has no history of asthma or other respiratory disease)

- Make sure the administered tablet is not choking the patient.
- Give antihistamines (see dosage schedule above).
- If symptoms are not controlled or worsen, refer patient to appropriate health facility.

In all cases explain to the patient that the adverse event is almost certainly not a reaction to the medicine itself, but due to the killing of the parasite by the medicine. Emphasize that it is a sign that the medicine works and was needed.

2.3 When to refer patients to a district or teaching hospital

When any of the symptoms progresses or persists beyond 24 hours or if an unexpected reaction or SAE is observed, refer the individual to a health facility that is equipped to deal with such situations. Use locally available and previously identified channels for referring patients to health facilities.

3. RESPONDING TO COMMUNITY NEEDS: COMMUNICATION SKILLS FOR MANAGING AEs-f-MDA

3.1 Communicating with the communities

3.1.1. Principles of Crisis Management (see Section 7.4)

3.1.2 Reinforcing Community Understanding

- Remind the community of the objectives and expected benefits of the MDA, as well as the known AEs and SAEs that may occur during intervention.
- During MDA preparation use prepared materials for specific audiences to ensure that the targeted community is well motivated and all eligible individuals will accept treatment.
- Ensure that staff and communities are aware of and know how to manage possible adverse events.
- Develop messages that do not scare or make the community uncomfortable about the mass treatment intervention.
 - Stress that preventive chemotherapy is highly beneficial and AEs-f-MDA that are self-limiting and treatable using simple remedies could occur.
 - Point out that occasionally a serious event may happen at the same time or immediately after the treatment and should not be falsely attributed to the treatment.
 - Inform the community and drug administrators about the availability of rapid response teams and their phone numbers so that they report directly to these teams at times of emergency.
- Communication about SAEs should mainly target health workers and provide practical hints on where and how to refer patients to appropriate care levels.

3.1.3. Informing Communities about progress of investigation of SAEs

- When an investigation of SAEs is being done, inform communities at every stage of the investigation (refer to flow chart) to re-establish trust in preventive chemotherapy and those who manage the programs.
- It is not necessary to discontinue the MDA while awaiting the completion of the investigation unless SAEs continue to occur or the quality of the drug is suspect.
- Consider the following while developing messages to address concerns about a medicine or treatment approach when communicating with communities and the media:
 - Provide statements on the important benefits of preventive chemotherapy for the disease and on the uncertainty of the specific cause of the adverse event(s).
 - Emphasize that operational errors or coincidental illness are much more likely than the medicine to have caused the AE-f-MDA since it is very rare that these medicines cause such reactions.
 - Assure that appropriate action is being taken to safeguard the public to eliminate every possibility of operational error.

3.1.4. Informing communities about results of investigation of any AE-f-MDA

- The conclusions reached by the investigators on the cause of the event(s) must be communicated to the community.
- The steps for carrying out the investigation and assessing causality are detailed in Chapter 7.
- The following points may help developing messages at the end of the investigation/assessment depending on the conclusion reached; *e.g.*:
 - the AE has been caused by the medicine(s), but appeared at the expected rate
 - nothing unexpected is happening, the benefits of preventive chemotherapy outweigh the adverse events it causes.

- the AE is coincidental
 - Present convincing data showing that the event truly was coincidental.
 - Involve key persons, who enjoy community's trust, to review the investigation process and conclusions and seek their help to convince/ensure the community that the event truly was coincidental.
- the AE has been caused by the medicine(s) and appeared at a 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.
- 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 X months' time to ensure that errors have actually been corrected.
- 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.

3.2 Communicating with the media

- Be proactive with the media and seek them out with positive stories. Wherever possible reach out to professional organizations, health professionals and field staff before the media to advise them on how to deal with public concerns and

how to minimize potential harm to preventive chemotherapy interventions.

- Emphasize that preventive chemotherapy is highly beneficial and that the vast majority of AEs-f-MDA are self-limiting, treatable using simple remedies, and are expected to occur.
- Enlist the support of groups and individuals that have public respect and authority to make public comments to endorse preventive chemotherapy and get key messages through to the communities.

It is very important that a spokesperson be designated to communicate with the media.

3.2.1 What to tell the media?

- In responding to any concern about safety of preventive chemotherapy you must be seen to be compassionate and, at the same time, highly professional with careful investigation of the problem.
- Avoid improvisation and casual remarks. Always emphasize the rationale and the proven benefits of preventive chemotherapy and avoid dwelling on negative examples.
- Avoid, as much as possible, use of negative terms such as 'adverse event' but increase use of 'preventive treatment safety' and reiterate that some AEs-f-MDA normally occur.

3.2.2 Hold a media 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.
- Organize a media conference 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, announce a further conference within a suitable number of days. Keeping regular contact with the media helps create confidence and contributes to preventing 'scoops'.
- Invite professional organizations and NGOs to 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.
- Preparation for a press conference includes at least the following:
 - Written messages to be communicated and provided to all spokespersons.
 - Agreed upon, standardized statements to answer unexpected questions that have not been discussed among the institutions/organizations participating in the press conference.
 - 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.

3.2.3. Preparing a press release

- When dealing with the media, it is extremely important to prepare materials in advance.
- Use 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.

- Consider including the following in the press release:
 - A description of the events and their context (e.g. an isolated event, a coincidental event, etc.).
 - A description of whether or not the adverse event is still on-going (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. WAS THIS A SERIOUS ADVERSE EVENT (SAE)?

It is important to distinguish common, expected, transient and easily manageable AEs-f-MDA from SAEs that result in death or disability.

4.1 AEs-f-MDA

An AE-f-MDA is a medical event that takes place in an MDA program, causes concern in the medical and wider community and is believed to be caused by the drug(s) used. It can be caused by either administration of the drug or by a coincidental event that by chance happened after drug administration. Most AEs-f-MDA are self-limiting and treatable using simple remedies and are not usually required to be reported to national or international regulatory authorities.

4.2 SAEs

On the other hand, a **Serious Adverse Event (SAE)** is a regulatory term describing any untoward medical occurrence with any of the following characteristics:

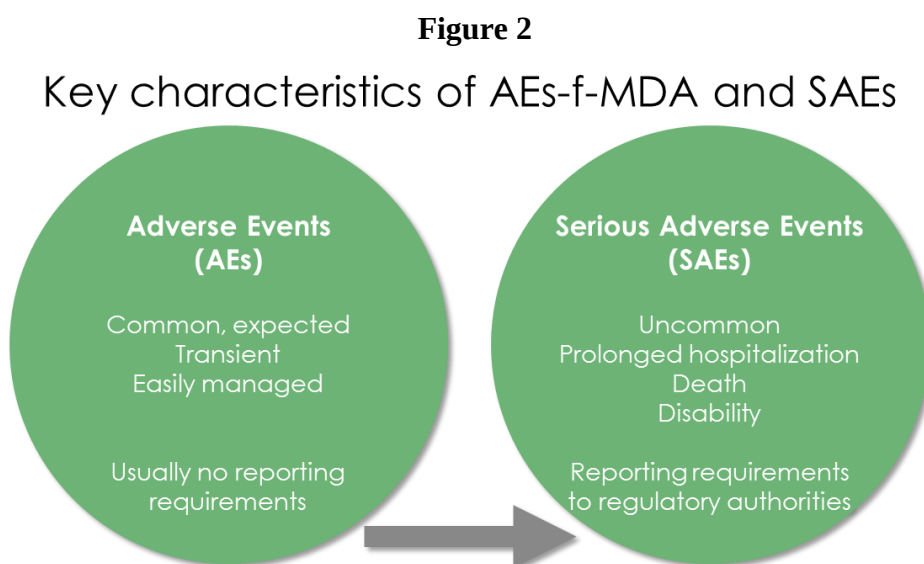
- Results in death;
- Requires in-patient hospitalization;
- Results in persistent or significant disability;
- Is life-threatening; or
- Results in a congenital anomaly/birth defect.

In addition, preventive chemotherapy programs encourage reporting of events that cause significant concern in the community and are perceived to have been due to the medicines used in the MDA program.

SAEs may appear up to several days after the administration of the drugs and may resolve only after several months. When SAEs do occur, they usually begin as AEs-f-MDA and subsequently evolve into SAEs.

SAEs are required to be promptly reported to regulatory authorities, institutional review boards/ethics committees (IRBs/ECs), corporate global drug safety groups and pharmacovigilance groups. In addition, they also need to be investigated to establish any linkage with the drugs used (causality assessment). Successful response to SAEs is dependent on early identification, early action, having a plan in place, and thorough reporting.

Figure 2 below shows key characteristics of AEs-f-MDA and SAEs and their relationship.



4.3 Severe vs. Serious adverse events

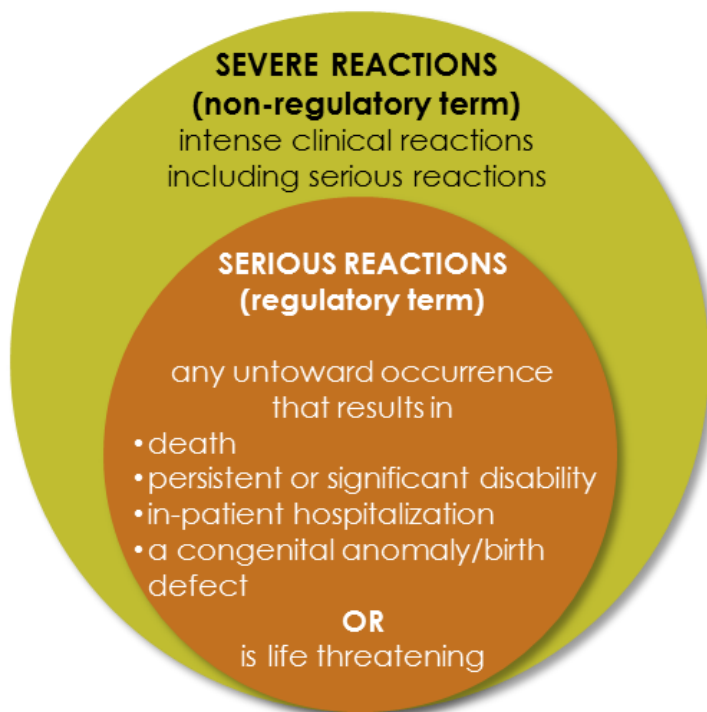
The terms "severe" and "serious" should be used with care when

applied to AEs-f-MDA. It is important to distinguish between severity and seriousness because they are easily confused and often (incorrectly) used interchangeably. Severity refers to a point on an arbitrary scale of intensity of the adverse event in question.

Figure 3 below illustrates the relationship between severe and serious reactions.

Figure 3

Relationship between Severe and Serious Reactions



‘Severe reaction’ is a broader term, which includes serious reactions but also other reactions that do not have the characteristics of those defined as ‘serious.’ **Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.**

5. REPORTING SAEs (and AEs)

Reporting of AEs-f-MDA and SAEs requires striking a balance between reporting all events occurring during and after MDA – something which could overwhelm the system – and identifying serious events that require investigation and regulatory reporting to all stakeholders. Commonly occurring and expected adverse events are usually not reported and captured by the health systems of most countries. Health workers should advise communities both that minor reactions are expected and how they can be managed.

5.1 What should be reported to whom?

- SAEs: to regulatory agencies and stakeholders
- Cases of serious community concern: to national NTD program management (as soon as possible)
- Any severe reactions (e.g., Stevens Johnson's syndrome, Mazzotti reaction), even when not meeting the regulatory definition of SAEs, especially if occurring in clusters: to national NTD program management
- Reactions occurring at increased frequency, even if not severe: to national NTD program management

An SAE report should trigger an immediate decision on the need for action and investigation and deployment of rapid response teams.

5.2 Who should report?

5.2.1 The following program personnel are primarily responsible for detection and reporting of AEs and SAEs:

- Health and other staff, including volunteers administering medicines in preventive chemotherapy interventions.
- Health workers providing clinical treatment of AEs in health facilities (any kind/level).

5.2.2 In addition reports may be received from

- Relatives/parents who report AEs affecting members of their family.
- Researchers conducting clinical studies or operational research.

5.2.3 Training to report and treat

- Primary care health workers: Primary health care workers should be adequately trained to assess the patient, manage simple adverse reactions and fill out WHO-standardized form (in Annex 2 of this Handbook) for non-serious adverse reactions. They should recognize possible SAEs and refer them to the PHC medical officers for management. All barriers to reporting (for example feeling of guilt) need to be identified in the preparation of the intervention and can be addressed during training of peripheral health workers.
- PHC (primary health center): The health personnel at the PHC hospital should be trained to assess and manage all cases of AEs and to recognize and refer SAEs to the district hospital if necessary.
- District hospital: Physicians and nursing staff at district hospitals and medical college hospitals should assess and manage all AEs and SAEs referred to them. District hospital personnel could utilize a pool of experts for the management of SAEs and draw up a plan of action for the management of unusual reactions.

5.3. Program Managers

The standard form developed by WHO (adapted locally if necessary) for reporting AEs and SAEs should be used and can be found in Annex 2 of this handbook. Program managers should submit copies of the SAE reports to national and international agencies as early as possible (ideally within 24 hours). These agencies include:

- National health services;
- Drug donor companies (GlaxoSmithKline, Merck & Co., Inc., etc.);
- National pharmacovigilance organization (if there is one in the country);
- World Health Organization; and
- Donors supporting programs.

File these reports as soon as the SAEs have been identified and recorded ***without waiting for the outcome of investigations.***

Prompt submission of reports to the partners not only permits them to update their databases about SAEs and track them globally but more importantly allows them to satisfy regulatory requirements governing SAE reporting. In addition, when they are informed early, these agencies may provide valuable support for carrying out the investigations to determine causality.

6. INVESTIGATING TO DETERMINE CAUSALITY

6.1 Determine which reports should be investigated

- 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; and/or
 - is causing or is likely to lead to significant community concern.
- In addition, national programs may define the type of AEs that require investigation and assure that adequate expertise exists to conduct a proper epidemiological investigation.
- An initial assessment should be conducted to determine whether or not there is a real increase in the number of events and whether an investigation is needed.

6.2 Determine 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 throughout 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 Conduct an AE investigation

An AE investigation follows standard epidemiological investigation principles. In addition, it requires investigation of the specific medicinal product(s) as well as how the drugs were administered to individuals participating in the MDA.

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
 - Type of event, date of appearance, duration, and treatment of the clinical event
 - History of the patient including past medical conditions, previous reactions to medicines
 - 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, as full an autopsy report as possible (or reason why not available), toxicological screening, and pathological findings
- c) **Make a direct examination of preventive treatment site.**
 - Ask to be shown treatment procedures, medicine administration techniques, how the dose was calculated, and how water used in administering the medicines was obtained and checked.

- Investigate the details of staff training (When were they trained? To do what? Was there any verification of their skills?).
 - Determine if the number of persons to treat was greater than usual.
 - Determine whether any container is not the original or carries no readable label.
 - Check for up-to-date guidelines on medicine handling and treatment procedures.
 - Examine the storage facilities.
 - Determine whether any (open) container looks particularly dirty, and whether the physical environment is compatible with administration of medicines.
 - Check the presence and completeness of records of medicines that are received and used in treatment operations.
- d) **Gather information on the suspected medicine and obtain a sample** (preferably from and with the container of the suspected medicine):
- Note the brand, batch number, and expiry date.
 - Describe any unusual appearance (broken tablets, unusual tablet colour/shape, etc.).
 - Describe the conditions under which the medicine was shipped, its present storage condition, storage of medicine before it arrived at treatment site, and where it came from (who imported, who sent to treatment site and how).
 - Prepare a list of sites that have received and used the same batch.
- e) **Gather information on clinical features of suspected AEs-f-MDA at same treatment site, at other sites and in non-treated persons:**
- Identify other people who received the same medicine from the same batch and developed illness.

- Identify other people who received the same medicine but a different batch and developed illness.
 - Identify people who did not receive the medicine that was distributed but had a similar illness.
 - Ask if they took any other medicine earlier.
 - Ask them if they took any medicines to treat their illness.
 - Count the total number of people who received the same batch of medicine at the site and at other sites during this round of MDA
 - Count the total number of people who did not receive the same batch of medicine at the site of investigation and, if possible, at other sites during this round of MDA
- 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).**

6.4 Assess causality

The assessment of causality is not the responsibility of the program manager alone. The national preventive chemotherapy safety committee (where it exists) has the role of confirming the causality assessments of selected investigations and, where required, assisting investigators to determine causality. Other national programs will use WHO-prescribed guidelines.

Use the following WHO Drug Monitoring Programme guidelines to determine causality:

Causality term	Assessment criteria ^{4*}
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.

⁴ World Health Organization. *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*. Geneva: WHO, 2011.

6.4.1 Causes of AEs-f-MDA

Causes of adverse events that occur following large-scale preventive chemotherapy interventions can be due to:

- the medicine;
- destruction of parasites killed by the medicine;
- operational errors: Errors and accidents in treatment procedures, logistics, medicine manufacturing, handling, or administration;
- coincidental event: unrelated to the medicines or preventive chemotherapy procedures (temporal association with the intervention); or
- unknown cause.

6.5 Conclude the investigation

The investigation to determine causality will result in one of the following possible conclusions:

- **The event is definitively related to the drugs used.**
- **The event is definitively not related to the drugs used.** Some clinical cases simply coincide with the MDA; that is, the event might have occurred even if the person had not received the drug. If such an event is suspected as coincidental to the MDA, if possible, it should be demonstrated that the same event also occurred in a population group that was not treated. Although the AE-f-MDA has not been linked to the drugs used, it may require adequate medical monitoring, and thus a mechanism for referral to the necessary health services should be established.
- **The event is related to the process of administering the drug.** If the event is related to the operational aspects of the program, corrective measures should be initiated immediately in logistics, training, and supervision.

- **The investigation is inconclusive.** When causality cannot be determined, in addition to reporting the findings of the investigation to the interested parties, the reason that no conclusion was drawn should be indicated, along with whatever progress was made.

6.6 Complete a SAE Investigation Form (see Annex 3)

6.7 Take corrective action, and recommend further action (see Section 7)

6.8 Share results of the investigation

Share the outcome of the investigation with the health workers, program personnel, communities and media. When it has been determined that the event was not related to the drugs used, it renews the confidence in the continued safety of the drugs. Identification of operational errors can be used to reinforce supplemental training.

Communities should also be informed about the results of the investigation, and the safety of preventive chemotherapy programs should be highlighted.

Inform the national and international agencies (including WHO, drug donor companies and donors supporting programs) about the results of the investigation. Send them a copy of the investigation report to keep them informed even if the investigation shows no relationship to the drugs used or is inconclusive.

7. CORRECTING THE PROBLEM

7.1 Fix the underlying problem

Careful monitoring and supervision will ensure safe distribution of the drugs. However, expected AEs-f-MDA or coincidental events that occur during MDAs may threaten the sustainability of these programs. Prompt care of affected individuals and investigation of SAEs will help to overcome the threat posed by AEs-f-MDA.

7.1.1 Expected AE-f-MDA or coincidental event

- When the cause of an AE is an expected adverse reaction or when the investigation points to a coincidental event, the main task for program managers is care for the patient and communication.
- The program manager should convey to the communities, in simple terms, the concepts underlying coincidental events and always emphasize the safety of the drugs being used in the campaigns.

7.1.2 Operational errors

- An investigation may eventually identify an operational error as the main cause of an AE. Make this widely known so that others can also learn from the experience.
- Use the investigation itself as a teaching resource in training investigators in the future.
- Correct all operational errors and implement a checking mechanism to ensure that they don't happen again.
- Inform the media about the solution and outcome.

7.2 Improve training of health workers

- Appropriate training of health workers is a key component of running safe MDA programs.

- Operational errors are best remedied by providing training to ensure such errors do not occur again, using these errors as examples and tools for discussion.
- Train health workers to be better informed about the drugs, the expected reactions that can occur and how they can be managed to increase the success of drug distribution.
- Identification of operational errors can be used to reinforce supplemental training.

7.3 Improve social mobilization

- A well prepared community will have a higher likelihood of accepting the distributed drugs if they are informed about the safety of the drugs and made aware that mild adverse events are normal, transient and easily manageable.
- Develop social mobilization messages that strike the right balance between highlighting the benefits of the MDA drugs and openly sharing information about possible adverse events.
- Organize an orchestrated media campaign to encourage acceptance that emphasizes the safety of the drugs, the mild adverse events that could occur and the provisions made for managing adverse events.

7.4 Crisis management

A crisis can arise for reasons that are outside the direct control of the program (for example, the publication of an article in the press) and can jeopardize the conduct of MDA and the long-term success of the program. Take the following steps in advance to prevent the occurrences of crises:

Anticipate

Do not wait until a crisis occurs. Anticipate and prepare by:

- Having a media packet on the SAE(s) in question
- Making sure relevant people at all levels (from CDD

and up) know what to say/not say to the media, and to whom the media should be referred.

- Having contacts in place for those information channels.
- Determine who will be responsible for answering questions.
- Develop relationships with the media, especially with journalists specializing in health issues, and distribute press releases before beginning the campaign that includes information about AEs-f-MDA to be expected.
- Establish accredited information channels by issuing public awareness messages on health over the radio or in a health journal.

Train personnel at all levels to respond adequately.

- The program manager must train himself or herself and the other senior managers.
- Include training of staff members at the local levels to acquaint them with the media.

Confirm all the facts before making any public statements.

- Decide if the AE-f-MDA is indeed genuine and not an unfounded rumor.

Prepare a plan to react to a crisis when it occurs.

- Create a crisis working group in which representatives of the population participate, if appropriate. Examine the legal, technical, and communication aspects.
- Designate the person who will be responsible to communicate with journalists.
- Issue a preliminary statement within a few hours. Communicate with receptive journalists with whom a relationship already exists.
- Launch a technical investigation and keep the press

informed about the progress made.

- If the incident is of great magnitude, call a press conference daily. Try to meet the expectations of the media in every way possible.
- Organize and herald support measures for the people affected – i.e., covering expenditures or setting up a telephone consultation service – without acknowledging any blame.
- Consider the possibility of eliciting the support of celebrities or other well-known individuals who are willing to support MDA publicly.
- Conduct a rapid opinion poll to understand the public's opinion and develop messages accordingly.
- Evaluate the event and assimilate the lessons it offers about how things could be handled better the next time

7.5 Develop links with pharmacovigilance programs

Successful identification, management and investigation of SAEs in preventive chemotherapy programs require the active involvement of several stakeholders and linkages with national pharmacovigilance systems. In general, public health personnel of NTD endemic countries are not equipped in monitoring the safety of medicines that are distributed. In addition, pharmacovigilance systems may not be well developed to handle the requirements of large-scale field operations. Where they exist, they may not be effectively linked with preventive chemotherapy programs.

Clearly, while the program manager is expected to respond rapidly and appropriately to AEs and SAEs that occur during preventive chemotherapy programs he or she will require the support of the district and state health services in organizing the medical care and support. More importantly, he or she will need to be assisted by clinical pharmacologists, epidemiologists and statisticians when SAEs are investigated and causality determined. Finally, he or she needs to work closely with national pharmacovigilance

organizations (or their equivalents) to ensure that safety data is accurately captured by both national and international agencies.

The key to a successful and safe preventive chemotherapy program is careful planning.

A checklist like the one in Annex 1 can help in planning MDA campaigns.

ANNEX 1

CHECKLIST FOR PLANNING AND MANAGEMENT OF SAFETY DURING MDA CAMPAIGNS⁵

1. Be prepared

- ☐ Understand the relevant guidelines for management of AEs-f-MDA.
- ☐ Recognize the standard case definition for AE-f-MDA and standard investigation procedures.
- ☐ Form medical teams at strategic places and inform the community and drug administrators about the availability of such teams.
- ☐ Create a pool of experts who can guide the program in managing investigating SAEs.
- ☐ Ensure that local health facilities are prepared to receive and manage individuals with AEs-f-MDA and SAEs.
- ☐ Designate and train staff to conduct an AE-f-MDA investigation using the investigation form (see Annex 3).
- ☐ Inform all health workers/clinicians of the need to report immediately an AE-f-MDA that meets the case definition.
- ☐ Identify a person to notify all stakeholders. Identify a spokesperson for public communications.

2. Receive report of an AE-f-MDA

- ☐ Decide if the report is a genuine AE-f-MDA according to your definition, and whether it needs investigating and/or

⁵ Based on a checklist developed for immunization programs drawn from World Health Organization Regional Office for the Western Pacific. Appendix J: Checklist for immunization safety surveillance system of *Immunization safety surveillance: guidelines for immunization programme managers on surveillance of adverse events following immunization (Second Edition)*. Manila: WHO WPRO, 2013

announcing to the public.

- ☐ Arrange to travel to the location of the AE-f-MDA, or delegate responsibility to another trained person or team to do this.

3. Investigate and collect data

- ☐ Ask about the drug.
- ☐ Ask about services.
- ☐ Ask about the patient.
- ☐ Observe the service in action.
- ☐ Formulate a hypothesis as to what was the cause of the AE-f-MDA.
- ☐ Collect specimens from the patient, if necessary.
- ☐ Collect the drugs used, if possible and necessary.

4. Dispatch specimens of drugs, if collected

5. Analyze the data

- ☐ Obtain laboratory results.
- ☐ Review clinical findings.
- ☐ Review on-site investigation.
- ☐ Review epidemiological findings e.g. clustering of cases in time or space or by manufacturer or lot.
- ☐ Summarize and report findings.

6. Take action

- ☐ Communicate with health staff (e.g. treatment, information).
- ☐ Communicate findings and action to the public.
- ☐ Correct problem (based on the cause) by improving training, supervision, and/or distribution of drugs.
- ☐ Replace drugs if appropriate.

ANNEX 2

ADVERSE EVENT (AE) REPORT FORM (FOR USE AT DRUG ADMINISTRATION SITE IN PREVENTIVE CHEMOTHERAPY PROGRAMMES)

Country:	Date of report: / /	ID No. (if applicable):
Patient name and contact details:		
	Age:	Sex (M/F):
Treatment site:		

Which drugs were administered?	Dose administered	Brand and manufacturer name	Batch number	Time and date of treatment (hour, day/month/year)
☐ Albendazole				
☐ Azithromycin				
☐ Diethylcarbamazine (DEC)				
☐ Ivermectin				
☐ Mebendazole				
☐ Praziquantel				
☐ other				

Explain when and circumstances of past and concomitant treatment(s) with same or other medicines (if applicable):

Please collect a sample of the drug and label it with brand name, batch number, date of collection and send it to District Medical Officer or Ministry of Health for on forwarding to WHO office or National Drug Regulatory Authority.

Done (date): ____/____/____

Could not do (date): ____/____/____

Time and date of onset of the adverse event:

Description of adverse event (please tick boxes as appropriate):

- ☐ death
- ☐ life-threatening
- ☐ in-patient hospitalization or prolongation of an existing hospitalization
- ☐ persistent or significant disability/incapacity
- ☐ none of the above

Clinical signs and symptoms (please describe):

Past medical history and other relevant information (e.g. other diseases, suspected parasitic infections such as malaria or loiasis, laboratory results, dates of hospitalization or death, alcohol intake within 24 hours of treatment, pregnancy):	
Any treatments administered to manage adverse event:	
Patient currently recovered: Yes / No / Unknown	Which treatment do you think was a possible cause of the adverse event?
Reporter's name and contact details:	Signature and date:

Please send this form to your District Medical Officer or Ministry of Health to forward to the National Drug Regulatory Authority and the WHO office in your country, which will conceal the patient's name and forward a scanned copy to pctdata@who.int. WHO will immediately share this information with the concerned manufacturers.

ANNEX 3

AE INVESTIGATION FORM⁶

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:		

⁶ World Health Organization. *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*. Geneva: WHO, 2011.

(continued on next page)
AE Investigation Form (continued)

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 4
IMPORTANT CONTACT NUMBERS

(Use this page to note down important contact numbers. A few useful contacts have been indicated but you can add other relevant numbers, in addition.)

National Program Manager: _____

District Health Officer: _____

District Hospital: _____

_____:

_____:

_____:

_____:

_____:

_____:

GLOSSARY⁷

Adverse event following mass drug administration (AE-f-MDA)	A medical incident that takes place after a preventive chemotherapy mass drug administration 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 program managers should decide upon a more precise and locally meaningful definition.

⁷ This glossary has been derived from World Health Organization. *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*. Geneva: WHO, 2011.

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.
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)	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. Medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious. 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. from: <i>Adverse drug reactions: definitions, diagnosis, and management.</i> I Ralph Edwards, Jeffrey K Aronson - <i>Lancet</i> 2000; 356: 1255–59
Severe adverse event	See serious adverse event. The term “severe” is often used to describe the intensity (severity) of a medical event, as in the grading “mild”, “moderate”, and “severe”.
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.

ACRONYMS

AE-f-MDA	Adverse event following mass drug administration
CDD	Community drug distributor
MDA	Mass drug administration
NGO	Non-governmental organization
NTD	Neglected tropical disease
PC	Preventive chemotherapy
PHC	Primary health center
SAE	Serious adverse event
WHO	World Health Organization

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