



Safety in administering medicines

for neglected tropical diseases



World Health
Organization



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Glossary

The definitions given below apply to the terms used in this manual. They are derived from existing publications by the World Health Organization (WHO), including *Ending the neglect to attain the Sustainable Development goals: a road map for neglected tropical diseases 2021–2030 (1)* and a forthcoming guideline on taeniasis and cysticercosis.

Adverse event: Any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment. It can be caused by either administration of the medicine, or by a coincidental event that by chance happened after drug administration (See also serious adverse event).

Community drug distributors: Volunteers frequently utilized by neglected tropical disease programmes to deliver preventive chemotherapy to the individuals in their community as a part of mass drug administration.

Community mobilization: A process of capacity-building through which communities, individuals, groups or organizations plan, conduct and evaluate activities on a participatory and sustained basis to improve their health and other needs, either on their own initiative or stimulated by others.

Control: Reduction of disease incidence, prevalence, morbidity and/or mortality to a locally acceptable level as a result of deliberate efforts; continued interventions are required to maintain the reduction. Control may or may not be related to global targets sets by WHO.

Drug coverage: Proportion of individuals in a targeted population who swallowed a medicine or a combination of medicines. Drug coverage is expressed as a percentage.

Mass drug administration: Distribution of medicines to the entire population of a given administrative setting (for instance, state, region, province, district, subdistrict or village), irrespective of the presence of symptoms or infection; however, exclusion criteria may apply. (In this manual, the terms mass drug administration and preventive chemotherapy are used interchangeably.)

Monitoring and evaluation: Processes for improving performance and measuring results in order to improve management of outputs, outcomes and impact.

Neglected tropical diseases: A diverse set of 20 primarily infectious diseases and disease groups that thrive in impoverished settings, especially in the heat and humidity of tropical climates. These diseases have been largely eliminated elsewhere and thus are often forgotten. They include Buruli ulcer; Chagas disease; dengue and chikungunya; dracunculiasis; echinococcosis; foodborne trematodiasis; human African trypanosomiasis; leishmaniasis; leprosy; lymphatic filariasis; mycetoma; chromoblastomycosis and other deep mycoses; onchocerciasis; rabies; scabies and other ectoparasitoses; schistosomiasis; snakebite envenoming soil-transmitted helminthiasis; taeniasis and cysticercosis; trachoma; and yaws.

Pharmacovigilance: The science of and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible problems related to medicines. Pharmacovigilance is an aspect of patient care that aims to optimize the use of medicines in order to treat or prevent disease. Good pharmacovigilance identifies risks and risk factors in the shortest possible time to avoid or minimize harm.

Preschool-aged children: All children aged between 1–5 years who are not yet attending (primary) school.

Preventive chemotherapy: Large-scale use of medicines, either alone or in combination, in public health interventions. Mass drug administration is one form of preventive chemotherapy; other forms could be limited to specific population groups such as school-aged children and women of childbearing age. (In this manual, the terms preventive chemotherapy and mass drug administration are used interchangeably.)

School-aged children: All children aged between 6–15 years (usually), regardless of whether they are attending school. In some countries, a primary school's enrolment may include individuals aged older than 15 years.

Serious adverse event: A medical event that is fatal, life-threatening, disabling, results in hospitalization or in congenital anomaly or birth defect after intake of medication. It is important to distinguish between “severe” and “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 adverse event is not necessarily serious.

Side-effect: Any unintended effect of a pharmaceutical product occurring at doses normally used in humans that is related to the pharmacological properties of the medicine. Essential elements in this definition are the pharmacological nature of the effect, that the phenomenon is unintended and that there is no overt overdose.

Treatment coverage: The proportion of individuals in a defined population who swallowed a medicine or, as is the case in preventive chemotherapy, a combination of medicines. The defined population can be (i) a target group for treatment, for instance school-aged children, (ii) the people in a geographical region or administrative area or in communities highly endemic for specific diseases or (iii) the population of an entire country. These three types of coverage are referred to as programme coverage, geographical coverage and national coverage respectively.

1. Introduction



Photo credit: International Trachoma Initiative

1.1 Objective

The objective of this manual is to provide practical tools, including training modules and job aids, to help national programmes for neglected tropical diseases (NTDs) plan, prepare and monitor the safe administration of medicines for treatment of these diseases. The materials consolidate and emphasize critical aspects of existing guidance published by WHO; they do not make new recommendations.

1.2 Target audience

The target audience for these materials includes programme managers, national and subnational public health workers, community drug distributors and community health workers, WHO

regional and country office staff, nongovernmental organizations and other implementing partners and donors supporting such activities.

1.3 Intended use

This manual summarizes key issues related to the safety of NTD medicines and their administration, with a focus on essential medicines used in mass drug administration (MDA), also called preventive chemotherapy. It can be used as a standalone reference manual, but is intended to be used in conjunction with the accompanying training modules, which provide practical instruction, and the aide-mémoires. Versions of the aide-mémoires and training modules are available respectively for both (i) programme managers and district-level health officials (Annex 1 and Web Annex A); and (ii) community drug distributors and community health workers (Annex 2 and Web Annex B).

2. Background



Global health programmes have ethical responsibilities not only to deliver health benefits to populations but also to prevent harm to individuals (2,3). Reflecting both of these responsibilities, WHO, in its Thirteenth General Programme of Work, 2019–2023, established an ambitious goal of universal health coverage, which requires the availability of safe, effective and affordable essential medicines and their correct administration and use (4). The cross-cutting targets of the WHO road map for 2021–2030 (1) align with this goal through the promotion of high-quality, safe, people-centred interventions against NTDs, including individual case-based treatment as well as MDA.

The safety of public health and medical interventions is critical for their acceptance and success. Patient safety is essential for effective, high-quality universal health coverage and for creating trust in health services (5). In 2019, the World Health Assembly adopted resolution WHA72.6 on global action on patient safety, urging Member States to “promote a safety culture” and requesting WHO

to develop “normative guidance on minimum standards, policies, best practice and tools for patient safety” and provide support to Member States in training and building technical capacity to assess, measure and improve patient safety (6). WHO also coordinates surveillance for serious adverse events associated with health interventions and promotes safety of medicines for children (7).

Safety is also a primary concern for NTD programmes. For example, medicines that are donated for treatment are manufactured under stringent regulatory authority guidelines or are prequalified by WHO, with considerable effort in determining safety for mass treatment and in conducting surveillance for serious adverse events. WHO has issued formal and informal guidance on assuring the safety of preventive chemotherapy and the prevention, detection and management of serious adverse events (8,9). In addition, before approving co-administration of existing medicines such as ivermectin, diethylcarbamazine and albendazole for lymphatic filariasis, WHO required intensified surveillance for adverse reactions in thousands of people (10).

Despite these substantial efforts, maintaining safety requires ongoing vigilance by NTD programmes, particularly as they scale up. More than one billion people participate in MDA each year, which has significantly reduced disease transmission and morbidity associated with five diseases suitable for preventive chemotherapy: soil-transmitted helminthiases, schistosomiasis, lymphatic filariasis, onchocerciasis and trachoma (11). Serious adverse events after preventive chemotherapy, although uncommonly reported, still occur. People with *Loa loa* infection who receive ivermectin for onchocerciasis control are at risk of encephalopathy, which can be fatal (12–14). Deaths from choking, primarily in young children, also occur; they are related to how medicines are administered rather than to their pharmacology (7,9). Available evidence, although limited, suggests that forcing children to swallow tablets against their will is the main risk factor for choking (9,15). Safety is also an issue for diseases that require individual case management with medicines that are associated with significant toxicity. For these patients, treatment often must be carefully administered in a clinical setting and monitored for safety (16,17). The safety and toxicity of snakebite antivenoms are also a concern (18).

Related threats to programme safety include incomplete reporting and investigation of serious adverse events; inadequate coordination with national pharmacovigilance centres; lack of safety training for community drug distributors; and challenges to clear, effective risk communication with stakeholders, including communities and the mass media. The negative publicity and media attention surrounding reports of adverse reactions, whether caused by the medicines used in MDA or not, can adversely affect programmes for many years. In the spirit of WHA72.6 and the 2030 NTD road map, programmes should foster a “culture of safety” and adopt a continuous cycle of assessing current practices and attending to individual and systemic safety gaps that are identified. Safety should be embedded in, and permeate, all aspects of NTD programmes, including training; supervision; drug supply and management; individual treatment and preventive chemotherapy; communication with communities; programme monitoring; and prompt investigation and reporting of serious adverse events. Safety-related goals, objectives and activities should be articulated in national NTD master plans.



The safety of public health and medical interventions is critical for their acceptance and success. Patient safety is essential for effective, high-quality universal health coverage and for creating trust in health services (5).

The following sections address key areas for improving safety, and are further developed in the training modules annexed to the guidance manual. They include safe management of medicines (section 3); safe administration of preventive chemotherapy and prevention of choking (section 4); collaboration with pharmacovigilance agencies (section 5); recognizing, managing and reporting serious adverse events (section 6); and communication and rumour control (section 7).

3. Safe management of medications



Photo credit: International Trachoma Initiative

3.1 Manufacture

Safety begins with the development and testing of high-quality medicines that are manufactured according to product specifications which comply with stringent regulatory authority guidelines or criteria established by WHO for prequalification. Pharmaceutical companies donate medicines for 12 NTDs (Table 1). Health ministries use a WHO joint application package to request donated medicines for preventive chemotherapy against soil-transmitted helminthiases, lymphatic filariasis, onchocerciasis and schistosomiasis (19). Other medicines, such as azithromycin for trachoma, niclosamide or praziquantel for taeniasis, and triclabendazole for fascioliasis, are available from the manufacturer or the medicine donation programme. For programmes that rely on generic medicines that are not donated by pharmaceutical companies, such as for schistosomiasis in adults or, in some cases, soil-transmitted helminthiases in preschool-aged children, the quality and effectiveness of available medicines can be a

source of concern, as found in a nationwide survey in Ethiopia (20). Whenever possible, programmes should use medicines that have been prequalified by WHO.

Table 1. Medicines donated for use against neglected tropical diseases, by disease

Company	Medicine	Quantity donated	Disease	Commitment	Donation coordinator
Bayer	Nifurtimox	7 750 000 tablets total	Chagas disease	2021–2025	WHO
	Nifurtimox (120 mg)	300 000 tablets annually	Human African trypanosomiasis	2021–2025	WHO
	Nifurtimox (30 mg)	20 000 tablets annually	Human African trypanosomiasis	2021–2025	WHO
	Suramin	10 000 vials annually	Human African trypanosomiasis	2021–2025	WHO
	Niclosamide (400 mg)	2 800 000 tablets total	Taeniasis and cysticercosis	2020–2024	WHO
	Praziquantel (600 mg)	1 339 000 tablets total	Taeniasis and cysticercosis	2020–2024	WHO
Chemo Ibérica S.A. (Fundación Mundo Sano)	Benznidazole (12.5 mg)	3000 tablets total	Chagas disease	2020–2022	WHO
	Benznidazole (100 mg)	105 000 tablets total	Chagas disease	2020–2022	WHO
Eisai	Diethylcarbamazine citrate	2 200 000 000 tablets total	Lymphatic filariasis	Until elimination	WHO
Gilead Sciences	Liposomal amphotericin B	380 000 vials total	Visceral leishmaniasis	2016–2021	WHO
Sanofi	Eflornithine	Unlimited	Human African trypanosomiasis	Until 2025	WHO
	Melarsoprol	Unlimited	Human African trypanosomiasis	Until 2025	WHO
	Pentamidine	Unlimited	Human African trypanosomiasis	Until 2025	WHO
	Fexinidazole	Unlimited	Human African trypanosomiasis	Until 2025	WHO
Novartis	Multidrug therapy ¹	Unlimited	Leprosy	2021–2025	WHO
	Clofazimine	Unlimited	Severe erythema nodosum leprosum reactions	2021–2025	WHO

	Triclabendazole	600 000 tablets total	Fascioliasis	2016–2022	WHO
EMS	Azithromycin	Up to 153 000 000 tablets	Yaws	2021–2025	WHO
Pfizer	Azithromycin	Unlimited	Trachoma	1998–2025	International Trachoma Initiative
Johnson & Johnson	Mebendazole	200 000 000 tablets annually	Soil-transmitted helminthiases (SAC) ²	Until 2025	WHO
GlaxoSmithKline	Albendazole	600 000 000 tablets annually	Lymphatic filariasis	Until elimination	WHO
		400 000 000 tablets annually	Soil-transmitted helminthiases (SAC) ²	Until elimination	WHO
Merck KGaA	Praziquantel	250 000 000 tablets annually	Schistosomiasis (SAC) ²	Unlimited	WHO
MSD	Ivermectin	Unlimited	Onchocerciasis	Until elimination	Mectizan Donation Program
		Unlimited	Lymphatic filariasis in co-endemic countries	Until elimination ³	Mectizan Donation Program
		Up to 100 000 000 treatments annually	Lymphatic filariasis for triple-therapy MDA	Until 2025	Mectizan Donation Program

Source: reference (1).

¹ Rifampicin, clofazimine, dapsone.

² For school-aged children (SAC).

³ In Yemen and African countries where lymphatic filariasis and onchocerciasis are co-endemic.

3.2 Shipping and storage

Standard operating protocols and procedures have been developed to coordinate supply chains and ensure safe, secure transport and storage of medicines (19,21). For medicines used in preventive chemotherapy, the Neglected Tropical Diseases Supply Chain Forum – the supply chain behind the world’s largest public health donation programme – has issued guidelines for management of inventory to minimize loss, damage, contamination and misuse and to avoid expiration of medicines (21).

3.3 Drug formulation

For medicines being given to young children, age-appropriate formulations (liquid, granules or rapidly dispersible tablets) are preferred to avoid choking (7). These formulations are not always available for all NTDs.

3.4 Administration

Safety is a central concern during drug administration, even with high-quality pharmaceuticals that have been shipped and stored appropriately.

- As much as possible, medicines should be kept in their original, clearly-labelled containers during preventive chemotherapy or individual treatment. Repackaging should be avoided, as containers can be mislabelled and repackaging can adversely affect the quality and integrity of medicines.
- Coadministration of drugs during MDA is increasingly common as NTD programmes become more integrated. Without careful planning, co-administration increases the risk of mix-ups, incorrect dosing and, possibly, choking. Care should be taken to organize and conduct MDAs to ensure that all drugs to be co-administered are available and that dosing is correct.
- Only drug combinations that are approved by WHO for co-administration should be given together. For lymphatic filariasis, this includes ivermectin and albendazole; diethylcarbamazine and albendazole; or ivermectin, diethylcarbamazine and albendazole (10). For schistosomiasis and soil-transmitted helminthiasis, this includes praziquantel with albendazole or mebendazole (22).
- If water is used to reconstitute powder for oral suspension or to facilitate swallowing of tablets, it should be clean and given in a way that does not promote cross-contamination.
- Before the COVID-19 pandemic, little attention was given to minimizing the risk of transmission of respiratory or gastrointestinal infections during MDA, although lack of hygiene, crowding and shared cups or utensils undoubtedly facilitate such transmission. Greater attention to infection control is warranted.

4. Safe administration of preventive chemotherapy



Photo credit: International Trachoma Initiative

Although the clinical manifestations of many NTDs develop mainly in adults and older children, preschool children (that is, children aged under 5 years) can become infected, develop sub-clinical disease and contribute to transmission. For this reason, preschool-aged children are included in preventive chemotherapy for trachoma, soil-transmitted helminthiasis and lymphatic filariasis, and, with the availability of an age-appropriate formulation of praziquantel, schistosomiasis.

4.1 Prevention of choking

The medicines used in preventive chemotherapy are pharmacologically safe. However, some of the tablets are larger in diameter than the trachea (windpipe) of young children (Table 2). A study has demonstrated the potential of a paediatric tracheal growth model for deciding treatment paths for

patients (23). If tablets are not administered properly, children can aspirate, or choke on them, blocking the airway. Available evidence suggests that about 1% of young children experience non-fatal choking during treatment for soil-transmitted helminth infections (9,15). Although fatal choking during MDA is uncommon, it occurs most often when tablets completely block the airway and cannot be dislodged (7).

Table 2. Tablet size of medicines for preventive chemotherapy and windpipe diameter at youngest recommended eligible age for treatment, by disease

Disease	Age	Windpipe diameter (23)	Medicine	Form	Typical dimension
Lymphatic filariasis ^a	≥ 2 years	6 mm	Albendazole	Tablet	19 x 9 x 6 mm
			Diethylcarbamazine	Tablet	9 x 9 x 2 mm
	≥ 5 years	7 mm	Ivermectin	Tablet	1 x 6 x 6 mm
Schistosomiasis	≥ 2 years	5 mm	Praziquantel	Dissolvable tablet ^b	To be determined
	≥ 6 years	7 mm	Praziquantel	Tablet	22 x 8 x 6 mm
Soil-transmitted helminthiases	≥ 12 months	5 mm	Mebendazole	Dissolvable tablet	20 x 20 x 3 mm
			Albendazole	Tablet	19 x 9 x 6 mm
Trachoma	≥ 6 months	3 mm	Azithromycin	Oral suspension	Liquid
	≥ 7 years	8 mm	Azithromycin	Tablet	14 x 6 x 5 mm

^a Albendazole is administered with either diethylcarbamazine or ivermectin.

^b Under development.



Choking-related deaths in young children are preventable through careful planning and training, and age-appropriate formulations and proper administration of medicines.

4.1.1 Risk factors

Risk factors for choking include large tablet size, young age and forcing children to swallow tablets against their will (9,15). The most important of these risk factors appears to be forcing children to swallow tablets when they are crying or trying to resist taking them. Risk declines, but does not disappear, above 3 years of age (15). Indeed, older adults may also have problems swallowing or chewing large tablets.

4.1.2 Prevention

Choking-related deaths in young children are preventable through careful planning and training, age-appropriate formulation and proper administration of medicines.

4.1.3 Planning and policy

Choking during MDA is a form of operational error which is associated with clearly defined risk factors, such as fatigue, crowding, poor communication, being rushed and task overload (24). In support of the WHO-led initiative on patient safety (6), NTD programmes can treat fatal choking as a preventable adverse event and proactively implement the following prevention policies and practices.

- The push to reach high drug coverage to reduce transmission should not override concerns for safety. Children should never be forced to swallow tablets during MDA in an effort to achieve high drug coverage (9). High drug coverage need not conflict with the safety of MDA; high-quality programmes can achieve both.
- Supportive supervision of community drug distributors should reinforce the importance of safety by encouraging and reassuring those distributors who prioritize safety – even at the cost of slightly lower drug coverage – and when necessary, retraining them to reinforce this practice (25).
- Preventing choking ultimately depends on the quality of interaction between the community drug distributor and the person taking the medicine (or, in the case of young children, the child’s parent or guardian). Distributors should follow the safety precautions for administering medicines (page 15) and be trained, prepared and able to communicate effectively with parents and children. Safety training should emphasize role-playing, problem-solving, communication and orderly workflow.
- Community drug distributors should be familiar with manoeuvres, such as the Heimlich manoeuvre, to dislodge foreign bodies from the airway (9).
- NTD programmes should periodically conduct observational assessments of MDA to evaluate safety practices and refine prevention strategies. For example, in 2018 an observational assessment found that 24% of children aged under 3 years had received whole, rather than crushed, albendazole tablets for treatment of soil-transmitted helminthiases; 12% were forced to take the tablets against their will (15).
- Prompt investigation, management and reporting of serious adverse events are not only legal and regulatory requirements but serve also to decrease rumours, restore trust and sustain high drug coverage. Investigation of serious adverse events should include detailed information on the circumstances involved so that the data can be used to prevent future occurrences.

4.2 Drug formulation

Since 2007, WHO has recommended that young children participating in preventive chemotherapy be given age-appropriate formulations of NTD medicines (7). For trachoma, azithromycin is provided as a powder for oral suspension (reconstituted with water), which is recommended for all children aged under 7 years or less than 120 cm in height, or anyone who has difficulty swallowing tablets (26). Albendazole and mebendazole are not commonly available for preventive chemotherapy as powders for oral suspension. For soil-transmitted helminthiases (and in the case of albendazole for lymphatic filariasis), WHO recommends that deworming tablets be “broken and crushed” for all children aged under 3 years, and given with water (9). For clinic-based treatment of schistosomiasis in preschool-aged children, WHO recommends crushing praziquantel tablets (27). It is unclear how widely these recommendations are followed. A new chewable “child-friendly” formulation of mebendazole is now available for soil-transmitted helminthiases, a tablet that rapidly disintegrates or dissolves when added to a drop of water (28). A paediatric formulation of praziquantel is under development for schistosomiasis.



4.3 Administration

The following guidance is recommended for community drug distributors and other people who administer preventive chemotherapy medicines to young children.

- Adhere to the recommended dosing guidelines on dosing and formulation.
- Offer powder for oral suspension of medicines for trachoma and crushed tablets of albendazole, praziquantel or non-dispersible mebendazole to anyone eligible for the treatment, who has difficulty swallowing tablets. For praziquantel, tablets should be swallowed with a little liquid, preferably during or after meals
- For trachoma, give azithromycin oral suspension to all children aged under 7 years or less than 120 cm in height, and to anyone who has difficulty swallowing tablets (26).
- For soil-transmitted helminthiases and lymphatic filariasis, crush albendazole tablets before giving them to children aged under 3 years.
- Directly observe *all* treatments.
- *Never* force children to swallow medicines, hold their nose to make them swallow or force their head back to give them the medicine: this increases the risk of choking. Never allow parents, guardians, relatives or bystanders to do these things either.
- For children who are fussy, irritable or resist taking medicines, encourage the parent or guardian to calm them so they can receive the treatment.
- If the child continues to resist, *do not* treat the child during this round of preventive chemotherapy.
- When multiple medicines are co-administered during preventive chemotherapy, to avoid choking, do not give participants all the tablets at the same time and instruct them not to swallow all the tablets simultaneously.

5. Collaboration with pharmacovigilance agencies

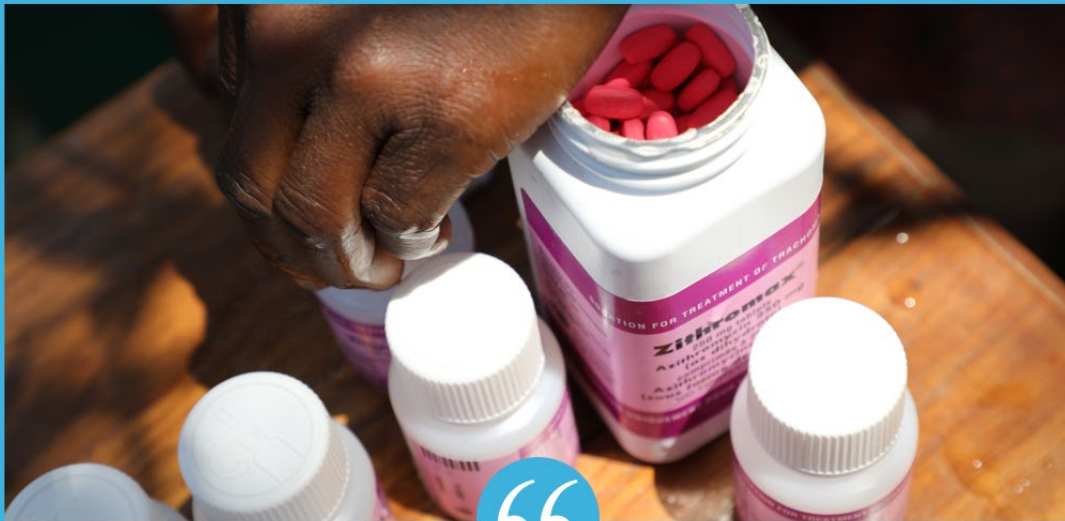


Photo credit: Mectizan Donation Program

National NTD programmes have long recognized the importance of investigating and reporting serious adverse events associated with NTD medicines. WHO has published guidance to help NTD programmes prevent, detect and manage such events (8), which has been adapted and documented (29). Most countries also have national pharmacovigilance centres, located within or affiliated with the health ministry, which are responsible for safety of medicines and the investigation, analysis and reporting of serious adverse events.

5.1 Cross-sectoral collaboration

During the early years of control and elimination, NTD programmes often took the lead in investigating and reporting serious adverse events, particularly those events that occurred during preventive chemotherapy. In many countries, close collaboration was difficult because NTD programmes and pharmacovigilance programmes are often situated in different governmental



As NTD programmes are increasingly integrated and concerned with strengthening health systems, it has become important to collaborate closely with programmes responsible for pharmacovigilance nationally, subnationally, regionally and globally.

Photo credit: International Trachoma Initiative

departments, and the capacity for engagement between both programmes was limited. Furthermore, pharmacovigilance programmes had limited experience with MDA. Today, however, NTD programmes reach more than 1 billion people every year (30), and the capacity of many pharmacovigilance programmes has improved since NTD programmes were established. As NTD programmes are increasingly integrated and concerned with strengthening health systems, it has become important to collaborate closely with programmes responsible for pharmacovigilance nationally, subnationally, regionally and globally. Such collaboration may take time and require changes in organizational dynamics or structures, but it is critical for advancing the safety of NTD medicines, and it has already yielded benefits for control in several countries.

5.2 Advantages to collaboration

While stakeholders in NTDs and pharmacovigilance may have different responsibilities and objectives, they often have the same ultimate goals: to improve people's health and well-being and to contribute to a safe, flourishing society. They also share specific aims, including assuring safety,

preventing unintended harm, protecting public health, improving the quality of information for decision-making and optimizing use of resources (31,32).

By combining forces, both programmes can share responsibilities, increase safety awareness and model the power of collaboration within health ministries. As demonstrated with recent collaboration between the WASH (water, sanitation and hygiene) and NTD programmes, collaboration can enable both sectors to achieve their own specific goals and objectives more quickly and effectively (33).

The first step in effective collaboration is to define shared goals and aims among partners.

Advantages to collaboration for NTD programmes include:

- specialized expertise in adverse drug reactions and their investigation and management, as well as guidance and resources;
- official regulatory authority for addressing serious adverse events;
- independent review of NTD programme safety, which can instill public trust;
- expertise in analysing safety data, which complements the greater capacity of NTD programmes, in general, to collect safety data;
- awareness of data on NTD-related serious adverse events that are not available to NTD programmes;
- open access to the WHO Global Pharmacovigilance Database and access to the WHO global database (VigiBase) of individual case safety reports (34), which can provide national and global pictures of NTD-related serious adverse events;
- help in demonstrating the NTD programme's commitment to safety and cross-sectoral collaboration; and
- expertise and experience in communicating information on risk to communities, and in mitigating and stopping misinformation about adverse events; this can help build public trust in NTD programmes.

Advantages of collaboration for pharmacovigilance programmes include:

- improved safety of MDA as well as management and investigation of serious adverse events, in line with regulatory requirements;
- improved awareness of pharmacovigilance and understanding of simultaneous mass exposure to medicines through preventive chemotherapy;
- greater awareness of individual NTD case management, which requires use of medicines with significant side-effects;
- improved analysis of data and timeliness of reporting serious adverse events;
- opportunities to increase awareness on safety of medicines among the public (i.e. the populations served by NTD programmes), which can improve advocacy and support for pharmacovigilance and strengthen reporting structures;
- increased opportunity to collect and report information during investigations of serious adverse events that will directly address efforts to prevent them (for instance, circumstances in which a child choked) and/or assess and improve the safety of the drug by the pharmaceutical company;

- more efficient allocation and use of resources as a result of sharing responsibilities with NTD programmes;
- reduced duplication of work;
- a denominator for calculating risk of serious adverse events, as MDA programmes report the number of persons treated; and
- a forum for rapidly standardizing and refining reporting tools and systems, such as electronic and mobile systems, improving data collection standards, and fostering seamless data flow and sharing.

5.3 How to start collaboration

Collaboration can start where it is simplest, or easiest to fund, and be expanded at a later stage as a joint work plan develops and resources become available. Simple entry points include:

- inviting pharmacovigilance agencies to NTD meetings (and, if relevant, to join NTD task forces or working groups);
- including national pharmacovigilance centres in planning for and correspondence related to MDA;
- attending meetings and working groups on pharmacovigilance;
- sharing information on NTD medicines, disease prevalence, drug coverage, and experience with adverse events and serious adverse events;
- ensuring that the NTD safety committee includes representatives from both NTD and pharmacovigilance programmes to deliberate over reports of serious adverse events during MDA campaigns;
- identifying potential sources of funding for comprehensive programme delivery;
- seeking out and engaging with a specific counterpart or ally from the pharmacovigilance programme with whom you could collaborate closely;
- inviting a representative of the pharmacovigilance agency to participate in national-level NTD training of trainers; and
- adding messaging on pharmacovigilance in NTD training and community sensitization materials.

Collaboration is not just about setting up a coordination structure such as a committee or working group: it requires a team of people working together towards the same goal. Consider a shared achievable goal that both teams can work together on. Who should be involved, what expertise and experience do they bring, and to what extent can they commit to being actively engaged over the necessary period?

In an initial series of meetings between the NTD and pharmacovigilance programmes, you may wish to:

- become familiar with each other's programmes, responsibilities, goals, timelines, strategies, objectives and regulatory requirements, with an emphasis on safety;
- discuss common implementation challenges (e.g. collecting information on details surrounding serious adverse events in a timely fashion; using reports of serious adverse events to develop prevention strategies; addressing community unrest following such events; and developing common protocols to ensure a unified response);
- identify clear roles, responsibilities and opportunities, particularly where there is good overlap and measurable results can be achieved quickly;
- identify practical areas where engagement of pharmacovigilance personnel can improve NTD safety and where NTD personnel can facilitate the goals of pharmacovigilance;
- ask pharmacovigilance staff to review messaging by NTD programmes on safety and risk;
- invite pharmacovigilance staff to observe or participate in preventive chemotherapy campaigns;
- begin plans to establish or strengthen working groups or task teams, including district-level teams, to investigate and manage serious adverse events within specific time frames;
- develop and commit to a preliminary scope of work; and
- create a core team responsible for ongoing communication and development of closer collaboration through a situation analysis and a formative assessment of opportunities for collaboration.

6. Recognizing, managing and reporting serious adverse events



Despite the pharmacological safety of the essential medicines used to treat NTDs, adverse events may occur; most are transient in duration and mild in intensity. Some adverse events are direct side-effects of the medicines; others are caused by their effect on the organism being targeted, particularly for helminths. These are commonly referred to as “side-effects” or “adverse drug reactions.” Adverse events may also be caused by improper administration or other factors.

National policies for informed consent should be followed. If patients and communities are well-informed in advance, and people who experience adverse reactions know where to seek help, most events can be managed without negative impact on the programme or on the health of individuals. Occasionally, clusters of mild adverse events during MDA can cause unease or even panic, which disrupts NTD programmes. Concern about adverse events remains a major reason why people refuse to participate in preventive chemotherapy (35-37).

A small proportion of adverse reactions are classified as serious. A “serious adverse event” is a regulatory term describing a medical event that results in death; is life-threatening; requires in-

patient hospitalization or results in prolongation of hospitalization; results in significant or persistent disability/incapacity; or results in a congenital anomaly or birth defect. Regulations requiring reporting of serious adverse events were developed for clinical trials and research on human subjects rather than for population-level exposures that occur with public health programmes such as preventive chemotherapy. These regulations require that all serious adverse events be promptly reported to regulatory authorities, such as national pharmacovigilance centres, regardless of whether they are considered to be causally related to medicines or programmes. Reports of serious adverse events alert public health officials and pharmaceutical company to unexpected safety threats and help to quantify their magnitude and pattern, which are known to be associated with treatment. If properly investigated and analysed, such reports can also contribute to developing strategies and practices to improve the safety of NTD medicines.

The frequency of adverse events and serious adverse events varies with the distribution and prevalence of NTDs as well as with the specific medicine(s) being used and the NTD(s) being targeted. For example, *Loa loa*-related encephalopathy following MDA for onchocerciasis occurs in central Africa, where loiasis is co-endemic. The settings in which serious adverse events are detected and the routes through which they are reported to regulatory authorities may differ between NTDs suitable for preventive chemotherapy and those that require individual treatment. For example, serious adverse events following individual treatment in clinics or hospital settings are more likely to be recognized and reported by attending physicians than community health workers administering community MDA campaigns. WHO has issued detailed guidance to programme managers for preventing, detecting and managing serious adverse events during preventive chemotherapy (8), which has been incorporated into a handbook (29). Programme managers should consult these documents for further information.

6.1 Serious adverse events and preventive chemotherapy

Serious adverse events are of particular concern in the context of preventive chemotherapy, since entire populations – including people who are healthy and not affected by NTDs – are presumptively treated. Reporting of serious adverse events has identified two major safety issues. First, reports of serious adverse events from Central Africa during MDA with ivermectin for onchocerciasis control led to the recognition that coinfection with *Loa loa* was responsible for unexpected cases of encephalopathy and coma, as well as to a series of research studies and efforts to prevent and improve the outcome of these cases (12–14,38). Secondly, reports of fatal choking led to WHO recommendations that young children receive crushed, rather than whole, deworming tablets and that they not be forced to take them while crying or resisting (9).

Much less frequent is Stevens–Johnson syndrome, a serious skin condition sometimes associated with certain medicines (39), and seizures in people with neurocysticercosis who receive praziquantel for schistosomiasis or albendazole for control of soil-transmitted helminthiasis (40,41). Even less common in MDA settings are adverse events reported in patients receiving other medicines. For example, haematoma of the tongue was reported in a man treated with ivermectin for scabies who was also receiving the anticoagulant warfarin (42), and a small outbreak of Stevens–Johnson syndrome was reported in Filipino labourers in Taiwan, China who were treated with both mebendazole and metronidazole (39). Because such apparent drug–drug interactions are rare and causality is uncertain, they have not led to generalized exclusion criteria for MDA.



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Exclusion criteria (8,43-48)

Individuals with serious illness should be excluded from preventive chemotherapy because drug-related adverse events in these individuals may be severe and because they are more likely to experience adverse health events unrelated to preventive chemotherapy. Seriously ill individuals are defined as those who:

- have an illness that makes them too sick or weak to get out of bed; or
- are currently hospitalized.

Azithromycin is an exception to this general rule, in light of recent findings suggesting that it may reduce overall mortality in young children in areas where infant mortality is high (49).

Additional general exclusion criteria include:

- age (the lower eligible age varies for different medicines; see Table 3);
- pregnant women (with exceptions; see Table 4);

- patients diagnosed with neurocysticercosis or with compatible symptoms, such as a history of seizures or epilepsy, or intense, severe and progressive headaches, should be excluded from preventive chemotherapy with albendazole or praziquantel (44); and
- people who have previously suffered from serious adverse events caused by a reaction to the medicine, such as Stevens–Johnson syndrome (8,47).

Table 3. Youngest age recommended for preventive chemotherapy, by medicine

Medicine	Disease	Eligibility for treatment (age or height)	Rough age equivalent
Albendazole (45,47)	Lymphatic filariasis Soil-transmitted helminthiases	≥ 12 months (age)	
Azithromycin (26,48)			
Oral suspension	Trachoma	≥ 6 months (age)	
Tablets		≥ 7 years (age) or > 120 cm (height)	
Ivermectin (43,47)	Lymphatic filariasis Onchocerciasis	≥ 90 cm (height)	≥ 5 years
Diethylcarbamazine (43,47)	Lymphatic filariasis	≥ 2 years (age)	
Mebendazole (45,47)	Soil-transmitted helminthiases	≥ 12 months (age)	
Praziquantel (27,46,47)			
Tablets	Schistosomiasis	≥ 94 cm (height)	≥ 6 years
Dissolvable oral tablets		≥ 2 years (age)	

Table 4. Pregnancy- and lactation-related exclusion criteria for preventive chemotherapy, by medicine

Medicine	First trimester	Second and third trimesters	Lactating
Albendazole (8,43,57,59)	Exclude	Treatment recommended in areas endemic for soil-transmitted helminthiases	Treatment recommended in areas endemic for soil-transmitted helminthiases
Azithromycin (26,60)	Exclude – probably safe	Safe	Safe
Diethylcarbamazine (8,43,59)	Exclude	Exclude – probably safe	Exclude - possibly safe
Ivermectin (8,43,59)	Exclude	Exclude – probably safe	Exclude for first week after delivery
Mebendazole (8,43,57,59)	Exclude	Treatment recommended in areas endemic for soil-transmitted helminthiases	Treatment recommended in areas endemic for soil-transmitted helminthiases
Praziquantel (8,46,57,59)	Exclude	Treatment recommended in areas endemic for schistosomiasis	Treatment recommended in areas endemic for schistosomiasis

6.2 Serious adverse events and individual treatment

Effective treatment for several NTDs requires multi-day regimens that are administered in clinical settings by experienced medical personnel, with careful monitoring for toxicity. These include visceral leishmaniasis, human African trypanosomiasis, Chagas disease, Buruli ulcer, neurocysticercosis and echinococcosis (16,17,50–54). Table 1 lists the medicines donated for treatment of these diseases. Multi-drug treatment of leprosy (Hansen’s disease), which is given for 6–12 months, is associated with neuritis as well as immunological “type I and type II reactions” (55, 56). Treatment should always be administered by trained personnel, following recommended protocols for administration and monitoring of adverse events. For decades, lack of financial incentive for development of safer, more effective regimens stalled progress, but in the past several years, considerable research has been conducted to develop alternative treatments.

Reliable data on adverse reactions associated with treatment for these NTDs come largely from clinical studies rather than population-level adverse event reporting. The most common adverse events associated with treatment for NTDs are summarized in Annex 5.

Preventive chemotherapy with single-dose niclosamide or praziquantel, or three consecutive days of albendazole is being considered for prevention of *Taenia solium* taeniasis and neurocysticercosis (57); post-exposure prophylaxis, a form of targeted preventive chemotherapy, has been proposed for treatment of leprosy, using single-dose rifampicin (58,59). The safety profile of the medicines in these settings is less well-established than for other medicines commonly used in preventive chemotherapy.



Photo credit: International Trachoma Initiative

6.3 Being prepared for serious adverse events

A rapid, professional, and effective response to serious adverse events is possible only with advance planning and preparation, which should involve all levels of the health system as well as communities.

- Community drug distributors, health workers and district health officers should all be familiar with, and able to rapidly recognize, serious adverse events associated with the different diseases and medicines.
- Local clinics and referral centres should be informed of MDA in advance so they can be prepared to address adverse events and provide support.
- A chain of reporting should be agreed upon and practiced in advance, based on the existing system for reporting serious adverse events and the processes, structures and provisions for notifying and seeking immediate help from the appropriate health officials; telephone numbers should be available to all NTD programmes. Community drug distributors should be confident in reporting criteria and processes. District health officers and treating clinicians should be aware of reporting criteria and who to contact at the national level for immediate assistance; this is particularly important in MDA settings where treating personnel leave the community at the end of the day. National and subnational pharmacovigilance agencies should be informed in advance of preventive chemotherapy, of the location, dates, medicines used, diseases targeted and estimated number of participants; this should be done at several levels to ensure there is comprehensive public awareness through mass media, written materials, community awareness-raising activities and liaison with community leaders.
- The community, or in the case of individual treatment, the patient, should be informed about the possibility of adverse events as well as where they should seek help if adverse events occur. Such communication generates trust and demonstrates concern for quality people-centered care, a core element of universal health coverage.
- Particularly in the setting of MDA, in which persons participate for the benefit of the community, public health programmes have a “duty to care” for people who experience adverse events and serious adverse events. A national policy should be in place that specifies who will be responsible for their care.

6.4 Responding to serious adverse events

The immediate priority in responding to serious adverse events is to provide care for the patient and reassurance to the community (8,29). In settings of preventive chemotherapy, community drug distributors should have immediate access to supervisors or district health staff to arrange for referral and medical care as needed.

A second urgent priority is communication, which must be based on known facts and occur quickly, smoothly and at multiple levels. Patients and their families must be reassured that they are safe and being cared for. Formal and informal community leaders, community members and the media must be provided with accurate information to prevent the spread of rumours and misinformation, which can harm NTD programmes. Technology and social media make the spread of rumours much more rapid, damaging and harder to control. NTD programmes must therefore use social media promptly and skillfully. Health officials must also be notified, both to provide necessary medical care and to initiate appropriate response and investigation; they, in turn, must file official reports to national and international regulatory agencies. For more information, see section 7 on communication and rumour control.

6.5 Investigating serious adverse events

The steps for investigating and reporting serious adverse events are similar for diseases addressed through preventive chemotherapy and individual treatment. Soon after the event occurs, an investigation should be conducted if (i) there is suspicion that the event may have been caused by “operational error”; (ii) required by national regulations; (iii) the cause is unknown or unexplained; (iv) there is a cluster of events; or (v) there is significant community concern or disruption (29). Typically, investigations are conducted by national and subnational health and regulatory officials who interview witnesses, review the chain of events that led to the event, and assess whether it was causally related to NTD medicines. They may send samples of the medicine(s) used during preventive chemotherapy to a reference laboratory to be tested for quality and purity. These officials submit a standardized report, usually provided by the national pharmacovigilance centre, to the national NTD programme and the Centre, pharmaceutical companies and international regulatory agencies. Serious adverse events reporting forms could vary from country to country, although they comply with WHO standards; an example of such a form is shown in Annex 3.

These forms are designed for systematic recording of events related to serious adverse events in general; they may be less useful for collecting information that can lead to prevention of specific serious adverse events such as choking. Thus, for certain serious adverse events of interest, additional information can be collected using specific forms. For example, in cases of choking, information should be gathered on drug formulation (e.g. whole tablet or powder for oral suspension) and form (i.e. crushed or whole tablet, granules or rapidly dispersible tablet); how the medicine was given (e.g. with water); whether the child was forced to take the medicine while resisting or crying; the position of the child (i.e. upright or supine); who gave the medicine (i.e. health worker, parent or the child her or himself); and whether the treatment was observed by a community drug distributor or health worker. An example of such a form is shown in Annex 4.

7. Communication and rumour control



Photo credit: International Trachoma Initiative

Communication and community engagement have long been recognized as essential for preventive chemotherapy programmes. Effective communication is also required for optimal individual treatment of patients with NTDs and their families in order to ensure compliance with medication and other treatment measures. Despite years of experience, programme managers highlight the need for ongoing preparedness, support and communication skills, particularly when panic erupts in communities or in the media following adverse events, even when not causally associated with treatment. Special skill and training may be needed to address the rare but challenging instances of “mass psychogenic illness” in which several people develop similar, often dramatic, symptoms that are pharmacologically unrelated to the medicines.



Communication and community engagement have long been recognized as essential for preventive chemotherapy programmes. Effective communication is also required for optimal individual treatment of patients with NTDs and their families in order to ensure compliance with medication and other treatment measures.

Effective communication remains challenging for several reasons. Continued growth in the number of people participating in preventive chemotherapy, some for the first time, may contribute to increased numbers of adverse events. In addition, the success of programmes in reducing the prevalence of infection and disease means that the need for intervention, particularly preventive chemotherapy, is less obvious to communities. The relative infrequency of serious adverse events makes it difficult to retain and practice related communication skills. The COVID-19 pandemic has created further health-related communication challenges that affect programmes.

7.1 Planning and preparation

At the community level, health workers and drug distributors should be trained to share information about the safety and effectiveness of preventive chemotherapy for NTDs as well as the risk of adverse reactions. This should include messages on where and how to seek care for adverse reactions if they occur; it may require tailoring messages to different groups within the community. Communication with communities should establish trust in preventive chemotherapy and in those who manage the intervention.

Mass and social media can be allies in mobilizing community participation in preventive chemotherapy, or they can rapidly amplify rumours that threaten NTD programmes. Skillful engagement and cultivation of the media *in advance* of preventive chemotherapy will be helpful for conveying accurate information if safety is called into question. Communicating effectively with the media requires training and practice. Together with the National Pharmacovigilance Centre, NTD programmes should designate a spokesperson, develop a communications plan and draft press statements prepared *before* MDA in case of community concern over adverse events. All programme officials should be familiar with key messages. Close collaboration with and involvement of the national pharmacovigilance agency can help to generate public confidence and trust and reinforce preparedness for adverse events.

7.2 Response

In the event of an adverse event that affects the health of people receiving medicines or threatens the programme, the immediate priority is attending to the patient and ensuring that they receive appropriate medical attention. Compassionate, professional, calm communication with the patient and family member is essential. As noted above, a second urgent priority is to communicate with the community and the media to provide essential information, restore trust, and counteract misinformation and rumours. Regardless of whether the event is truly related to the MDA or only perceived to be, it can become a crisis if not managed properly or planned for in advance (8,29,43).

Recommended steps for effective communication in response to adverse events include the following (8,29,43,60).

- Activate the communication strategy and adapt it to the current crisis.
- Identify a spokesperson to interact with the media (consider geographical location of the serious adverse event; language groups; respected leaders; health personnel).
- Define the audiences that need to receive information (there may be several, e.g. public, media, health professionals).
- Identify delivery mechanisms for each major audience (e.g. in-person meetings, radio, newspaper, television, social media).
- Design a few simple key messages for each audience, which may include the following:
 - concern and empathy for the person experiencing the serious adverse event;
 - overall excellent safety track record of NTD medicines globally;
 - reactions to treatment during MDA are usually mild and self-limiting;
 - safety is a chief concern of the programme and a reporting system (surveillance) has been established to detect, manage and prevent serious adverse events;
 - the incident is being taken seriously and is under investigation;
 - the investigation will address the causes or factors contributing to the serious adverse event so that they can be prevented in the future. It will include investigation at all levels, from the source of medicines, through their chain of custody, to their administration;
 - in general, many serious adverse events are coincidental, i.e. the event is not causally related to the medicine or its administration;
 - the quality of the medicines is assured (provided this is true); and
 - specific actions are being taken to respond to the serious adverse event (give examples).

Recommended tips for effective communication in response to adverse events include the following (8,29,43,60).

- Project a strong, compassionate, competent image for yourself and the NTD programme.
- Avoid improvization and casual remarks (stick to the facts).
- Prepare answers and practise for the likely and awkward questions.
- Identify which issues not to respond to (e.g. blaming an individual or speculating on the cause before the investigation is complete).
- Be 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.”).
- Avoid jargon; use simple phrases and give examples to clarify your meaning.
- Be serious – jokes can be disastrous.
- Be aware of body language, which is critically important for perceptions.
- Be responsible: do not be defensive, but accept responsibility appropriate to your position.
- Avoid blaming someone.
- Be 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
- Be positive: reframe the situation in positive terms; use terms such as “safety” (which has a positive connotation) rather than adverse event.
- When facing a hostile interviewer, prepare to use these “ABCD” techniques:
 - *Assure*. 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, of whom 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 to something linked but positive.
 - *Correct what is wrong*. Immediately correct information from the interviewer that is wrong.
 - *Deliberate*. Take time to think about your response to questions; do not be rushed or forced. Be deliberate.

8. Summary points and suggestions



All global health programmes have ethical responsibilities both to provide health benefits and minimize harm. In recognition of the high financial and health costs of operational error (24), the World Health Assembly called for a WHO-led initiative on patient safety in 2019 (6). Safety has long been a primary concern of NTD control. In alignment with WHA72.6, the NTD road map 2021–2030 (1) and the WHO Thirteenth General Programme of work 2019–2023 (4), this “culture of safety” should permeate all aspects of NTD programmes, including training; supervision; medicine supply and management; individual treatment and preventive chemotherapy; community engagement; programme monitoring; and investigation and reporting of serious adverse events. Ideally, safety-related goals, objectives and activities should be articulated in national NTD master plans.

Managers of NTD programmes already have access to excellent reference materials produced by WHO and partners to guide them in securing high-quality NTD medicines, protecting the supply chain, collaborating with pharmacovigilance agencies, preventing choking and *Loa loa*-related

encephalopathy associated with preventive chemotherapy, investigating and reporting serious adverse events, and developing effective communications with communities and the media. The following suggestions and the accompanying training modules and job aids are intended to reinforce existing guidance and support a “culture of safety.”

- Co-administration of NTD medicines, which is increasingly common, should be carefully planned and executed to avoid mix-ups, incorrect dosing and choking. Only combinations of medicines that are approved by WHO for co-administration should be co-administered.
- Children should *never* be forced to take medicine during MDA in an effort to achieve high coverage (9). If the child continues to resist, *do not* treat the child during this round of preventive chemotherapy. High drug coverage need not conflict with MDA safety: high-quality programmes can achieve both.
- Community drug distributors should be trained, prepared and able to communicate effectively with parents and children to prevent choking, and they should be familiar with manoeuvres, such as the Heimlich manoeuvre, to dislodge foreign bodies from the airway (9).
- Safety training for community drug distributors should emphasize role-playing, problem-solving, communication, recognizing and addressing serious adverse events, and orderly workflow.
- NTD programmes should periodically conduct observational assessments of MDA to evaluate safety practices and to refine prevention strategies.
- Pharmaceutical companies should be encouraged to further develop and make available age-appropriate formulations of NTD medicines.
- Oral suspension or crushed tablets should be offered to all children aged under 3 years and to anyone, of any age, who has trouble swallowing tablets.
- *All* treatments should be directly observed during preventive chemotherapy.
- When multiple medicines are co-administered during MDA, participants should not be given all the tablets at the same time and should be discouraged from taking all the tablets together.
- Even after the pandemic of COVID-19 subsides, continued measures should be taken to prevent transmission of respiratory or gastrointestinal infections during treatment, e.g. through poor hygiene, crowding, and shared cups or utensils.
- Practical steps should be taken to develop strong collaboration with pharmacovigilance agencies in detecting, managing, investigating and reporting serious adverse events.
- National and subnational pharmacovigilance centres as well as health centres should be informed in advance of preventive chemotherapy, including the location, dates, medicines used, diseases targeted and estimated number of participants.
- A chain of reporting serious adverse events should be agreed upon, documented and practiced in advance, and provisions made for escalation to notify and seek immediate help from the appropriate health officials, whose telephone numbers should be available to all people in NTD programmes, including community drug distributors.
- NTD programmes should designate a spokesperson, develop a communications plan, refine and practise communication skills, and draft press statements *before* MDA in case of community concern over adverse events.

Safety requires ongoing vigilance and preparation. In official and unofficial documents, WHO has provided guidance on most, if not all, of the issues addressed here. Yet gaps in safety persist. To be effective, safety principles must be embedded in the policies, procedures and structures of NTD programmes. Cross-sectoral collaboration (for instance, with pharmacovigilance agencies) and multi-level communication (from the national to the community level and back) are required. Visionary and committed leadership is essential. Programme managers must be able to allocate resources to prioritize safety and preparedness, even though serious adverse events occur infrequently. Together, these and other actions can position NTD programmes to create “cultures of safety” that model the intention and realize the potential of WHA72.6.

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Annex 1. Aide-mémoire for programme managers

Ensuring the safety of preventive chemotherapy campaigns for control and elimination of neglected tropical diseases

The safety of preventive chemotherapy for control and elimination of neglected tropical diseases (NTDs) is critical to the success of programmes. Safety is also essential to fulfill the ethical obligation of public health programmes to “do no harm” while delivering health benefits. Safety should be embedded in, and permeate, all aspects of NTD programmes, including training; supervision; drug supply and management; preventive chemotherapy; communication with communities; programme monitoring; and prompt investigation and reporting of serious adverse events.

Preventive chemotherapy is the periodic (usually annual) distribution of medicine to at-risk populations. The aims of preventive chemotherapy are to provide treatment for people with NTDs and reduce transmission of disease. Thus, preventive chemotherapy offers benefits to both individuals and populations. Preventive chemotherapy is usually offered during a short period of time, and may be conducted outside the normal health care settings. This necessitates careful planning and good supervision.

Safety has long been a key consideration for NTD programmes. For example, the medicines that are donated for preventive chemotherapy are manufactured according to the highest standards of quality, and WHO has included safety in its preventive chemotherapy guidelines for specific diseases. Considerable effort has been put into determining the safety of combinations of medicines for use in preventive chemotherapy and in establishing surveillance for serious adverse events. Despite these substantial efforts, maintaining safety as preventive chemotherapy reaches more than 1 billion people per year requires ongoing vigilance and explicit attention.

This aide-mémoire is intended to help NTD programme managers and other stakeholders ensure safety as an integral part of preventive chemotherapy. It accompanies the manual on safety in administering medicines for NTDs and the associated training modules (Web Annexes A and B). A similar aide-mémoire is available for community drug distributors and their supervisors (Annex 2).

The following checklist is organized chronologically, highlighting essential safety activities during the planning, implementation and follow-up periods of preventive chemotherapy. Components of safety within these periods include organizational and systems preparedness; drug supply and management; communications and community mobilization; safety training; and managing adverse events.

I. Preparing for preventive chemotherapy

Organizational and systems preparedness

- Safety-related goals, objectives and activities articulated in national NTD master plan
- National and subnational pharmacovigilance agencies informed of preventive chemotherapy location, dates, medicines used, diseases targeted, and estimated number of participants
- Protocols and procedures for managing, reporting and investigating adverse events and serious adverse events, including standard case definitions, are clearly established and communicated to all relevant stakeholders (particularly the national pharmacovigilance centre)
- Medical teams are prepared to respond rapidly to adverse events and serious adverse events

Drug supply and management

- Supplies of medicines to be used in preventive chemotherapy are available, of high quality, and are safely and securely stored and ready for shipment to communities
- Medicines have been stored safely and securely and managed according to best practices (e.g. first-in, first-out)
- Medicines to manage adverse events and serious adverse events are available in health facilities and, if appropriate, to drug distributors

Communication and community mobilization

- Communications plan developed and rehearsed, covering community mobilization, key messaging for various groups (e.g. community leaders, public, media), and communications in the event of serious adverse events or rumours
- Communications spokespeople identified and trained at national and regional levels
- Draft press statements prepared to address various scenarios and communications challenges (e.g. serious adverse events and rumours)
- Key messages pilot tested and refined with input from community and other stakeholders
- Drug distributors (which can include teachers, community health workers, or volunteer community drug distributors, among others) are trained to share information with community about the disease targeted, the safety and effectiveness of the medicines, and the risk of adverse reactions (see training, below)

Ensuring safety: training and practice

- Drug distributors are trained to recognize, manage and refer adverse events and serious adverse events associated with different NTDs and NTD medicines
- Drug distributors know what to do in case of choking (e.g. familiar with Heimlich manoeuvre)
- Drug distributors know the contraindications and exclusion criteria for administering NTD medicines

Managing adverse events

- Arrangements have been made by community drug distributors and district health staff to provide patients with immediate medical care if needed
- Medicines and supplies for managing adverse events are available and in place
- Referral facilities for serious adverse events are identified and prepared to receive patients
- System for immediate notification and response to serious adverse events established, disseminated, and all people involved know who to contact

II. Conducting preventive chemotherapy campaigns

Organizational and systems preparedness

- Clinics and hospitals notified and prepared to manage adverse events
- Response to serious adverse events and associated reporting system prepared

Drug supply and management

- Medicines stored safely and securely and managed according to best practices (e.g. first-in, first out)
- Medicines inspected in advance of administration to ensure that they are not broken or disintegrated
- Medicines inspected to ensure that they have not reached the expiration date
- In the case of repackaging of medicines, all containers appropriately and clearly labelled

Communication and community mobilization

- Key messages delivered to community and other stakeholders about the diseases targeted, the safety and effectiveness of the medicines, and the risk of adverse reactions (see training modules)
- Communications team monitoring social media for rumours and misinformation

Ensuring safety: training and practice

- Community drug distributors equipped to organize a safe working environment for delivering preventive chemotherapy and skilled in crowd control
- Community drug distributors rapidly recognize adverse events and serious adverse events associated with different NTDs and NTD medicines and immediately contact supervisor in order to know what to do
- If campaign is planned during a time when a pandemic, such as COVID-19 is suspected, personal protective equipment, social distancing, and other precautions have been implemented
- Adherence to recommended dosing guidelines for medicines administered
- Adherence to recommended exclusion criteria for medicines administered
- Adherence to WHO-approved combinations for medicines co-administered
- All treatments directly observed by community drug distributors
- Supervisors of community drug distributors monitor for safety as well as other aspects of programme performance, such as drug coverage

Managing adverse events

- Patients informed of the possibility of adverse events and where they should seek care if an adverse event were to occur
- If adverse events occur:**
 - provide patients with immediate medical care;
 - contact and reassure families of patients that they are safe and being cared for;
 - report serious adverse events to WHO, regulatory agencies and pharmaceutical manufacturers within 24 hours;
 - notify district health officers, NTD programme personnel and pharmacovigilance agencies if reactions are more severe or are of concern to the community;
 - activate communication strategy with media that addresses the factors contributing to the serious adverse events and dispels any circulating misinformation; and

- follow up on the investigation of serious adverse events conducted by national and subnational health and regulatory authorities.

III. After preventive chemotherapy

Organizational and systems preparedness

- Review, analyse and discuss serious adverse events, drug coverage, processes and challenges
- Identify what worked well and what improvements are needed for next round of preventive chemotherapy

Medicine supply and management

- Determine remaining stocks and return unused medicines to medical stores
- Request medicines for next round(s) of preventive chemotherapy
- Review protocols for safe and secure medicine management and supply chain

Communication and community mobilization

- Review key messages delivered to community and other stakeholders about the diseases targeted, the safety and effectiveness of the medicines, and the risk of adverse reactions
- Review adequacy of the communications plan; review rumours and misinformation and adjust communications plan as needed

Ensuring safety: training and practice

- Identify gaps in training; incorporate specific training exercises into preparations for subsequent preventive chemotherapy

Managing adverse events

- Debrief on adverse events, and response and reporting of serious adverse events, with NTD task force and pharmacovigilance centre, with full review of processes
- Determine how to improve management and reporting of serious adverse events to prevent them in the future
- Incorporate serious adverse events into ongoing analysis at the national level
- Ensure that appropriate reports are shared with regulatory and other agencies and organizations

Annex 2. Aide-mémoire for community drug distributors

Ensuring the safety of preventive chemotherapy campaigns for control and elimination of neglected tropical diseases

Preventive chemotherapy is the periodic (usually annual) distribution of medicine to people at risk of neglected tropical diseases (NTDs). The aims of preventive chemotherapy are to treat infected people and reduce disease transmission. Safety – the principle of “do no harm” – is critical for the success of preventive chemotherapy programmes.

This aide-mémoire is intended to help NTD drug distributors, including community health workers, community drug distributors, teachers, or other people, ensure safety during preventive chemotherapy. The following checklist is organized in three main sections, highlighting essential safety activities before, during and after preventive chemotherapy.

I. Safety *before* preventive chemotherapy

Drug distributors should:

- Share key information with the community about the diseases targeted, the safety and effectiveness of the medicines, and the risk of adverse events. These messages include:
 - Medicines for NTDs are safe and effective.
 - To protect the community, most eligible people must take the medicine.
 - In the day or two after treatment, people may experience adverse reactions, which are usually mild, and last less than two days. Common adverse reactions include headache, stomach ache, fever, muscle aches and nausea. They are most commonly caused by the effect of the medicine against the NTD.
 - Medicines will be distributed on [days] at [place].
- Know what to do to prevent choking (see below)
- Know what to do in the event of choking (e.g. Heimlich manoeuvre)
- Know what to do in the event of adverse events, including serious adverse events, which require medical attention

II. Safety *during* preventive chemotherapy

Safe setting or environment

Drug distributors should:

- Establish a safe, organized work environment
- Control crowds to allow for smooth workflow
- Use personal protective equipment, social distancing and other precautions as required during pandemics

Drug administration

Drug distributors should:

- Obtain consent from adults and children prior to treatment
- Adhere to recommended dosing guidelines
- Directly observe treatment
- Adhere to recommended exclusion criteria for:
 - age (depends on disease and medicine)
 - serious illness – person too sick or weak to get out of bed
 - women in the first trimester of pregnancy
 - people with a history of seizures or epilepsy
 - people who have previously suffered from serious adverse events from the medicine

Choking prevention

Drug distributors should:

- Crush deworming tablets and give them with water to children aged under 3 years
- Never* force children to take medicine against their will. If a child continues to resist, he or she should not be treated during this round of preventive chemotherapy
- Ensure that participants do not swallow all tablets together at the same time when multiple drugs are co-administered
- Know what to do if a child chokes (e.g. Heimlich manoeuvre; see Figs. A2.1 and A2.2 below).

Managing adverse events

Drug distributors should:

- Inform participants of the possibility of adverse events and where they should seek care if any such event were to occur
- Know which adverse events require immediate notification of supervisors and the rapid response team and how to contact them. These include:
 - any severe reaction that threatens health
 - any cluster of cases involving several people
 - any reactions that cause community concern or disruption

- If adverse events occur:
 - a. Provide patients with immediate first-aid care or treatment for minor adverse events
 - b. For more severe reactions, refer the patient to the nearest health facility and immediately contact supervisor or/and the rapid response team
 - c. Reassure and provide support to families of people affected
 - d. If needed, pause preventive chemotherapy in order to reestablish order and calm

III. Safety *after* preventive chemotherapy

Organizational and systems preparedness

- Review and discuss any problems with drug administration, drug coverage or adverse events
- Identify what worked well and what improvements are needed for the next round of preventive chemotherapy

Communication and community mobilization

- Review key messages delivered to the community and other stakeholders about the diseases targeted, the safety and effectiveness of the medicines and of the risk of adverse reactions, and adjust them if needed.

Ensuring safety: training and practice

- Incorporate lessons learned into preparations for subsequent preventive chemotherapy



Fig. A2.1 Heimlich manoeuver on a choking child



Fig. A2.2 Heimlich manoeuver on a choking baby

Annex 3. Example of a general form for reporting serious adverse events

Country:		Date of report: (day/month/year) / /			
1. Patient information					
Name (first/middle/last):			Age:	Sex (M/F):	
Location:	District:		Province/State:		
2. Pre-existing conditions					
<i>Health status before treatment with preventive chemotherapy medicines:</i>					
<input type="checkbox"/> Good <input type="checkbox"/> Poor <input type="checkbox"/> Unknown If "Poor", give details:					
Disease	Confirmed	Suspected	Negative	Unknown	Details
1. Soil-transmitted helminthiases	<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"/>	
5. Trachoma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Other parasitic infections, known or suspected:</i>					
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):
<i>Other medications being taken (concurrently or recently):</i>					
<i>Is patient pregnant?</i> <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown					
3. Medicines administered					
<i>Which of the following medicines were administered to the patient?</i>	Dose	Brand and name of manufacturer	Batch number	<i>Date of treatment:</i> (day/month/year)	
albendazole					
azithromycin					
diethylcarbamazine (DEC)					
ivermectin					
mebendazole					

praziquantel				
<i>Source of treatment:</i> <input type="checkbox"/> Mass treatment programme <input type="checkbox"/> Clinic or physician treatment <input type="checkbox"/> Other method		Patient's height (cm)	Patient's weight (kg)	
<p><i>Was this a first treatment with any of the medicines selected above?</i></p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown</p> <p>If "Yes", which of the following medicines were first treatments?</p> <p><input type="checkbox"/> albendazole <input type="checkbox"/> azithromycin <input type="checkbox"/> diethylcarbamazine (DEC) <input type="checkbox"/> ivermectin <input type="checkbox"/> mebendazole <input type="checkbox"/> praziquantel</p> <p>If "No", explain when, and circumstances of past treatment(s) of each medicine:</p>				
4. Description of the serious adverse event				
<i>Date of onset</i> (day/month/year):		<i>How long after medicines were taken?</i> <input type="checkbox"/> hours OR <input type="checkbox"/> days		
<i>Clinical signs and symptoms</i> (please describe)				
<p><i>Do you think this adverse event is/was life-threatening?</i> <input type="checkbox"/> Yes <input type="checkbox"/> No</p>				
<i>Laboratory results</i> (please provide name of test)			<i>Dates of tests</i> (day/month/year)	

<p>a) Hospitalization</p> <p>If "Yes", indicate:</p> <ol style="list-style-type: none"> 1. Date of admission (day/month/year) 2. Reason(s) for admission: 3. Date of discharge (day/month/year) <p>b) Medical treatments administered to treat adverse event:</p> <p>c) Clinical course:</p> <p style="text-align: center;"><i>(Attach any relevant reports)</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
5. Condition/outcome at time of last observation	
<p>Full recovery:</p>	<p>Yes No <input type="checkbox"/> Unknown</p>
<p>Ongoing illness:</p> <p>"Yes", describe current condition:</p>	<p>YesIf No <input type="checkbox"/> Unknown</p>
<p>Persistent/significant disability/incapacity:</p> <p>If "Yes", describe:</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No Unknown</p>
<p>Death:</p> <p>If "Yes", indicate:</p> <ol style="list-style-type: none"> 1. Date of death (day/month/year): 2. Cause of death: 3. Circumstances at the time of death, in detail: <p>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):</p>	<p>Yes No</p>
6. Conclusions (to be completed by the health-care provider)	
<p><i>Presumptive diagnosis:</i></p>	

Do you think the combined treatment with the medicines selected in Box 3 was a possible causative factor in this serious adverse event?

Yes No 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 and title:	
Address:	
Phone, mobile phone and fax numbers <i>(including country code and area code):</i>	
Signature and date:	

Source: Adapted from reference 47.

Annex 4. Template form for reporting serious adverse events involving choking during preventive chemotherapy

Date of report (dd/mm/yyyy): _____

Date of adverse event (dd/mm/yyyy): _____

Patient information

Name: _____ Age (years): _____ Sex: M __F__

Adverse event location

Setting (check appropriate box):

- Child health day
- Mass drug administration
- Other (describe) _____

District _____ Province _____

Medicine(s) administered just prior to choking (check all boxes that apply)

- Albendazole
- Azithromycin
- Diethylcarbamazine
- Ivermectin
- Mebendazole
- Praziquantel
- Other (describe) _____

Formulation(s) of medicine(s)

Tablet (check appropriate boxes)

Form: Whole Broken Crushed

Number of tablets given ____

Tablet(s) given together at same time, or one by one

Oral suspension

Dispersible tablet

Other (describe) _____

Administration of medicine(s)

Who administered the medicine? (check all boxes that apply)

- Child (or patient)
- Community drug distributor
- Other health worker
- Parent or caregiver
- Volunteer (describe) _____

Was administration directly observed by a community drug distributor or health worker (check box that applies)?

- Yes
- No
- Unknown

What was the position of the child (patient) at the time of administration (check box that applies)?

- Sitting or standing upright
- Supine
- Held in someone's arms

What was the demeanor of the child immediately before and during administration (check all boxes that apply):

- Content, quiet
- Fussy
- Agitated or fearful
- Crying
- Resisted taking medicine

Was water or other liquid given with the medicine (check box that applies)?

- Yes, after the medicine
- Yes, medicine mixed with water/liquid
- No

What efforts were taken to resolve choking? (check all boxes that apply)

- Heimlich manoeuver or "abdominal thrust"
- Slap on back
- Attempt to remove obstruction from mouth
- Other (describe) _____

Other factors

What other factors might have contributed to choking? (describe)

Annex 5. Adverse events associated with treatment, by disease

	Disease	Medicine used	Adverse events due to action of the medicine	Adverse events due to operational error	Reference document
Preventive Chemotherapy	Lymphatic filariasis	Diethyl-carbamazine	Encephalopathy (confusion, lethargy, stupor or coma), Death in patients with heavy <i>Loa loa</i> infection. Mazzotti reaction: intense itching, enlargement of lymph nodes, papular rash, fever, tachycardia, arthralgia, headache, major ocular complications (occasionally fatal) in patients with onchocerciasis.		https://apps.who.int/iris/bitstream/handle/10665/44683/97892415021_91_eng.pdf
		Albendazole	Albendazole in patients with heavy <i>Loa loa</i> infection has the same reactions as DEC but much less frequent (only sporadic case reports). Albendazole is not contraindicated in areas with loaiasis.	Choking on large tablets. Anxiety reactions (e.g. clusters of vomiting episodes), especially in children, that arise from the fear of treatment	
	Onchocerciasis	Ivermectin	Same as DEC but less frequent (about 1 serious adverse event in 800,000 persons treated) in patients with heavy <i>Loa loa</i> infection		
	Schistosomiasis	Praziquantel	Fever, meningismus (headache, photophobia, neck stiffness), intracranial hypertension (occasionally fatal), seizures in patients with neurocysticercosis (especially those with hydrocephalus and parenchymal brain cysts). Destruction of the parasite may cause severe eye damage in patients with ocular cysticercosis	Choking on large tablets. Anxiety reactions (e.g. clusters of vomiting episodes), especially in children, that arise from the fear of treatment	
	Soil-transmitted helminthiasis	Albendazole	Worm migration to and occasional expulsion through nose or mouth in patients with heavy ascariasis infections. Albendazole in patients with neurocysticercosis has the same reactions as praziquantel	Choking on large tablets. Anxiety reactions (e.g. clusters of vomiting episodes), especially in	

Preventive chemotherapy (continued)		Mebendazole	Transient abdominal pain, diarrhoea, headache, dizziness	children, that arise from the fear of treatment	
	Taeniasis	Nicosamide	Mild gastrointestinal disturbances may occur.		https://apps.who.int/iris/handle/10665/41765
		Praziquantel	Occasionally causes abdominal discomfort, nausea, headache, dizziness and drowsiness. Rarely, it is reported to have induced pyrexia, urticaria and rectal bleeding. In people with neurocysticercosis, there is a potential risk to cause the death of the cysts, which can result in local inflammation, oedema, headaches, seizures and dizziness.	Choking on large tablets. Anxiety reactions (e.g. clusters of vomiting episodes), especially in children, that arise from the fear of treatment	https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0007873 . PLoS Negl Trop Dis 14(1): e0007873.
	Clonorchiasis and opisthorchiasis				https://doi.org/10.1371/journal.pntd.0007873
	Fascioliasis and paragonimiasis	Triclabendazole	Adverse reactions are usually mild. The most common are abdominal pain, epigastric pain and sweating. Less common are nausea, vomiting, dizziness, cough, fever, urticaria and pruritus. Skin rash is uncommon.		https://www.who.int/neglected_diseases/resources/who_cds_ntd_pct2007.1/en/ • https://apps.who.int/iris/bitstream/handle/10665/75209/WHO_HTM_NTD_PCT_2011.3_eng.pdf?ua=1
Trachoma	Azithromycin	Nausea, abdominal discomfort, vomiting, diarrhea		https://apps.who.int/iris/handle/10665/43405	

Human African Trypanosomiasis	Nifurtimox + eflornithine	Abdominal pain, diarrhoea, nausea, vomiting and headache are frequent. There is a risk of seizures, and occasionally psychotic reactions and hallucinations. Other described adverse effects are fever, anorexia, tremor, ataxia, bone marrow suppression (anaemia, leucopenia), insomnia, vertigo, mood alteration (asthenia, lethargy, confusion, malaise), musculoskeletal pain, ear troubles, arrhythmia, arterial hypertension, edema, thoracic pain.		https://www.who.int/neglected_diseases/resources/who_trs_984/en/
	Suramin	Pyrexia is frequent. Nephrotoxicity (with albuminuria, cylindruria and haematuria) is frequent but usually mild and reversible. Other adverse effects observed rarely are early hypersensitivity reactions like urticaria and circulatory collapse, late hypersensitivity reactions like exfoliative dermatitis and haemolytic anaemia, peripheral neuropathy and bone-marrow toxicity with agranulocytosis, thrombocytopenia and reactive encephalopathy.	Severe hypersensitivity reaction if test dose not given or in patients with onchocerciasis	
	Fexinidazole	Vomiting, nausea, asthenia, decreased appetite, headache, insomnia, tremor and dizziness. Neuropsychiatric adverse reactions (insomnia, hallucination, agitation, logorrhea, abnormal behaviour, anxiety, psychotic disorder), neutropenia, QT interval prolongation		
	Melarsoprol	Encephalopathic syndrome (occurs in 5–18% of all treated cases and is fatal in 10–70%). General malaise and gastrointestinal (nausea, vomiting and diarrhoea) and skin reactions (pruritus); Severe complications, such as exfoliative dermatitis, occur in fewer than 1% of cases.	Phlebitis and subcutaneous necrosis because extravasation	
	Pentamidine	Hypotension, dizziness and sometimes collapse and shock. Occasional adverse reactions are nausea or vomiting and pain at the injection site. Sterile abscesses or necrosis may occur at the site of intramuscular injection. Systemic reactions reported include azotaemia due to nephrotoxicity, leukopenia, raised liver function enzymes, hypoglycaemia and hyperglycaemia. Persistent diabetes is a rare but feared event. Severe adverse events such as anaphylaxis and acute pancreatitis are extremely rare.	Hypotension collapse after rapid intravenous injection, Abscesses or necrosis at the site of intramuscular injection.	

Leishmaniasis	Liposomal amphotericin B	Chills/rigors, fever, nausea, vomiting, hypertension, a faster heart rate than normal, breathlessness, and hypoxia, rash, anaemia, insomnia, feeling sick, feeling tired, confusion, having muscle weakness or cramps. Diarrhoea, nausea, vomiting. Increased alkaline phosphatase, blood urea nitrogen and creatinine. High blood sugar, low potassium, low magnesium, low calcium, low sodium		https://www.who.int/neglected_diseases/resources/who_trs_949/en/
	Amphotericin B deoxycholate	Fever (sometimes accompanied by shaking chills usually occurring within 15 to 20 minutes after initiation of treatment), malaise, weight loss, hypotension, tachypnea, pain at the injection site with or without phlebitis or thrombophlebitis, generalized pain, including muscle and joint pains. Anorexia, Nausea, Vomiting, Diarrhea, Dyspepsia, Cramping, epigastric pain. Decreased renal function and renal function abnormalities including azotemia, hypokalemia, hyposthenuria, renal tubular acidosis; and nephrocalcinosis.		
	Miltefosine	Vomiting, diarrhoea, increase in liver enzymes (SGOT, SGPT, AP)		
	Paromomycin	Headache, lethargy, mild injection site pain		
	Sodium stibogluconate	Flushing, sweating, fever, rash, yellow skin and eyes, pain and thrombosis on intravenous administration, pain at injection site if given intramuscular, abdominal pain, anorexia, malaise, myalgia, arthralgia, headache and lethargy. Fatal cardiac arrhythmias, ECG changes, including reduction in T-wave amplitude, T-wave inversion and QT prolongation. Transient coughing.		
	Meglumine antimoniate	Headache, General malaise, difficulty in breathing, skin rash, facial edema. Special Precautions before systemic administration-A protein rich diet must be given throughout the duration of treatment and iron deficiency anemia or specific deficiencies corrected before the treatment. ECG, hepatic and renal functions must be monitored throughout the treatment (instructions from product package insert)		

Individual Case (continued)	Leprosy	Clofazimine	Brown discoloration of the skin, gastro-intestinal upset		https://www.who.int/lepro/resources/SEAGLP20062.pdf
		Rifampicin	Red urine, skin rash, urticaria, drug allergy, jaundice, purpura, shock, renal failure. Flu-like syndrome (chills, fever, headache and muscle and bone pain)		
		Ofloxacin	Abdominal pain, flushing or redness of the skin (especially on the face and neck), Convulsions		
		Minocycline	Headache, diarrhoea, dizziness, dysphagia, epigastric discomfort. Rarely, hives (urticaria) with or without fever and wheezing or tightness in the chest of throat		
		Dapsone	Haemolytic anaemia, various skin rashes including exfoliative dermatitis, urticaria, nephrotic syndrome, hepatitis, dapsone syndrome, agranulocytosis, psychosis		
	Yaws	Azithromycin	Nausea, abdominal discomfort, vomiting, diarrhea		https://apps.who.int/iris/bitstream/handle/10665/259902/9789241512695-eng.pdf
	Rabies	PEP rabies vaccines	Minor, transient erythema, pain or swelling occurs at the site of injection; mild systemic adverse events, such as transient fever, headache, dizziness and gastrointestinal symptoms. Serious adverse events are rare, including include Guillain–Barré syndrome and allergic reactions.		https://apps.who.int/iris/bitstream/handle/10665/272364/9789241210218-eng.pdf
	Taeniasis and cysticercosis	Praziquantel	Headache, intestinal colic, diarrhea, nausea, feeling of fatigue, drowsiness and dizziness. Risk of seizure in patients with neurocysticercosis. Destruction of the parasite may cause severe eye damage in patients with ocular cysticercosis	Choking on large tablets. Anxiety reactions (e.g. clusters of vomiting episodes), especially in children, that arise from the fear of treatment	https://apps.who.int/iris/bitstream/handle/10665/44683/9789241502191_eng.pdf
		Albendazole	Mild reactions including headaches, vertigo, breathing difficulties and gastrointestinal discomfort. Albendazole in patients with neurocysticercosis has the same reactions as praziquantel		
	Buruli ulcer	Rifampicin	Red urine, skin rash, allergy, urticaria, jaundice, shock, purpura, renal failure		https://www.who.int/publications/i/item/9789241503402
Clarithromycin		Jaundice, nausea and altered taste, anorexia, nausea, abdominal pains		https://www.who.int/publications/i/item/9789241503402	

ECG: electrocardiogram; PEP: post-exposure prophylaxis



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