

Mass drug administration for neglected tropical disease control and elimination: a systematic review of ethical reasons

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ABSTRACT

Background Neglected tropical diseases (NTDs) are a diverse group of debilitating diseases and conditions afflicting more than one billion people in impoverished communities. Control of these diseases is crucial to achieve Sustainable Development Goal 3 and the pledge to 'leave no one behind'. Relying on large-scale delivery of wide-spectrum drugs to individuals in at-risk communities irrespective of their health status, mass drug administration is a core strategy for tackling half of the NTDs targeted by the latest WHO roadmap (2021–2030). However, ethical challenges surround its implementation and long-term impact. This systematic review aims to give a comprehensive picture of the variety of ethical reasons for and against mass drug administration for NTD control and elimination, facilitating further debate in ethics and policy.

Methods PubMed and Web of Science Core Collection were searched for all relevant publications. Of the 486 retrieved records, 60 met the inclusion criteria for qualitative analysis. Ethical reasons discussing the topic at hand were extracted from full texts and synthesised through the Kuckartz method of qualitative content analysis.

Results Data extraction revealed 61 ethical reasons, of which 20 (32.7%) had positive, 13 (21.3%) had ambivalent and 28 (45.9%) had negative implications regarding mass drug administration for NTDs. The health benefits and cost-effectiveness of the measure were extensively highlighted. However, equity, autonomy and sustainability emerged as the domains with the most pressing ethical concerns. Many issues related to implementation are yet to be adequately addressed in policy documents.

Conclusions This is the first systematic review of ethical reasons pertaining to mass drug administration for NTD control and elimination. Due to the diversity of included studies, no general recommendations can be made. Instead, context-specific strategies seem necessary. Alternative approaches tackling socioecological determinants of ill health are needed for long-term sustainability. Future research could benefit from contributions of non-Western philosophies and perspectives by local researchers.

BACKGROUND

Neglected tropical diseases (NTDs) are a medically diverse group of chronic and debilitating conditions afflicting more than 1.6 billion people.¹ Present in all parts of the world, they are most prevalent and frequently

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mass drug administration for neglected tropical disease (NTD) control and elimination is one of the largest public health interventions globally and is implemented in vulnerable communities worldwide. However, ethical guidance documents lack in policy.

WHAT THIS STUDY ADDS

⇒ This is the first systematic review of ethical reasons for mass drug administration for NTD control and elimination. It highlights pressing ethical concerns in the domains of autonomy, equity and sustainability.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings highlight that mass drug administration raises numerous ethical concerns that are yet to be addressed by policy-makers and encourage further bioethical debate around public health measures for NTD control and elimination.

coendemic in tropical and subtropical areas. The collective burden of NTDs, of an order of magnitude similar to that of one of the 'Big Three' (tuberculosis, malaria and HIV/AIDS),² disproportionately affects the most impoverished communities globally where it remains politically 'unattended'.³ NTDs result from and contribute to poverty, as they create disability, social stigma and exclusion of affected individuals and their communities. Sustained in complex cycles at the interface between human, animal and environmental health, they are intrinsically linked to the state of human livelihoods and can trap most vulnerable livestock-dependent groups, among others, in self-reinforcing poverty dynamics.⁴ Their control thus seems essential to achieve many Sustainable Development Goals (SDGs), including health equity promoted by SDG3 and the pledge to Universal Health Coverage.^{5 6} In line with these ambitions, the WHO aims to reduce or eliminate the burden of 20 NTDs of infectious and non-infectious aetiologies by 2030,

through a set of control measures outlined in its latest roadmap.⁵

Control strategies for half of these NTDs include mass drug administration (MDA).⁵ MDA—also referred to as ‘preventive chemotherapy’ (PC)—entails the regular large-scale delivery of wide-spectrum drugs to individuals of at-risk communities, irrespective of their health status.⁷ Drug distribution usually occurs either through teachers at local schools or through volunteers named community drug distributors (CDDs), at central locations or from door to door in the community. The NTDs targeted by MDA (PC-NTDs) bear significant differences in terms of their overall burden, associated morbidity and mortality and the effectiveness of drug treatment. For instance, trachoma and onchocerciasis are leading causes of infectious blindness, while lymphatic filariasis (LF) can result in severe disability and stigma in the form of lymphoedema and hydrocele. On the other hand, some PC-NTDs such as soil-transmitted helminthiases (STH) or scabies usually present more benign forms of morbidity. MDA, designed to contribute to the burden reduction of all targeted diseases, serves different purposes and holds differing importance and urgency for affected communities. The WHO addresses MDA as one of the possible

interventions for NTDs, encompassing drug distributions of varying realities in the context of all these diseases.⁵ To highlight distinctions, disease-specific drug combinations, target groups and levels of targeted control are detailed in table 1.

It is noteworthy that MDA for NTD control is not a recent development and was historically driven by private stakeholders from the Global North. In the 1910s, the Rockefeller Sanitary Commission successfully eliminated hookworm disease, found very prevalent in school-aged children in the Southern USA, through the sponsorship of MDA campaigns. The success of these interventions and their positive effects on long-term school attendance and income supported the MDA rationale for the rest of the world.⁸ When drugs for other NTDs were developed, such as ivermectin by Nobel laureate William Campbell in the 1980s, it became evident that these diseases of poverty would not enable a commercial market due to the lack of purchasing power of afflicted populations.⁸ In 1987, Merck committed to providing ivermectin for ‘as much and as long as needed’ for the elimination of onchocerciasis,⁹ thereby establishing the first donation programme of its kind. It was followed by donor commitments for the control of four other NTDs

Table 1 PC-NTDs targeted by the WHO 2021–2030 roadmap

Name of the NTD	Level of targeted control	Drugs of choice for MDA	Recommended target group for MDA
Lymphatic filariasis	Elimination as a PH problem	Albendazole, diethylcarbamazine, ivermectin	Entire community in endemic areas
Onchocerciasis	Elimination (interruption of transmission)	Ivermectin	Entire community in endemic areas
Schistosomiasis	Elimination as a PH problem	Praziquantel	At-risk groups: mainly school age children, also recommended for preschool age children and adults in high-risk occupations In highly endemic areas: entire community
Soil-transmitted helminthiases	Elimination as a PH problem	Albendazole/mebendazole (intestinal parasites and hookworms) and ivermectin (if <i>Strongyloides</i> present or high prevalence <i>Trichuris</i>)	At-risk groups: mainly school age children, also recommended for preschool age children, women of reproductive age and adults in high-risk occupations
Trachoma	Elimination as a PH problem	Azithromycin, tetracycline eye ointment	Entire community in endemic areas
Foodborne trematodiasis	Intensified control	Triclabendazole (fasciola), praziquantel (others)	Entire community in highly endemic areas
Leprosy	Elimination (interruption of transmission)	Rifampicin	Contacts of confirmed cases (postexposure prophylaxis)
Scabies	Intensified control	Ivermectin	Entire community in highly endemic areas
Taeniasis and cysticercosis	Intensified control	Praziquantel, niclosamide, albendazole	Entire community in endemic areas
Yaws	Eradication	Azithromycin	Entire community in endemic areas

MDA, mass drug administration; NTDs, neglected tropical diseases ; PC, preventive chemotherapy; PH, public health.

(STH, schistosomiasis, LF and trachoma), throughout the 1990s, that were coordinated by the newly created WHO NTD department from 2005 onwards.¹⁰ The effort to control NTDs through MDA gained momentum through the London Declaration in 2012, in which signatories including pharmaceutical companies and non-governmental organisations pledged to contribute to the control or elimination of 10 NTDs by 2020.¹¹ The recent Kigali Declaration (2022) builds on these commitments, while involving a larger diversity of stakeholders and prioritising country ownership of NTD programmes.^{12 13} From 2015 to 2019, more than 1 billion people were treated by MDA annually, making it one of the largest public health (PH) interventions globally.⁷

Controversy around MDA arose in 2015 when data from a seminal econometrics article from 2004¹⁴ were reanalysed by an independent group of researchers¹⁵ who questioned their conclusions about the positive impact of MDA treatment for STH on school attendance. As this analysis, based on a study in Kenya, had largely made the case for MDA,¹⁶ the debate caught press and social media attention beyond the science world.¹⁷ Importantly, the debate (also referred to as ‘worm wars’) shed light on how little evidence was available on the social impacts of mass deworming.¹⁸ Concerns about the ethics of such an indiscriminate measure were brought up¹⁶ and some scholars started advocating for the adoption of a biosocial lens in the evaluation of NTD control measures.¹⁹ To this day, however, very few publications fully dedicate to discussing ethical issues surrounding MDA for NTD control and elimination, and ethical guidance documents lack in policy.²⁰

The complex social environments in which MDA is conducted give rise to numerous ethical issues centred on health equity, beneficence and autonomy. Locally, matters such as the adequate collection of informed consent or mediation of social stigma are essential. On a global level, ethical questions about the judicious use of drugs and the impact of potential drug resistance on future generations arise,²¹ along with challenges of country ownership in a context of structural inequalities with donors and international organisations mainly dominated by stakeholders from the Global North.

To our knowledge, this systematic review is the first to provide a full synthesis of the ethical debate around MDA in the NTD context. It systematically depicts ethical reasons for and against the use of MDA for NTD control and elimination given in published academic literature to date. It does not provide an analysis that distinguishes between targeted NTDs. Instead, it offers a comprehensive overview of ethical considerations associated with MDA when viewed as a singular PH measure in the NTD context. Highlighting the variety of standpoints and knowledge gaps in the debate, this study might serve as a foundation for further bioethical investigation and inform discussions of local and international PH experts and decision-makers.

METHODS

Aims

Systematic reviews of reasons identify and present published ethical reasons relevant to a normative research question, aiming at providing the most comprehensive overview possible of an ethical debate. They imply a systematic (reproducible) search, selection and qualitative analysis of the published literature related to the topic at hand and have been increasingly used in bioethics.²²

This review aims at drawing a comprehensive picture of the current ethical debate around the use of MDA for NTD control and elimination in at-risk communities. It documents the variety of reasons in favour and against the intervention that has been published in academic journals to date. The study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-Ethics reporting guideline.²³ It was preregistered with Open Science Framework (<https://osf.io/vctjh>).

Identification of studies

For this study, in line with the WHO,⁵ we defined NTDs as a diverse group of debilitating conditions persisting among populations living in poverty, mainly in low-income and middle-income countries. We focused on the diseases amenable to MDA, listed in [table 1](#).

The search strategy was developed and refined through hand and exploratory database searches. The systematic search was then carried out in two comprehensive medical databases: PubMed and Web of Science Core Collection, by JH-B in February 2023. No book or grey literature search was performed due to time constraints. Developed search strings were made up of three semantic clusters. The NTD cluster mentioned all PC-NTDs listed in the WHO NTD roadmap (2021–2030), including pathogen and disease names and their synonyms. Symptom names were included when disease specific. The MDA cluster comprised synonyms for MDA as used by official bodies and found in the literature by exploratory search. Lastly, the ethics cluster was composed of synonyms and antonyms of commonly used terms and principles of medical ethics—including the well-established principles by Beauchamp and Childress.²⁴ The full search string is provided in [table 2](#). The search was limited to title/abstract or topic fields for increased accuracy.

Eligibility criteria were defined in advance (see [table 3](#)). All publications mentioning ethical issues related to the use or implementation of MDA for NTD control or elimination were included in the study. In the title-abstract screening, we included records that explicitly labelled the discussed issues as ‘ethical’ or that mentioned MDA in relation to medical ethics-related terms. MDA had to be examined in the broad context of possible PH interventions in the NTD field. Articles solely comparing outcomes of different MDA regimens were excluded. All types of publications stemming from peer-reviewed scientific journals were considered, except conference

Table 2 Search string used in PubMed

Semantic cluster	Search terms	Add with:
NTD	"Neglected tropical disease"*(Title/Abstract)OR NTD(Title/Abstract)OR "neglected disease"*(Title/Abstract) OR "unattended disease"*(Title/Abstract) OR ("Lymphatic filariasis"(Title/Abstract)OR LF(Title/Abstract)OR elephantiasis(Title/Abstract)OR "lymphoedema and hydrocele"(Title/Abstract)OR "lymphedema and hydrocele"(Title/Abstract)OR adenolymphangitis(Title/Abstract)OR "Wuchereria bancrofti"(Title/Abstract)OR Brugia(Title/Abstract) OR (Onchocerciasis(Title/Abstract)OR "river blindness"(Title/Abstract)OR "Onchocerca volvulus"(Title/Abstract) OR (Schistosomiasis(Title/Abstract)OR bilharzia*(Title/Abstract)OR Schistosoma(Title/Abstract) OR ("Soil-transmitted helminthiasis"(Title/Abstract)OR STH(Title/Abstract)OR strongyloidiasis(Title/Abstract)OR trichuriasis(Title/Abstract) OR acariasis(Title/Abstract)OR "Ascaris lumbricoides"(Title/Abstract)OR "Trichuris trichiura"(Title/Abstract)OR whipworm*(Title/Abstract)OR "Necator americanus"(Title/Abstract)OR "Ancylostoma duodenale"(Title/Abstract) OR hookworm*(Title/Abstract)OR Strongyloides(Title/Abstract) OR (Trachoma(Title/Abstract)OR "trachomatous trichiasis"(Title/Abstract)OR "Chlamydia trachomatis"(Title/Abstract) OR ("Foodborne trematodiasis"(Title/Abstract) OR opisthorchiasis(Title/Abstract)OR clonorchiasis(Title/Abstract)OR fascioliasis(Title/Abstract)OR paragonimiasis(Title/Abstract)OR "Clonorchis sinensis"(Title/Abstract)OR Opisthorchis(Title/Abstract)OR "small liver fluke"*(Title/Abstract) OR Fasciola(Title/Abstract)OR Paragonimus(Title/Abstract) OR (Leprosy(Title/Abstract)OR "Hansen's disease"(Title/Abstract)OR "Mycobacterium leprae"(Title/Abstract)OR "Mycobacterium lepromatosis"(Title/Abstract) OR (Scabies(Title/Abstract)OR ectoparasitose*(Title/Abstract)OR "Sarcoptes scabiei"(Title/Abstract)OR mite*(Title/Abstract) OR (Taeniasis(Title/Abstract)OR cysticercosis(Title/Abstract)OR neurocysticercosis(Title/Abstract)OR Taenia(Title/Abstract) OR tapeworm(Title/Abstract) OR (yaws(Title/Abstract)OR "endemic treponematose"*(Title/Abstract)OR "Treponema pallidum"(Title/Abstract))	AND
MDA	"mass drug administration"(Title/Abstract)OR "massive drug administration"(Title/Abstract)OR "mass antibiotic administration" OR MDA(Title/Abstract)OR "preventive chemotherapy"(Title/Abstract)OR PC(Title/Abstract)OR "mass drug treatment"(Title/Abstract)OR "mass deworming"(Title/Abstract)OR "total community treatment"(Title/Abstract)	AND
Ethics	Ethics (MeSH Terms) OR philosophy (MeSH Terms) OR ethic*(Title/Abstract)OR bioethic*(Title/Abstract)OR bio-ethic*(Title/Abstract)OR moral*(Title/Abstract)OR unethic*(Title/Abstract)OR immoral*(Title/Abstract) OR (autonom*(Title/Abstract)OR consent(Title/Abstract)OR dependen*(Title/Abstract) OR (beneficence(Title/Abstract)OR benefit(Title/Abstract) OR (non-maleficence(Title/Abstract)OR harm(Title/Abstract) OR (justice(Title/Abstract)OR injustice(Title/Abstract)OR unjust(Title/Abstract)OR fair*(Title/Abstract)OR unfair*(Title/Abstract)OR equit*(Title/Abstract)OR inequit*(Title/Abstract)OR dilemma(Title/Abstract)OR acceptability(Title/Abstract)	AND
MDA, mass drug administration ; NTD, neglected tropical disease.		

abstracts, due to their short length. Likewise, no restrictions were applied to publication years or scientific disciplines. The search was restricted to publications written in English, German and French, due to the authors' proficiency in these languages.

Selection process

Records retrieved from the queries were imported into Zotero, a bibliography management software and duplicates were discarded. JH-B reviewed the titles and abstracts of the identified publications, against the

above-mentioned eligibility criteria. 26 ambiguous cases were discussed by both authors in regular meetings until consensus was reached. Due to time constraints, no full screening of included articles' reference lists was performed. An overview of the selection process is provided in [figure 1](#).

The full texts of eligible publications were then retrieved and screened by JH-B. Publications were searched for ethical reasons pertaining to the use of MDA for the control or elimination of NTDs in at-risk communities.

Table 3 Eligibility criteria

Inclusion criteria	Exclusion criteria
Addresses ethical aspects of MDA use or implementation for NTD control or elimination in at-risk communities	<ul style="list-style-type: none"> Does not address MDA strategies Addresses MDA for the control or elimination of other diseases (not NTDs) Does not address ethical aspects Ethical aspects mentioned are not directly related to MDA
MDA is examined as a possible PH intervention for NTD control or elimination	Publication solely compares different MDA regimens (e.g., drug types, dosages, target groups)
All PC-NTDs listed in WHO roadmap (2021–2030)	Diseases not targeted by WHO roadmap for NTDs (e.g., malaria)
Written in English, German or French languages	Written in languages other than English, German, French
All types of publications in scientific journals, except conference abstracts	Texts not published in scientific journals (e.g., book chapters) or conference abstracts
All publication years, all countries	N/A
MDA, mass drug administration; N/A, not applicable; NTD, neglected tropical disease; PC, preventive chemotherapy; PH, public health.	

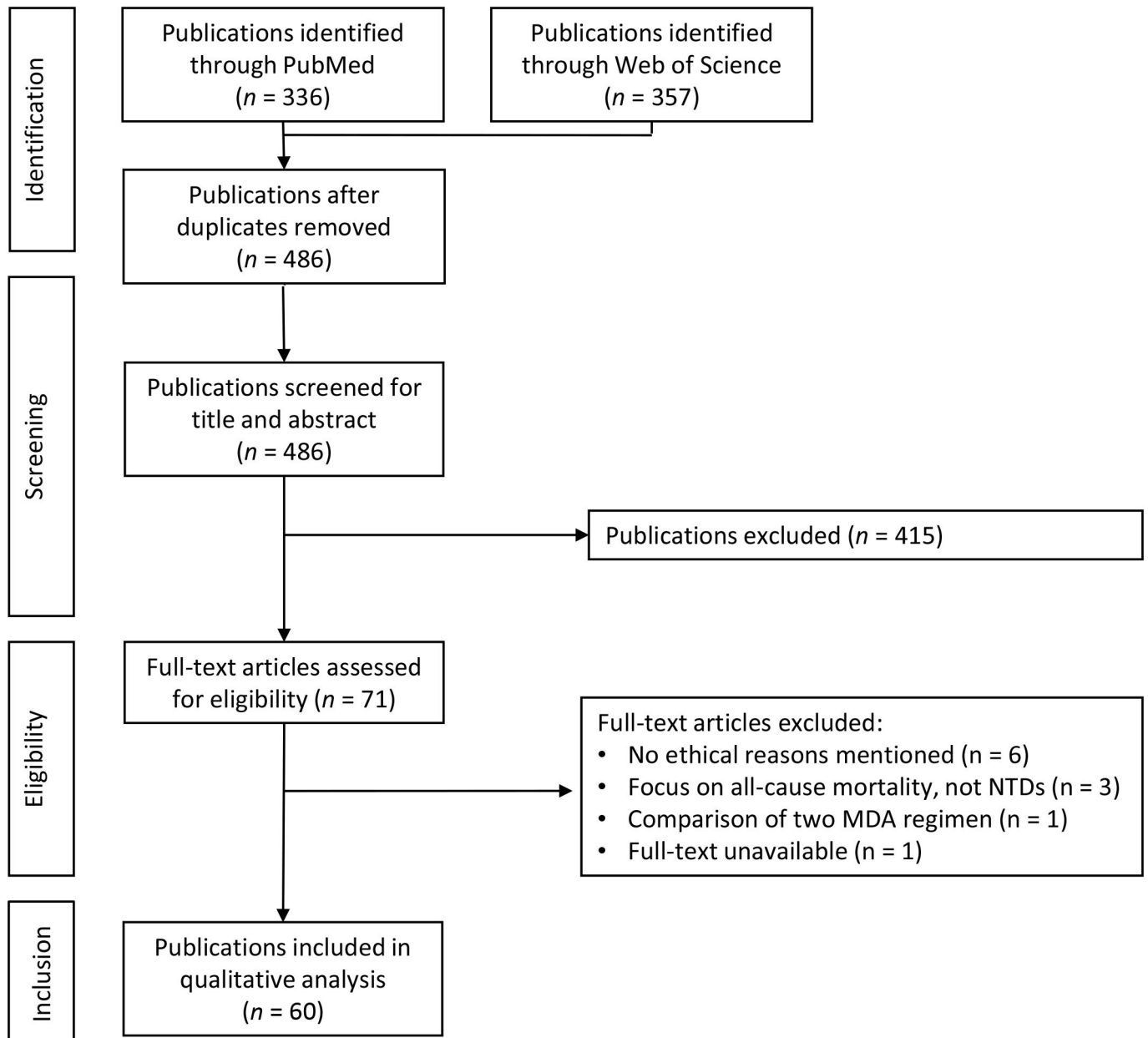


Figure 1 Flow chart of the selection process. MDA, mass drug administration; NTDs, neglected tropical diseases.

In the context of this study, a reason was understood as the first part or premise of an argument, inferring and justifying its conclusion. Publications were excluded if no reasons were found, or if they did not meet the above-mentioned eligibility criteria (see [table 3](#)). Four ambiguous cases were again discussed by the authors until consensus was reached.

Data extraction and synthesis

Eligible full texts were investigated through qualitative content analysis as described by Kuckartz,²⁵ using the software MAXQDA 2020. The employed method by Kuckartz relies on the selection of concept-driven (deductive) main categories that are progressively refined by data-driven (inductive) subcategories during the content analysis. Each identified ethical reason was assigned a code

reflecting its content and alleged implication regarding the research question (positive/negative/ambivalent). Codes were classified into predefined main categories, comprising the five principles of PH ethics by Marckmann (expected benefits, potential harm, autonomy, equity, efficiency),²⁶ complemented by the principle of ‘sustainability’ that captured the long-term implications of MDA. Reasons that did not fit in the above-mentioned categories were classified as ‘other’. Data-driven subcategories were defined until theoretical saturation was reached. The code system was then reviewed to eliminate overlaps and refine the analysis. Coded segments were revised to ensure their correct classification. The coding was performed by JH-B, a master’s student with backgrounds in infectious diseases and social sciences.

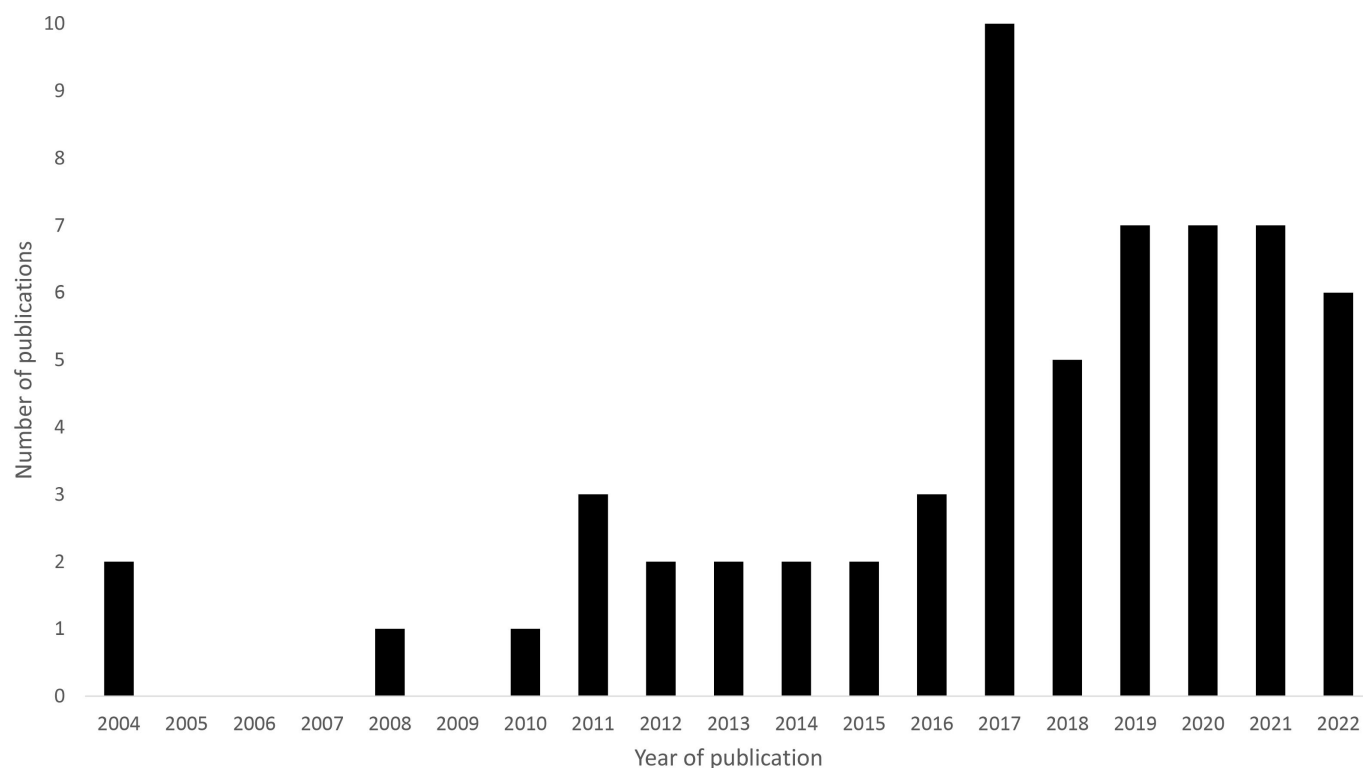


Figure 2 Number of included publications per year.

Intercoder reliability was tested in regular meetings with SS, a full professor with backgrounds in clinical medicine and philosophy.

Relevant metadata from included publications were further documented. These included first and last author affiliation country, competing interests, type and location of study, and targeted diseases.

Quality appraisal

No quality appraisal was performed, due to the current lack of consensual scientific standards to evaluate reasons in the ethics field²⁷ and the diversity of article types and scientific disciplines included in this study.

Patient and public involvement

The research question addresses central issues for NTD patients and individuals of at-risk populations targeted by MDA. Qualitative studies, that allow affected individuals to genuinely express their opinions, form substantial part of this review. No patients or affected people were involved in the design or conduct of this study.

RESULTS

Sample description

A total of 486 publications were retrieved from the database search after duplicate removal, 60 of which met the inclusion criteria for qualitative analysis (see online supplemental file 1 for full list). Publication years, as shown in figure 2, ranged from 2004 to 2022 with a surge of relevant publications after 2016.

Figure 3 details the types of included publications in this very heterogeneous study sample.

Most included studies focused on NTDs in general (n=18) or on three major PC-NTDs: LF (n=17), schistosomiasis (n=16) and STH (n=16). Scabies and onchocerciasis were thematised in very few publications (n=2) and 5 of the 10 PC-NTDs were not specifically addressed in our study sample. Most publications had a worldwide scope (n=37) and among the geographically more focused studies, Africa was the most represented geographic region by far (n=18). In contrast to the subject matter examined in this study, the majority of first authors in included publications were affiliated with institutions based in high-income countries, mainly the UK and the USA (figure 4).

A total of 820 relevant text passages were identified within the included publications. These segments were pooled into 61 ethical reasons, of which 20 (32.7%) had positive, 13 (21.3%) had ambivalent and 28 (45.9%) had negative implications concerning MDA for NTD control or elimination. The major aspects associated with each of these ethical principles are described hereafter. All identified reasons and the publications they stem from are listed in online supplemental file 2.

Main categories

Most positive reasons are associated with the **expected benefits** arising from MDA in health, quality of life and economic aspects, at the community level. In terms of health, MDA is endorsed for reducing prevalence and morbidity of the target disease:

Between 2016 and 2019, more than 1 billion people received PC each year, resulting in significant reductions in

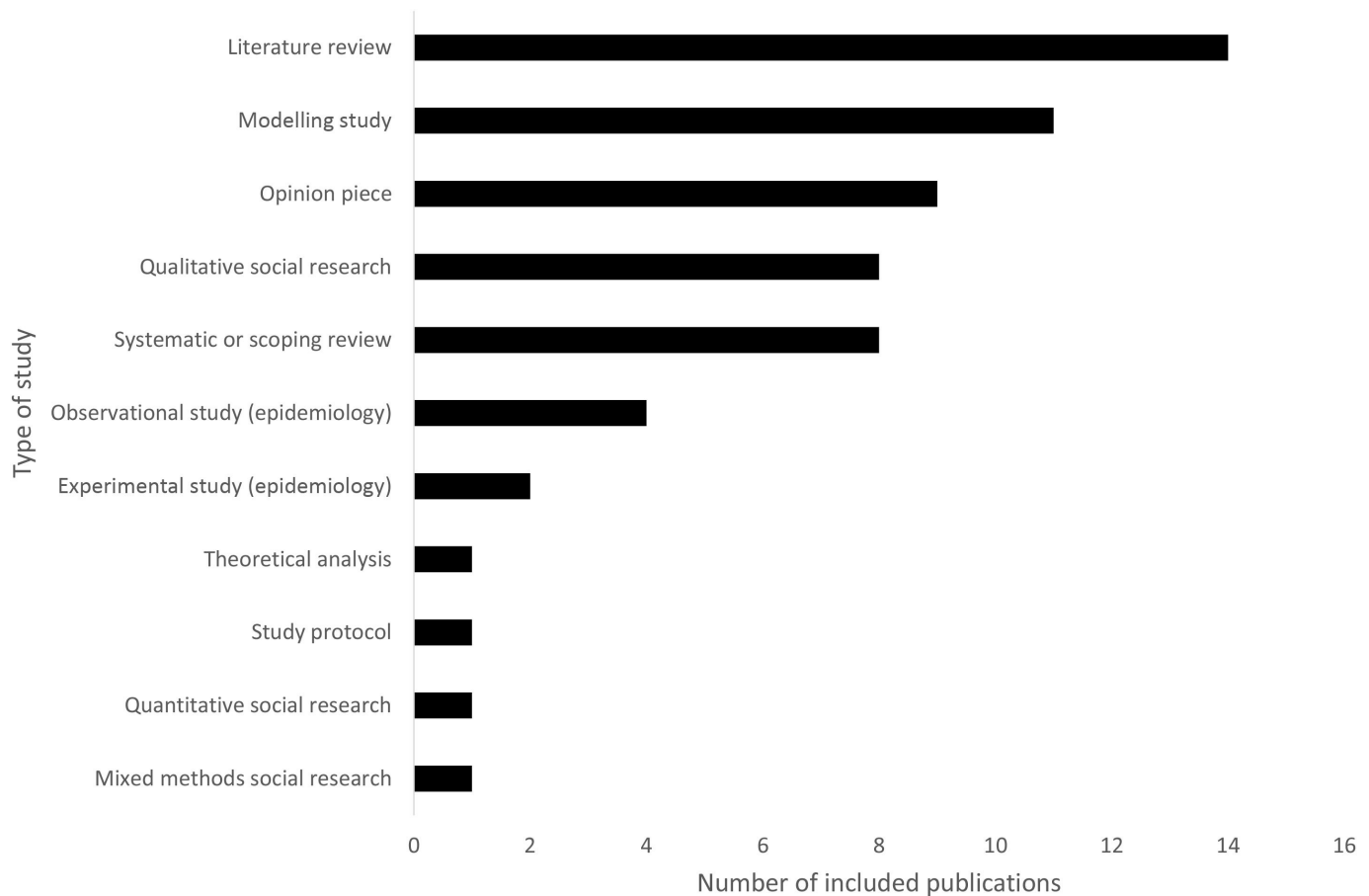


Figure 3 Number of included publications by type.

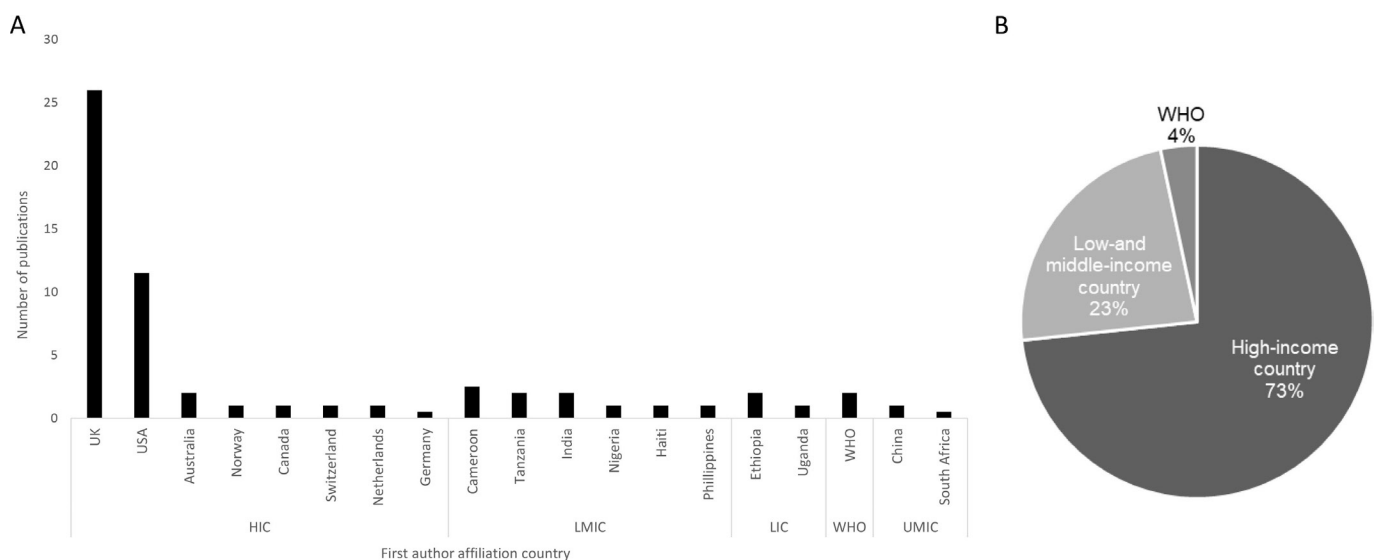


Figure 4 First author affiliation country in included publications. (A) Countries were clustered according to the World Bank classification and sorted by the number of occurrences in included publications. (B) Distribution of the countries according to World Bank major categories. Low-and middle-income country: aggregation of LIC, LMIC and UMIC categories. HIC, high-income country; LIC, low-income country; LMIC, lower-middle-income country; UMIC, upper-middle-income country.

morbidity, reduced transmission, and for some NTDs, regional elimination as a public health problem.²⁸

Moreover, decrease of disease transmission averts DALYs in many population groups including uninfected people and future generations.

Ancillary health benefits comprise the burden reduction of untargeted coendemic infectious diseases such as other NTDs and parasites:

since two of the three drugs used for LF elimination have broad anti parasite properties, treated populations are freed from both intestinal worms and from skin infections with onchocerca, lice, and scabies.²⁹

This positive health impact leads to economic benefits as it alleviates the strain on local healthcare systems and provides direct returns to impoverished target populations:

it has led to cost savings for the world's poorest people, by reducing catastrophic health expenditures.³⁰

On the flipside, MDA is criticised for the lack of benefit it provides, on an individual level, to chronic disease patients and the uninfected majority subjected to the treatment:

People with late-stage LF were those with the physical conditions of hydrocoele and elephantiasis, they suffered the most from the disease and yet did not benefit from the treatment.³¹

In line with the 'worm wars' controversy, included publications conflict about the effects of MDA on general health and school performance.

Potential harm is discussed in relation with drug pharmacology and MDA programme implementation. Most of the mentioned harms occur at the individual level. Although drugs are depicted as being mostly pharmacologically safe, many authors are concerned with occurring side effects ranging from mild adverse events (dizziness, nausea) to serious adverse events such as Loa-induced encephalopathy, allergies or autoimmune disorders. These pharmacological harms are reportedly poorly managed and economically burden affected people:

In Ghana, community members who had experienced side effects complained that when they report to the health facility with the symptoms, they are not attended to in time and they also must pay for necessary treatments to manage side effects.³²

Additionally, various harms result from programme implementation, among which the risk of fatal choking on medication that mainly occurs in young children. Major risk factors appear to be forcing children to swallow medications and the frequent absence of age-appropriate drug formulations. Further, damage can arise from the lack of guidelines surrounding drug coadministration in integrated MDA programmes targeting several PC-NTDs at once.

Many publications address **sustainability** of MDA. The measure is mainly criticised for being ineffective on

long-term disease dynamics, as it does not mitigate root causes of ill health. This allows for sustained transmission:

treatment without improving the water, sanitation and hygiene (WASH) provision does not stop transmission of the parasites. Some of the children still have to cross schistosome-infective rivers to get to and from school.³³

Thus, drug distributions must be repeated frequently to maintain benefits, prevalence bouncing back to baseline levels when drug distribution programmes are discontinued. It also raises the concern of a potential emergence of drug resistance:

The experience gleaned from programs to control veterinary nematodes clearly demonstrates that it is simply a matter of time before resistance will emerge in populations repeatedly exposed to broad spectrum anthelmintics.³⁴

Moreover, relying on a recurring measure could threaten social sustainability as it reinforces aid-dependency of endemic countries and could be discontinued in the absence of available funds. The impact of MDA on local healthcare systems seems ambivalent. Many authors call for integrated control strategies that address underlying causes of ill health and improve livelihoods in multi-infection settings:

sustained commitment and vigilance are needed to detect and respond to recrudescence of infection and develop the infrastructure, such as sanitation, vector control and primary health services, needed to sustain public health gains.²⁰

Equity is another debated aspect. Some authors regard MDA as a pro-poor intervention since the programme sponsors drugs the most precarious populations could not otherwise afford. MDA also makes low-priority treatments available and sometimes attends communities beyond healthcare system reach.

community-wide MDA would be widely beneficial to those who typically could not afford treatment or to afford to send their children to school where they would be treated by the school-based distribution programs.³⁵

On the other hand, many publications highlight issues around equity arising from the way MDA is implemented in practice. Treatment is exclusively provided to the groups targeted by the distribution, entailing that in the absence of a supportive primary healthcare system, individuals who are infected but not within the specified target groups cannot access free treatment. Further, targeted populations themselves are unequally reached by MDA programmes, in practice. Geographical and socioeconomic disparities are often reflected in drug distribution rates and specific population groups are systematically absent from the distributions. These include some of the most exposed and fragile groups such as out-of-school children, farmers, migrants, marginalised individuals and women of reproductive age. Finally, studies mostly led by authors affiliated to LIC/LMIC institutions, pointed out that CDDs bear a substantial burden in ensuring

the effective functioning of the programmes. Although recruiting community volunteers seems crucial to the implementation and acceptance of these programmes, their working conditions are often neglected, and their efforts are usually uncompensated, creating a disproportionate burden:

some CDDs are sacrificing food to deliver medicines and refer to the work as a 'type of slavery work without payment'.³⁶

Most publications critically view the impact of MDA on **autonomy**. While some authors argue that the programmes can improve knowledge and prevention practices in treated populations, many qualitative studies included in this review observe that most communities do not receive appropriate sensitisation before the distributions. Poor prevention practices and lack of trust in provided drugs can arise. Individuals can also be subjected to social pressure in favour or against drugs in their communities, which can restrict their decision-making capacity. Further, many MDA programmes are criticised for poor informed consent collection, particularly when they rely on opt-out policies in schools:

Communication with targeted populations is poor, and health education materials are inadequate. As a result, the involvement of those being expected to swallow medications in the planning and implementation of programmes is minimal, raising a serious question when it comes to treating children. To expect pupils to consume tablets without the permission and support of their parents would not be possible in most parts or (sic) the world. Why should it be acceptable in Africa?¹⁶

Community ownership is another prominent subaspect. While some authors argue that community-based MDA empowers communities towards their own actions, most publications criticise the lack of engagement of targeted groups in goal setting and implementation:

The target population was rarely seen to have any active participatory role or decision-making power. Their participation generally appeared to be limited to remaining in their houses until distributors turned up with drugs.³⁷

The active engagement of target communities is also pivotal in cultivating trust that is essential for MDA, given that it relies on wide adherence to function.

Similarly, endemic countries have a limited voice in programme governance due to power imbalances with donors and international organisations:

National governments 'own' NTD programmes within their borders, but the goals, strategies and interventions are often developed at the global level, significantly influenced by partners in the global north, and authorized through resolutions at the World Health Assembly in Geneva.²⁰

The debate around **efficiency** is less varied, MDA being widely assessed as a cost-effective measure:

One of the great benefits of MDA is that the drugs and delivery are relatively cheap.³⁸

It is praised to generate quick wins towards many SDGs detrimentally impacted by NTDs. However, certain publications highlight that alternative interventions lack proper evaluation because of the attractiveness of pharmaceutical large-scale donations towards MDA.

DISCUSSION

Most of the included publications have a broad focus both in terms of diseases and geographical areas they discuss. However, context-specific details could significantly affect ethical reasoning. First, only 5 out of the 10 PC-NTDs are specifically addressed in the publications. This is unexpected because various diseases have distinct health risks and require different drugs, which may have varying side effect profiles. Second, the majority of included publications have a worldwide scope. However, context-specific details, which are often overlooked by studies with a wide focus, can have important ethical relevance. The social organisation of communities, which differs across urbanisation rates, can determine the importance of CDDs in drug delivery for instance.³⁷ Additionally, the availability of nearby healthcare centres that can handle adverse events influences the benefit–risk ratio of the intervention. Furthermore, values may significantly differ across cultures, particularly regarding community and patient autonomy, which are crucial considerations when it comes to MDA.

It is also noteworthy that few first authors were affiliated to institutions based in NTD endemic countries. This joins the broader concern on dominance of Western institutions in the definition of research agendas and normative frameworks guiding global institutions.³⁹

In line with Addiss *et al.*,²⁰ we found that only a small number of publications specifically focus on the ethics of MDA. Instead, ethical issues often come up as side points in discussions or arise in qualitative interview studies with different primary aims. Considering that MDA targets stigmatising diseases in resource-constrained environments where ethical attention seems particularly important, it is surprising that this field of research is still relatively under investigated. The discourse on MDA is intricately linked to the balance between individual and communal interests, which are central considerations in PH ethics.⁴⁰

MDA is widely endorsed for its potential to generate substantial benefits for communities, ranging from the reduction of disease transmission to the elimination of certain PC-NTDs. The measure, thus, averts DALYs for at-risk populations and even future generations. However, exclusively relying on MDA for PC-NTD mitigation can pose problems.

Amidst the positive community impact, individual harms, notably adverse effects, have been highlighted in numerous publications. Those often receive insufficient attention within programmes, leaving individuals to cope individually and incur economic losses through direct treatment costs and lost labour time.^{31 32 36 41} These

individual harms stand in contrast with collective benefits and they demand attention due to their significant burden on affected people. This is particularly crucial given that many individuals receiving MDA are uninfected, and therefore, derive no direct individual benefit from the intervention. Moreover, benefits derived from MDA are most often temporary and programmes rely on regular iterations of drug distributions to maintain low levels of disease transmission, repeatedly exposing drug recipients to adverse effects. This review, therefore, underscores the necessity of considering both individual and community interests within the MDA discourse.

Given that the MDA rationale is supported by official policy documents, it seems natural to compare the ethical issues highlighted in our review with those addressed in the WHO roadmap.⁵ While they address similar ethical principles, our study identifies several ethical concerns in the implementation of MDA that are not discussed in the roadmap.

In particular, included publications criticise the lack of attention given to equity in programme implementation. Our review highlights that drug delivery often fails to reach certain disadvantaged population groups, potentially due to both delivery challenges and issues on the demand side. Insufficient coverage rates are a pivotal concern in MDA, as the measure heavily relies on extensive coverage to diminish disease transmission rates. Some authors in the malaria field emphasise that MDA's benefit-to-risk ratio is significantly influenced by coverage, with limited coverage potentially tilting the balance towards risks for the uninfected majority subjected to the treatment.⁴² Therefore, fostering community engagement to enhance population coverage seems crucial.^{43 44} Additionally, ensuring that treatment options are accessible and affordable to infected individuals outside of MDA campaigns is necessary for ensuring equity, as MDA may not target entire at-risk populations and does not prevent reinfection. Moreover, this review underscores that the burdens associated with programme implementation are unequally distributed within at-risk communities. CDDs reportedly bear a significant portion of this burden, yet their working conditions receive insufficient attention from the programmes.^{36 37} Enhancing working conditions and providing financial incentives for CDDs seems essential, as it could not only contribute to reinforcing community engagement⁴³ but would also align with ethical considerations for these community workers.

These aspects receive limited attention in policy, which primarily endorses MDA for its perceived impact on equity, understood as poverty alleviation and attendance of underserved communities. The roadmap mainly considers the absence of MDA as the barrier to equity, rather than addressing implementation issues as discussed in our review.

Unsurprisingly, as it is central to the roadmap, autonomy is another prominent aspect in our review. We found multiple challenges to autonomy at community level that are not explicitly mentioned in the roadmap.

Those encompass issues such as inadequate provision of health education, insufficient informed consent procedures, and a lack of ownership at the community and country levels. Prioritising better community sensitisation seems essential, as health education is a prerequisite for proper informed consent and has been reported to lack by numerous publications in our review (for full list, refer to online supplemental file 2). This could not only support the consent process but could also enhance prevention practices. Depending on the distribution context, involving traditional or civil leaders could also be key to fostering community engagement.⁴³ Moreover, engaging community stakeholders as partners and sharing responsibilities can demonstrate respect for local resources⁴⁵ which is essential to safeguard community autonomy.

While the roadmap does touch on autonomy, its primary focus is on promoting country ownership through integration and prioritisation of NTD programmes within national health systems and budgets of endemic countries. Along with the recent Kigali declaration,¹² it aims to involve countries more in planning and decision-making around implementation. However, this review highlights important power imbalances with donors from the Global North, who strongly influence decision-making, as they provide significant funding for NTD control and elimination. These findings raise questions about the feasibility of increasing country's decision-making power, particularly when MDA, heavily dependent on drug donations from the pharmaceutical industry, is the predominant measure for combating half of the NTDs. Vested interests and dominance of Western stakeholders in the international Global Health agenda seem to impede involvement of endemic countries especially when it comes to defining relevant health issues to tackle, setting goals and determining appropriate measures to address NTDs.^{16 20}

In terms of sustainability, our review emphasises that MDA programmes often fail to address the socioecological determinants of ill health. Many publications highlight the need to improve livelihoods through interventions like Water, Sanitation and Hygiene (WASH). This aligns with the aspirations of the roadmap to more cross-cutting, interdisciplinary, and One Health approaches to tackle NTDs. However, it is worth noting that while NTDs are now included in the quadripartite One Health Joint Plan of Action,³⁹ the World Organisation for Animal Health currently has no action plan for PC-NTDs, although many of them, such as schistosomiasis, are sustained through zoonotic transmission. Additionally, drug resistance to broad-spectrum anthelmintics used in MDA can have implications beyond the human health sector, such as environmental contamination.⁴⁶ Importantly, it could jeopardise the treatability of the targeted diseases for future generations, raising important ethical questions.²¹ The ethical dimensions of these One Health aspects of MDA are largely absent from the publications included in our review. Given that most PC-NTDs are sustained in complex cycles involving animals and the environment, it

is urgent to jointly consider issues of animal and human welfare which are known to be intertwined in marginalised multispecies collectives.⁴⁷

More broadly, it is important to be aware of the strengths and limitations of technical solutions in the form of vertical drug delivery approaches. Although MDA has proven its benefits in diminishing transmission rates of several PC-NTDs in many areas, over years of implementation, this measure cannot be expected solve all problems arising from these diseases. Relying solely on 'magic bullet' interventions, which are expected to solve multifactorial 'syndemics'⁴⁸ including social problems like stigma and poverty, can have unforeseen consequences. Multifactorial issues require multifaceted solutions, and the cost-effectiveness of drug distributions should not overshadow the need for alternative measures addressing socioecological determinants of ill health.⁴⁹ These could include improving primary healthcare systems, WASH, vector control and veterinary PH, as advocated in the WHO roadmap. It is crucial to bear in mind that ethical goals do not necessarily guarantee ethical outcomes. Interventions can have unintended effects, especially when insufficient attention is given to the specificities of their implementation.⁵⁰ Therefore, it is essential to enhance community engagement and to evaluate MDA against the specifics of its implementation context to ensure that set objectives can be ethically achieved.

Limitations

The purpose of this review was to explore the diversity of ethical considerations discussed in the literature about MDA for NTD control and elimination. The analysis did not differentiate between PC-NTDs, as the aim of this study was to analyse MDA as a singular PH intervention within the NTD context, in line with the WHO roadmap. Additionally, it did not include ethical aspects related to MDA for childhood mortality, another type of intervention that has been extensively debated on. The qualitative literature analysis conducted does not allow us to draw conclusions about the frequency with which certain ethical aspects occur, as it does not correlate with their significance. Moreover, certain limitations of this work should be acknowledged. First, although we adopted a broad definition of ethics, the analysis was done through a Western bioethical lens, influenced by established frameworks and the backgrounds of the authors. Consequently, some important local and context-specific ethical issues could have been overlooked. Second, search strings were designed to capture as much relevant literature as possible. Nevertheless, given the highly interdisciplinary nature of the field, it is possible that certain relevant publications were missed. Additionally, the review focused solely on scientific publications indexed in two databases, which excluded potentially relevant grey literature or case reports. Third, while no publications were excluded based on their language, the search strings were constructed solely with English terms, which might have

missed relevant literature published in other languages. Lastly, no quality appraisal of the mentioned reasons was done, due to the lack of guidelines for this endeavour in the bioethics field.²⁷ Readers are thus invited to critically judge the presented aspects considering their prior knowledge or experience.

CONCLUSION

In conclusion, this systematic review sheds light on the diversity of ethical considerations surrounding MDA for NTD control and elimination. Despite the limited number of publications specifically focused on the ethics of MDA, reasons have been identified across various ethical principles. Among these, equity, autonomy and sustainability of MDA emerged as the domains with the most pressing ethical concerns. Many of these pertain to the implementation of MDA and have yet to be adequately addressed in policy documents. While MDA has demonstrated its benefits in reducing the burden of PC-NTDs in numerous settings over years of implementation, it is crucial not to overlook the ethical challenges that arise when the measure reaches vulnerable communities. These concerns should be addressed through a context-specific lens rather than viewing MDA as a one-size-fits-all solution. Moreover, it seems essential to stop perceiving MDA as a 'magic bullet' and explore alternative interventions to achieve long-term sustainability. These should encompass structural changes addressing root causes of ill health. This could involve WASH, strengthening primary healthcare systems to address chronic cases and a focus on veterinary PH, considering that many of these diseases are sustained through animal reservoirs. Regardless of the approach, there should be a focus on implementation research and community engagement. Tailoring interventions to contexts is crucial to ensure ethical implementation and enhance their overall impact.

International organisations play a vital role in empowering endemic countries and placing them at the forefront of decision-making processes concerning NTD control, which should result in a real ability of these nations to shape the agenda and guide interventions on NTDs. Moreover, concrete ethics recommendations should be developed at the international level for MDA implementation and evaluation in the NTD context, considering human, animal and environmental health implications. This process could involve a multidisciplinary panel of experts, weighing out benefits and risks of MDA use in different contexts (diseases and geographical areas), taking example of the WHO guideline for azithromycin MDA to mitigate childhood mortality.⁵¹

Future research could expand the bioethical discourse on MDA by incorporating non-Western philosophies and ethical perspectives. It seems crucial to involve local researchers and give them a prominent role in investigating MDA ethics. Finally, exploring subaltern perspectives of NTD endemic communities on their most

pressing health issues could be essential for improved problem-framing.

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