

Antimalarial mass drug administration: ethical considerations

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Received 12 February 2016; revised 25 April 2016; accepted 23 May 2016

Plasmodium falciparum malaria is a major cause of death and illness in tropical countries, particularly in childhood. In endemic countries, a significant proportion of the community is infected with malaria asymptomatically. One promising way to eliminate malaria in low transmission settings is to give the entire population malaria treatment. This is called mass drug administration (MDA) and it raises a number of ethical issues, as possible long-term benefits are uncertain. The effectiveness of MDA is critically dependent on level of participation, so the promised benefits to the community can be annulled by non-participation of a small number of individuals. These potential benefits range, from the permanent elimination of malaria (success) to a transient reduction in the prevalence of infection and the incidence of illness (failure). The drawbacks of MDA are inconvenience, potential toxicity, loss of confidence in the elimination campaign, possible drug resistance (though unlikely) and the potential for a rebound of malaria illness (if immunity is lost and malaria is reintroduced later). Other ethical issues relate to balancing individual and public health interests, and potentially limiting individual autonomy by making MDA compulsory.

Keywords: Antimalarials, Elimination, Ethics, Malaria, Mass drug administration, Public health

Introduction

The health and quality of life of human populations can be improved by ensuring exposure to adequate nutrition and essential elements. This can be accomplished by adding vitamins to food, iodine to salt and fluoride to water. ‘Opting out’ is almost impossible, and individual informed consent is inapplicable in cases where the benefits generated by these interventions are considered public goods.¹ In combatting infectious diseases, vaccines are used for prevention and drugs are given for treatment. Most vaccines are given in childhood. There is a choice for the family who may not wish their child to receive a vaccine; however, there is strong societal pressure against opting out because herd immunity is important. Thus, not having your child vaccinated makes illness more likely in other children as well as your own (for example, in the case of measles). Sometimes when the infectious disease threat from an individual is serious, governments may prevent their entry or isolate them, if necessary against their will, until the threat diminishes. Such public health measures have been justified based on an ethical obligation not to harm others, and the preservation of public goods, such as herd immunity (in the case of vaccination).^{2,3} Malaria, the most important parasitic disease of mankind, is a major cause of death in tropical countries, and an

important cause of illness, particularly in childhood.⁴ Over the past 60 years there has been one failed attempt at global eradication of malaria, launched by WHO. There is now a resurgence of support for malaria elimination, with substantial recent progress. It has been estimated that global malaria mortality has been reduced by half.⁵ This progress is now threatened by a familiar foe, resistance. The mosquitoes that carry malaria and the parasites that cause it are both becoming resistant to the chemicals we use to kill them. Nowhere is antimalarial drug resistance worse than in Southeast Asia. Resistance of *Plasmodium falciparum*, the parasite that causes most of the deaths, to all classes of antimalarial drugs is now established in the Greater Mekong area.^{6,7} Resistance was an important contributor to the resurgence of malaria that followed the previous failed attempt to eliminate malaria. Mosquitoes became resistant to the insecticide DDT (dichlorodiphenyltrichloroethane), and parasites became resistant to chloroquine, a remarkably effective, well-tolerated and inexpensive medicine. Resistance to chloroquine, and to sulfadoxine-pyrimethamine (the drug which followed chloroquine), both emerged in the Greater Mekong area and then spread across the rest of Asia to Africa, at the cost of millions of lives.⁸ There is now a race against time to eliminate malaria from the region before malaria again becomes untreatable.

One promising way to eliminate malaria is to give the entire population of a malaria affected area antimalarial treatment.^{9–11} This is called mass drug administration (MDA). It is a crude and difficult approach with a chequered history, but it can be very effective. MDA is done because a significant proportion of the population harbour malaria parasites without being ill. These people have previously been infected repeatedly and develop sufficient immunity to control their infections at a low level, which does not cause overt illness. These asymptomatic individuals act as a reservoir for malaria and a source of infection to others. They are generally well, do not seek medical attention and are not readily identified by current tests (even expensive, new and highly sensitive DNA or RNA tests will miss some cases). The only way to clear the infection rapidly from populations with a significant proportion of asymptomatic individuals is antimalarial MDA. In general MDA should only be considered when sustained elimination is a realistic prospect, there is good access to treatment and surveillance, effective implementation of vector control and surveillance, and a minimal risk of reintroduction of infection.^{9,10,12} Exceptional circumstances in which antimalarial MDA has been used include the containment of epidemics; for example, in the recent Ebola virus epidemic in West Africa where MDA was used to prevent confounding by malaria of the Ebola containment effort.

Currently, MDA in the Greater Mekong area comprises three rounds, at monthly intervals, of a three-day treatment course of dihydroartemisinin-piperaquine.¹¹ This is a well-established antimalarial treatment, although its use in MDA is still exploratory. Despite documented resistance in Myanmar, Cambodia, Thailand and southern Vietnam, artemisinin-based combination therapies were shown to be highly efficacious, presumably because of increased reliance on the efficacy of the partner drug, particularly piperaquine, due to its long half-life.^{7,9} A low dose of primaquine is added in some deployments. MDA is best done in the dry season when malaria transmission is lowest.¹³ This treatment should clear all *P. falciparum* infections in the community. Primaquine, a gametocidal agent, should reduce gametocyte transmission from already infected humans to mosquitoes. Concurrently, the slowly eliminated piperaquine prevents acquisition of new malaria infections for over a month (post-treatment chemoprophylaxis).⁹ This form of MDA does not eliminate vivax malaria, which traditionally causes about half the malaria illness in the region. It is possible to eliminate *Plasmodium vivax* as well, but this involves giving a 14-day course of primaquine (termed ‘radical cure’) with the attendant risk of drug-induced haemolysis in individuals who are glucose-6-phosphate dehydrogenase (G6PD) deficient (3–30% prevalence).¹⁴ A simple method of testing for G6PD deficiency rapidly is not generally available, therefore, current MDA does not include a radical curative regimen with primaquine.

Before starting MDA there should be intensive community engagement to inform the potential participants of the benefits and risks, and to encourage active participation and good adherence. What are the benefits for the MDA participants? For the infected individual there is removal of low-grade infections, which may cause subclinical morbidity (mainly mild anaemia) and prevention of new infections. There should be a substantial reduction in the subsequent risk of malaria for the whole community and, if the campaign is successful, malaria would be eliminated from the

community, which would be an enormous benefit. But what are the ethical issues, including the risks involved, in treating entire communities who are asymptomatic, particularly as the MDA may not be effective if participation is poor? Here we examine the main ethical issues associated with MDA.

Ethical issues

The main ethical issues related to MDA in malaria elimination can be considered in terms of the risk-benefit balance, public health ethics and individual autonomy. These are recurring themes in many public health initiatives.

Risk-benefit balance

MDA is given to people who may not have malaria, although they would later become infected without MDA. Effective MDA would hopefully eliminate falciparum malaria, contain artemisinin resistance and, if a radical course of primaquine was given, would eliminate the majority of the malaria that affect humans: *P. falciparum* and *P. vivax*. There are enormous benefits of malaria elimination, both for the current population as well as for future generations: prevention of malaria related mortality and morbidity, and the related social and economic costs. At the very least, a well-executed MDA should reduce the risk of malaria substantially, as well as providing other indirect benefits, such as improved health infrastructure or a better-informed community. The drawbacks of MDA include inconvenience, potential toxicity, the potential for a rebound illness if immunity is lost then malaria is reintroduced, and a very low risk of selecting for drug resistance due to drug pressure. The risk of perpetuating drug resistance is thought to be low because MDAs are implemented in those with submicroscopic infections rather than in patients with levels of parasitemia that are often over a thousand times higher where there may be a chance of de novo emergence of resistant parasites.^{11,15} This risk must be balanced against its contribution to accelerated malaria elimination in the absence of other measures and the threat of untreatable falciparum malaria in the near future if there is total resistance to the drugs.

There is a complex but critical relationship between participation and outcome. If participation (‘coverage’) is poor the efficacy of MDA is reduced substantially.¹⁶ If an individual opts out, he/she risks jeopardising the entire effort by reintroducing malaria to the treated community. If MDA is effective, the benefits considerably exceed the risk, but with ineffective MDA risk may exceed benefit. MDA needs to be administered at the same time to the entire community so while the preceding community engagement may well have identified individuals who are unwilling to participate, the coverage will not be known until the day the MDA starts. If participation is poor then all the promised benefits that persuaded the community to participate in the first place, may not be realised. As high coverage is so important to realising the benefits of MDA, everything possible must be done to encourage active participation. But how far should health agencies go to persuade individuals who are not willing to participate? How much should community pressure be instigated? Could non-participants later be blamed for malaria

suffering or death? The MDA participants and the future health of the community are both potentially damaged by the continued presence of malaria parasite carriers. Taking an extreme example, what if there was a single malaria parasite carrier who refused to be treated in an island of a million people that had previously been racked by malaria? At what point, if ever, should MDA become compulsory? In the war on malaria, and in particular the struggle to contain multidrug-resistant malaria in the Greater Mekong area, we are a long way from this level of success, but it is important to plan ahead for success as well as failure.

In addition to low participation, which may prevent the benefits being realised, there is the risk of adverse drug reactions from MDA. The safety profile of the drug, and evidence from years of experience using dihydroartemisinin-piperaquine and primaquine, suggest that the short-term risks directly related to drug ingestion are very low. However, in MDA we are potentially treating tens of thousands of individuals in a short period of time. Adverse drug reactions that are rare, serious and perhaps not previously encountered could appear because of the sheer numbers involved. These might include serious allergic reactions, which may be more severe on subsequent exposures. In addition, incidental cases of unrelated severe illness, freak accidents and deaths in any community could also be confused with drug related events. It is never easy to attribute causality to an intervention. The only way is rechallenging with the drug, which would carry further risks. If these serious events are attributed to the drug when they are, in fact, unrelated, then subsequent MDA programmes will be halted prematurely and confidence in the health system may be diminished. Rumours are common with any mass campaign and can be very damaging. By contrast if the events are not attributed to the drug, when in fact they are related to the drug, then we will advertently expose more people to serious drug reactions.

Perception of risks and benefits are important both for the success of MDA and for confidence in the health system that delivered it. It is very important that there is continual active engagement to address concerns, deal with unfounded rumours, and clarify objectives. For example, many people living in endemic areas are unaware that there are different types of malaria, so may be confused and disappointed when MDA directed against falciparum malaria does not eliminate subsequent vivax malaria. Maintaining trust in the system and the method is essential, particularly as elimination of vivax malaria may require further MDA.

Balancing individual and public interest

With MDA, entire communities, with the exception of pregnant women in the first trimester, children under 6 months old and the severely ill, are treated. That means that many individuals who are neither ill nor carriers of the parasite, will be asked to take drugs and therefore experience potential adverse drug reactions. The ethical justification is not dissimilar to public health initiatives, such as vaccination campaigns, in which the focus is directed to populations or communities instead of individuals.² In contrast to MDA participants, some of who are disease carriers, individuals undergoing vaccinations are all healthy, and will gain protection against future infection if exposed. The similarity between vaccinations and MDA is that in both cases some

people treated benefit directly, while others do not, but everyone is exposed to the potential side effects. This moral challenge is one related to public health ethics. In many public health initiatives, there is an enduring dilemma of balancing individual benefits and risks with the advancement of good health outcomes for the entire public. The interesting point with MDA is that the balance of individual and public interest changes with the effectiveness of treatment. The individual who opts out of MDA potentially damages his or her participating neighbours. The amount of potential damage ranges from negligible in a failed MDA, to enormous in a highly successful campaign. Returning to the earlier extreme example of a single individual with the potential to reinfect a large population with malaria, at what point, if ever, are we justified in coercion for treatment or quarantining the individual? Governments are generally willing to take tough measures if the threat to society is large. For example draconian measures have been taken to contain dangerous contagions such as H5N1 influenza, SARS, MERS-CoV, Ebola virus, Lassa fever and multidrug-resistant TB, which involved restriction of liberty in order to protect the public. Malaria is a major cause of death in tropical countries. In the Greater Mekong region falciparum malaria is becoming untreatable due to drug resistance. Drug resistance has been recognised as an important ethical issue as it has implications for the global public good.¹⁷ How forcefully should we act for the public interest?

Autonomy

For appropriately targeted MDAs to be successful, the public must be persuaded to take part in MDAs—both for their own good and for the good of current and future populations. In the former, there is an element of medical paternalism but it seems to be the middle path. Paternalism is a familiar strategy in public health such as increasing cigarette tax and vaccination, but an individual has the right to refuse to take drugs. The latter is a matter of public health ethics discussed in the previous section. The importance of communication, community participation, political involvement and other forms of public engagement preceding and during MDA has been shown to be critical in previous successful MDA programmes,¹⁸ but a full community understanding of the complexities of malaria transmission is unlikely. The benefits will have to be taken on trust, and as explained above, cannot be guaranteed. At present, making MDA compulsory is not considered justified, but we should consider if this might change. Antimicrobial resistance in general, and antimalarial resistance in particular, are increasingly recognised as threats to global health and security, posing an ethical issue in their own right.¹⁷ Individuals infected with resistant organisms pose a societal threat. As malaria elimination proceeds successfully, the threat from malaria resurgence increases as communities in once endemic areas lose their immunity. If MDA is necessary for this success then, at some point, and it is not clear when, the individual may lose their right to 'opt out,' in order to achieve public health ends. It is generally agreed that in public health, the full force of state authority and power should be reserved for exceptional circumstances.² In the case of malaria elimination and eradication and curbing the threat of drug resistance, when this will become exceptional is a matter of debate.

Conclusions

Multidrug-resistant falciparum malaria, originating from the Greater Mekong Area, poses an enormous and uncontained threat to the tropical world. MDA, together with effective vector control, and surveillance and case management, is thought to be a promising strategy to eliminate malaria from entire circumscribed populations rapidly.^{9–11} MDA has several associated ethical issues; the most challenging of these is the balance of risk versus benefit, which depends largely on the degree of community participation. The risks posed to the community by individuals who opt out from MDA increase if the treatment is successful in eliminating disease, particularly in areas with highly drug resistant malaria parasites. This may threaten their autonomy, as they may be compelled to take medication in the name of public interest. There needs to be careful assessment of the risk and benefits, and of the balances between individual and public interest, as well as a careful consideration of any restrictions placed on autonomy.

Authors' contributions: PYC and NJW contributed equally to the preparation of the manuscript. Both authors read and approved the final manuscript. PYC and NJW are guarantors of the paper.

Funding: This work was supported in part by a Wellcome Trust Strategic Award (096527). The Mahidol Oxford Tropical Medicine Research Unit is funded by the Wellcome Trust (106698/Z/14/Z). PYC is funded by a Wellcome Trust Engaging Science grant (105032/Z/14/Z) and NJW is a Wellcome Trust Principal Fellow.

Competing interests: NJW is the Principal Investigator of a currently ongoing mass drug administration initiative in the Greater Mekong Region.

Ethical approval: Not required.

References

- O'Neill O. Informed consent and public health. *Philos Trans R Soc Lond B Biol Sci* 2004;359:1133–6.
- Upshur RE. Principles for the justification of public health intervention. *Can J Public Health* 2002;93:101–3.
- Dawson A. What are the moral obligations of the traveller in relation to vaccination? *Travel Med Infect Dis* 2007;5:90–6.
- WHO. World Malaria Report. Geneva: World Health Organization; 2014.
- Murray CJ, Ortblad KF, Guinovart C et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;384:1005–70.
- Dondorp AM, Nosten F, Yi P et al. Artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med* 2009;361:455–67.
- Ashley EA, Dhorda M, Fairhurst RM et al. Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med* 2014;371:411–23.
- Barnes KI, Watkins WM, White NJ. Antimalarial dosing regimens and drug resistance. *Trends Parasitol* 2008;24:127–34.
- Tanner M, Greenwood B, Whitty CJ et al. Malaria eradication and elimination: views on how to translate a vision into reality. *BMC Med* 2015;13:167.
- Poirot E, Skarbinski J, Sinclair D et al. Mass drug administration for malaria. *The Cochrane Database Sys Rev* 2013;12:CD008846.
- von Seidlein L, Dondorp A. Fighting fire with fire: mass antimalarial drug administrations in an era of antimalarial resistance. *Expert Rev Anti Infect Ther* 2015;13:715–30.
- WHO. Malaria Policy Advisory Committee and Secretariate. Malaria Policy Advisory Committee to the WHO: conclusions and recommendations of eighth biannual meeting (September 2015). *Malar J* 2016;15:117.
- Jamrozik E, de la Fuente-Nunez V, Reis A et al. Ethical aspects of malaria control and research. *Malar J* 2015;14:518.
- WHO. Guidelines for the treatment of malaria. Geneva: World Health Organization; 2015.
- White NJ, Pongtavornpinyo W, Maude RJ et al. Hyperparasitaemia and low dosing are an important source of anti-malarial drug resistance. *Malar J* 2009;8:253.
- Newby G, Hwang J, Koita K et al. Review of mass drug administration for malaria and its operational challenges. *Am J Trop Med Hyg* 2015;93:125–34.
- Selgelid MJ. Ethics and drug resistance. *Bioethics* 2007;21:218–29.
- Kaneko A. A community-directed strategy for sustainable malaria elimination on islands: short-term MDA integrated with ITNs and robust surveillance. *Acta Trop* 2010;114:177–83.