Published in final edited form as:

Expert Rev Anti Infect Ther. 2012 February ; 10(2): 237–242. doi:10.1586/eri.11.165.

Preventive chemotherapy and the fight against neglected tropical diseases

Antonio Montresor,

Department of Control of Neglected Tropical Diseases (NTD), World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland, Telephone +41227913322

Albis Francesco Gabrielli,

Department of Control of Neglected Tropical Diseases (NTD), World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland, Telephone +41227911876

Lester Chitsulo,

Department of Control of Neglected Tropical Diseases (NTD), World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland, Telephone +41227913862

Kazuyo Ichimori,

Department of Control of Neglected Tropical Diseases (NTD), World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland, Telephone +41227912767

Silvio Mariotti,

Department of Prevention of Blindness and Deafness (PBD), World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland, Telephone +41227913491

Dirk Engels, and

Department of Control of Neglected Tropical Diseases (NTD), World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland, Telephone +41227913824

Lorenzo Savioli

Department of Control of Neglected Tropical Diseases (NTD), World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland, Telephone +41227912664

Abstract

Preventive chemotherapy is the public health strategy recommended by WHO against a set of Neglected Tropical Diseases that includes 4 groups of helminth infections (lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis) and one chlamydial (trachoma) infection.

This article presents the characteristics of preventive chemotherapy interventions directed against each disease targeted by this strategy and provides an update on the status of their implementation worldwide.

Keywords

Preventive chemotherapy; Lymphatic Filariasis; Onchocerciasis; Schistosomiasis; Soil Transmitted Helminthiasis; Trachoma

Characteristics of PC

Preventive Chemotherapy (PC) consists of the regular, large-scale administration of drugs - either alone or in combination, to entire population groups, with the aim of reducing transmission and associated morbidity; PC is the public health strategy recommended by WHO against a set of Neglected Tropical Diseases (NTDs): 4 groups of helminth infections (lymphatic filariasis, onchocerciasis, schistosomiasis and soil transmitted helminthiasis) and one chlamydial infection (trachoma). (1)

From an operational perspective, PC is characterized by population-level diagnosis and treatment and by an implementation at regular intervals (2). The burden of a given target infection in a given area is therefore assessed through surveys conducted in a sample of its population, following which treatment is administered at regular intervals on a large scale and by teams that include non-medical personnel (teachers, volunteers, or community drug distributors).

The size of the population targeted by a PC intervention can vary according to the disease that is targeted, based on the epidemiological characteristics of such disease and the aimed public health goal (the more conservative control of morbidity or the more ambitious interruption of transmission). When the entire population of an endemic area is targeted, the intervention takes the name of mass drug administration (MDA); when the target is limited to specific risk-groups in the population, (e.g. school-age children, fishermen), the intervention is called targeted treatment; when only individuals testing positive to screenings regularly conducted in a given area are targeted, the intervention is referred to as selective treatment (1–3).

The suitability of lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis and trachoma to be addressed by a PC intervention is justified by the fact that these diseases are characterized by a chronic evolution of morbidity that gives rise to late or non-specific symptoms, with the consequence that individuals are not exposed to early or high risk of death or of severe complications, and are actually frequently unaware of being infected. Treatment must therefore be provided actively, without waiting for the time when advanced symptoms alert the infected individuals and take them to the health centre, as at this stage treatment itself might be ineffective. Such active intervention does not need to be repeated frequently, but, by virtue of the previously mentioned slow disease evolution, treatment can be offered from every few months in highly endemic areas to every few years in low-endemic areas, with a frequency that is specific to the level of infection in the population. The population-based nature of PC relies on the high safety of the drugs used, that can therefore be administered by supervised non-medical personnel in "campaigns" similar to those carried out for vaccination purposes. All this ensures lower costs than those required by clinical case-management, thus making PC a viable intervention in resource-poor settings; the resulting high cost-effectiveness of PC makes it one of the most successful public health interventions.(4)

Integration of PC

The diseases targeted by PC affect similar populations, namely those living in settings where poverty is widespread, resources are limited, and access to sanitation is poor. In 2003 the international community recognized that such diseases required more attention and a collective response to combat them emerged as a new concept in light of economic considerations, social progress and human rights.

The new key strategy (integrated preventive chemotherapy) was released in 2006 (1) and is based on the coordination of the large scale drug administration efforts that up to then had been implemented in an isolated fashion against lymphatic filariasis, onchocerciasis, schistosomiasis or STH singularly. Trachoma was later added to the package, since its control strategy includes large scale administration of the antibiotic azithromycin.(5) Because of this operational overlapping, interventions directed against helminth infections can be implemented in a coordinated fashion among them and also with those directed against trachoma; the aim is that of attaining higher coverage rates and make the best use of available resources.

There are, nevertheless, significant barriers and challenges to the integration of PC; the discussion of these issues is however beyond the scope of this paper.

Drugs used in PC and their co-administration

Integrated PC for the control of the mentioned NTDs is based on the large scale distribution of 6 drugs, alone or in combination (Table 1). Millions of doses of anthelmintic drugs and azithromycin have been used in the last years and each of these drugs has an excellent safety record: adverse reactions are minimal and transient and serious adverse events are extremely rare (1). In the case of anthelmintic drugs adverse reactions have been shown to result from the body's response to dying worms rather than from a direct effect of the medicine itself; heavily infected individuals are therefore more likely to experience such reactions (1). In treatment of trachoma, the low frequency and significance of side effects associated with azithromycin ensures a high compliance profile. The only potential severe adverse effect is the Mazzotti-like reaction in patients with loiasis when treated with ivermectin. At the moment areas where LF and loiasis are co-endemic are not covered by PC (6).

In case of co-endemicity of several NTDs in a given area, different drugs can be co-administered to the same individuals with the aim of combating all the prevalent diseases simultaneously. A number of studies have investigated the safety of drug co-administration in the treatment of NTDs:

- albendazole and praziquantel can be safely co-administered (7);
- mebendazole and praziquantel have been widely co-administered in many countries and reported to be safe (8);
- albendazole and ivermectin can be safely co-administered (9);
- albendazole and diethyl carbamazepine are also safe for co-administration (8);

- the co-administration of albendazole, ivermectin and praziquantel is safe in areas where lymphatic filariasis, onchocerciasis, soil-transmitted helminthiasis and schistosomiasis are co-endemic and where several rounds of treatment with one or two drugs have been implemented in the past. (10–13);
- co-administration of azithromycin and anthelmintic drugs is being currently studied; for the time being it is recommended to implement large-scale distribution of this drug roughly one week apart from any helminth control or elimination intervention.

Coverage of preventive chemotherapy

As mentioned, PC is currently being implemented on a worldwide scale for the control/elimination of a set of diseases. Figure 1 presents the progress of the global coverage of population at-risk for each disease (101).

For elimination of **lymphatic filariasis**, in 2009 PC with albendazole + ivermectin or albendazole + DEC has been implemented in 53 of the 81 endemic countries covering a total of 385 million individuals (101). Albendazole and ivermectin have been donated for several years in quantities sufficient to cover the global needs, while a donation of DEC sufficient to cover all endemic countries with the exception of India, is expected to be operational from 2012 onwards.

For elimination and control of **onchocerciasis**, PC with ivermectin has been implemented in all the 30 endemic countries worldwide, covering a total of over 68 million of individuals in 2009. Donated ivermectin is sufficient to cover the global needs.

For control of **schistosomiasis**, PC has been implemented in 21 of the 78 endemic countries (52 of which are eligible for PC) and a total of 19 million treatments (each one on average of 2 ½ tablets) were distributed in 2009 when the donation of PZQ was only covering 10% of the need (101).

For control of **STH**, PC has covered over 300 million pre-school-age and school-age children. Small-scale donations have been in place for some years, but large-scale commitments have recently been undertaken by major pharmaceutical companies and it is expected that from 2012 onwards donations of albendazole and mebendazole will significantly increase the global coverage (101).

For elimination of **trachoma** over 37 million doses of azithromycin were distributed in 2009 in 30 countries across the world (101).

Globally, over 700 million individuals are estimated to be treated every year for one or more NTDs. The increasing success of this approach is boosted by a number of factors: the clear demonstration of the association of such infections with poverty and the increasing evidence on their socio-economic burden (14); the geographical overlap of the targeted diseases (15); the contribution of preventive chemotherapy not only to morbidity reduction but also to sustained decrease of transmission (16); its flexibility, which allows the expansion of its target to other diseases with characteristics similar to those of the four original ones, as in

the case of trachoma as well as in that of other helminth infections such as fascioliasis, clonorchiasis and opisthorchiasis (foodborne trematode infections) (17, 18). These factors pave the way for a further expansion of this public health intervention, which now shares, from an organizational and logistics perspective, many common features with immunization.

In the past ten years, there has been a significant boost in commitment by a increasingly wider donor community, that is seeing the worth of fighting NTDs: not only have financial contributions increased, but - as mentioned - specific drug donation programmes have been set up or announced, and national governments in endemic countries have started implementing or have reinforced their good efforts to progressively scale-up NTD control and elimination activities on a national scale.

Expert commentary

PC demonstrated to be a strategy efficient in rapidly controlling morbidity and - under some conditions - in eliminating target diseases from target areas within a reasonable timeframe (19); it also proved to be simple and low cost intervention, thus allowing its successful implementation in contexts where minimal resources are available for health. (20) This evidence convinced the global partners' community of the validity of this approach and was instrumental in securing the donation of significant amounts of the WHO-recommended medicines by manufacturers to programmes in endemic countries; it also encouraged a number of bilateral and multilateral donors to invest in supporting the cost of drug distribution and of other public health measures complementary to PC.

Control and elimination of diseases for which resources have been made available for a significant number of years (i.e. onchocerciasis and lymphatic filariasis) is presently in a more advanced phase (global coverage between 37% and 56%), whilst control of diseases for which resources have been made available more recently (i.e. soil-transmitted helminthiasis and schistosomiasis) is currently characterized by a lower coverage (between 12% and 31%); the effects of the recent, significant drug donations is however expected to become evident in the next few years. The prevalence of trachoma has dramatically decreased since 1998, when the global elimination campaign (WHO-GET2020) was established. The global number of cases has decreased from an estimated 146 millions to 40 millions nowadays, with an increasing number of countries reporting the achievement of elimination and moving into post endemic surveillance (21) This was made possible by the azithromycin donation and by the engagement of many international partners in funding and supporting the implementation of the SAFE strategy.

Five years view (2012-2016)

We expect to see the global coverage achieved by PC interventions to increase in the next five years, with results of different magnitude for each NTD.

Considering that from 2012 onwards, all drugs used for control and elimination of **lymphatic filariasis** (albendazole, ivermectin and DEC) will be available in sufficient quantities to cover global needs and in the large majority of the cases as a donation; that a number of donors are willing to invest resources in the Global Programme to Eliminate

Lymphatic Filariasis (GPELF); and that more and more countries are completing the mapping exercise and are ready to start MDA, we consider that in the next 5 years a continuous increase of the PC coverage will be registered, and that full geographical coverage will be reached by 2015 for countries without co-endemic loasis and by 2016 by countries with co-endemic loasis (22). We also expect that the remaining challenge in distributing ivermectin in LF endemic areas where also loasis is transmitted will be solved.

As the drug used in PC for the control of **onchocerciasis** (ivermectin) is donated in sufficient quantity to cover the global needs, we expect to reach full global geographical coverage and the achievement of interruption in transmission in the Americas by 2016.(23)

The scarce availability of the drug used for controlling **schistosomiasis** (praziquantel) is presently considered one of the main limiting factors for a rapid scaling up of the geographical coverage of PC interventions directed against this disease. If a large-scale donation will materialize in the next future, there are hopes that the PC global coverage for this disease will increase significantly in the next 5 years to reach 30-45%. Without such donation, the PC coverage will probably increase marginally to 10-12%.

Following recent commitments, drugs used to control **STH** (albendazole or mebendazole) are now donated in sufficient quantities to implement PC targeting all school-age children at-risk globally. More drugs are however necessary to control these infections in pre-school-age children and women of child bearing age. We expect the combined PC coverage of pre-school-age and school-age children to reach 50% in the next five years and progress towards the 75% threshold by 2020.

The availability of the drug used in PC for the control of **trachoma** (azithromycin) is ensured by the commitment of the producer (Pfizer, Inc.) and of the organization that oversees its distribution to endemic countries (ITI); the challenges are the effective and timely use of the available drug, the timely submission of requests by national Governments, the coordination of resources with the aim of linking together drug treatment, surgery provision, hygiene education and environmental interventions, necessary to ensure the steady progress towards global elimination, foreseen by the year 2020.

Reference List

- (1). WHO. Preventive chemotherapy in human helminthiasis. Coordinated use of anthelmintic drugs in control interventions: a manual for health professionals and programme managers. Geneva: World Health Organization; 2006. [** *This WHO manual is the essential strategic reference for control and elimination of the main helminth infections.*]
- (2). Gabrielli AF, Montresor A, Chitsulo L, Engels D, Savioli L. Preventive Chemotherapy in Human Helminthiasis:Theoretical and Operational Aspects. *Trans R Soc Trop Med Hyg.* 2011; 105(12): 683–693. [PubMed: 22040463] [* *This review explores in details all the aspects of preventive chemotherapy.*]
- (3). WHO. Report of the WHO Informal Consultation on the use of chemotherapy for the control of morbidity due to soil-transmitted nematodes in humans. Geneva: World Health Organization; 1996.
- (4). Hotez PJ, Molyneux DH, Fenwick A, et al. Control of neglected tropical diseases. *N Engl J Med.* 2007; 357(10):1018–1027. [PubMed: 17804846]

- (5). WHO/LSHTM/ITI. Trachoma control. A guide for programme managers. World Health Organization; Geneva: 2011. [*** These guidelines provides all the necessary information to start a trachoma control programme.*]
- (6). Taylor MJ, Hoerauf A, Bockarie M. Lymphatic filariasis and onchocerciasis. *Lancet*. 2010; 376(9747):1175–1185. [PubMed: 20739055]
- (7). Olds GR, King C, Hewlett J, et al. Double-blind placebo-controlled study of concurrent administration of albendazole and praziquantel in schoolchildren with schistosomiasis and geohelminths. *J Infect Dis*. 1999; 179(4):996–1003. [PubMed: 10068597]
- (8). Engels D, Ndiricimpa J, Nahimana S, Gryseels B. Control of *Schistosoma mansoni* and intestinal helminths: 8-year follow-up of an urban school programme in Bujumbura, Burundi. *Acta Trop*. 1994; 58(2):127–140. [PubMed: 7887338]
- (9). Awadzi K, Edwards G, Duke BO, et al. The co-administration of ivermectin and albendazole--safety, pharmacokinetics and efficacy against *Onchocerca volvulus*. *Ann Trop Med Parasitol*. 2003; 97(2):165–178. [PubMed: 12803872]
- (10). Mohammed KA, Haji HJ, Gabrielli AF, et al. Triple co-administration of ivermectin, albendazole and praziquantel in zanzibar: a safety study. *PLoS Negl Trop Dis*. 2008; 2(1):e171. [PubMed: 18235853]
- (11). Eigege A, Pede E, Miri E, et al. Triple drug administration (TDA), with praziquantel, ivermectin and albendazole, for the prevention of three neglected tropical diseases in Nigeria. *Ann Trop Med Parasitol*. 2008; 102(2):177–179. [PubMed: 18318940]
- (12). Namwanje H, Kabatereine N, Olsen A. A randomised controlled clinical trial on the safety of co-administration of albendazole, ivermectin and praziquantel in infected schoolchildren in Uganda. *Trans R Soc Trop Med Hyg*. 2011; 105(4):181–188. [PubMed: 21353271]
- (13). Anto F, Asoala V, Anyorigiya T, et al. Simultaneous administration of praziquantel, ivermectin and albendazole, in a community in rural northern Ghana endemic for schistosomiasis, onchocerciasis and lymphatic filariasis. *Trop Med Int Health*. 2011; 16(9):1112–1119. [PubMed: 21689221]
- (14). Hotez PJ, Fenwick A, Savioli L, Molyneux DH. Rescuing the bottom billion through control of neglected tropical diseases. *Lancet*. 2009; 373(9674):1570–1575. [PubMed: 19410718]
- (15). Clements AC, Deville MA, Ndayishimiye O, Brooker S, Fenwick A. Spatial co-distribution of neglected tropical diseases in the east African great lakes region: revisiting the justification for integrated control. *Trop Med Int Health*. 2010; 15(2):198–207. [PubMed: 20409287]
- (16). Croce D, Porazzi E, Foglia E, et al. Cost-effectiveness of a successful schistosomiasis control programme in Cambodia (1995-2006). *Acta Trop*. 2010; 113(3):279–284. [PubMed: 19962364]
- (17). Keiser J, Duthaler U, Utzinger J. Update on the diagnosis and treatment of food-borne trematode infections. *Curr Opin Infect Dis*. 2010; 23(5):513–520. [PubMed: 20683264]
- (18). Hu VH, Harding-Esch EM, Burton MJ, Bailey RL, Kadampeul J, Mabey DC. Epidemiology and control of trachoma: systematic review. *Trop Med Int Health*. 2010; 15(6):673–691. [PubMed: 20374566]
- (19). Linehan M, Hanson C, Weaver A, et al. Integrated implementation of programs targeting neglected tropical diseases through preventive chemotherapy: proving the feasibility at national scale. *Am J Trop Med Hyg*. 2011; 84(1):5–14. [PubMed: 21212194]
- (20). Sinuon M, Tsuyuoka R, Socheat D, et al. Control of *Schistosoma mekongi* in Cambodia: results of eight years of control activities in the two endemic provinces. *Trans R Soc Trop Med Hyg*. 2007; 101(1):34–39. [PubMed: 17028047]
- (21). WHO. Report of the fifteenth meeting of the WHO alliance for the elimination of blinding trachoma by 2020. Geneva: World Health Organization; 2011.
- (22). WHO. Lymphatic Filariasis, Progress report 2000-2009 and strategic plan 2010-2020. Geneva: World Health Organization; 2011.
- (23). OEPA. Epidemiology. 2011. <http://www.oepa.net/epidemiologia.html>

Websites

- (101). WHO. [Accessed 30 November 2011] Neglected Tropical Diseases - PCT Databank. 2010.
http://www.who.int/neglected_diseases/preventive_chemotherapy/databank/en/index.html

Key issues

- Preventive chemotherapy is the regular, large-scale administration of drugs - either alone or in combination, to entire population groups living in areas where helminth infections (lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminthiasis) and trachoma are prevalent, with the aim of reducing their morbidity and transmission.
- Different anthelmintic drugs (albendazole, DEC, ivermectin, mebendazole, praziquantel) can be co-administered to the same target population, based on the type and number of diseases that are transmitted in a given area. Information on co-administration of any anthelmintic drug and azithromycin for trachoma is limited, and as a precautionary measure this drug should be administered a week apart from the others. In all cases, coordination among control and elimination efforts against helminth infections and trachoma should be fostered.
- Preventive chemotherapy is currently implemented on a worldwide scale, and over 700 million individuals are administered at least an anthelmintic drug or the antibiotic azithromycin every year. Nevertheless, much remains to be accomplished in order to achieve full coverage and reach all those in need.
- The fact that preventive chemotherapy is a safe, simple, efficient and highly cost-effective interventions, similar in many aspects to immunization campaigns, has gained the attention of a number of partners and donors. Notably, most of the drugs used are nowadays donated. It is expected that the coverage of preventive chemotherapy will gradually increase in the years to come. This will contribute to control morbidity and - under some conditions - interrupt transmission of the target infections.

Figure 1.
Population requiring preventive chemotherapy (PC) world wide and progress of global coverage 2007-09

Table 1

Drug, dosages, implementation threshold in PC interventions. From (1) modified

Disease	Drug and dosage	Modality of application of PC	Threshold for implementation of PC	Frequency of intervention
Lymphatic Filariasis (in countries where onchocerciasis is co-endemic)	Ivermectin 400 µg/kg <i>plus</i> Albendazole 400 mg	MDA	Prevalence of infection 1%	Once a year
Lymphatic Filariasis (in countries where onchocerciasis is not co-endemic)	DEC 6 mg/kg <i>plus</i> Albendazole 400 mg	MDA	Prevalence of infection 1%	Once a year
Onchocerciasis	Ivermectin 400 µg/kg	MDA	Prevalence of infection 40% or Prevalence of palpable nodules 20%	Once a year
Schistosomiasis	Praziquantel 40-60 mg/Kg	Targeted chemotherapy (school children and workers with water contacts)	Prevalence of infection 10%	According prevalence of infection
Soil transmitted Helminthiasis	Albendazole 400 mg <i>or</i> Mebendazole 500 mg	Targeted chemotherapy (pre-school children, school children and women of child bearing age)	Prevalence of infection 20%	Once or twice a year according prevalence of infection
Trachoma	Azithromycin 20 mg/kg	Targeted chemotherapy (school children)	Prevalence of Active trachoma 5% in 1-9 years old	Once a year

Table 2

PC implementation status by disease (101)

Disease	Target	Number endemic countries	Number of countries where implemented in large scale	Number of individual in need of treatment	Number of individual treated in 2009 (Coverage)
Lymphatic Filariasis	Total population	81	53	1 341 047 000	385 270 000 (28%)
Onchocerciasis	Total population				
Schistosomiasis	School children and adults	78	21	236 165 000	19 570 000 (8%)
Soil transmitted Helminthiasis	Pre-school children	112	50	273 333 000	109 749 000 (40%)
	School children	112	61	609 211 000	204 344 000 (33%)
	Women of child bearing age	112	-		
Trachoma	School children	42	26	340 000 000	45 000 000 (13%)