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Projected benefits from integrating NTD programs in sub-Saharan Africa

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The integration of preventive chemotherapy programs (PCPs) targeting multiple neglected tropical diseases (NTDs) with similar strategic approaches offers opportunities for enhanced cost-effectiveness. To estimate the potential cost savings and health outcomes of integrated programs, the data available for five NTDs (lymphatic filariasis, onchocerciasis, intestinal helminthiasis, schistosomiasis and trachoma) can be used to define eligible target populations, the probable overlap of at-risk populations, and the cost per person treated in stand-alone and integrated programs. If all targets for 2006 in sub-Saharan Africa are met, then savings of 26–47% can be projected from such integration (a cost of US $58–81 million versus $110 million for stand-alone PCPs). These first estimates can be refined as empirical data become available from integrated PCPs in the future.

Integrating programs targeting NTDs

Much attention in global health has recently focused on the three most widely recognized devastating diseases – namely, malaria, tuberculosis and AIDS – but lesser-known infections or 'neglected tropical diseases' (NTDs) relentlessly persist in exacting severe physical, psychosocial and economic toll on the poorest, most marginalized populations of the developing world [1]. For some of these NTDs, however, preventative solutions are now at hand, and active global initiatives have been created with the aim of controlling or even eliminating them. At national and international levels, such initiatives have operated largely as stand-alone vertical programs, but recent experiences in coordinating or 'integrating' program activities suggest that appreciable savings in both financial and personnel costs can be achieved, along with enhanced program effectiveness, through the wider adoption of integration strategies [1].

Five of these NTDs – lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis (STH) and trachoma (Table 1) – all share a similar strategy of 'preventive chemotherapy' (i.e. the large-scale treatment of at-risk populations once or twice yearly), which is often termed mass drug administration (MDA) when whole endemic populations are targeted. Although the specific details of these preventive treatment programs (Table 2) differ in several important ways (e.g. target populations, frequencies of drug administration and specific means of distributing the drugs), there are numerous similarities. For example, the use of community volunteers, the training of health personnel and volunteers, social mobilization of the community, drug distribution, assessment of adverse reactions, and aspects of monitoring and evaluation are often very similar in the programs.

Furthermore – and very importantly – because co-administration of the drugs used for treatment has been shown to be safe (albendazole plus ivermectin [2], albendazole plus praziquantel [3], albendazole plus praziquantel plus ivermectin [4], and azithromycin plus ivermectin [G.W. Amsden *et al.*, pers. commun.]), we can anticipate that taking advantage of program similarities to integrate program activities should lead to significant cost savings as compared with current approaches to drug delivery, which are based largely on separate disease-specific treatments [5].

How much saving might be achieved through such integration remains uncertain. Thus, the principal goal of the exercise presented here has been to review the information available and to estimate the potential savings likely to be gained through the integration of five NTD-specific programs, focusing on sub-Saharan Africa where the prevalence and overlap of these NTDs are particularly high. Estimates are made first for the population sizes already targeted for implementation by each individual program in 2006, and then at the level of implementation required to reach the complete target population for each program. In addition, the health benefits expected to be achieved through such integrated preventive chemotherapy programs (PCPs) have been projected.

Analyzing cost savings

To estimate the cost savings from program integration, it is necessary to identify the target populations eligible for treatment for each disease-specific program, to estimate the overlap of populations targeted for each disease-specific program, and to determine the cost per person receiving drugs both in stand-alone programs and in the integrated programs.

Target populations eligible for treatment

For each disease-specific program, we identified the total population eligible for treatment, along with the

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Table 1. Overview of selected NTDs and the PCPs targeting them

Disease/ program	Global at-risk population	No. of endemic countries	Clinical features	Transmission	Refs
Lymphatic Filariasis Global Programme to Eliminate Lymphatic Filariasis (LF)	1.3 billion	83 countries in Africa, Asia, the Americas, and the western Pacific	A leading cause of disability, LF can lead to manifestations such as grossly swollen genitals (hydrocele) and limbs (lymphedema), often with hardened, thickened skin (elephantiasis)	The larval stage of LF parasites (microfilariae) circulate in the blood of infected persons and are picked up by mosquitoes (*Anopheles*, *Culex* and *Aedes*), where they develop into infective forms, which are then transmitted to others	[27]
Onchocerciasis (i) Mectizan Donation Program (ii) African Programme for Onchocerciasis Control (iii) Onchocerciasis Elimination Program for the Americas	120 million	37 (30 countries in Africa plus Yemen, and 6 countries in the Americas)	Onchocerciasis (river blindness) is a highly disfiguring and disabling disease in which adult worms induce formation of nodules under the skin and produce millions of small microfilariae, which cause intense itching, acute and chronic skin reactions, and severe eye lesions that may progress to blindness.	The larval stage of *Onchocerca volvulus* parasites (microfilariae) are found in the skin of infected people and picked up by vector blackflies, where they develop into infective forms that are transmitted to others through bites of the blackfly	[28]
Schistosomiasis (i) Partners for Parasite Control (ii) Schistosomiasis Control Initiative	652 million	76 countries in Africa, the Middle East, the Americas, and the Pacific	Two principal clinical types of schistosomiasis reflect the parasite species causing the infection: one affects the liver and gastrointestinal system, the other affects the urinary tract; morbidity varies from severe (hepatic fibrosis, urinary obstruction, bladder cancer) to subtle (anemia, growth stunting, cognitive impairment) conditions	Infective larvae (cercariae) develop in fresh-water snails that had been infected earlier by parasites coming from human stool or urine; people become infected after contact with cercariae released from the snails, while bathing, washing or working in the water	[12,29]
Soil-transmitted helminths (STH) Partners for Parasite Control	4.2 billion	Most countries in Africa, Southeast Asia, China, India and South Asia, and the tropical regions of the Americas	STHs include hookworm, roundworm and whipworm; infection with these worms causes stunting, anemia, vitamin A deficiency and malnutrition, which results in impaired growth, intellect and cognition in children and low-birth-weight babies in pregnant women	Hookworm larvae hatch from parasite eggs deposited on the ground in human stools and then infect others by penetrating the skin through the hands, feet, legs and buttocks; infective roundworm and whipworm eggs are transmitted by ingestion in a human stool-contaminated environment or through person-to-person contact	[9,30]
Trachoma International Trachoma Initiative	540 million	55 countries, primarily in Africa and Asia but also in pockets of the Americas and Australia	The world's leading cause of preventable blindness, trachoma manifests as inflammation of the upper eyelid with progressive corneal irritation and scarring; in the advanced stage (trichiasis), the eyelid becomes so severely scarred that it contracts, causing the eyelashes to turn inwards; repeated irritation from these in-turned eyelashes damages the cornea, ultimately causing blindness	The microorganism responsible for trachoma, *Chlamydia trachomatis*, is highly infectious and can be spread on an infected person's hands or clothing, or can be transmitted by flies that have been in contact with discharge from the eyes or nose of an infected person	[31]

Abbreviation: LF, lymphatic filariasis.

population specifically targeted for treatment in 2006 (Table 3). The 'total eligible population' numbers reflect both the prevalence of these infections in sub-Saharan Africa and the inclusion/exclusion criteria of the programs, as specified or referenced in Table 2.

Soil-transmitted helminth and schistosomiasis programs are already integrated in many countries [6]; therefore, to separate the target populations for combined STH and schistosomiasis (STH/schistosomiasis) treatment from those for STH-only treatment, we estimated that schistosomiasis would also be treated in 50% of the populations where STH programs operate.

Overlap of target populations

Figure 1 illustrates the overlap of the five NTDs in sub-Saharan Africa at a country level: most countries are endemic for various combinations of four or more of the infections [7–11]. To estimate the potential cost savings from integrating PCPs, however, it is the extent of the actual overlap of the distribution of these diseases that is important. For our calculations, we used the lymphatic filariasis program as the 'platform' on which to add the integrated programs, because lymphatic filariasis has the largest target population (Table 3). The at-risk population for onchocerciasis was assumed to lie completely within that for lymphatic filariasis. The percentage of geographic overlap between other diseases and lymphatic filariasis was approximated in consultation with coordinators of the disease-specific programs, and was assumed to reflect the extent of potential program overlap.

Cost per person treated

Estimates of cost per person treated for each disease-specific program (Table 4) were derived both from published studies [11–13] and from consultation with coordinators for each disease-specific program. These values reflect the actual costs experienced by programs

Table 2. PCPs in sub-Saharan Africa

Disease targeted	Program goal	Ages targeted	Drug regimen	Frequency	Drug source	Refs
LF[a]	Elimination as a public health problem by 2020	5–80 years	Albendazole + ivermectin	1×annually	GlaxoSmithKline donates albendazole; Merck and Co., Inc. donates ivermectin (Mectizan®)	[32,33]
Onchocerciasis	Establishment of community-based sustainable yearly treatment in areas with moderate/high intensity by 2010	5–80 years	Ivermectin	1×annually	Merck and Co., Inc. donates ivermectin (Mectizan®)	[34]
STH/schistosomiasis	Regular treatment of 75% of at-risk school-age population by 2010	6–15 years	Albendazole/ mebendazole + Praziquantel	STH: 2× annually Schisto: 1× annually[b]	Albendazole/ mebendazole is purchased at roughly US $0.02 per dose; Praziquantel is purchased at roughly $0.20 per dose	[12,35]
STH	Regular treatment of 75% of at-risk school-age population by 2010	6–15 years	Albendazole/ mebendazole	2×annually	Albendazole/ mebendazole is purchased at ~$0.02 per dose	[12,35]
Trachoma	Elimination of blinding trachoma as a public health problem by 2020	6 months to 80 years	Azithromycin	1×annually	Pfizer donates azithromycin (Zithromax®).	[11]

[a]Current assessment relates only to those countries in sub-Saharan Africa where LF and onchocerciasis are co-endemic.
[b]Frequency varies according to prevalence.

in sub-Saharan Africa (which can differ from those in other regions of the world). The costs assume once-yearly intervention for each disease except STH infection, for which the program cost of US $0.25 per person reflects twice-yearly treatment (Table 2) at $0.125 per intervention (this price includes the per-person cost of the drug [albendazole or mebendazole], social mobilization, drug distribution, training, and monitoring and evaluation).

Although it is uncertain exactly how much saving can be achieved by integrating PCP activities, our assumption is that the costs for programs with very similar delivery strategies can be reduced to between 10 and 50% of the stand-alone costs of the programs. Underlying this estimate is the assumption that most of the costs for administration and personnel, for drug transport and distribution, for adverse reaction assessment, and for much of the monitoring and evaluation will be included in the 'platform' (lymphatic filariasis) program cost; there will be additional costs for add-on programs to modify or to increase social mobilization (including information, education, and communication materials), personnel training and specific monitoring and evaluation activities. In the lymphatic filariasis and onchocerciasis stand-alone programs currently running in sub-Saharan Africa, these costs (for training, mobilization and monitoring and evaluation) account for 25–50% of the cost per person treated (Ref. [13]; and A.S. Goldman *et al.*, unpublished), and it is reasonable to assume that other stand-alone programs will spend similar percentages on these items.

With these assumptions, we can estimate how programs added to a 'platform' of lymphatic filariasis MDA activities will affect the 'base' costs of the lymphatic filariasis stand-alone program. For onchocerciasis and trachoma, the additional costs from integration with the lymphatic filariasis program were calculated at the 10, 30 and 50% estimates for costs of add-on programs (Table 5). For those STH programs overlapping with the lymphatic filariasis programs, the additional 'delivery' cost for the first of the twice-yearly treatments was estimated at 10, 30 and 50% of $0.105 (half of the stand-alone program cost

Table 3. Stand-alone program targets and program overlap in sub-Saharan Africa

Disease	Total target population eligible for treatment (million)	Refs	2006 target population eligible for treatment (million)[a]	Estimated % of target population in LF endemic zone
LF	387.3	[36]	81.5	100
Onchocerciasis	82	[28]	73.4	100
STH/Schistosomiasis	86.5	[12]	22	85
STH	86.5	[12]	22	60
Trachoma	131	[a]	27.4	67

[a]Estimates provided by managers of the respective programs (see Table 1).

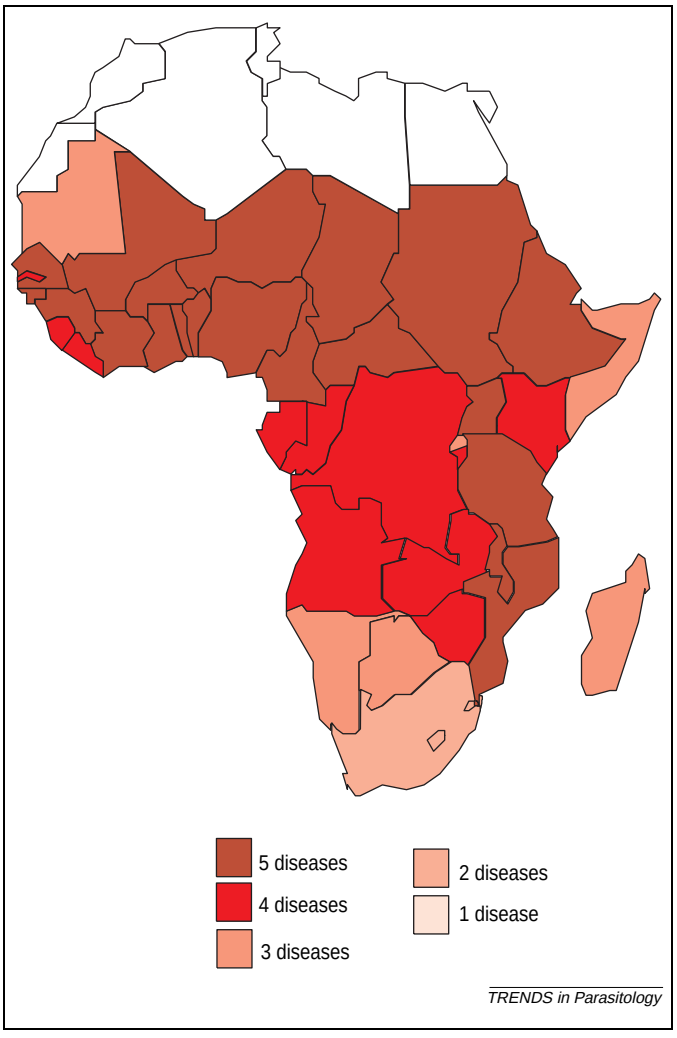

Figure 1. Overlap of five selected NTDs at a country level in sub-Saharan Africa. The NTDs are lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis and trachoma. Most countries are endemic for four or more of these NTDs in various combinations. Owing to the focal nature of some of the NTDs, information is needed to determine the specific geographic overlaps at a district level.

minus the $0.02 cost of the drug itself because albendazole distribution is already a part of the lymphatic filariasis elimination program). For the second of the twice-yearly treatments for STH disease, costs were estimated at $0.125.

Because praziquantel is the only one of the NTD program drugs not currently being donated, the cost of adding an overlapping STH/schistosomiasis program to an lymphatic filariasis program was estimated at $0.20 to purchase praziquantel plus 10, 30 and 50% of $0.155 (the stand-alone program cost of $0.50 minus $0.125 for the second treatment with albendazole or mebendazole minus $0.22 for the cost of praziquantel and albendazole or mebendazole). For each program targeting populations outside the lymphatic filariasis endemic zone, the whole stand-alone per-person cost (Table 4) would apply.

Table 4. Costs to implement PCPs separately for each disease in sub-Saharan Africa in 2006

Disease	No. to be treated in 2006 (million)	Cost per person treated (USD)	Total cost (million USD)	Refs
LF	81.5	0.45	36.7	[a]
Onchocerciasis	73.4	0.58	42.6	[13]
STH/schistosomiasis	22	0.50	11.0	[12]
STH	22	0.25	5.5	[12]
Trachoma	27.4	0.50	13.7	[11]
Projected total cost for stand-alone PCPs in 2006			**109.5**	

[a]A.S. Goldman *et al.*, unpublished. Abbreviation: USD, US dollars.

Analyzing outcomes

Projecting health outcomes of the integrated disease control packages in sub-Saharan Africa relies on the PCP treatment to prevent the major clinical manifestations of each disease, including blindness (onchocerciasis and trachoma), severe skin disease and itching (onchocerciasis), lymphedema and hydrocele (lymphatic filariasis), liver, kidney, and bladder disease (schistosomiasis), anemia (STH and schistosomiasis) and protection from infection with STHs. We estimated the number of cases prevented by multiplying the estimated rates of incidence of each clinical manifestation by the percentage of the at-risk population in sub-Saharan Africa covered by the integrated PCPs.

To estimate the incidence of disease (Table 6), we divided prevalence (assumed to be stable within the population) by duration of the clinical manifestation. Life expectancy in sub-Saharan Africa was estimated at 48.6 years (see http://www.census.gov/ipc/www/idbnew.html). The percentage of the whole at-risk population targeted for treatment in 2006 was used to calculate the projected health outcomes of the programs currently underway. Where the published estimates varied, we determined low and high approximations for each outcome by applying different prevalence or duration estimates, and used the average value as a final estimate. The percentage of the at-risk adult population covered for STH control was based on the lymphatic filariasis program target for adults divided by the number of adults at risk for STH disease, because the lymphatic filariasis drugs for MDA (albendazole and ivermectin) are also highly effective treatments for STH infections [14,15].

Costs

Estimating the target populations eligible for treatment (Table 3), the per-person cost of drug treatment in stand-alone programs (Table 4), the overlap of the NTD programs, and the per-person cost of drug treatment in integrated programs (Table 5) enabled us to calculate the total cost savings that can be made from disease program integration in sub-Saharan Africa. The projected cost of treating each disease separately in 2006 is $110 million (Table 4). By contrast, the estimated total cost for an integrated NTD intervention package in 2006 (if all 2006-targeted populations were to be incorporated into the integrated programs), including lymphatic filariasis, onchocerciasis, STH disease, schistosomiasis and trachoma, ranges from $58 million at a 10% 'add-on cost' to $81 million at a 50% 'add-on cost' (Table 5); that is, $29–52 million less, or a projected

Table 5. Costs of integrated PCPs in sub-Saharan Africa in 2006

Disease	Costs outside LF endemic zone				Add-on costs inside LF endemic zone				Total cost (million USD)			
						1st yearly round of treatment						
	No. to be treated in 2006 (million)	No. outside LF endemic zone (million)	Cost per person treated outside LF zone (USD)	Total cost outside LF zone (million USD)	No. inside LF endemic zone (million)	At 10% of stand-alone cost (USD)	At 30% of stand-alone cost (USD)	At 50% of stand-alone cost (USD)	Additional cost for 2nd yearly treatment (USD)	At add-on costs of 10% of stand-alone (USD)	At add-on costs of 30% of stand-alone (USD)	At add-on costs of 50% of stand-alone (USD)
LF	81.5	–	–	–	81.5	0.45[a]	0.45	0.45	–	36.68	36.68	36.68
Onchocerciasis	73.4	0	0.58	0.00	73.4	0.058	0.174	0.290	–	4.26	12.77	21.29
STH/Schisto	22	3.3	0.50	1.65	18.7	0.216	0.248	0.280	0.125	8.03	8.63	9.22
STH	22	8.8	0.25	2.20	13.2	0.011	0.032	0.053	0.125	3.99	4.27	4.54
Trachoma	27.4	9.0	0.50	4.50	18.4	0.050	0.150	0.250	–	5.42	7.26	9.10
Projected total cost for integrated PCPs in 2006										**58.37**	**69.60**	**80.83**

[a]A.S. Goldman *et al.*, unpublished.

saving of 26–47% through integrated PCP packages. The projected average cost per person treated (for diseases for which each individual is at risk) through an integrated drug delivery strategy in sub-Saharan Africa ranges from $0.57 to $0.79.

Using the same assumptions and logic, we can make similar projections of cost savings from program integration at full scale-up (i.e. for each program reaching 100% of its overall target population in sub-Saharan Africa); stand-alone costs are projected at $350 million annually, but integration could achieve savings of between $55 and $102 million (calculations, carried out as in Table 5, not shown), with the cost per person treated estimated at $0.53 to $0.62.

Health outcomes

Box 1 shows the projected outcomes anticipated from integration of the five NTD PCPs that we have 'costed' for sub-Saharan Africa in 2006 (Table 5). Many of these outcomes can be realized immediately (i.e. within the first year of the PCP); others, whose more chronic manifestations of disease take years to develop (e.g. hydrocele or blindness) will be realized only after many years. All of the outcomes, however, must be recognized as products of the integrated PCPs.

Refining the projections

We have estimated that the savings achieved through 'integrating' the PCPs for five NTDs in sub-Saharan Africa could approximate 26–47% of the cost of carrying out the individual, stand-alone PCPs. Given the current lack of substantive data, however, a great many uncertainties remain about our estimates and their underlying assumptions, of which the following are particularly important.

(i) There is uncertainty about the true geographic distributions and prevalence of the infections. These distributions determine which of the five PCPs really can be integrated at an operational (district) level and also what additional integration can be undertaken among non-lymphatic filariasis programs in areas outside the lymphatic filariasis endemic zones (i.e. outside the 'platform' used for our calculations).
(ii) There is uncertainty about true costs of the individual PCPs activities, which, with some exceptions (e.g. Ref. [13]; and A.S. Goldman *et al.*, unpublished), have been rarely quantified. These costs affect the estimates of how much can be saved by integrating specific activities within the PCPs.
(iii) There is uncertainty about the existence of 'programmatic barriers' that might prevent integration despite otherwise feasible situations (e.g. organizational impediments at local, national and international levels, or the rate at which program integration can be initiated and then scaled up).
(iv) There is uncertainty about potential 'biological barriers' that might prevent PCP integration in some situations (e.g. presence of loiasis, which complicates implementation of the lymphatic filariasis and

Table 6. Estimates and sources used to calculate health outcomes resulting from integrated PCPs in 2006 in sub-Saharan Africa

Clinical outcome of the NTDs	Prevalence (in millions)	Refs	Estimated duration (years)	Refs	% of at-risk population expected to be covered[a]
Lymphedema	4.64	[37]	30–40	[16]	21
Hydrocele	10.2	[37]	30–40	[16]	21
STH infection (age ≤15 yr)	56–94.3	[9]	1	–	14
STH infection (age >15 yr)	67.9–142	[9]	1	–	14
Anemia in pregnant women	5.96–7.54	[38]	1	–	14
Blindness (trachoma)	0.5–1.3	[39][b]	20	[40]	15
Blindness (onchocerciasis)	0.29	[39]	11–20	[41,42]	90
Skin disease	4.4–5.8	[41]	5	[41]	90
Kidney or bladder disease	28	[43]	10–20	[43]	5
Liver disease	1.22	[43]	10–20	[43]	5

[a]See Table 3.
[b]http://www.sightsavers.org/html/eyeconditions/trachoma_extent.htm

Box 1. Projected outcomes resulting from integrated PCPs in 2006 in sub-Saharan Africa

- 10.5 million children protected from STH disease
- 14.7 million adults protected from STH disease
- 5 million cases of skin disease and itching prevented
- 569 000 women who will get pregnant in the next year protected from anemia
- 105 000 people prevented from getting severe kidney or bladder disease
- 62 500 cases of hydrocele prevented
- 28 400 cases of lymphedema prevented
- 25 500 cases of blindness prevented
- 4600 people prevented from getting life-threatening liver disease

onchocerciasis MDAs, or undefined drug interactions that might restrict some types of PCP integration).

(v) There is uncertainty about future costs; for example, additional drug donations might abolish the need to purchase drugs for the STH and schistosomiasis PCPs (albendazole or mebendazole for STH, praziquantel for schistosomiasis), resulting in a considerable decrease in the cost of these programs.

In each of these areas, improved data are needed to refine the estimates of the cost savings that can be potentially achieved through integration. In addition, it might be that integrating only two or three of these NTD programs will be more feasible or cost-effective than integrating all five programs; examining such possibilities in the future would certainly make an important contribution to ongoing discussions of PCP integration and its value.

Furthermore, as impressive as the projected clinical outcomes of such integrated PCPs are (Box 1), these estimates identify only a fraction of the total health benefit achieved by such programs. For lymphatic filariasis, for example, the burden estimates are undoubtedly undervalued, because much of the endemic area remains to be mapped, and important clinical manifestations other than lymphedema and hydrocele [16] have not been considered. For onchocerciasis and trachoma, outcomes related to low vision and other complications have not been assessed; these outcomes will also be reduced by PCPs [11,17,18]. For schistosomiasis and STH, lives saved by treating people have not been estimated, because the rates of deaths caused by these conditions are still poorly defined [19,20].

In addition – and very importantly – all of these NTD helminth infections are now recognized as important cofactors that affect susceptibility and clinical response to co-infections with malaria, HIV and tuberculosis [21], and none of these outcomes has been considered. Finally, studies have shown that adding (i.e. integrating) health activity responsibilities to community drug distributors of ivermectin for the treatment of onchocerciasis can lead not only to success of these new health activities but also to improved effectiveness and greater likelihood of sustainability of the onchocerciasis program itself [22]. Such programmatic enhancements will translate into greater public health efficiency and probably into additional cost savings.

Concluding remarks

Despite its significant limitations, this exercise to estimate the potential cost savings and impact of integrating the PCPs for five of the most significant NTDs has focused on an issue of great importance that must be addressed. As integrated activities are undertaken and implemented on an ever-larger scale, an increasing amount of data will become available to improve the necessarily imprecise estimates of our current analysis. Indeed, the goal of this exercise has been not only to provide a first approximation of the savings and outcomes that might be achieved through PCP integration for the five NTDs, but also to identify the specific issues and types of data that will be needed to refine these estimates in the future.

It might seem intuitive that benefits and efficiencies will accrue from integrating or linking these individual public health initiatives, but it is essential to gather the necessary empirical data to define the best ways both to carry out such integration and to assess its costs, cost savings and cost-effectiveness. Although treating each of these NTDs individually has been recognized already as an efficient and cost-effective way to make a major health and productivity impact on affected populations [23–26], the case for investment in overcoming all of them will become even stronger if, by integrating drug distribution programs, the process can become more efficient and even more affordable. Indeed, thorough documentation of both costs and cost savings must be an integral part of these PCP integration efforts. It is absolutely essential to make the most effective use of the all-too-limited funds now available to enhance health and productivity among the world's most underserved populations by taking advantage of today's unique opportunities to implement integrated PCPs targeting at least five of the most important, and completely preventable, NTDs [5].

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