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Scaling up integrated prevention campaigns for global health: costs and cost-effectiveness in 70 countries

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ABSTRACT

Objective: This study estimated the health impact, cost and cost-effectiveness of an integrated prevention campaign (IPC) focused on diarrhoea, malaria and HIV in 70 countries ranked by per capita disability-adjusted life-year (DALY) burden for the three diseases.

Methods: We constructed a deterministic cost-effectiveness model portraying an IPC combining counselling and testing, cotrimoxazole prophylaxis, referral to treatment and condom distribution for HIV prevention; bed nets for malaria prevention; and provision of household water filters for diarrhoea prevention. We developed a mix of empirical and modelled cost and health impact estimates applied to all 70 countries. One-way, multiway and scenario sensitivity analyses were conducted to document the strength of our findings. We used a healthcare payer's perspective, discounted costs and DALYs at 3% per year and denominated cost in 2012 US dollars.

Primary and secondary outcomes: The primary outcome was cost-effectiveness expressed as net cost per DALY averted. Other outcomes included cost of the IPC; net IPC costs adjusted for averted and additional medical costs and DALYs averted.

Results: Implementation of the IPC in the 10 most cost-effective countries at 15% population coverage would cost US$583 million over 3 years (adjusted costs of US$398 million), averting 8.0 million DALYs. Extending IPC programmes to all 70 of the identified high-burden countries at 15% coverage would cost an adjusted US$51.3 billion and avert 78.7 million DALYs. Incremental cost-effectiveness ranged from US$49 per DALY averted for the 10 countries with the most favourable cost-effectiveness to US$119, US$181, US $335, US$1692 and US$8340 per DALY averted as each successive group of 10 countries is added ordered by decreasing cost-effectiveness.

Conclusions: IPC appears cost-effective in many settings, and has the potential to substantially reduce the burden of disease in resource-poor countries. This study increases confidence that IPC can be an important new approach for enhancing global health.

Strengths and limitations of this study

- Synthesises a large volume of epidemiological data from disparate sources into a unified method for projecting the consequence of integrated prevention campaign (IPC) implementation in 70 countries.
- Links the 'opportunity index' concept with cost-effectiveness.
- Provides a more comprehensive assessment of intervention potential than assessment of cost-effectiveness alone.
- Methods presented here may be applied to other disease areas and facilitate more objective resource allocation decision-making for global health.
- Incomplete availability of data relevant to the large number of countries analysed.
- Infeasible to develop cost-effectiveness thresholds that reflected the full array of local public health options against which IPC could be considered.
- Regions or urban areas within countries may have costs and health benefits that depart from the overall country assessments.

BACKGROUND

For many years, vertical (disease-specific) programming has dominated the sphere of global health funding in an effort to tackle the areas of greatest need.[1] However, there is increasing recognition that, among diseases with complementary prevention strategies and overlapping populations, single-disease approaches to population health improvement create duplication of effort and miss important opportunities for synergies in health benefits and economies of scope.[2] Recent initiatives have therefore sought to integrate programmes for multiple diseases, and many have demonstrated feasibility, efficiencies and success.[3 4]

A particularly promising example of integrated programming was a prevention campaign in Western Province, Kenya that targeted diarrhoea, malaria and HIV,[5] three diseases that account for a substantial portion of the total disease burden in many parts of the developing world.[6] Over the course of 1 week, the campaign provided

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general health education, condoms, insecticide-treated bed nets, point-of-use water filters and HIV testing and counselling to more than 80% of the target population.[5] Those testing positive for HIV were offered on-site CD4 count determination, cotrimoxazole prophylaxis and referral to comprehensive HIV care and treatment. The campaign yielded large health benefits and net economic savings.[7 8] Large-scale expansion of this integrated prevention campaign (IPC) has the potential to deliver substantial health benefits and cost savings. In a separate study, we reviewed country-specific data for 70 low-income and middle-income countries, finding that the opportunity for a diarrhoea, malaria and HIV IPC is not limited to Kenya.[9] It is plausible that IPCs can have a large impact on health in many resource-limited settings.

While the cost-effectiveness of this IPC in Western Kenya has been established[8] the economic and health effects of a multicountry IPC initiative are unknown. Using data appropriate for providing an initial indication of the conditions under which IPC is likely to be cost-effective, we estimated the costs, health outcomes and cost-effectiveness of IPC implementation in the same 70 low-income and middle-income countries. To support decision-making for IPC implementation, we also estimate the increases in budgets that would be required to cover increasing numbers of countries.

METHODS

Overview

We modelled the health impact, cost and cost-effectiveness of a diarrhoea, malaria and HIV IPC in 70 countries by adapting a previously published spreadsheet-based model that was applied to the original IPC in Western Kenya.[8] Countries were chosen for inclusion in the analysis based on two factors: they were classified as low-income or middle-income as defined by the World Bank[10]; and they had a total disability-adjusted life-year (DALY) burden for the three diseases addressed by the IPC in the highest tertile of the 214 World Bank-defined economies (ie, ≥87 000 DALYs); as described in a companion paper.[9] We refer to this ordering of countries by the combined disease burden as the 'opportunity index'. For a break-down of the relative contribution by disease to each country's total burden see Jiwani 2014 and table S4 of the online technical supplement. We derived incidence and case death rates for each country from published reports, using regional averages and other approximations when country-specific estimates were missing. We developed a mix of empirical (where available) and modelled (projected from empirical data) cost estimates applied to all 70 countries. Key outcomes examined included the cost of the IPC; net IPC costs adjusting for averted and additional medical costs; deaths and disease episodes averted; DALYs averted due to prevention, and to earlier and more HIV care; and finally, cost-effectiveness expressed as net cost per DALY averted. We used a healthcare payer's perspective, and discounted long-term costs and DALYs at 3% per year.[11] Costs were denominated in 2012 US dollars. The time frame of the analysis is 3 years for the empirical data. Modelled results depend on the age-dependent life expectancy at the time death would otherwise have occurred in Kenya. This is 61 years for diarrhoeal diseases and malaria, and 37 years for HIV.

Detailed model features

We adapted a Microsoft Excel spreadsheet that we had previously constructed to analyse the cost-effectiveness of the Kenya IPC. Details of the model have been published elsewhere.[8] The model estimates the health and cost benefits of prevention for malaria, diarrhoea and HIV separately. For HIV, it also estimates the DALYs averted and costs incurred due to earlier diagnosis and treatment arising from HIV testing. Cost-effectiveness of the IPC was compared to the cost-effectiveness of antiretroviral therapy (ART) in each of the 70 countries. This metric was selected since, with the current aspiration of universal access to ART,[12] provision of ART is on the active policy agenda for most HIV-affected countries.

Cost estimates and projection methods

Campaign costs for the Kenya IPC were obtained from published empirical data supplemented by filter repair and replacement costs.[7 8] We estimated campaign costs for each country using the Kenya IPC as a benchmark, translating to other countries according to type of cost, as follows. Programme costs were classified as commodity, personnel and other costs. Commodities were further categorised as tradable and non-tradable. Tradable commodities are those purchased on the international market and include bed nets, filters and condoms, and required no adjustment from the dollar-denominated costs incurred by the Kenya IPC.[7] The cost of non-tradable items, primarily personnel, were adjusted according to the per capita gross domestic product (GDP) ratio, in International dollars, between Kenya and each study country.[13] For each country, we estimated the costs of averted medical care due to the IPC by adjusting the costs for healthcare incurred per fatal and non-fatal case in the Kenya campaign by the ratio of GDP per capita in the target country versus Kenya. We selected per capita GDP rather than per capita healthcare spending as the basis for these adjustments, because the latter reflects overall access to care and our model accounts for access separately. (For a comparison of 3 cost adjustment methods and evidence of similar resulting cost estimates, see online technical supplement.)

There are few country-specific data on access to care for malaria except for some of the more-affected countries, mostly in Africa. We therefore used global average rates of treatment access, estimated at 68.4% based on published literature.[14–19] (See online technical appendix for the country-specific figures underlying this value.) As

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noted in table 2, the value of 68.4% was varied from 51.3% to 85.5% in sensitivity analyses. For access to care for diarrhoea, we used country-specific estimates based on demographic and health survey data on the percentage of children under 5 years of age with diarrhoea in the 2 weeks preceding the survey who received any kind of treatment for diarrhoea.[20] We used an average rate of access to ART of 70%. This is considerably higher than the 56% access reported for sub-Saharan Africa[21] and reflects likely increases in the context of the global commitment to access.[12]

We calculated the per person-year cost of ART for each country by using published estimates for countries where available.[22–42] The non-drug portion of each published unit cost figure was inflated to 2012 US dollars using the USA Consumer Price Index.[43] We then derived from the set of published figures an average figure for low income, lower middle income excluding India and upper middle income countries as defined by the World Bank.[44] We applied these country income-category averages to the larger set of countries for which published ART unit cost estimates were unavailable, according to their respective income categories. ART cost-effectiveness for each country was estimated by adjusting US$883 per DALY averted which is the average for 45 sites studied in Zambia.[26] To arrive at country-specific estimates we calculated the ratio of per capita income between each country and Zambia and applied this factor to the average portion of overall ART costs for low-income countries which is non-tradable, 36.9%. This figure was derived from the ART unit cost studies described above which includes the breakdown of costs by major component.

First versus second campaign health benefits

The health benefits of a second campaign are likely to be lower than that of the initial campaign. For malaria this is due to residual benefits from nets, beyond their average functional life of 3 years. In the absence of a second campaign, we assume a malaria risk in years 4–6 equal to 75% of the risk at baseline (before the first campaign). For diarrhoeal disease the filters themselves are not expected to confer benefit after 3 years, though there may be residual benefit from the behavioural component; we assume that the risk is 87.5% of baseline. New nets and filters in a second campaign reduce disease risks to the levels expected after the first campaign. Thus the second campaign reduces the incidence of malaria from 75% to 50% of baseline (a 1/3 relative reduction). Similarly, diarrhoea decreases from 87.5% to 37% of baseline (a relative drop of 58%; details in online technical supplement).

Disease-specific data and projection methods

We obtained country estimates of the prevalence of HIV in the adult (15–49 years) population.[42 45 46] For each country, we derived estimates of the baseline cases of malaria per person-year by dividing WHO-adjusted estimates of the annual number of cases[47] by the total country population.[48] For diarrhoea, we estimated the average number of cases per person-year in the overall population using DHS data on the number of cases per year in children under 5[49] (details in online technical supplement).[50 51] Multiplying each estimate by the total population[48] yields the estimated number of cases in each country.

We calculated country-specific case death rates for malaria and diarrhoea as the number of deaths due to the disease[52 53] divided by the number of cases. We set an upper-bound malaria case death rate of 15% based on published findings of a Delphi survey of malaria experts.[54] We assumed a case death rate for HIV of 100%.

Using a discount rate of 3%[55] we estimated the DALYs incurred with each fatal case of malaria and diarrhoea at 28 based on life expectancy at age 25 in Kenya (the estimated average age of death from malaria and diarrhoea) of 61 years.[56] We derived estimates of the DALYs incurred per non-fatal case of each disease as the product of the disability weight (0.191 for malaria and 0.105 for diarrhoea)[57] and the average duration of each case (7 days for malaria[58]; 4.43 days for diarrhoea, a severity weighted duration for children and adults[59]; or 0.0037 and 0.0013 DALYs for each non-fatal case of malaria and diarrhoea, respectively. Assuming 70% access to ART, we estimated 10.6 DALYs incurred per HIV infection, and 8.8 discounted DALYs averted per treated case of HIV, an assumption based on 22 years of ART, average age of ART initiation of 35 years, and a life expectancy at age 35 in Kenya of 37 years.[56] Each untreated HIV case incurs 15.1 discounted DALYs.

Household size and beneficiaries per household

Using country-specific data of rural household size as reported in the most recent Demographic and Health Survey, divided by the number of participants per household as observed in the Kenya IPC campaign, we obtained the number of beneficiaries per campaign participant. For bednets, we assumed fewer incremental beneficiaries per participant on the assumption that there was some prior access to bednets, 15.1% on average, as observed in the Kenya campaign. For HIV we assumed the same number of adult participants on average, 2.5, as the basis for calculating the number of beneficiaries per campaign participant.

For the remaining health inputs, we assumed values equal to those used in the Kenya analysis for all countries.[8] See table 1 for base case values and sources for data inputs.

Relationship of opportunity to cost-effectiveness

In a companion article, we identified the countries in which scale-up of a diarrhoea, malaria and HIV IPC would be most beneficial, by summarising country-specific epidemiological data related to the disease burden and shortfall in current intervention coverage (Jiwani *et al*, under review, 2013). We created three

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Table 1 Base case values and sources for data inputs

	Malaria	Diarrhoea	HIV		Source(s)		
	LLIN	Filters	VCT	Condoms	LLIN	Filters	VCT/condoms
Health in[61]puts							
Campaign participant per household	2.5				Postcampaign survey		
Number benefiting per campaign participant	**1.563**	**1.840**	0.950	0.361	Postcampaign survey		
Baseline cases per year per individual benefiting	**0.057**	**0.542**	0.004	0.009	[47, 48]	[49–51]	[8, 62–64] Postcampaign survey (see text)
Proportion of cases that are fatal	**0.012**	**0.001**	1	1	[47, 52, 54]	[48, 49, 51, 59, 62]	Assumption
DALYs incurred with each fatal case	28.0	28.0	15.1	15.1	[56]	[56]	[56]
DALYs incurred with each non-fatal case	0.0037	0.0012	NA	NA	[57, 58]	[57, 59]	NA
Protective effect against mortality	0.50	0.63	0.50	0.26	Expert opinion[65]	[66]	[67, 68]
Protective effect against non-fatal cases	0.5	0.63	NA	NA	[65]	[66]	NA
Multiplier to capture secondary benefits	NA bit	NA	2	2	[69]	NA	[70] (see text)
Years of benefit	3	3	1	1	Adjusted to 3 years per postcampaign evaluation[71 72]	Adjusted to 3 years per postcampaign evaluation[73]	[68]
Access to care	0.684	**0.678**	0.700	0.700	[14–19]	[20]	Assumption
Cost inputs							
Campaign cost	**US$34 280**				US$31 980 plus additional US$2300 in maintenance costs[7]		revised filter
Discount rate	3.0%				[10]		
Healthcare incurred with each death	**US$65**	**US$104**	**US$12 213**	**US$12 213**	[64, 74]	[75]	Authors' construction based on 22 years on ART at US$766 per person-year discounted at 3% per annum.
Healthcare incurred with each non-fatal case	**US$7.80**	**US$7.00**	NA	NA	[76]	[75]	NA

Bold figures represent values that change with each country.
DALY, disability-adjusted life-year; NA, not applicable.

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Table 2 Sensitivity analysis variables, base case, minimum and maximum values

Input parameter	Nigeria			Kenya			Bangladesh		
	Base case	**Min**	**Max**	**Base case**	**Min**	**Max**	**Base case**	**Min**	**Max**
Campaign cost	**US$40 479**	**US$20 239**	**US$60 718**	**US$34 280**	**US$17 140**	**US$51 420**	**US$35 658**	**US$17 829**	**US$53 486**
Cost per death malaria	**US$97.50**	**US$48.75**	**US$146.25**	**US$65.00**	**US$32.50**	**US$97.50**	**US$72.22**	**US$36.11**	**US$108.33**
Cost per death diarrhoea	**US$156.00**	**US$78.00**	**US$234.00**	**US$104.00**	**US$52.00**	**US$156.00**	**US$115.56**	**US$57.78**	**US$173.34**
Cost per non-fatal case malaria	**US$11.70**	**US$5.85**	**US$17.55**	**US$7.80**	**US$3.90**	**US$11.70**	**US$8.67**	**US$4.33**	**US$13.00**
Cost per non-fatal case diarrhoea	**US$10.50**	**US$5.25**	**US$15.75**	**US$7.00**	**US$3.50**	**US$10.50**	**US$7.78**	**US$3.89**	**US$11.67**
Annual cost ART	**US$938**	**US$469**	**US$1407**	**US$766**	**US$383**	**US$1150**	**US$766**	**US$383**	**US$1150**
Discount rate	0.03	0.015	0.045	0.03	0.015	0.045	0.03	0.015	0.045
Access to care diarrhoea	**0.565**	**0.424**	**0.706**	**0.678**	**0.509**	**0.848**	**0.663**	**0.497**	**0.829**
Access to care malaria	0.684	0.583	0.855	0.684	0.583	0.855	0.684	0.583	0.855
Access to ART	0.7	0.42	0.98	0.7	0.42	0.98	0.7	0.42	0.98
Years on ART	22	11	33	22	11	33	22	11	33
HIV prevalence	**0.036**	**0.018**	**0.054**	**0.063**	**0.032**	**0.095**	**0.0006**	**0.0003**	**0.0009**
Baseline cases p1000py Malaria	**351.6**	**175.8**	**527.5**	**57.0**	**28.5**	**85.5**	**6.13**	**3.06**	**9.19**
Baseline cases p1000py diarrhoea	**765.3**	**382.7**	**1148.0**	**542.0**	**271.0**	**813.0**	**299.81**	**149.91**	**449.72**
Propor fatal malaria	**0.008**	**0.004**	**0.012**	**0.012**	**0.006**	**0.018**	**0.004**	**0.002**	**0.006**
Propor fatal diarrhoea	0.001	0.001	0.002	0.001	0.001	0.002	0.0007	0.0004	0.0011
Participants per HH	2.5	1.25	3.75	2.5	1.25	3.75	2.5	1.25	3.75
DALYs fatal malaria	27.8	13.9	41.7	27.8	13.9	41.7	27.8	13.9	41.7
DALYs fatal diarrhoea	27.8	13.9	41.7	27.8	13.9	41.7	27.8	13.9	41.7
DALYs non-fatal malaria	0.366	0.183	0.549	0.366	0.183	0.549	0.366	0.183	0.549
DALYs non-fatal diarrhoea	0.127	0.064	0.191	0.127	0.064	0.191	0.127	0.064	0.191
Protect. mortality malaria	0.500	0.250	0.750	0.500	0.250	0.750	0.500	0.250	0.750
Protect. mortality diarrhoea	0.630	0.315	0.945	0.630	0.315	0.945	0.630	0.315	0.945
Protect. non-fatal malaria	0.500	0.250	0.750	0.500	0.250	0.750	0.500	0.250	0.750
Protect. non-fatal diarrhoea	0.628	0.314	0.941	0.628	0.314	0.941	0.628	0.314	0.941
Protect. mortality HIV transmission	0.500	0.250	0.750	0.500	0.250	0.750	0.500	0.250	0.750
Protect. mortality HIV acquisition	0.255	0.128	0.383	0.255	0.128	0.383	0.255	0.128	0.383
Multiplier: secondary effects HIV	2	1	3	2	1	3	2	1	3
Duration of benefit malaria	3	1.5	4.5	3	1.5	4.5	3	1.5	4.5
Duration of benefit diarrhoea	3	1.5	4.5	3	1.5	4.5	3	1.5	4.5
Duration of benefit HIV	1	0.5	1.5	1	0.5	1.5	1	0.5	1.5

All variables have β distributions with α and β parameters of 2. Minimum and maximum values are 0.5 and 1.5 of base case values, respectively, except for access to diarrhoea disease care and malaria care which have minimum and maximums of 0.6 and 1.4, and access to HIV ART which has a minimum and maximum of 0.75 and 1.25. Bold figures represent values that change with each country.
ART, antiretroviral therapy; DALY, disability-adjusted life-year.

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'opportunity indices,' ranking countries by (1) DALYs per capita across the three diseases of the IPC, (2) a sum of burden ranks for each disease and (3) a composite of burden and intervention opportunity. We extend this opportunity analysis by examining the relationship between a country's opportunity rank (in DALYs per capita) and its cost-effectiveness for IPC implementation.

Sensitivity analyses

To assess the effect of uncertainty in inputs, we conducted one-way and multiway Monte Carlo sensitivity analyses for three countries: Kenya, a low-income country where the IPC trial was performed and is at the 44th centile for cost-effectiveness of the 70 countries analysed; Nigeria, a lower-middle income country at the 75th centile (relatively favourable); and Bangladesh, a low-income country at the 25th centile. Each of the 31 model inputs examined in the sensitivity analyses (table 2) was assigned a β distribution with α and β parameters of 2, in order to ensure symmetry around the mean. Maximum and minimum values were set as 1.5 and 0.5 times the base case, except for access to malaria and diarrhoea treatment (0.75–1.25 of base case) and access to HIV treatment (0.6–1.4 times base case). Figures in bold font reflect parameter values that vary by country. Finally, we examined the effect of variations in important inputs on the cost-effectiveness of IPC in all 70 countries grouped in order of cost-effectiveness.

RESULTS

Across the 70 high-opportunity countries, the cost-effectiveness of the first campaign ranges from US$7 (Guinea-Bissau) to US$15 886 (China) per DALY averted (IQR US$96–US$1071 per DALY averted; table 3). At US $182 per DALY averted, Pakistan is at the 50th centile for cost-effectiveness. With the exception of Afghanistan, the 30 counties with the most favourable cost-effectiveness are in sub-Saharan Africa. The cost-effectiveness of IPC compares favourably to the cost-effectiveness of ART in 51 countries. The 30 countries with the lowest cost-effectiveness estimates are geographically more diverse and include only three in sub-Saharan Africa (Swaziland, South Africa and Namibia).

As shown in figure 1, per capita disease burden as measured by the opportunity index is highly correlated with cost-effectiveness. See figure 1 of the online technical supplement for relationship between opportunity index and cost-effectiveness for campaign 2.

Table 4 displays the cumulative results, grouped in 10-country increments, assuming 15% population coverage and moving from most to least attractive cost-effectiveness. IPC in the top 10 countries would cost US $583 million for the 3-year campaign, with a net cost after adjusting for effects on healthcare spending of US $398 million for the first 3-year campaign and US$468 million for the second and subsequent campaigns. The first and second campaigns would avert 8.0 and 5.7 million DALYs, respectively, with an average cost-effectiveness of US$49 and US$82 per DALY averted, respectively. As shown in the right-hand two columns, the incremental cost-effectiveness rises rapidly (becomes less favourable) after coverage of the top 50 countries. In particular, if expanding from the top 50 to 60 countries and from 60 to all 70 countries, large net incremental costs are associated with relatively modest increases in health benefits. The cost per DALY averted in expanding from 60 to 70 countries is US$8340 and US$19 728 for campaigns 1 and 2, respectively.

For each stratum of 10 countries ranked from most to least cost-effective, table 5 displays the median cost-effectiveness for the first 3-year campaigns, for possible second campaigns, and for ART. The cost-effectiveness of the first campaign compares more favourably to ART by a wide margin for each of the 10-country strata. For the second campaign ART is more cost-effective than IPC for the 51st–60th and for the 61st–70th country, as ranked by IPC cost-effectiveness.

Results for Kenya, Bangladesh and Nigeria illustrate reasons for variation across countries.

In Nigeria, the IPC cost-effectiveness ratio is US$94 per DALY averted, 18th of 70 countries ranked by cost-effectiveness. This result represents high health benefits for malaria and diarrhoea, and modest benefits for HIV. For every 1000 IPC participants, the first campaign averts an estimated 13.4 deaths: 6.0 due to malaria, 3.4 due to diarrhoea and 4.0 due to HIV. The campaign costs are US$40 479, with net costs of US$34 769 after offsetting savings from averted care needs.

In Kenya, cost-effectiveness is somewhat less attractive, at US$157 per DALY averted, 31st of 70 countries. This is due to lower malaria and diarrhoea benefits than in Nigeria, and more discovered HIV. For every 1000 IPC participants, the campaign averts an estimated 10.9 deaths: 1.6 due to malaria, 2.4 to diarrhoea and 7.0 to HIV. The campaign costs US$34 280. Although reduced disease creates offsetting savings in care needs, there are US$81 000 in *added* HIV costs due to earlier and additional detection of HIV. The net cost of the campaign is US$46 149, or US$157 per DALY averted. This is less than the US$883 per DALY averted for ART in Kenya.

In Bangladesh, the IPC cost-effectiveness ratio is US $1168 per DALY averted, 53rd of 70 countries. This is due to lower health benefits overall. For every 1000 IPC participants, the campaign averts an estimated 0.9 deaths: 0.1 due to malaria, 0.8 due to diarrhoea, and only 0.1 due to HIV. The campaign costs are US$35 658. When adjusted for modest offsetting savings from averted care, the net cost of the campaign is US$30 236. Cost-effectiveness is comparable with the estimated US $1046 per DALY averted for ART for HIV. See table 5 of the online technical supplement for detailed results for all three countries.

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Table 3 Summary costs and cost-effectiveness results per 1000 IPC participants for 70 countries ordered from most favourable to least favourable cost-effectiveness (net cost per DALY averted)

				Costs		Disease averted			CE		
	Country	World Bank income classification	DALYs per capita	IPC cost	Net cost	Deaths	Episodes	DALYs averted	Campaign cost per DALY averted	Net cost per DALY averted	CE of ART
1	Guinea-Bissau	Low	0.134	US$29 459	US$7814	40.7	10 523	1143.3	US$26	US$7	US$1005
2	Senegal	Lower middle	0.050	US$34 969	US$12 190	10.7	5735	306.0	US$114	US$40	US$768
3	Sierra Leone	Low	0.119	US$31 525	US$20 112	16.0	4118	446.7	US$71	US$45	US$764
4	Burkina Faso	Low	0.126	US$31 525	US$22 206	16.4	4124	459.4	US$69	US$48	US$819
5	Somalia	Low	0.121	US$26 015	US$22 754	16.8	3682	470.5	US$55	US$48	US$1535
6	Niger	Low	0.110	US$28 081	US$21 620	14.8	4967	419.7	US$67	US$52	US$1095
7	Mali	Low	0.124	US$29 459	US$23 016	15.9	4222	445.8	US$66	US$52	US$888
8	Afghanistan	Low	0.057	US$28 770	US$18 906	12.7	4146	356.6	US$81	US$53	US$935
9	Chad	Low	0.120	US$35 658	US$24 848	15.3	4335	424.6	US$84	US$59	US$807
10	Lesotho	Lower middle	0.115	US$35 658	US$47 366	31.3	1756	779.4	US$46	US$61	US$738
11	Guinea	Low	0.095	US$29 459	US$22 324	12.6	4272	353.8	US$83	US$63	US$928
12	Congo, DR	Low	0.112	US$24 637	US$25 488	13.4	3517	375.9	US$66	US$68	US$1493
13	Sudan	Lower middle	0.057	US$38 413	US$15 241	6.9	4907	198.8	US$193	US$77	US$703
14	Liberia	Low	0.092	US$26 704	US$25 526	11.9	3401	332.6	US$80	US$77	US$1025
15	Burundi	Low	0.118	US$26 015	US$33 639	14.3	2267	389.9	US$67	US$86	US$987
16	Benin	Low	0.083	US$33 591	US$25 345	10.0	3096	280.0	US$120	US$91	US$910
17	Côte d'Ivoire	Lower middle	0.084	US$33 591	US$35 069	14.1	4021	387.2	US$87	US$91	US$801
18	Nigeria	Lower middle	0.133	US$40 479	US$34 769	13.4	3102	369.3	US$110	US$94	US$747
19	Mozambique	Low	0.141	US$30 147	US$59 145	22.2	3816	590.0	US$51	US$100	US$1109
20	Cen. African Rep.	Low	0.105	US$27 392	US$37 525	13.8	2819	373.3	US$73	US$101	US$1230
21	Uganda	Low	0.105	US$31 525	US$40 192	14.9	3492	399.8	US$79	US$101	US$749
22	Congo, Rep.	Lower middle	0.067	US$54 254	US$33 944	11.5	2981	318.5	US$170	US$107	US$756
23	Togo	Low	0.075	US$29 459	US$32 147	10.4	2849	288.7	US$102	US$111	US$864
24	Angola	Upper middle	0.088	US$64 586	US$35 794	11.5	3268	320.8	US$201	US$112	US$674
25	Tanzania	Low	0.075	US$33 591	US$38 453	12.1	3122	326.9	US$103	US$118	US$935
26	Zambia	Lower middle	0.128	US$33 591	US$69 806	21.8	3107	564.3	US$60	US$124	US$826
27	Ethiopia	Low	0.057	US$30 147	US$29 630	8.6	1986	235.7	US$128	US$126	US$1139
28	Rwanda	Low	0.071	US$31 525	US$34 034	9.6	2216	266.1	US$118	US$128	US$768
29	Malawi	Low	0.110	US$28 081	US$59 745	18.3	2965	462.2	US$61	US$129	US$996
30	Cameroon	Lower middle	0.100	US$37 724	US$52 388	14.3	3115	388.4	US$97	US$135	US$741
31	Kenya	Low	0.065	US$34 280	US$46 149	10.9	2018	294.1	US$117	US$157	US$883
32	Mauritania	Lower middle	0.042	US$36 346	US$28 117	5.8	2607	164.2	US$221	US$171	US$955
33	Yemen	Lower middle	0.025	US$37 035	US$21 139	4.3	3128	122.9	US$301	US$172	US$719
34	Zimbabwe	Low	0.075	US$25 326	US$76 203	17.8	1682	428.8	US$59	US$178	US$1731
35	Pakistan	Lower middle	0.020	US$41 856	US$19 714	3.8	2748	108.1	US$387	US$182	US$904
36	Ghana	Lower middle	0.063	US$44 612	US$35 624	6.8	1966	189.9	US$235	US$188	US$746
37	Madagascar	Low	0.043	US$28 770	US$24 895	4.5	1910	127.8	US$225	US$195	US$1025
38	Eritrea	Low	0.033	US$27 392	US$26 438	4.3	1942	120.5	US$227	US$219	US$1753
39	Botswana	Upper middle	0.080	US$137 595	US$185 872	26.8	1111	734.1	US$187	US$253	US$577
40	Haiti	Low	0.028	US$30 836	US$31 570	4.4	3128	123.0	US$251	US$257	US$869

Continued

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Table 3 Continued

	Country	World Bank income classification	DALYs per capita	Costs		Disease averted		DALYs averted	CE		
				IPC cost	Net cost	Deaths	Episodes		Campaign cost per DALY averted	Net cost per DALY averted	CE of ART
41	Swaziland	Lower middle	0.150	US$58 387	US$198 392	29.1	2230	724.2	US$81	US$274	US$632
42	Guatemala	Lower middle	0.016	US$57 698	US$22 134	2.4	3143	70.1	US$823	US$316	US$627
43	South Africa	Upper middle	0.097	US$99 713	US$180 284	21.5	1150	561.0	US$178	US$321	US$582
44	Gabon	Upper middle	0.060	US$29 826	US$84 306	9.3	1876	255.0	US$117	US$331	US$613
45	India	Lower middle	0.027	US$48 744	US$34 973	3.7	1255	104.9	US$464	US$333	US$733
46	Myanmar	Low	0.026	US$31 525	US$28 249	2.9	1306	83.7	US$377	US$337	US$1354
47	Papua New Guinea	Lower middle	0.018	US$40 479	US$25 117	2.4	2868	71.2	US$568	US$353	US$864
48	Iraq	Upper middle	0.009	US$53 565	US$25 989	1.9	2587	55.8	US$960	US$466	US$758
49	Namibia	Upper middle	0.038	US$75 606	US$204 271	15.6	1528	402.7	US$188	US$507	US$606
50	Cambodia	Low	0.014	US$38 413	US$31 172	1.9	1341	54.3	US$708	US$574	US$739
51	Nepal	Low	0.010	US$30 836	US$28 994	1.4	1135	39.8	US$776	US$729	US$883
52	Morocco	Lower middle	0.006	US$58 387	US$42 818	1.9	1623	54.8	US$1066	US$782	US$650
53	Bangladesh	Low	0.007	US$35 658	US$30 236	0.9	1076	25.9	US$1377	US$1168	US$1046
54	Algeria	Upper middle	0.008	US$73 540	US$51 390	1.4	1304	41.0	US$1793	US$1253	US$606
55	Uzbekistan	Lower middle	0.006	US$45 989	US$25 637	0.6	2352	18.2	US$2523	US$1406	US$717
56	Ukraine	Lower middle	0.006	US$74 228	US$68 364	1.2	623	33.6	US$2210	US$2036	US$600
57	Thailand	Upper middle	0.005	US$90 759	US$100 377	1.8	455	48.7	US$1863	US$2061	US$622
58	Indonesia	Lower middle	0.008	US$56 321	US$46 677	0.7	814	20.8	US$2708	US$2244	US$793
59	Bolivia	Lower middle	0.010	US$56 321	US$30 994	0.4	2015	13.5	US$4178	US$2299	US$668
60	Vietnam	Lower middle	0.005	US$45 989	US$40 910	0.6	828	17.6	US$2616	US$2327	US$664
61	Colombia	Upper middle	0.003	US$95 580	US$63 657	0.6	1419	20.5	US$4652	US$3098	US$598
62	Peru	Upper middle	0.004	US$95 580	US$59 439	0.6	1497	19.0	US$5026	US$3126	US$613
63	Brazil	Upper middle	0.004	US$104 534	US$65 501	0.6	1385	19.2	US$5431	US$3403	US$581
64	Philippines	Lower middle	0.003	US$51 499	US$39 031	0.3	1289	10.9	US$4746	US$3597	US$724
65	Russian Federation	High: nonOECD	0.007	US$143 794	US$121 954	1.1	735	31.2	US$4607	US$3907	US$579
66	Argentina	Upper middle	0.003	US$147 238	US$101 854	0.6	1097	18.1	US$8155	US$5642	US$577
67	Malaysia	Upper middle	0.004	US$138 284	US$104 408	0.6	930	17.6	US$7858	US$5933	US$591
68	Turkey	Upper middle	0.001	US$29 459	US$58 058	0.1	1784	6.1	US$4821	US$9501	US$582
69	Mexico	Upper middle	0.003	US$127 264	US$134 901	0.3	0	9.6	US$13 197	US$13 989	US$583
70	China	Upper middle	0.001	US$84 560	US$74 564	0.1	486	4.7	US$18 015	US$15 886	US$638

The grey highlighted cells indicate CE ratio is less favourable than investment in ART. Results shown are for the first 3-year campaign.
ART, antiretroviral therapy; CE, cost-effectiveness; DALY, disability-adjusted life-year; IPC, integrated prevention campaign.

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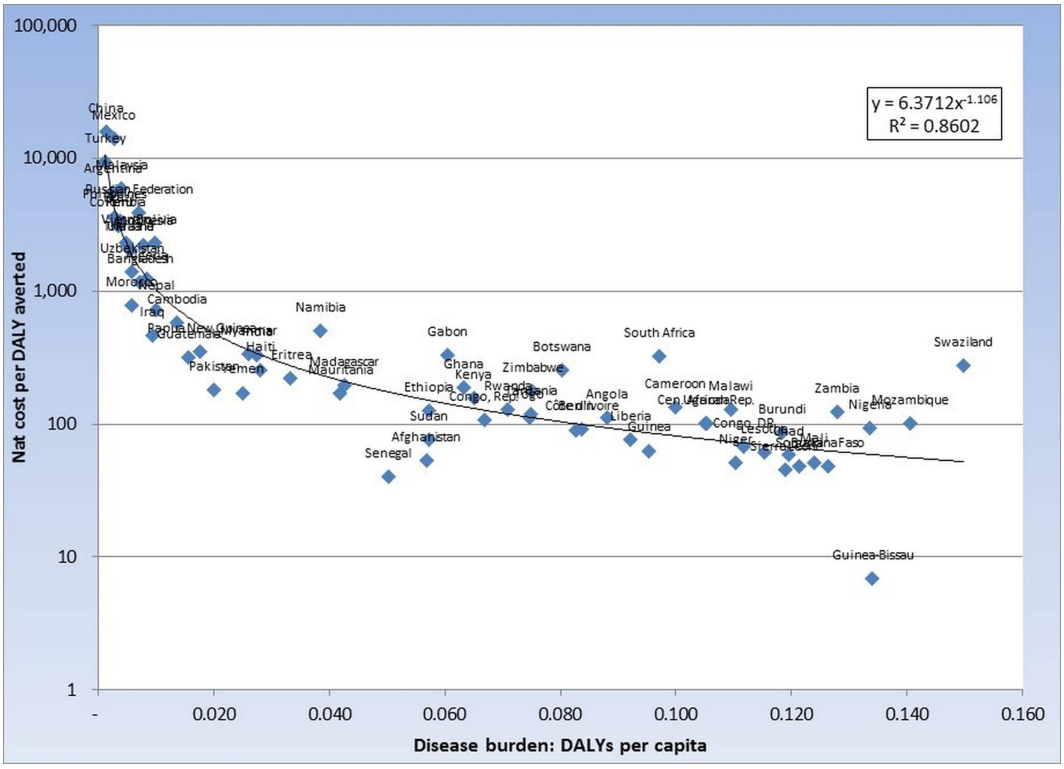


Figure 1 Cost-effectiveness (net integrated prevention campaign (IPC) cost per disability-adjusted life-year (DALY) averted) and Opportunity Index (DALYs per capita; Campaign 1, n=70).

Sensitivity analyses

One-way sensitivity analysis

Figure 2 is a tornado graph of the sensitivity of IPC cost-effectiveness to the model inputs displayed in table 2 for Nigeria. IPC participants per household had the greatest effect on IPC cost-effectiveness (range, US$126 per DALY averted), followed by the multiplier that reflects prevention of secondary HIV transmission, the duration of the prevention benefits of HIV interventions (range, US$122 per DALY averted each), cost of the IPC campaign (range, US$110 per DALY averted), and the reduction in mortality due to reduced HIV transmission (range, US$83 per DALY averted).

For Bangladesh, the inputs with the greatest effect on cost-effectiveness are duration of benefits for diarrhoea prevention and the baseline cases of diarrhoea per 1000 person-years (range, US$1506 per DALY averted for both), campaign cost (range, US$1377 per DALY averted), IPC participants per household (range, US $1305 per DALY averted) and protective benefit against diarrhoea mortality (range, US$1140 per DALY averted). For Kenya, the variables with the most influence on cost-effectiveness are the multiplier that reflects prevention of secondary HIV transmission and the duration of the prevention benefits of HIV interventions (range, US $236 per DALY averted each), the reduction in mortality due to reduced HIV transmission (range, US$161 per DALY averted), cost of the IPC campaign (range, US $117 per DALY averted) and the number of participants per household (range, US$103 per DALY averted). See online technical supplementary figures S2 and S3 for one-way sensitivity analysis tornado graphs for Bangladesh and Kenya, respectively.

Figure 3 shows how variation in three inputs affects incremental cost-effectiveness as each successive 10 countries are added to a scaled-up IPC programme. Up to 50 countries, IPC remains cost-effective compared with ART even if the least favourable end of the input estimate range is used.

Multivariate Monte Carlo sensitivity analysis

Table 6 displays the 80% CI for a 20 000-trial simulation for three outcomes: DALYs averted, net costs and net cost per DALY averted (cost-effectiveness). For Kenya and Nigeria the least favourable end of the cost-effectiveness range is more favourable than the cost-effectiveness of ART for HIV, US$304 vs US$883 per DALY averted for Kenya and US$208 vs US$747 per DALY averted for Nigeria. For Bangladesh, the least favourable end of the cost-effectiveness range, US$2547 is *less* favourable than the estimated US$1046 per DALY averted for ART. For Nigeria the five most important variables in order of their correlation with cost-effectiveness (net cost per DALY averted) are, the duration of the HIV prevention benefits (r=−0.51); prevention of secondary HIV transmission (r=−0.50), the number of IPC participants per household (r=0.33), cost of the IPC campaign (r=0.31), and the reduction in mortality due to reduced HIV transmission (r=−0.24; figure 4). See online technical supplementary figures S4

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Table 4 IPC costs, DALYs averted and cost-effectiveness compared with no intervention, and incremental cost-effectiveness for 70 countries in increments of 10, ranked by cost-effectiveness US$

Countries	Campaign cost	Net cost		DALYs averted		Cost-effectiveness (compared with no intervention)		Incremental cost-effectiveness (compared with previous row)	
		Campaign 1	Campaign 2	Campaign 1	Campaign 2	Campaign 1	Campaign 2	Campaign 1	Campaign 2
Top 10	5.832E+08	3.979E+08	4.685E+08	8.048E+06	5.708E+06	US$49	US$82	NA	NA
Top 20	2.387E+09	2.054E+09	2.068E+09	2.706E+07	1.629E+07	US$76	US$127	US$87	US$151
Top 30	3.715E+09	3.554E+09	3.338E+09	3.961E+07	2.382E+07	US$90	US$140	US$119	US$169
Top 40	5.614E+09	4.943E+09	4.858E+09	4.731E+07	2.916E+07	US$104	US$167	US$181	US$284
Top 50	1.624E+10	1.342E+10	1.395E+10	7.265E+07	4.983E+07	US$185	US$280	US$335	US$440
Top 60	2.226E+10	1.863E+10	1.941E+10	7.573E+07	5.186E+07	US$246	US$374	US$1692	US$2699
Top 70	5.129E+10	4.350E+10	4.629E+10	7.871E+07	5.322E+07	US$553	US$870	US$8340	US$19 728

'Net costs' consist of IPC campaign costs adjusted for medical costs averted or added due to the campaign. Results assume 15% of population covered by IPC in each country. Costs in 2012 US dollars.
DALY, disability-adjusted life-year; IPC, integrated prevention campaign; NA, not applicable.

and S5 for multivariate sensitivity analyses correlations coefficients for Kenya and Bangladesh, for projection of IPC costs and benefits in Kenya for 30 years (see online technical supplementary figure S6).

Scenario analysis

IPC cost-effectiveness with HIV costs and outcomes omitted. Finally, we report on the cost and cost-effectiveness of the IPC programme if HIV programme costs and health benefits are ignored. These results reflect the perspective of a payer who assumes responsibility for the diarrhoea and malaria components only. When future HIV-related costs and benefits are disregarded, including both additional care costs due to more and earlier detection and reductions in care costs due to prevention, the cost per DALY averted decreases from US$157 to US$129 in Kenya; from US$94 to US$31 in Nigeria and increases from US$1168 to US$819 in Bangladesh.

DISCUSSION

We examined the costs and health benefits of IPC for 70 countries with a high combined burden of diarrhoea, malaria and HIV. Together these countries comprise 76% of the world population[48 50] and 98% of its disease burden.[9] If implemented with 15% population coverage in the top 40 of the 70 countries as ordered by cost-effectiveness, 47.3 million DALYs could be averted at a net cost of US$4.9 billion, or US$104 per DALY averted. As shown in table 3, this compares favourably with the cost-effectiveness of ART in each of those 40 countries. The DALYs averted constitute 58% of the disease burden due to HIV, malaria and diarrhoeal disease in these countries. US$4.9 billion is considerably less than the President's request to the USA Congress for FY 2013 for US$6.4 billion for the PEPFAR programme[60] and thus might be affordable from a donor's perspective, especially if the current trend of greater host country financial contribution to HIV programmes continues. With the exception of Afghanistan, all 30 of the countries in which IPC was most cost-effective are in sub-Saharan Africa and in 51 countries, the cost-effectiveness of IPC compared favourably to ART.

The cost-effectiveness of IPCs varies greatly among the 70 countries we examined. This wide divergence is due primarily to differences in disease burden and therefore to the higher levels of incremental health benefit generated per incremental dollar spent for prevention. For example, Nigeria ranks 4th of the 70 countries based on DALYs per capita in the three diseases of the IPC, and Bangladesh ranks 55th. As shown in figure 1, per capita disease burden as measured by the opportunity index is highly correlated with cost-effectiveness. In the case of a single disease-intervention pair such a finding would be unsurprising since the cost-effectiveness of most prevention interventions depend importantly on incidence. It is more noteworthy here since the relative prevalence of the three diseases varies greatly between the countries

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Table 5 Median cost-effectiveness (net cost per DALY averted) by 10-country increments in order of cost-effectiveness

Countries ranked by IPC cost-effectiveness	Campaign 1	Campaign 2	Antiretroviral therapy for HIV
Top 10	US$50	US$102	US$854
11–20	US$88	US$141	US$958
11–30	US$121	US$197	US$797
31–40	US$185	US$318	US$894
41–50	US$335	US$591	US$683
51–60	US$1721	US$3514	US$666
61–70	US$4774	US$17 068	US$587

DALY, disability-adjusted life-year.

we studied, and the effect on medical care costs of intervening also varies substantially among the three diseases. In spite of this variability, the opportunity index is a reasonably good guide to cost-effectiveness.

Costs of programme delivery also matter. Swaziland, Botswana and South Africa have relatively unfavourable cost-effectiveness in relation to their disease burden. This is due primarily to their high per capita GDP and thus the higher estimated non-commodity (mainly personnel) portion of their campaign costs. However, IPC cost-effectiveness still compares favourably to that of ART in all three countries.

Sensitivity of findings within each country reflects how the IPC interacts with local disease burden. Diarrhoea is the largest contributor to the disease burden in Bangladesh, accounting for 87% of the DALYs averted by the IPC campaign. Not surprisingly, the most important determinant of cost-effectiveness was the estimated duration of the benefits of the water filter and the baseline incidence of diarrhoea. Kenya has a far larger HIV

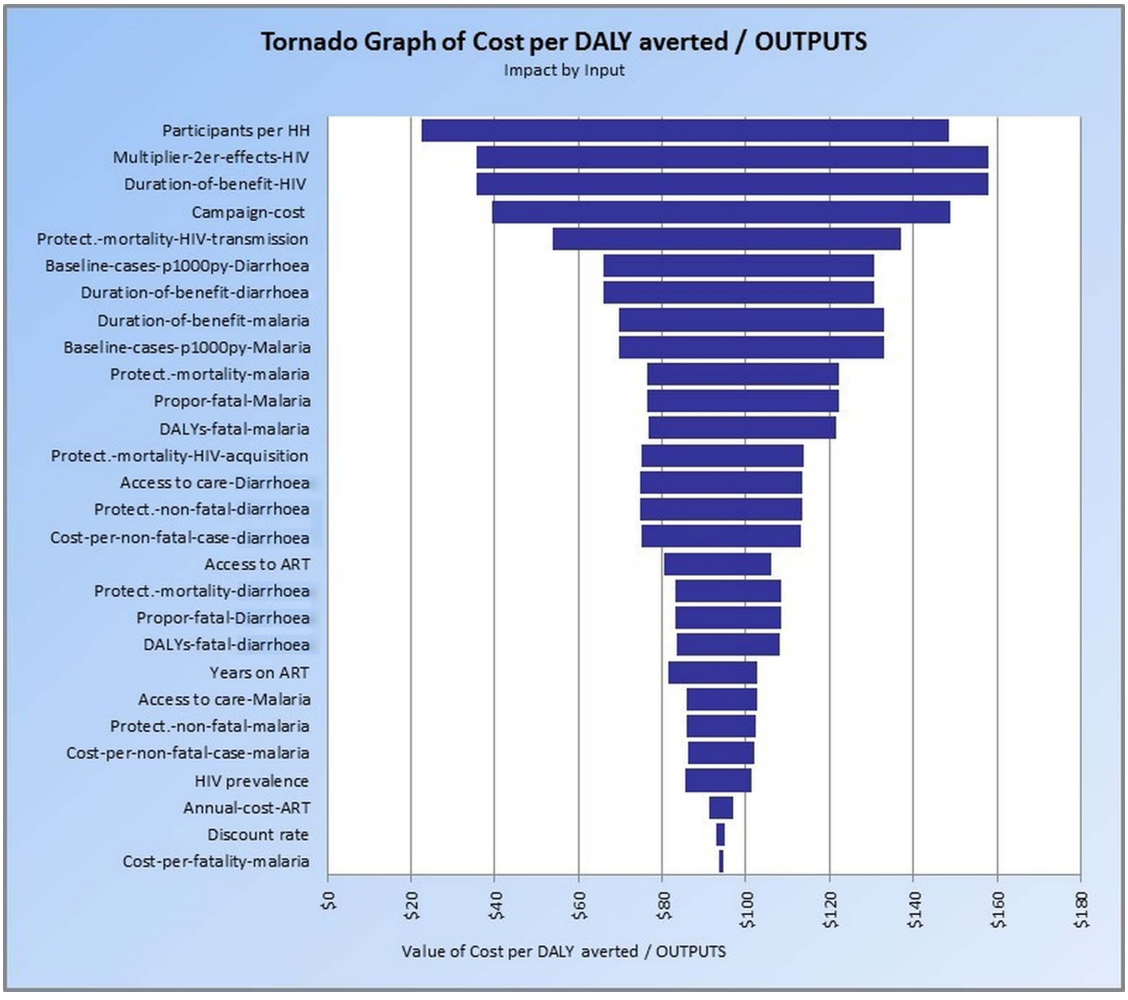


Figure 2 Tornado graph of Cost per DALY averted—Nigeria: impact by input (ART, antiretroviral therapy; DALY, disability-adjusted life-year).

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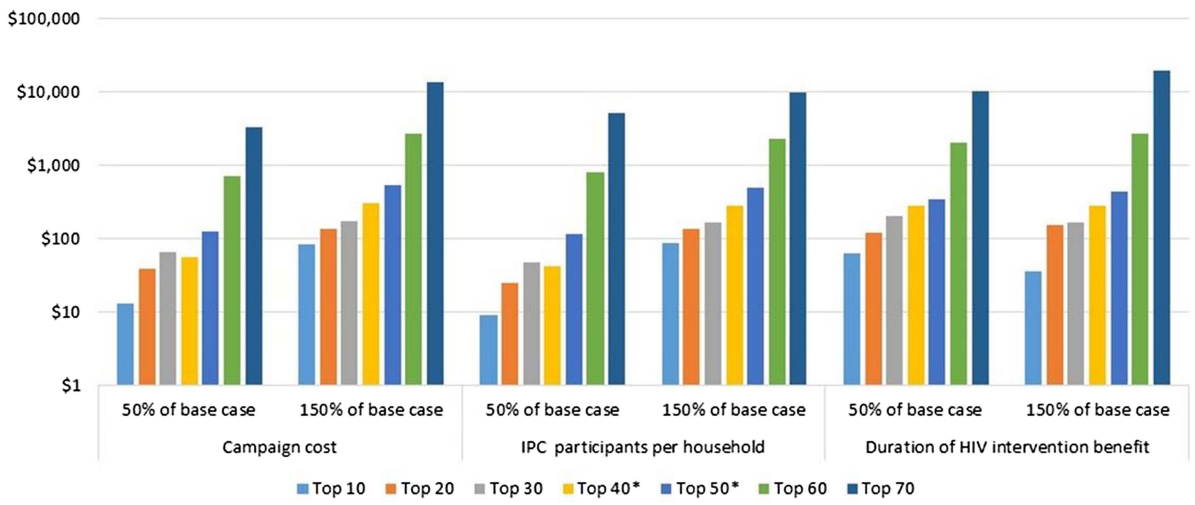


Figure 3 One-way sensitivity analysis of incremental cost-effectiveness by three key variables in 10-country increments ranked by integrated prevention campaign (IPC) cost-effectiveness.

epidemic, with a prevalence of 6.3% rather than 0.06% of adults as in Bangladesh. Accordingly, the largest determinants of IPC cost-effectiveness in Kenya were HIV-related in both one-way and multivariate sensitivity analyses. Nigeria's HIV prevalence of 3.6% is close to the average of 3.5% of the 70 countries examined. Nigeria's high IPC cost-effectiveness ranking is due to its high incidence of malaria and diarrhoea, 252 and 765 cases per 1000 person-years, respectively, compared with median values of 52 and 521 for malaria and diarrhoea respectively for the 70 countries studied.

Among the strengths of the current study are its synthesis of a large volume of epidemiological data from disparate sources into a unified method for projecting the consequence of IPC implementation in 70 countries, and the linking of the 'opportunity index' concept with cost-effectiveness. This provides a more comprehensive assessment of intervention potential than assessment of cost-effectiveness alone. This data-driven process may be applied to other disease areas and facilitate more objective resource allocation decision-making.

Limitations of our approach include incomplete availability of data relevant to the large number of countries analysed. Methods for approximation were therefore necessary. For example, the costs of the campaigns themselves were extrapolated from empirical Kenya-specific data using per capita GDP ratios between Kenya and the other countries to estimate the non-tradable commodity portion of costs. For other variables such as the protective effects of HIV prevention, bed nets and water filters where country-specific information was absent we employed wide ranges in the sensitivity analyses to ensure that we accounted for uncertainty, and this produced wide CIs around the model outcomes.

This study provides substantial evidence that IPC campaigns can be cost-effective in a large number of low-income and middle-income countries epidemic settings. However, it leaves unanswered important questions that need to be addressed when these broad findings are translated into programmes and policies. For example, in settings with high prevalence of both HIV and malaria, as community HIV prevalence is reduced, malaria susceptibility may decline, thus reducing the benefits associated with malaria prevention. Such interactions are not accounted for in our analysis. In some countries the relative contributions of each disease to the total burden imposed by all three diseases is uneven[9] (see table S4 of the online technical supplement for a breakdown of the contribution of each disease to the total for all three diseases). Swaziland, for example, has a high burden of HIV and a low burden of malaria. In Swaziland and similar settings, it may be sensible to focus the IPC campaign in areas of relatively

Table 6 Multiway sensitivity analysis; 20 000-trial Monte Carlo simulation, 80% CI for three IPC outcomes and cost per DALY averted by ART for HIV in Kenya, Bangladesh and Nigeria

Outcomes	Kenya	Bangladesh	Nigeria
DALYs averted	206–407	13.1–45.8	228–564
Net costs	US$7810–US$79 885	US$18 566–US$41 473	US$2241–US$61 448
Net cost per DALY averted (cost-effectiveness)	US$23–US$304	US$519–US$2547	US$5–US$208
Cost per DALY averted by ART for HIV	US$883	US$1046	US$747

ART, antiretroviral therapy; DALY, disability-adjusted life-year; IPC, integrated prevention campaign.

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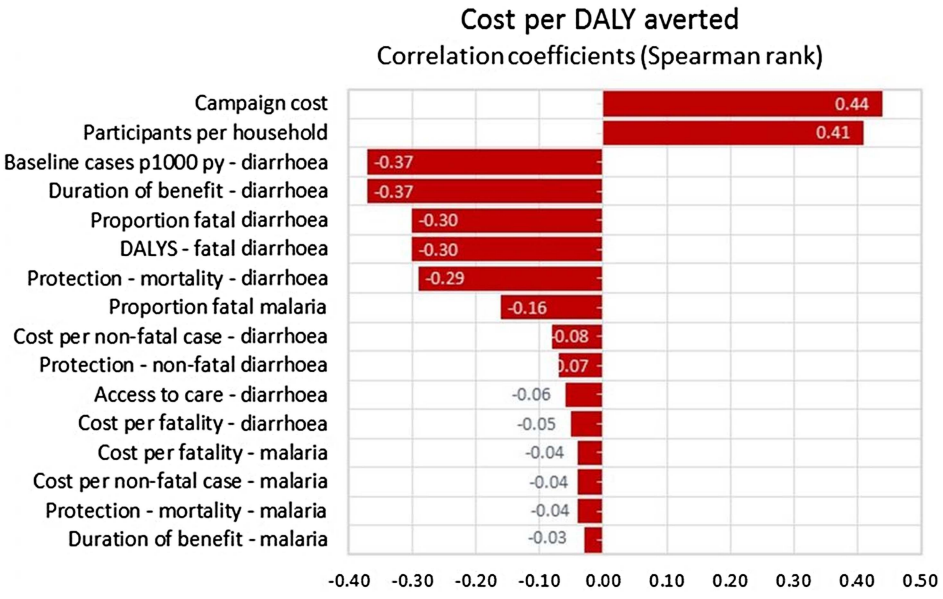


Figure 4 Result of 20 000-trial Monte Carlo simulation: correlation between input values and cost per disability-adjusted life-year (DALY) averted—Nigeria.

high malaria endemicity, by other means to target the malaria prevention component. Our cost projections posit relatively low IPC coverage of 15%. At this level it is reasonable to assume that in most countries, many high-prevalence areas would not be fully covered and planners need not be concerned that a point of diminishing returns would be met in which it becomes more costly to cover the next community, while the benefit of covering that community might decline. However, prior to implementation, country-specific analyses would be required to determine for which subset of countries it would be more cost-effective to scale up to higher coverage levels even if it means that some countries are excluded from implementation altogether. The current study also was not designed to consider how programme costs and effectiveness might vary according to whether a more vertical or more integrated approach is adopted, or depending on the level of prior scale of existing diarrhoeal disease, malaria or HIV programmes. These important programme design considerations will depend on the organisation of the healthcare system in each of the countries considering an IPC programme.

Since we looked at a large number of countries, we could not explore specific countries in detail. It was infeasible to develop cost-effectiveness thresholds that reflected the full array of local public health options against which IPC could be considered. Comparing IPC with the estimated cost-effectiveness of ART for HIV does not account for the potential intervention options that are more efficient than both IPC and ART. In addition, there may be substantial regions or urban areas within countries that have costs, health benefits that depart from the overall country assessments to which our analysis is confined. Finally, we were not able to evaluate the cost to patients of seeking care and were thus unable to adopt a full societal perspective. Since disease prevention averts the need for these expenditures, our results may underestimate net costs and thus cost-effectiveness. The current analysis should not displace investigation of potential opportunities for efficient IPC implementation in high disease burden areas within countries.

This study increases confidence that IPC can be an important new approach for enhancing global health. IPC appears to be cost-effective compared to ART for HIV in many settings, and has the potential to substantially reduce the burden of disease in poor countries. If implemented with 15% population coverage in the top 40 of the 70 countries as ordered by cost-effectiveness, 47.3 million DALYs could be averted at a net cost of US $4.9 billion, or US$104 per DALY averted. The specific countries, or number of countries, a donor may want to fund will depend on resource availability, and this analysis provides substantial guidance to decision makers aiming to predict the costs and benefits of various levels of investments in IPC programmes. If taken to scale, IPC can be a highly efficient strategy for improving global health.

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Contributors EM conceived and designed the study, conducted the analyses and drafted and revised the paper. AJ provided data for the study, helped with the analyses and drafting and revision. AR provided data for the study and revised the draft paper. SV and JW critiqued the analysis helped with specifying data inputs, and revised the draft paper. JGK helped guide design and implementation of the study, helped with specifying data inputs and edited the paper.

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