PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Scaling up integrated prevention campaigns for global health: Costs and cost-effectiveness in 70 countries
AUTHORS	Marseille, Elliot; Jiwani, Aliya; Raut, Abhishek; Verguet, Stephane; Walson, Judd; Kahn, James

VERSION 1 - REVIEW

REVIEWER	Valerie Crowell Swiss Tropical and Public Health Institute Switzerland
REVIEW RETURNED	17-Oct-2013

GENERAL COMMENTS	This is an interesting and important paper. The manuscript seems to be scientifically sound, and the methods and results are clearly presented. Background On page 4, lines 36-37, the authors state that they have used the best available data. I wonder if this is true, as it seems it would have been possible (albeit not feasible for the present study) to gather more country-specific data. i.e. on human resources costs, treatment costs, care-seeking for malaria. The authors could clarify that their approximations were sufficient for the purpose of this modelling study, which was to provide an initial indication of where and under which conditions IPC is likely to be cost-effective. The sensitivity analysis is of course critical to increasing confidence in the study conclusions, given the reliance on so many assumptions. Methods A societal perspective considers costs to patients as well. Are these included in the campaign costs and costs for health care incurred? The time frame of the analysis is not specified. It is not clear to me why the authors used country-specific DHS data on care-seeking for diarrhea, while using global average rates of treatment access for malaria. Could the authors provide a reference or method for calculating age 25 as the estimated average age of death from malaria and diarrhea (line 47)? The authors state that one of the main strengths of the paper is that it links the opportunity index with cost-effectiveness. A brief

	explanation in the methods section on how each country's opportunity rank was generated would be useful. It is not clear to me what the opportunity index in Figure 1 represents. Results There is no justification for the assumption of 15% population coverage of IPC. Presumably, if this is a cost-effective intervention package, it would be scaled up more widely. Lines 44-45: Are the figures for median cost-effectiveness for the last two strata correct in Table 5? If so, it seems that ART is more cost-effective than IPC for the last 2 strata. Line 39: in the case of Bangladesh, should the sentence read "decreases"? Discussion The authors could comment a bit more on the limitations of the study. For example, the authors make no mention in this manuscript of the interactions between the diseases and interdependence of intervention effects, and how this might affect cost-effectiveness ratios. The effects of interventions will depend on a number of factors such as local epidemiology, transmission patterns and human behaviour which are not accounted for in this analysis. It would also be interesting to surmise about the costs and feasibility of taking such an intervention to scale in countries and reaching remote or marginalized populations. Given funding limitations, would it be more desirable, from a cost-effectiveness perspective, to achieve 15% coverage in 40 countries or to aim for 70 or 80% coverage in the countries with the best cost-effectiveness results? What factors should be considered when making resource allocation decisions? Tables In the caption for Table 1, the authors should state that "Bold figures represent values that change with each country."

REVIEWER	Morel, Chantal LSE, UK
REVIEW RETURNED	24-Mar-2014

GENERAL COMMENTS	Overall comment: This study describes results of a cost-effectiveness model focussing of an integrated package of health interventions. This is indeed of significant interest. However, the cost and effectiveness data used to populate the model come predominantly from only one, Kenya-specific, field-based study. The use of findings from this one study to draw conclusions for cost-effectiveness across 70 different countries that vary significantly in terms of pathogen type, disease pattern, existing type and level of intervention, financing arrangements, etc. is questionable and, in this case, insufficiently justified. I recommend rejecting this paper in its current form and reconsidering an adaptation based on findings of the same model focussed on a more limited set of countries, including substantive justification for each

	country's inclusion. Specific comments: Text reads: "Countries were chosen for inclusion in the analysis based on two factors: they were classified as low- or middle-income as defined by the World Bank [9]; and they had a total DALY (Disabilityadjusted-life-year) burden for the three diseases addressed by the IPC in the highest tertile of the 214 World Bank-defined economies (i.e., ≥ 87,000 DALYs; assessed in a companion paper (Jiwani et al., under review, 2013 [9])." There is no indication of the relative importance of these diseases in these countries respectively. This would add much to the understanding of the relative merits of the package of interventions. "We calculated the per person-year cost of ART for each country by using published estimates for countries where available [21-42]." For how many countries did you actually have data and for how many did it need to be inferred? "The cost of non-tradable items, primarily personnel, were adjusted according to the per-capita GDP ratio, in International dollars, between Kenya and each study country [12]." …in order to… "For each country, we estimated the costs of averted medical care due to the IPC by adjusting the costs for health care incurred per fatal and non-fatal case in the Kenya campaign by the ratio of GDP per capita in the target country versus Kenya." Health costs are known to vary significantly from place to place. While I understand the logic and indeed the expedience desired in your approach I do also question whether it is sufficiently valid. Are there any preceding studies that suggest that differences in health spending in such cases are sufficiently similar across countries to be comparable when only controlling for GDP per capita? Sounds a bit simplistic and certainly runs counter most costing exercises in the field. In any case, how do your estimates fit in with previously estimated country-specific health cost differences (e.g. WHO CHOICE)? "For malaria, we used global average rates of treatment access, estimated at 68% for malaria based on published literature." Coverage rates differ significantly. Assuming an average for your entire area is overly simplistic. While it could be understood that country-specific estimates are difficult to collect, perhaps at least regional statistics could be used. First versus second campaign health benefits What are the health effects of the first campaign? "The health benefits of a second campaign would be lower than that of the initial campaign. For malaria and diarrhea, this is due to the limited functional life of nets and filters." This is a bit confusing. What exactly does a campaign entail if it does not include re-impregnation of nets and repair/replacement of water filters? "For the second campaign we estimate that the incidence of malaria and HIV would decrease to 33% of baseline levels and that of diarrhea to decrease to 58%. (Details in technical supplement)." These estimates are quite optimistic. Should include at least a bit of detail here on how this was calculated. Disease specific data and projection "Using a discount rate of 3% [10], we estimated the DALYs incurred with each fatal case of malaria and diarrhea at 28 based on life expectancy at age 25 in Kenya (the estimated average age of death from malaria and diarrhea) of 61 years [55]." The malaria parasite species (e.g. P falciparum, P vivax) differ from place to place but especially by continent. They cause different physical symptoms, namely having very different severity, chances of death. Their main health effects also affect age groups differently. Are you using this

	average from Kenya for ALL of the countries in your study. If so, I think this is very problematic. Other It is great to look at integrated solutions to improving health. However, it is not clear from the description of the IPC how it can/could tie with an overall health system approach. Presumably whether it is embedded in an HS approach or independent would have significant impact on costs as well as sustainability. Individually these (or similar) health interventions already exist in most of the countries in question. Did you look at the cost implications of scaling up of (and possible integration) of existing interventions in the respective contexts?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Valerie Crowell
Institution and Country Swiss Tropical and Public Health Institute
Switzerland
Please state any competing interests or state 'None declared': None declared

This is an interesting and important paper. The manuscript seems to be scientifically sound, and the methods and results are clearly presented.

Background

On page 4, lines 36-37, the authors state that they have used the best available data. I wonder if this is true, as it seems it would have been possible (albeit not feasible for the present study) to gather more country-specific data. i.e. on human resources costs, treatment costs, care-seeking for malaria. The authors could clarify that their approximations were sufficient for the purpose of this modelling study, which was to provide an initial indication of where and under which conditions IPC is likely to be cost-effective. The sensitivity analysis is of course critical to increasing confidence in the study conclusions, given the reliance on so many assumptions.

Authors' response: A fair point. We have now revised the relevant sentence to read: "Using international databases appropriate for providing an initial indication of the national 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- and middle-income countries."

Methods

A societal perspective considers costs to patients as well. Are these included in the campaign costs and costs for health care incurred?

Authors' response: No, we do not evaluate patients' time and money in seeking care. The comment is therefore correct. Our cost-effectiveness results are thus likely to be somewhat less favorable than one that did include these costs. We replace the term "societal perspective" with "health care payers' perspective", and added these two sentences to the Discussion --

"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 under-estimate net costs and thus cost-effectiveness."

The time frame of the analysis is not specified.

Authors' response: Good point. The empirical data are derived from three years' experience with the IPC campaign. The modeled consequences of the intervention compare the lifetime DALYs that would be incurred with IPC compared with no IPC. In calculating DALYs averted due to reduced mortality, we use the life expectancy at disease-specific average age of death In Kenya. For diarrheal disease and malaria this is 61 years and for HIV it is 37 years. We therefore added the following to the methods section:

"The time frame of the analysis is three years for the empirical data. Modeled results depend upon the life expectancy in Kenya at the age when disease deaths are averted. This is 61 years for diarrheal diseases and malaria and 37 years for HIV."

It is not clear to me why the authors used country-specific DHS data on care-seeking for diarrhea, while using global average rates of treatment access for malaria.

Authors' response: There are insufficient country-specific data available except for some of the more-affected countries, mostly in Africa. We therefore used the average of the following care seeking or access data from the studies cited in the text. As noted in Table 2, this value of 0.684 was varied from 0.513 to 0.855 in sensitivity analyses.

Could the authors provide a reference or method for calculating age 25 as the estimated average age of death from malaria and diarrhea (line 47)?

Authors' response: Thank you. This is a typo. The right number is 2.5 years. Corrected now.

The authors state that one of the main strengths of the paper is that it links the opportunity index with cost-effectiveness. A brief explanation in the methods section on how each country's opportunity rank was generated would be useful. It is not clear to me what the opportunity index in Figure 1 represents.

Authors' response: We agree that elaboration is necessary and have added the following to the Methods section's paragraph with the subheading "Overview":

" . . . 214 World Bank-defined economies (i.e., ≥ 87,000 DALYs); as described in a companion paper.1 We refer to this ordering of countries by the combined disease burden as the "opportunity index".

Results

There is no justification for the assumption of 15% population coverage of IPC. Presumably, if this is a cost-effective intervention package, it would be scaled up more widely.

Authors' response: True. In addition, the extent of coverage that is feasible and cost-effective will vary by country. Assuming rational targeting, cost-effectiveness will worsen as people at lower risk are

included in the covered population. Thus, access to IPC by 15% of the entire population is significant, and strikes us as a reasonable benchmark against which to measure costs.

Lines 44-45: Are the figures for median cost-effectiveness for the last two strata correct in Table 5? If so, it seems that ART is more cost-effective than IPC for the last 2 strata.

Authors' response: That's correct. IPC implementation in these last 20 countries would not be cost-effective. The first para of the discussion section points this out.

Line 39: in the case of Bangladesh, should the sentence read "decreases"?

Authors' response: I don't think so. For Bangladesh, the IPC has a net cost of $30,236 per 1000 participants (Table 3). Although there are offsetting medical care costs, net costs are still positive.

Discussion

The authors could comment a bit more on the limitations of the study. For example, the authors make no mention in this manuscript of the interactions between the diseases and interdependence of intervention effects, and how this might affect cost-effectiveness ratios. The effects of interventions will depend on a number of factors such as local epidemiology, transmission patterns and human behaviour which are not accounted for in this analysis.

It would also be interesting to surmise about the costs and feasibility of taking such an intervention to scale in countries and reaching remote or marginalized populations. Given funding limitations, would it be more desirable, from a cost-effectiveness perspective, to achieve 15% coverage in 40 countries or to aim for 70 or 80% coverage in the countries with the best cost-effectiveness results? What factors should be considered when making resource allocation decisions?

Given funding limitations, would it be more desirable, from a cost-effectiveness perspective, to achieve 15% coverage in 40 countries or to aim for 70 or 80% coverage in the countries with the best cost-effectiveness results?
Authors' response: These are valid points. We have added the following passage to the Discussion:

"This study provides substantial evidence that IPC campaigns can be cost-effective in a large number of low and middle-income countries epidemic settings. However, it leaves unanswered important questions that need to be addressed when these broad findings are translated into programs 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 disease is uneven.1 (See Table 4 of the 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 high malaria endemicity, by other means to target the malaria prevention component. Our cost projections posit relatively low IPC coverage, 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 program 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 diarrheal disease, malaria or HIV programs. These important program design considerations will depend on the organization of the health care system in each of the countries considering an IPC program."

Tables

In the caption for Table 1, the authors should state that "Bold figures represent values that change with each country."
Authors' response: Yes. Done.

Reviewer: 2
Reviewer Name C Morel
Institution and Country LSE, UK
Please state any competing interests or state 'None declared': None declared

Overall comment:
This study describes results of a cost-effectiveness model focussing of an integrated package of health interventions. This is indeed of significant interest. However, the cost and effectiveness data used to populate the model come predominantly from only one, Kenya-specific, field-based study. The use of findings from this one study to draw conclusions for cost-effectiveness across 70 different countries that vary significantly in terms of pathogen type, disease pattern, existing type and level of intervention, financing arrangements, etc. is questionable and, in this case, insufficiently justified. I recommend rejecting this paper in its current form and reconsidering an adaptation based on findings of the same model focussed on a more limited set of countries, including substantive justification for each country's inclusion.

Authors' response: These are important concerns and ones that we were cognizant of as we conceived, designed, and carried out this analysis. We agree that the available country-specific data are less than what an ideal analysis would include. However, we feel that we have been able to square the quantity and quality of the data that do exist with the broad cost-effectiveness assessments we aim to make in this paper. On a more specific point, we do not limited ourselves to data from the Kenya study. We use the experience of the Kenya IPC campaign to derive program costs in other countries. However the data on disease incidence and prevalence, case fatality rates, household size, access to care for diarrheal disease and the cost of care for diarrheal disease and partially for HIV are all country-specific values.

We agree that it might be possible to reduce the uncertainty in some of our estimates if we confine the analysis to a subset of countries for which more complete data are available. However, there's no reason to believe that the countries with the most complete data are those for which the IPC campaign would be most cost-effective; the opposite could well be true. Thus, such an approach would be inconsistent with the aim of our study.

Many, probably most, cost effectiveness analyses must contend with the issue of data from multiple sources and settings, significant portions of which were not generated to directly address the issue confronting the cost-effectiveness analyst. By acknowledging these issues, pointing out the likely direction of bias and making extensive use of sensitivity analyses, the analyst aims to levels of

accuracy and precision sufficient to answer the research question. Particularly with the clarifications and amendments suggested by both reviewers, we believe we have done so in this paper.

Specific comments:

Text reads: “Countries were chosen for inclusion in the analysis based on two factors: they were classified as low- or middle-income as defined by the World Bank [9]; and they had a total DALY (Disabilityadjusted-life-year) burden for the three diseases addressed by the IPC in the highest tertile of the 214 World Bank-defined economies (i.e., ≥ 87,000 DALYs; assessed in a companion paper (Jiwani et al., under review, 2013 [9]).” There is no indication of the relative importance of these diseases in these countries respectively. This would add much to the understanding of the relative merits of the package of interventions.
Authors’ response: True. Please see the additional passage we have added to the Discussion section as presented above on page 4 in responses to Reviewer #1.

“We calculated the per person-year cost of ART for each country by using published estimates for countries where available [21-42].” For how many countries did you actually have data and for how many did it need to be inferred?
Authors’ response: We were able to derive usable data from 15 countries as shown in this table which we are also adding to the Technical Supplement as Table 7:

“The cost of non-tradable items, primarily personnel, were adjusted according to the per-capita GDP ratio, in International dollars, between Kenya and each study country [12].” …in order to…
“For each country, we estimated the costs of averted medical care due to the IPC by adjusting the costs for health care incurred per fatal and non-fatal case in the Kenya campaign by the ratio of GDP per capita in the target country versus Kenya.” Health costs are known to vary significantly from place to place. While I understand the logic and indeed the expedience desired in your approach I do also question whether it is sufficiently valid. Are there any preceding studies that suggest that differences in health spending in such cases are sufficiently similar across countries to be comparable when only controlling for GDP per capita? Sounds a bit simplistic and certainly runs counter most costing exercises in the field. In any case, how do your estimates fit in with previously estimated country-specific health cost differences (e.g. WHO CHOICE)?

Authors’ response: There is no recognized ‘gold standard’ for adjusting program and health care costs by country setting. We therefore agree that the method we used should be compared with other possible approaches including WHO-CHOICE. We recognize that GDP per capita is an imperfect index for adjusting the non-tradable portion of costs of the IPC campaign and treatment costs. While per-capita GDP may reflect overall ability to pay it assumes that health care is a normal good in which consumption increases monotonically with income. It also lacks the specificity to capture both the unit cost and the relevant quantities utilized of various health inputs, such as inpatient days or outpatient visits. These utilization patterns can also be expected to vary by country partially independently of income. An alternative index is per-capita spending on health care. This is a more direct measure of overall health care spending, but also fails to capture the detailed inputs cost and utilization mix. Finally, as mentioned by the reviewer, WHO-CHOICE provides country-specific costs for inpatient days and outpatient visits at various levels of facilities (e.g. primary, secondary, and teaching hospitals). By comparing the WHO-CHOICE-derived costs for Kenya against the other 69 countries, yet a third index can be created. However, this WHO-CHOICE based index has its own short-comings. In addition to not reflecting the specific mix of inputs needed for the present analysis, the

methods used to derive the costs are somewhat opaque. The regression model used to predict country health care costs was based on per-capita GDP In the table below, we show each of these three indices along with the difference between them for the 70 relevant countries.

The variation in the results yielded by each method is modest. As shown in the tables and graph below, the mean and median differences between WHO-CHOICE and per-capita GDP are only 13.4% and 11.2% respectively; and the mean and median differences between WHO-CHOICE and per-capita health care spending are similar, 15.6% and 10.7% respectively. On balance, we believe that the per-capita GDP method we adopted is a reasonable approach. However, so that readers can compare the approaches, we have added tables 8 and 9 to the Technical Supplement. Table 8 shows the base-case results using the per-capita health care spending approach; Table 9 uses the index derived from WHO-CHOICE. These show very little difference in the cost-effectiveness results by country rankings when compared with the per-capita GDP approach (Table 3 in the main paper).

"Methods for estimating health care and campaign costs.
There is no recognized 'gold standard' for adjusting program and health care costs by country setting. While per-capita GDP may reflects overall ability to pay it assumes that health care is a normal good in which consumption increases monotonically with income. It also lacks the specificity to capture both the unit cost and the relevant quantity utilized of various health inputs, such as inpatient days or outpatient visits. These utilization patterns can vary by country partially independently of income. An alternative index is per-capita spending on health care. This is a more direct measure of overall health care spending, but also fails to capture the detailed inputs cost and utilization mix. Finally, WHO-CHOICE provides country-specific costs for inpatient days and outpatient visits at various levels of facilities (e.g. primary, secondary, and teaching hospitals). By comparing the WHO-CHOICE-derived costs for Kenya against the other 69 countries, yet a third index can be created. However, this WHO-CHOICE based index has its own short-comings. In addition to not reflecting the specific mix of inputs needed for the present analysis, the methods used to derive the costs are somewhat opaque. The regression model used to predict country health care costs includes per-capita GDP and, as our analysis shows may be similar to using a per-capita GDP-based index.

The variation in the results yielded by each method is modest. Table 8 shows the base-case results using the per-capita health care spending approach; Table 9 uses the index derived from WHO-CHOICE. These show very little difference in the cost-effectiveness results by country rankings when compared with the per-capita GDP approach (Table 3 in the main paper)."

"For malaria, we used global average rates of treatment access, estimated at 68% for malaria based on published literature." Coverage rates differ significantly. Assuming an average for your entire area is overly simplistic. While it could be understood that country-specific estimates are difficult to collect, perhaps at least regional statistics could be used.

Authors' response: The data on malaria treatment access are surprisingly sparse. We canvassed the relevant literature and summarized the useful data in the Table inserted in page 2 in this document in response to a very similar point made by Reviewer 1.

First versus second campaign health benefits

What are the health effects of the first campaign?
“The health benefits of a second campaign would be lower than that of the initial campaign. For malaria and diarrhea, this is due to the limited functional life of nets and filters.” This is a bit confusing. What exactly does a campaign entail if it does not include re-impregnation of nets and repair/replacement of water filters?

Authors’ response: Agree - this was poorly worded. What we meant to convey was that if there were no second campaign, the first campaign would continue to confer some benefit, but at a substantially lower level. Current bed nets have long-lasting impregnation (10 years), but suffer physical damage and thus are expected to have a useful life of only 3 years on average. The benefit of the additional campaign is the incremental benefit of new nets and filters adjusted for the residual benefit from the remaining functional filters and nets. This is more explained in more detail in the Technical Supplement. The paragraph with the sentence quoted above has now been re-written as:

“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 three 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 diarrheal disease the filters themselves are not expected to confer benefit after 3 years, though there may be residual benefit from the behavioral 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, diarrhea decreases from 87.5% to 37% of baseline (a relative drop of 58%). (Details in technical supplement).”

“For the second campaign we estimate that the incidence of malaria and HIV would decrease to 33% of baseline levels and that of diarrhea to decrease to 58%. (Details in technical supplement).” These estimates are quite optimistic. Should include at least a bit of detail here on how this was calculated. Disease specific data and projection

Authors’ response: I believe this is now addressed in the response given to the related point above.

“Using a discount rate of 3% [10], we estimated the DALYs incurred with each fatal case of malaria and diarrhea at 28 based on life expectancy at age 25 in Kenya (the estimated average age of death from malaria and diarrhea) of 61 years [55].” The malaria parasite species (e.g. P falciparum, P vivax) differ from place to place but especially by continent. They cause different physical symptoms, namely having very different severity, chances of death. Their main health effects also affect age groups differently. Are you using this average from Kenya for ALL of the countries in your study. If so, I think this is very problematic.
Authors’ response: First, as noted in response to reviewer 1, “age 25 in Kenya should be “age 2.5”. Apologies for the typo. It is true that incidence and death rates vary greatly by country and in fact, country-specific incidence and proportion of cases that are fatal are incorporated into our model. The sources of these data are shown in Table 1. The figure of 28 DALYS are the DALYs that occur in fatal cases only. It is not a weighted average of all cases. Because years at the end of life are heavily discounted, using country-specific life expectancies would make little difference. For example, the DALYS associated with death at age 2.5 for a person who would otherwise have lived to 90 would be 30.8 DALYS.

Other
It is great to look at integrated solutions to improving health. However, it is not clear from the description of the IPC how it can/could tie with an overall health system approach. Presumably

whether it is embedded in an HS approach or independent would have significant impact on costs as well as sustainability.
Individually these (or similar) health interventions already exist in most of the countries in question. Did you look at the cost implications of scaling up of (and possible integration) of existing interventions in the respective contexts?

Authors' response: These are valid points, but we believe that addressing them in a meaningful way lies outside the scope of what is already an extensive analysis. Please see the new passage added to the Discussion section.

Reference

1. Jiwani A, Matheson A, Kahn JG, Raut A, Verguet S, Marseille E, et al. Integrated disease prevention campaigns: assessing country opportunity for implementation via an index approach. BMJ open 2014;4(3):e004308.