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Economic evaluation of Wolbachia deployment in Colombia: A modeling study

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Abstract:	Background and Aims. Wolbachiaare bacteria that inhibit dengue virus replication within the mosquito. Previous studies found Wolbachia reduced virologically-confirmed dengue cases by 77% and was highly cost-effective. The World Mosquito Program in Colombia deployed Wolbachia in the Aburrá Valley from 2015-2022 and introduced it in Cali in 2020. To inform decisions about future extensions, we performed economic evaluations of potential expansion of Wolbachia deployments to 11 priority Colombian cities. Methods. Numbers and the distribution by severity of reported dengue cases were assembled from Colombia's national disease surveillance system and the health service provision registry (RIPS). An epidemiological panel of three experts provided consensus estimates for shares of non-medical cases and adjustments for under-reporting and misclassifications. Costs (in 2020 US dollars) of treating dengue illness were based on: (1) the benchmark tariff of the mandatory insurance for traffic accidents, (2) RIPS data on services provided per symptomatic dengue case and, (3) the national government database for establishing insurance premiums. A cluster randomized trial quantified the effectiveness of Wolbachia against symptomatic dengue cases. Results. Projecting impact over 10 years for Cali, we estimated a net health-sector savings of $4.95 per person. We also estimated averting 369 disability-adjusted life years (DALYs) per 100,000 population. From a societal perspective at 10 years, Wolbachia deployment is expected to have highly favorable benefit-cost ratios, with benefits per dollar invested of USD6.62 in Cali and USD5.61 over all priority cities. Conclusions. Over 10 years, Wolbachia is highly beneficial on economic grounds, and almost universally cost saving. That is, Wolbachia's savings in health care costs alone would more than offset deployment costs nationally and in all but one priority city. Even the least favorable parameter estimates generate at least USD2.00 in benefits per dollar invested, giving substantial confidence that Wolbachia deployment would be cost-beneficial in Colombia.
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Ethics Statement Enter an ethics statement for this submission. This statement is required if the study involved: • Human participants • Human specimens or tissue • Vertebrate animals or cephalopods • Vertebrate embryos or tissues	This modeling study did not involve any human studies data as it was based entirely on aggregate or publicly available anonymous data. These data could not allow any individual to be identified nor linked with any individual. The research team did not prospectively nor retrospectively recruit human participants nor did the team obtain tissues, data, or samples for the purposes of this study. The research team did not review existing medical records nor archived samples. Therefore, this study was outside the purview of the Committee for Protection of Human Studies in Research so ethical approval was not applicable. This statement also appears under "Ethics statement" at the end of the manuscript.

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Editors, *PLOS ONE*:

On behalf of my co-authors, I am pleased to submit the attached manuscript entitled "Economic evaluation of *Wolbachia* deployment in Colombia: a modeling study" for submission for possible publication in *PLOS ONE.*

We feel that this paper would make several important contributions to the scientific and policy literature. First, it would add to the very limited economic literature about this promising technology. From a societal perspective at 10 years, *Wolbachia* deployment is predicted to generate a highly favorable $5.61 in economic benefits for every dollar invested across all target cities in Colombia. Second, this study would be the first economic study about *Wolbachia* in the Americas, where a substantial portion of the world's dengue occurs. Third, the economic evaluation would be highly relevant to public sector policy makers at the municipal and national levels, as they would reap the savings but enjoy the benefits of this technology. Fourth, the paper reports findings separately by each priority city, providing information to inform the real choices of local and national policy makers, who currently face city-by-city decisions.

As our introduction states, we are aware of only three prior reports on the economics of *Wolbachia*. Both estimated the efficacy of this technology based on models and observational data. By contrast, this paper uses the actual efficacy from a well-conducted cluster randomized trial in one of the world's leading medical journals (Utarini et al., 2021).

Our submission is an original research article. We have not had any prior discussions with any editors about this submission. My co-authors and I chose to submit to *Plos One* thanks to our outstanding reviews behind a recent publication about Colombia in the journal (Shepard et al, 2023, https://doi.org/10.1371/journal.pone.0282786).

We feel that Luciano Andrade Moreira would be the best qualified academic editor based on his deep and long-standing expertise about dengue and his detailed understanding about *Wolbachia* in the Americas.

Statement of Proprietary Data: As a modeling study, this study was built on aggregate or public data and did not use any identifiable person-level data.

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Thank you for considering this manuscript.

Sincerely,

Donald S Shepard, PhD, FASTMH

Professor

Economic evaluation of *Wolbachia* deployment in Colombia: A modeling study

Short title: Economic evaluation of *Wolbachia* in Colombia

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ABSTRACT

Background and Aims

Wolbachia are bacteria that inhibit dengue virus replication within the mosquito. Previous studies found *Wolbachia* reduced virologically-confirmed dengue cases by 77% and was highly cost-effective. The World Mosquito Program in Colombia deployed *Wolbachia* in the Aburrá Valley from 2015-2022 and introduced *Wolbachia* in Cali in 2020. To inform decisions about future extensions, we performed economic evaluations of potential expansion of *Wolbachia* deployments to 11 priority Colombian cities.

Methods

Numbers and the distribution by severity of reported dengue cases were assembled from Colombia's national disease surveillance system and the health service provision registry (RIPS). An epidemiological panel of three experts provided consensus estimates for shares of non-medical cases and adjustments for under-reporting and misclassifications. Costs (in 2020 US dollars) of treating dengue illness were based on: (1) the benchmark tariff of the mandatory insurance for traffic accidents, (2) RIPS data on services provided per symptomatic dengue case and, (3) the national government database for establishing insurance premiums. A cluster randomized trial quantified the effectiveness of *Wolbachia* against symptomatic dengue cases.

Results

Projecting impact over 10 years for Cali, we estimated a net health-sector savings of $4.95 per person. We also estimated averting 369 disability-adjusted life years (DALYs) per 100,000 population. From a societal perspective at 10 years, *Wolbachia* deployment is expected to have highly favorable benefit-cost ratios, with benefits per dollar invested of USD6.62 in Cali and USD5.61 over all priority cities.

Conclusions

Over 10 years, *Wolbachia* is highly beneficial on economic grounds, and almost universally cost saving. That is, *Wolbachia's* savings in health care costs alone would more than offset deployment costs nationally and in all but one priority city. Even the least favorable parameter estimates generate at least USD2.00 in benefits per dollar invested, giving substantial confidence that *Wolbachia* deployment would be cost-beneficial in Colombia.

Key words:

Dengue, Colombia, *Wolbachia*, Cost-effectiveness analysis, Benefit-cost analysis, Mosquito control

1 INTRODUCTION

Dengue, responsible for dengue fever and dengue hemorrhagic fever, is the most widespread vector-borne virus in the southern hemisphere.[1] Colombia has experienced recent dengue epidemics in 2010, 2013, and 2019.[2]

Wolbachia are common bacteria that naturally infect fruit flies and many other insects. Researchers at the World Mosquito Program (WMP) discovered that they could infect *Aedes aegypti* mosquitoes with these bacteria[3] and that dengue, chikungunya and Zika viruses are then less able to replicate within the insects, thereby inhibiting the transmission of these mosquito-borne infections.[4] To use this method for disease control, governments, communities, and international organizations (e.g., the WMP) partner to grow mosquitoes infected with *Wolbachia* in insectaries and then deploy eggs or adult mosquitoes to establish the bacteria in the local mosquito population. *Wolbachia*-infected mosquitoes transmit the bacteria through their eggs to the next generation. This approach is termed the "replacement" strategy, as it seeks to replace wild mosquitoes by *Wolbachia*-infected ones. Thus, the establishment of *Wolbachia* becomes a sustainable and often long-term control mechanism at that site. The replacement approach was first applied near Cairns, Australia. Now a decade after initial deployment, mosquitoes there remain infected with the bacteria, supporting the long-term viability of the approach.[5] The replacement approach is being applied in countries in the Americas, Asia, and Oceania.[6]

Under a different approach, the *Wolbachia* suppression strategy, Singapore releases only male *Wolbachia* infected mosquitoes.[3] When these mosquitoes mate with wild mosquitoes, the eggs do not hatch, thereby reducing the number of potentially disease-carrying insects. While experiments to date have found this approach efficacious, the need for annual releases will likely make the suppression approach more costly.

A landmark cluster randomized trial reported that *Wolbachia* reduced all virologically-confirmed symptomatic dengue cases by 77.1% and hospitalized cases by 86.2% in Yogyakarta, Indonesia.[7] A subsequent cluster randomized trial is underway in Belo Horizonte, Brazil. A quasi-experimental study from Niterói, Brazil found that *Wolbachia* reduced incidence of dengue by 69%, of chikungunya by 56%, and of Zika by 37%.[8] Research in Rio de Janeiro has shown that the technique is generally robust. Even in neighborhoods where *Wolbachia* coverage was low, such in favelas where access was difficult, dengue infections were still reduced by 38% and chikungunya by 10%.[9]

In Colombia, the WMP began implementing the *Wolbachia* project with pilot releases in 2015. In 2017 the WMP expanded to city-wide deployments in the Aburrá Valley (Medellín, Itagüí and Bello).[10, 11] An evaluation based on routine disease surveillance data reported reductions in notified dengue incidence of 95% to 97% in the three cities following *Wolbachia* introduction, compared to the prior decade; a parallel case-control study in Medellín also showed significantly lower dengue incidence in *Wolbachia*-treated neighborhoods compared to untreated ones.[11-13] Deployment progressed to Cali, with phased releases since 2020 reaching approximately half of the city's population by May 2023. That month, the departmental and municipal governments announced the expansion of *Wolbachia* to Yumbo municipality, 13 km northeast of Cali.[14]

Wolbachia is predicted to be a highly cost-effective intervention for controlling mosquito-borne illnesses, especially when released in high-density urban areas. In Indonesia, *Wolbachia* was projected to have a cost-effectiveness ratio in US dollars (USD) of USD1500 per disability-adjusted life year (DALY) averted, offsetting costs to the health system and to society with benefit-cost ratios ranging from 1.35

to 3.40.[15] In Vietnam, another study found the technology similarly cost effective based on the 10-year time horizon, and cost-saving at the 20-year time horizon.[16] In Suva, Fiji, a much smaller city, *Wolbachia* was acceptably cost-effective, but in Port Vila, Vanuatu, the relatively small target population and lower population density would not make the approach cost-effective there.[17]

To inform decision making within Colombia, we evaluated the large-scale implementation of the *Wolbachia* replacement strategy for controlling dengue in selected Colombian cities. Here we present the resulting cost-effectiveness and benefit-cost analyses.

2 METHODS

Framework

The WMP identified 11 target Colombian cities that might be suitable for *Wolbachia* based on population size, population density, and dengue incidence rates, and provided information about each city (Supporting Information S1 Table). Altogether, these cities accounted for a third of Colombia's reported dengue cases from 2010 through 2019. We conducted economic analyses for each of these target cities. The analyses were done by city, as implementation and funding decisions lie partly at the municipal level. We focus on Cali first as it is the furthest along, after the Aburrá Valley, in the deployment of *Wolbachia*. Our analysis began by estimating the current burden of dengue-related illness in each of these priority cities in terms of average annual numbers of cases, health care costs, and loss of health from non-fatal dengue cases. We then estimated the expected gains from *Wolbachia* based on the Yogyakarta cluster randomized trial. Next, we examined the cost of implementing *Wolbachia* based on the WMP's recent Colombian projects. Finally, we calculated cost-effectiveness and benefit-cost ratios showring the ratio of predicted health care gains to estimated costs by city.

Parameters

The parameters in Table 1 provide the national data for the economic analysis conducted on the *Wolbachia* deployment with monetary amounts in 2020 USD, or in 2019 dollars (which were similar) if information for 2020 was not available.

Table 1. National Parameters

Label	Parameter	Value
(P1)	Average health system cost per dengue case in 2019 (SOAT *tarifa*) for cases treated in the medical sector), USD	\$202.11
(P2)	Average health system cost per dengue case in 2019 (SOAT *tarifa*) for cases treated in the medical and non-medical sectors), USD	\$116.90
(P3)	Cost of *Wolbachia* per km^2 in Cali. USD	\$96,698
(P4)	Estimated % savings in conventional vector control spending, year 1,	0%
(P5)	Estimated % savings in conventional vector control spending, year 2	20%
(P6)	Estimated % savings in conventional vector control spending, year 3	30%
(P7)	Estimated % savings in conventional vector control spending, year 4	40%
(P8)	Estimated % savings in conventional vector control spending, year 5+	50%
(P9)	Efficacy of Wolbachia intervention (%), year 1 from date of deployment	37.5%
(P10)	Efficacy of Wolbachia intervention (%), year 2+ from date of deployment	75.0%
(P11)	Efficacy of *Wolbachia* intervention (%), 10-year average	71.3%
(P12)	DALY/case (mortality [33%] and morbidity [67%])	0.0476
(P13)	Share of Wolbachia deployment cost that is incurred in year 1	100%
(P14)	Share of Wolbachia deployment cost needed for long term monitoring, year 2+	1%
(P15)	Annualization factor for 10 years at 3% per year	0.117

(P16)	Cumulative present value factor over 10 years (inverse of annualization factor)	8.53
(P17)	Colombia GDP/capita (2020), World Bank, market prices, USD	$5,312
(P18)	Share of dengue cases correctly reported in surveillance system	29%
(P19)	Share of *Wolbachia* costs for preparation, before deployment	20.54%

Notes: DALY=disability-adjusted life year; GDP=gross domestic product; km=kilometers; SOAT=Seguro Obligatorio para Accidentes de Tránsito] Compulsory Insurance for Traffic Accidents]; USD=United States dollars. Monetary amounts in 2020 USD (or the closest year available) at market exchange rates. Sources: P15 from Excel (=pmt(3%,10,-1); P16 = 1 / P15; P17 from the World Bank,[18] and all others from authors' calculations.

Disease burden of dengue

The disease burden of dengue in a specified geographical area in a year is best conceptualized as the product of its number of dengue cases times the disease burden per case. Global research has found that a substantial share of dengue cases are treated outside the formal health sector, and thus not captured in existing databases.[19] To apply this concept to Colombia, we assessed the breakdown of dengue cases by severity and reporting status. We relied on the expertise of three epidemiologists: Luz Inés Villarreal Salazar (independent consultant in Colombia), Carlos Willian Rincon (University Los Andes), and Maria Patricia Arbelaez Montoya (World Mosquito Program, Colombia). We adjusted for underreporting of the number of dengue cases using an adjustment factor derived from *el Sistema Nacional de Vigilancia en Salud Pública (SIVIGILA)* [the National Public Health Surveillance System] and *Registro Individual de Prestación de Servicios de Salud Municipio de Envigado (RIPS)* [Individual Registry of Provision of Health Services Municipality of Envigado].

The disease burden per case of dengue is the sum of its morbidity and mortality components. The morbidity component comes from Zeng et al.[20] The mortality component of disease burden of dengue per case was calculated first by dividing the average number of deaths due to dengue between the years 2012 through 2018 by the average incidence for these same years to find a weighted average case-fatality rate of 6.05×10^{-4}. Based on an estimated 50 years of remaining life and a discount rate of 3%, the discounted remaining life was calculated using the following formula:

$$\text{Discounted remaining life} = [1 - (1 + 0.03)^{-50}] / 0.03 = 25.73$$

Rounding the results from the Indonesian trial,[7] we estimated that the *Wolbachia* program in Colombia will result in a 75% reduction in dengue cases once *Wolbachia* is stably established in the mosquito population, estimated to be from the second year of implementation onwards based on projected time for deployment. Projecting a linear increase from zero to complete establishment of *Wolbachia* over the first year of implementation, we estimated a 37.5% reduction in dengue cases in that year.

<u>Current cost of a dengue episode</u>

The aggregate cost of dengue is the product of the average cost per case times the number of cases. We used two approaches to estimate the cost of a dengue case in Colombia. Under our main approach, the average direct cost of a dengue case treated in the formal health system in 2019 was estimated using the mandatory road traffic tariffs, *Seguro Obligatorio para Accidentes de Tránsito (SOAT*) [Compulsory Insurance for Traffic Accidents], for reported cases. We converted the amounts in Colombian pesos to US dollars at the average exchange rate for the years 2015-2020.[21] For most curative services in the health care system, RIPS provides a national claims system that captures the health care provided to the insured population by diagnostic codes, care provided, and care setting. The data include the number of consultations and procedures used, emergency room visits, and hospitalizations. RIPS categorized dengue cases as classic dengue and severe dengue. For verification we used the *Suficiencia* [Sufficiency] database, which provides service payments for calculating the *Unidad de Pago por Capitación (UPC)* [Capitation Payment Unit] and premium information.[22]

Using the SOAT tariff, we derived the cost per case through stratification by the severity of dengue and calculated a weighted average based on the estimated share of dengue cases by severity. To reflect the fact that a number of classical cases were hospitalized, we stratified by severity category and not by treatment setting for consistency among data sources. To report the cost of a typical dengue case in Colombia from the health system perspective, we adjusted for cases treated outside the health care system. To estimate the economic cost, we incorporated both the cost of cases treated outside the health care system and direct and indirect household expenditures during a dengue episode. To validate our SOAT-based estimate of the health sector cost per dengue case, we performed a supplemental calculation based on aggregate data (see Supporting Information S2 Text, Supporting Information S3 Table and Supporting Information S4 Table).[23-28]

We then analyzed the RIPS claims data to derive the average cost of a non-fatal dengue case for the years 2015 through 2020 and reported the average 5-year cost per case based on the severity of dengue, i.e., severe and non-severe dengue. The claims data included the total number and cost of dengue health care services based on the care setting: consultations, procedures, emergencies, and hospitalizations.

Cost of *Wolbachia* deployment

To estimate the cost of the *Wolbachia* program in the 11 priority cities in Columbia, we started by analyzing the program budget for Cali. The budget covered two programmatic phases, with each phase divided into three stages: prepare, release, and short-term monitoring (STM). The budget covered the administrative and management cost, communication, community engagement, data management, diagnostic, monitoring, mosquito rearing, the release of the *Wolbachia* mosquitoes, surveillance, site start-up, project oversight, and indirect (facilities and administrative) costs.

The preparation stage was 12 and 6 months for phases 1 and 2 of the Cali program, respectively; release stages each took 6 months, and the STM stage was 12 months. Initially, the WMP projected that implementation of the *Wolbachia* program would take three years per city. After further discussions, however, we agreed that expansion of the existing program to additional cities in Colombia, and likely in other countries in a scale-up phase, could be achieved with an accelerated timeline and reduced the projected duration.

Based on the shortened timeframes, we reduced the durations of projected staff requirements. We estimated indirect cost of the *Wolbachia* program at 15% of direct costs. This is the maximum global rate allowed to grantees by the Bill & Melinda Gates Foundation,[23] a major sponsor of *Wolbachia* development. Brandeis researchers also reduced the estimated time needed for preparation, release, and long-term monitoring from 30 months to 15 months. Both adjustments reduced the overall projected per square kilometer (km^2) cost of the *Wolbachia* program. To estimate the overall cost of the program in the 11 priority cities, we made the preceding two adjustments to the budgeted cost of Cali phase 2 deployments to derive an adjusted cost per km^2 (parameter P5). WMP provided estimates of the projected release area km^2 in each target city, including all built-up areas and excluding public spaces, which were multiplied by the adjusted cost per km^2 (parameter P3) to estimate the cost of implementation in the rest of Cali and the 10 other priority cities.

Our cost projections generated both best estimates and confidence bounds. The uncertainty reflected alternative estimates of the size of the deployment needed and the cost adjustment attributable to the pause in Cali phase 1 deployment due to the COVID-19 pandemic. The implementation costs occur primarily during the first and second years of release and STM, with an estimated 1% of the initial spending needed annually for long-term monitoring from the second year onward.

Economic appraisal

We calculated the present value of the *Wolbachia* program and all cost offsets in each city over a ten-year time horizon with a discount factor of 3% per year. The vector control offset was calculated through percentagewise cost savings estimated in Table 1. The medical cost offset comprises the estimated reduction of cases over the ten-year time horizon. The benefit-cost ratio was derived from the calculated total economic benefits (including the economic value of good health) divided by the cost of the deployment. Where this ratio exceeded 1.0, *Wolbachia* was considered a favorable economic investment. The incremental cost-effectiveness ratio (ICER) is the net present value cost of the *Wolbachia* program divided by its present value health gain in DALYs. A positive ICER below Colombia's per capita GDP[18] ($5,312) indicates that the intervention is highly cost-effective. A negative ICER indicates that the replacement strategy is cost saving, i.e., exceptionally cost-effective.

3 RESULTS

Current cost of dengue

The epidemiological panel provided the following five categories for the distribution of dengue cases in Colombia by severity and reporting to SIVIGILA: (1) 2% are severe cases and correctly diagnosed and reported to SIVIGILA, (2) 27% are non-severe dengue (including those with and without warning signs) and correctly reported to SIVIGILA, (3) 11% are non-severe dengue, diagnosed by medical providers but not reported to SIVIGILA due to time and administrative barriers, (4) 20% are non-severe dengue cases that are misdiagnosed (e.g., diagnosed as a non-specific viral fever), and (5) 40% are mild and do not interact with the formal healthcare system (i.e. home treatments).

Supporting Information S5 Table presents the average cost of a dengue case by severity and the proportion of dengue cases treated by setting. Only 29% of dengue cases are reported, almost all of which are non-severe dengue. Based on SOAT tariff, we estimated the medical cost of care for cases within the medical system as USD406.37 for a severe case (constituting 6.45% of medical cases) and USD188.02 for a non-severe medical dengue case (constituting 93.55% of medical cases). The weighted average cost per medical case was USD202.11 and USD1.50 for a non-medical dengue case. The societal cost per case, derived from Castro et al.,[1] averaged USD151.96, comprised of health sector costs (averaging USD116.90) and indirect costs (averaging USD35.06).

Disease burden of dengue per case

Based on the calculation provided for discounted remaining life, the years of life lost and years lived with disability per case are 0.0156 and 0.0320, respectively. The sum of these two metrics comprised the total disease burden per dengue case of 0.0476 DALYs.

Analytical results in priority cities

To illustrate our results, we have focused on Cali. It was the city with the greatest burden in reported dengue cases. After the Aburrá Valley, where *Wolbachia* had been deployed previously,[10] Cali is the one priority city in Colombia in which *Wolbachia* is already partly deployed. Table 2 displays the analytic results of *Wolbachia* releases for Cali, ten other priority cities, and the national level. Table 3 presents the costs and benefits as rates per person covered and gives final economic results. All benefit cost ratios are highly favorable, ranging from 1.62 to 10.60.

Table 2. Aggregate costs and DALYs for priority cities following the start of *Wolbachia* releases

Rank	Municipality	Adjusted population in release area	Adjusted release area dengue cases (including unreported)	Initial *Wolbachia* deployment costs	PV *Wolbachia* program costs[a]	PV Vector control offsets[a]	PV medical cost offsets[a]	PV net costs[a]	PV DALYs[a]
1	Cali	2,217,961	27,649	$8,973,571	$9,672,263	$563,261	$20,086,318	-$10,977,315	8,174
2	Ibagué	503,745	10,342	$2,269,484	$2,446,189	$238,873	$7,512,810	-$5,305,494	3,057
3	Villavicencio	506,145	10,161	$2,506,072	$2,701,197	$309,493	$7,381,782	-$4,990,078	3,004
4	Cúcuta	759,395	9,739	$4,363,719	$4,703,483	$1,195,491	$7,075,123	-$3,567,131	2,879
5	Bucaramanga	604,186	9,540	$1,989,085	$2,143,957	$803,501	$6,930,606	-$5,590,150	2,821
6	Neiva	343,194	7,035	$1,857,647	$2,002,286	$159,430	$5,110,385	-$3,267,529	2,080
7	Barranquilla	1,296,471	6,015	$5,783,242	$6,233,532	$226,281	$4,370,044	$1,637,207	1,778
8	Valledupar	477,763	3,937	$2,234,434	$2,408,410	$295,246	$2,860,029	-$746,866	1,164
9	Armenia	300,785	4,100	$1,253,036	$1,350,598	$124,653	$2,978,651	-$1,752,705	1,212
10	Pereira	404,270	3,262	$1,524,673	$1,643,386	$127,747	$2,369,401	-$853,762	964

11	Cartagena	926,747	2,460	$3,864,257	$4,165,132	$1,103,887	$1,786,889	$1,274,356	727
ALL	National	8,340,662	94,239	$36,619,221	$39,470,433	$5,147,863	$68,462,037	-$34,139,468	27,862

[a] 10-year present values.

Note: DALYs=disability adjusted life years; PV=present value over 10 years discounted at 3% per year; population in the release areas derived by the World Mosquito Program based on analyses of population density; monetary amounts are in 2020 US dollars.

Table 3. Ratios for priority cities following the start of *Wolbachia* releases

Rank	Municipality	PV *Wolbachia* deployment costs per person covered	PV conventional vector control offsets per person covered	PV medical care offsets per person covered	PV indirect benefits per person covered	PV overall gross benefits per person covered	PV DALYs averted per 100,000 population	Benefit-cost ratio	ICER
1	Cali	$4.36	$0.25	$9.06	$19.58	$28.89	369	6.62	-$1,343
2	Ibagué	$4.86	$0.47	$14.91	$32.24	$47.63	607	9.81	-$1,735
3	Villavicencio	$5.34	$0.61	$14.58	$31.53	$46.72	594	8.76	-$1,661
4	Cúcuta	$6.19	$1.57	$9.32	$20.14	$31.03	379	5.01	-$1,239
5	Bucaramanga	$3.55	$1.33	$11.47	$24.80	$37.60	467	10.60	-$1,982
6	Neiva	$5.83	$0.46	$14.89	$32.19	$47.55	606	8.15	-$1,571
7	Barranquilla	$4.81	$0.17	$3.37	$7.29	$10.83	137	2.25	$921
8	Valledupar	$5.04	$0.62	$5.99	$12.94	$19.55	244	3.88	-$642
9	Armenia	$4.49	$0.41	$9.90	$21.41	$31.73	403	7.07	-$1,446
10	Pereira	$4.07	$0.32	$5.86	$12.67	$18.85	239	4.64	-$885

11	Cartagena	$4.49	$1.19	$1.93	$4.17	$7.29	78	1.62	$1,752
ALL	National	$4.73	$0.62	$8.21	$17.74	$26.57	334	5.61	-$1,225

Note: DALYs = disability adjusted life years; ICER=incremental cost-effectiveness ratio; PV=present value over 10 years discounted at 3% per year; monetary amounts are in 2020 US dollars.

Fig 1 displays the cumulative projected economic benefits of the *Wolbachia* program in Cali by component and time horizon, where time is the number of completed years since *Wolbachia* deployment. *Wolbachia* is projected to replace some conventional vector control, avoid the need for medical care for treating dengue illness, and create economic value of additional healthy years. The overall economic benefits, the sum of these components, grows with increasing time horizons to USD51.73 per person covered with a 20-year horizon. Over this horizon, vector control offsets are the smallest benefit (USD0.50), followed by medical care offsets (USD16.20), and indirect benefits (the economic value of reduced illness, USD35.02).

<Insert Fig 1 about here>

The upper (dashed) line in Fig 2 shows the cost per person of implementing the *Wolbachia* program. The cost per person starts in year 0 with 20.54% of initial program costs (USD0.83) for planning and engagement of residents and local leaders. The remainder of initial costs occur in year 1, the year in which city-wide releases would occur, bringing initial program costs to USD4.05. Thereafter, annual monitoring occurs, if needed, costing 1% of the initial costs throughout the remainder of the time horizon. Thus, cumulative *Wolbachia* implementation costs per person rise to USD4.20 through 5 years and USD4.63 through 20 years. Whereas longer time horizons generated substantially larger benefits for each of the economic benefits, they added very little to the *Wolbachia* program costs. The lower (solid) line is the net health sector cost at each time horizon. In year 0, when there are no offsets, it is identical to costs of planning and engagement (USD0.83). In year 1, with some conventional vector control and medical care offsets, it reaches the maximum (USD3.50). Thereafter, health sector offsets exceed the additional vector control costs. At 4.3 years, *Wolbachia* begins to become cost saving. With longer time horizons, the cost savings continue to grow. Net costs per person become a substantial negative number (-USD12.08) with the 20-year horizon.

<Insert Fig 2 about here>

Fig 3 shows the summary outcome measures on health (DALYs averted) and economic impact (benefit-cost ratio) for Cali. Both increase with longer time horizons. With a 10-year horizon, the *Wolbachia* program averts 369 DALYs per 100,000 population with a benefit-cost ratio of 6.62. This highly favorable ratio indicates that every dollar invested generates USD6.62 in economic benefits for the city's residents through better health and averting health sector costs. With a 20-year horizon, these results become almost twice as favorable, averting 659 DALYs and a benefit-cost ratio of 11.18 to 1. Since the economic benefits from better health and offsets to health care expenses occur approximately uniformly over time, the break-even time horizons at which the benefits exactly offset the costs are 1.43 years (17 months) in Cali and 1.69 years (20 months) nationally. Both locations would offset their costs within 2 years.

<Insert Fig 3 about here>

Extending these results nationally, Fig 4 presents the benefit-cost ratios for all priority cities based on the 10-year horizon. All cities are favorable, as all the ratios exceed 1.00. Cali is close to the national average. Cartagena is the most marginal in economic terms, while Bucaramanga, with a ratio of 10.60, is almost twice as favorable as the national average.

<Insert Fig 4 about here>

Exploratory approach

We attempted to analyze the RIPS data by what we called the "tier," the most intensive setting in which a patient received services during a calendar. These were: hospital, emergency, consultations, and procedures. The resulting data, however, were not consistent with other information about dengue. The breakdown by tier showed only a small number of patients with a dengue hospitalization, but each person with a hospitalized case was reported to have had three dengue hospitalizations. As hospitalization for dengue in a year is relatively rare, having two in a year should be very rare and three extremely rare. For this reason, we felt that the RIPS data did not support the breakdown of RIPS utilization and costs by setting or "tier."

4 DISCUSSION

This study found that the favorable ICER and benefit-cost ratios strongly recommend the *Wolbachia* program. If implemented with efficacy mirroring the results from cluster randomized trial,[7] *Wolbachia* will substantially mitigate dengue incidence in the priority cities in Colombia. *Wolbachia's* costs mostly occur at the beginning, while the health and economic benefits accrue over time. Therefore, the cost effectiveness and economic benefits of *Wolbachia* increase based on the effective time horizon.

Colombia is hyperendemic with dengue.[2] We accounted for cases treated outside the medical system, misdiagnosed, or otherwise not reported and concluded that the burden of dengue is several times greater than official statistics. Our results reinforce previous research that

Colombia's dengue burden exceeds the global average.[19]

We used a supplemental method to validate the cost per case of dengue. The consistency with our main approach to cost estimation gives confidence in our results. The difference in the main health sector cost per case based on SOAT (USD117.50) and the supplemental approach based on macro costing (USD121.61) was only 3.5%. This small difference might be because while the RIPS data for this study account for procedures and consultations, they do not include the cost of medication in its estimates. However, we expect that the costs of medications are negligible for dengue. To relieve fever and discomfort, paracetamol is generally recommended. However, this long-established generic drug is very inexpensive. Because of the greater level detail in SOAT, we made that approach our preferred choice.

Our results show that the *Wolbachia* replacement strategy is highly favorable because it reduces health sector costs and has high benefit-cost ratios. In many cities, such as Cali, the economic benefits exceed USD5.00 for every dollar invested. With longer time horizons, the results are even more favorable. For example, for each dollar invested the average benefit across all priority cities grew from USD5.61 at 10 years to USD9.49 at 20 years. The study is especially applicable for policy as the first economic evaluation of *Wolbachia* to apply the results of the rigorous cluster randomized trial,[3] the first to apply *Wolbachia* to the Americas, the first offering a scaled approach in which national and city officials can choose any number of the target cities for deployment, and the first in a country with an almost universal national health insurance system. Thanks to Colombia's national health insurance system, the public sector would receive all the medical care cost offsets from *Wolbachia.*

Past cost-effectiveness studies suggest that in areas with high population densities, *Wolbachia* is comparable or more cost-effective than alternative dengue control interventions. Tschampl et al. found that community-based mobilization strategies in Nicaragua and Mexico were only marginally cost effective, with ICERs of USD29,618 and USD29,196 per DALY averted in Mexico and Nicaragua, respectively.[29] Vaccination and screening techniques in Colombia have cost-effectiveness ratios relative to GDP per capita ranging from 0.47 (with 90% dengue seropositivity among 9 year-olds) to 6.72 (with 10% dengue seropositivity).[30] *Wolbachia*'s deployment also has an ability to be scaled up from a community or regional deployment to all major endemic cities in Colombia.

Global experience and models raise a caution that *Wolbachia* may not work in isolated circumstances for varied reasons. In two nearby sites in Vietnam, *Wolbachia* coverage dropped in one (Tri Nguyan village) but not in the other (Vinh Luong). Researchers speculated that elevated temperature in water storage tanks where mosquitoes bred or an interaction with the built environment may have inhibited *Wolbachia* replication in the former.[31] In small-scale releases in Malaysia, *Wolbachia* were not permanently established because the selected strain (wAlbB) may have been less fit than the wild mosquitoes.[31] Modeling studies raise the possibility that dengue viruses could become resistant to *Wolbachia*. Because of the multiple mechanisms by which *Wolbachia* inhibit dengue transmission, any such resistance would likely evolve slowly.[32] Resistance could be identified by monitoring and possible corrective actions, such as new *Wolbachia* strains.

Our very favorable national benefit-cost ratio of 6.62 indicates that our findings are broadly resistant to such concerns. Suppose, as a worst case, that the efficacy of Wolbachia dropped from its central estimate of 77.1% to its lower confidence interval of 65.3%. This is a relative reduction of 15%. It could occur, for example, if *Wolbachia* failed to control dengue as projected at 10 years in 15% of the treated areas. Then the benefit-cost ratio would drop by 15% to 5.83. Still being substantially above 1.00, this adjusted ratio indicates that *Wolbachia* would still be very favorable. Comparable analyses for a 5-year horizon showed that even if protection lasted only that long, *Wolbachia* would still be highly beneficial. Similar calculations show that the replacement strategy would remain economically viable even if 10-year efficacy attenuated by 84.9%, calculated as (6.62 – 1)/6.62. At that point costs of USD1.00 would generate benefits of USD6.62 x (100.0% - 84.9%) or USD1.00, meaning that the program would just break even.

Several limitations should be acknowledged. The number of dengue cases varies between the RIPS and *Suficiencia* databases, pointing to inconsistencies and/or under-reporting. Additionally, the discrepancies between unit costing through the SOAT tariff prices of a dengue case and the macro-costing of a dengue case lend ambiguity to the actual cost of a dengue case to the Colombian economy. The difference between the SOAT tariff of USD116.90 (based on Table 1, P2) and the macro costing adds USD4.12 or 3.5% of the SOAT tariff for a total of USD121.01 per episode. This difference may have arisen because the SOAT tariff does not include the cost of medication, while the macro costing approach includes this cost. Finally, differences in numbers of dengue cases treated among epidemiological models, macro-costing, RIPS, and SIVIGILA creates uncertainty around the estimated healthcare cost offsets. However, the extremely favorable benefit-cost ratios indicate that *Wolbachia* deployment would still be highly favorable in most cities.

In an absolute sense, *Wolbachia* is beneficial with benefit-cost ratios exceeding 1.00. However, when discussing the implementation of the *Wolbachia* program, the Ministry of Health may also wish to consider other competing public health interventions to respond to dengue and other illnesses in Colombia. Coudeville et al. studied the impact of a screen-and-vaccinate strategy against dengue in Colombia.[30] From the perspective of the formal healthcare system, the median ICER for this strategy was equivalent to 42% of the GDP per capita. This strategy was more cost-effective (lower ICER) as the percentage of nine-year old seropositive individuals in the population increased. When examining the corresponding ICERs in the 11 municipalities in this study, the *Wolbachia* intervention ICERs are negative (extremely favorable as they are cost saving) in 9 of the 11 municipalities. In the remaining two municipalities (Barranquilla and Cartagena), the ICERs (USD921 and USD1,752, respectively) are positive, but they are 33% or smaller percentages of the GDP per capita (USD5,312). Even these positive ICERS are more favorable than the screen-and-vaccinate strategy with the Sanofi vaccine (Denvaxia).[30] *Wolbachia* also avoids the risk of adverse effects from vaccinating sero-negatives. In August 2022, a second dengue vaccine, Qdenga, manufactured by Takeda was licensed in Indonesia and by the European Medicines Agency and may become a candidate for public programs in the future. Published clinical results showed a reduction in dengue fever cases by 80%, and the Qdenga vaccine has not shown the risk associated with the Sanofi dengue vaccine.[33]

In the future, policy makers may have a portfolio of options. As our analysis shows, locations with a high number of dengue cases per square kilometer are ones where a lot of dengue cases can be averted at a limited cost. Thus, these will be the most favorable locations for *Wolbachia* deployment. This scalability of the intervention provides important considerations for municipal and regional governments for possible partnerships across multiple levels of government. Therefore, cities that can muster the resources would have the option of implementing

Wolbachia deployment. Other strategies, including vaccination, may be preferable for less densely populated locations. To address the uncertainties around each dengue control technique, some experts recommend integrating *Wolbachia*, vaccination, and case management.[34]

As resources for public health interventions are limited, it is useful to compare the cost-effectiveness of *Wolbachia* against that of public health interventions in Colombia. Two vaccines provide instructive examples. In 2013, Aponte-Gonzalez et al. published a cost-effectiveness analysis of Human Papillomavirus vaccines (HPV) in Colombia, from the societal perspective.[35] They found an ICER greater than three times the 2013 GDP per capita, so it was not cost-effective by routine criteria However, Colombia had already introduced HPV vaccination into its national vaccination program in 2012.[36] In 2023, Morales-Zamora et al. assessed the cost-effectiveness of high-prioritization and no prioritization strategies for COVID-19 vaccination campaigns in Colombia for 2023.[37] The high-prioritization strategy focused on the population at the highest risk. Their ICERs were USD3,339 for the high-prioritization strategy and USD5,224 for a no-prioritization strategy. Being cost saving in most priority cities, the *Wolbachia* program would be more cost-effective than both of these existing programs.

5 CONCLUSIONS

Our results show that *Wolbachia* is highly favorable because it reduces health sector costs and has high benefit-cost ratios. In all priority cities, the economic benefits per dollar invested exceed USD1.00, indicating that the economic value generated exceeds the costs. *Wolbachia* merits implementation in many of the 11 priority cities. *Wolbachia* does, however, present an initial fiscal challenge, as almost all the costs must be paid at the outset for preparation and deployment, while the benefits occur over time. Phasing deployment would mitigate up-front costs but delay the projected health benefits. Colombian officials will need to weigh these tradeoffs.

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Author contributions

Donald S. Shepard: conceptualization; formal analysis; funding acquisition; methodology; supervision; writing—review & editing. **Samantha R. Lee**: data curation; formal analysis; writing—original draft, review & editing. **Yara A. Halasa-Rappel**: data curation; formal analysis; writing—original draft, review & editing. **Carlos Rincon Perez**: methodology; data curation; formal analysis; writing—review & editing. **Arturo Harker Roa**: methodology; data curation; supervision; writing—review & editing. All authors have read and approved the final version of the manuscript. Donald S. Shepard had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest statement

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Data availability statement

Data access may be requested from the respective Colombian government agencies. For RIPS, see https://www.minsalud.gov.co/proteccionsocial/Paginas/rips.aspx. For population, see https://www.dane.gov.co/index.php/estadisticas-por-tema/demografia-y-poblacion/proyecciones-de-poblacion.

Ethics statement

This modeling study did not involve any human studies data as it was based entirely on aggregate or publicly available anonymous data. These data could not allow any individual to be identified nor linked with any individual. The research team did not prospectively nor retrospectively recruit human participants nor did the team obtain tissues, data, or samples for the purposes of this study. The research team did not review existing medical records nor archived samples. Therefore, this study was outside the purview of the Committee for Protection of Human Studies in Research so ethical approval was not applicable.

Transparency statement

The lead author Donald S. Shepard affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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FIGURE LEGENDS

Fig 1. Economic benefits of *Wolbachia* by component and time horizon

Fig 2. Gross and net health sector costs of *Wolbachia* by component and time horizon

Fig 3. Program impacts (DALYs and benefit-cost ratios) in Cali by time horizon

Note: DALYs denote disability adjusted life years

Fig 4. Estimated benefit-cost ratios by city with a 10-year horizon

SUPPORTING INFORMATION

S1 Table. Input data for priority cities

S2 Text: Macro-costing approach

S3 Table. Macro-costing approach to estimate the average cost of an outpatient visit and hospitalization (monetary amounts in 2020 USD)

S4 Table. Health care cost of dengue cases by type of dengue diagnosis and setting using macro-costing (amounts in 2020 USD)

S5 Table. Cost of dengue case by dengue type (Tarifa SOAT for reported), 2019 USD

Figure 1

Click here to access/download;Figure;Fig1a.tif

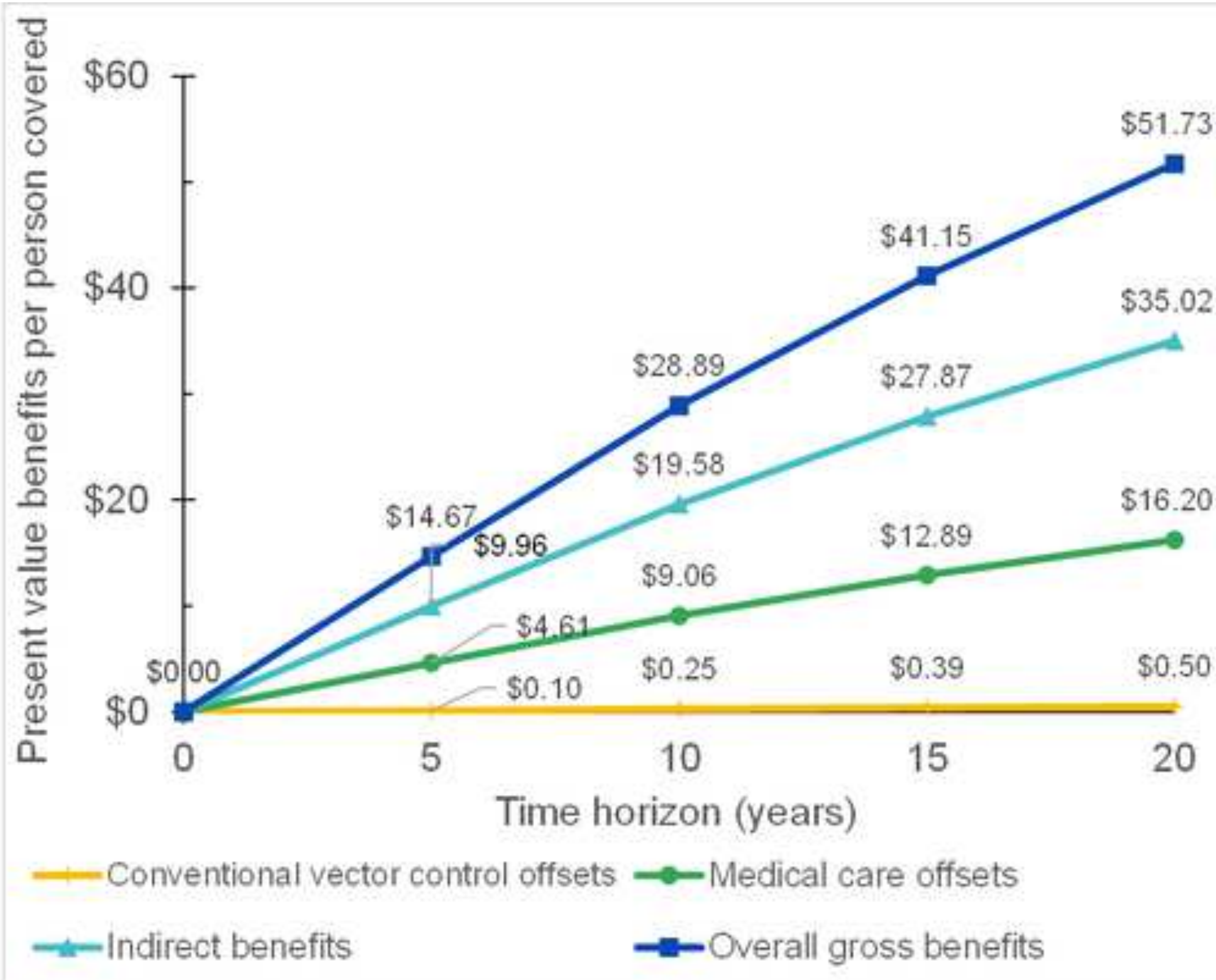


Figure 2

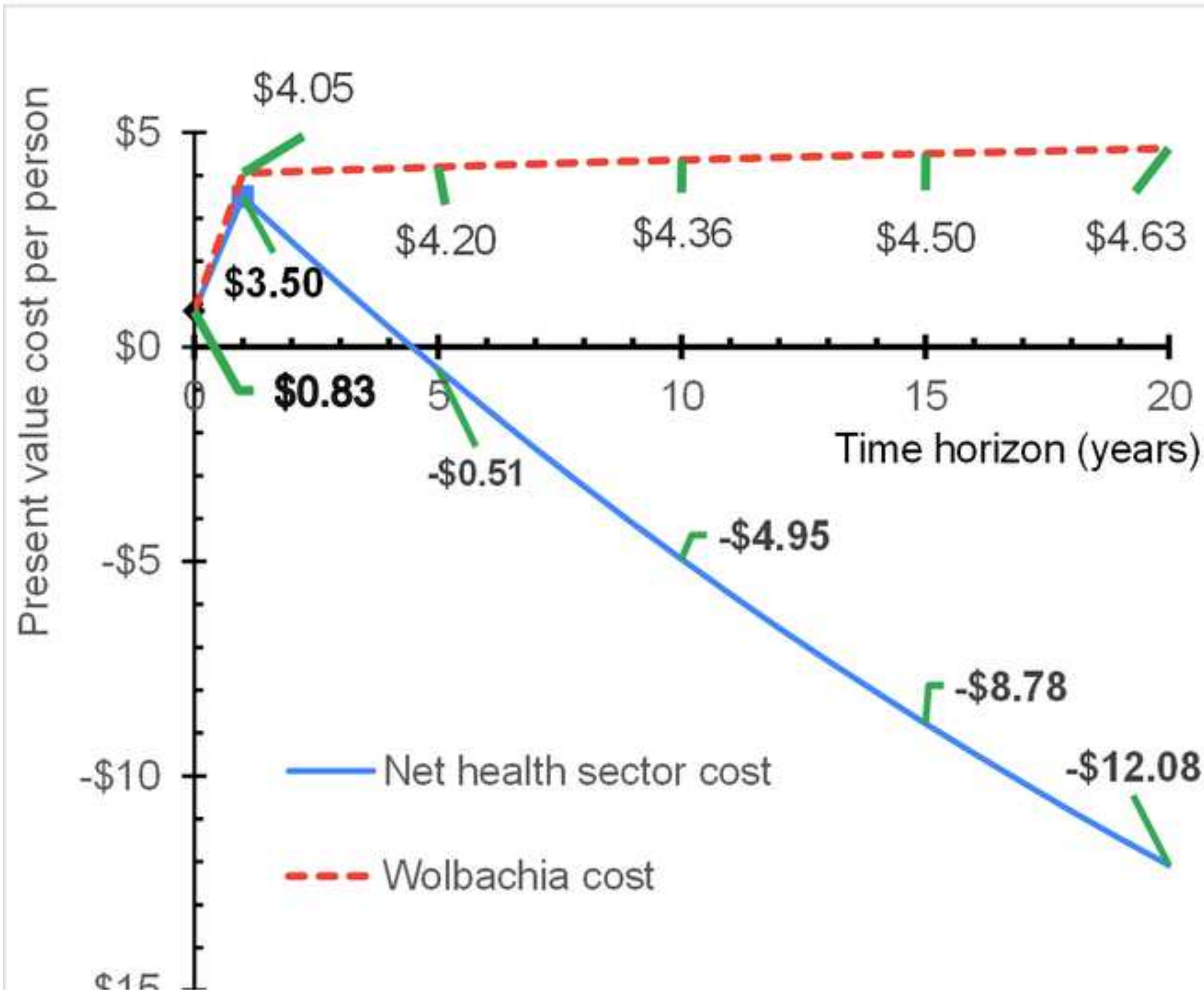
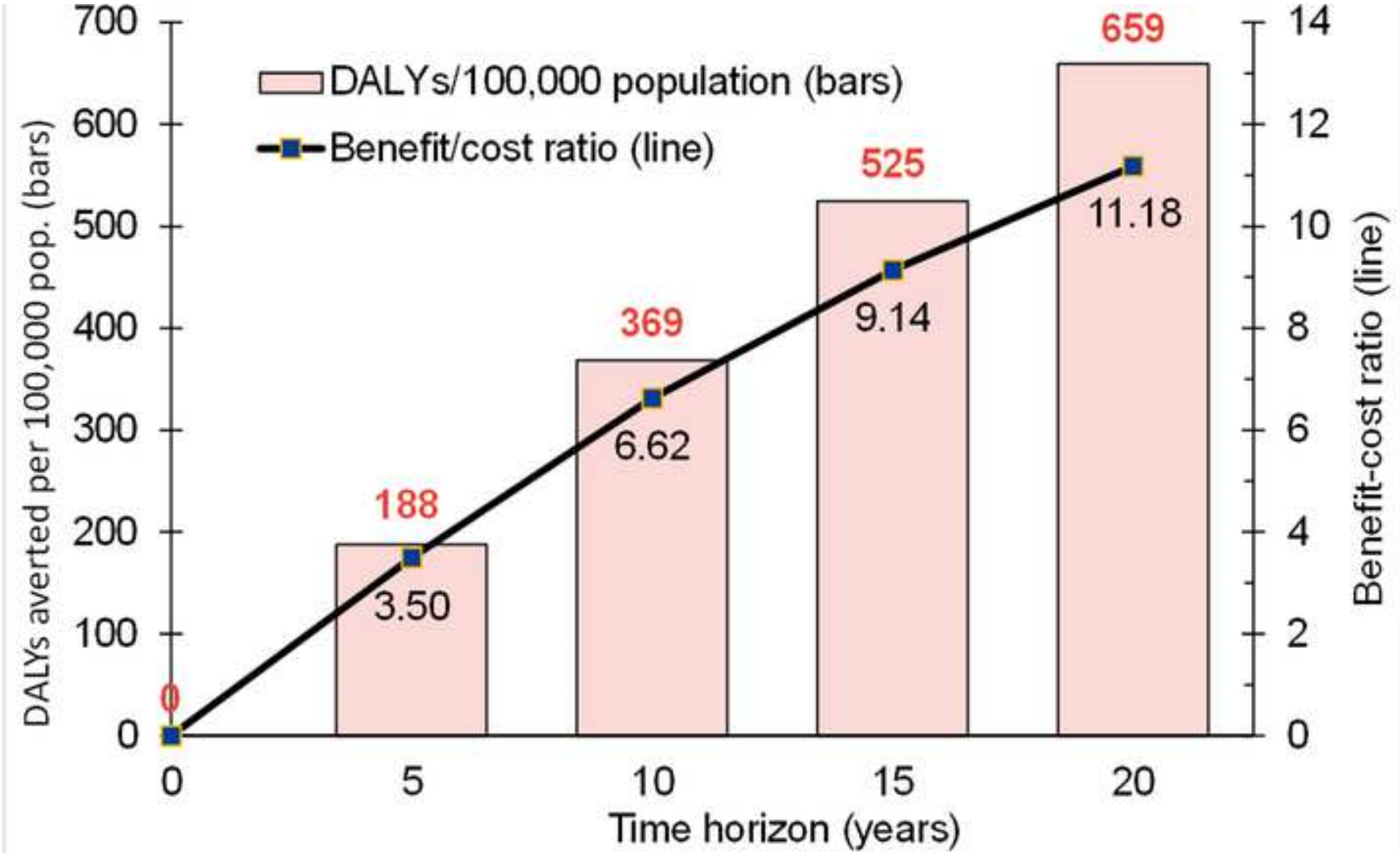

$4.05
$5
$0
-$5
-$10
-$15
Present value cost per person
$4.20
$4.36
$4.50
$4.63
$3.50
$0.83
0
5
10
15
20
Time horizon (years)
-$0.51
-$4.95
-$8.78
-$12.08
Net health sector cost
Wolbachia cost

Figure 3



DALYs/100,000 population (bars)
Benefit/cost ratio (line)
DALYs averted per 100,000 pop. (bars)
Benefit-cost ratio (line)
Time horizon (years)
0
188
369
525
659
3.50
6.62
9.14
11.18
0
100
200
300
400
500
600
700
0
2
4
6
8
10
12
14
0
5
10
15
20

Figure 4

Benefit-cost ratio
$12
$10
$8
$6
$4
$2
$0
$1.62
$2.25
$3.88
$4.64
$5.01
$5.61
$6.62
$7.07
$8.15
$8.76
$9.81
$10.60
Cartagena
Barranquilla
Valledupar
Pereira
Cúcuta
National
Cali
Armenia
Neiva
Villavicencio
Ibagué
Bucaramanga