Economic evaluation of *Wolbachia* deployment in Colombia

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Executive Summary

Introduction

The World Mosquito Program (WMP) in Colombia deployed *Wolbachia* in the Aburrá Valley (Medellín, Bello and Itagüí) from 2015-22 and began deploying *Wolbachia* in Cali in 2020, with Cali phase 3 underway in 2022. A randomized trial published in 2021 from Yogyakarta, Indonesia found that *Wolbachia* reduced symptomatic dengue cases by 77.1%. The Colombian national government is considering potential expansions to other endemic cities in Colombia. This report presents an independent economic analysis of a potential expansion of *Wolbachia* deployments to 11 priority cities (the rest of Cali and other high burden cities). Altogether, these cities accounted for a third of Colombia's reported dengue from 2010 through 2019.

Methods

Projected costs of *Wolbachia* deployment were initially based on estimates from the WMP from the experience in the Aburrá Valley and Cali Phase 1 per square kilometer. The projected costs were subsequently reduced based on the understanding that preparation and monitoring could be done in fewer months, and consequently at lower cost, than initially estimated. In addition, the projected overhead costs of general management from the WMP were reduced to 15%, the rate authorized in low- and middle-income countries by a major global donor for such work, the Bill & Melinda Gates Foundation. All economic data were presented in 2020 US dollars.

Numbers and the distribution by severity of reported dengue cases nationally and in target cities were assembled from the national disease surveillance system (SIVIGILA) for 2010-2019 and the health service provision registry (RIPS). An epidemiological panel of three experts interpreted these data. It provided consensus estimates of cases seen in the formal health system but not reported at all, or incorrectly reported, and cases seen outside the health care system that still pose a health burden to the population.

Costs of treating dengue illness were based on: (1) the benchmark tariff of the mandatory insurance for traffic accidents (SOAT), (2) RIPS data on services provided per symptomatic dengue case and, (3) the government data base for establishing insurance premiums (Suficiencia). The effectiveness of *Wolbachia* was based on the Yogyakarta trial results. In the base case, benefits were assumed to last for 10 years based on WMP experience in Australia, with sensitivity analyses projected to 20 years.

Results

The overall average medical cost per symptomatic dengue case was US$202.11 in the health care setting, and US$116.90 overall, including those treated in non-medical settings. The distribution of cases by severity and setting was 2% severe dengue (in medical setting), 58% non-severe dengue (both with and without alarm signs) treated in medical settings, and 40% dengue cases treated in non-medical settings. Over 10 years, *Wolbachia* deployment cost US$4.73, averted 0.0033 DALYs, offset $8.21 in health care costs and offset $8.83 including conventional vector control costs, and had a net present value cost of US$-4.10 per person in all target release areas in Colombia. The incremental cost-effectiveness ratio (ICER) was US-$1,225 per disability-adjusted life year (DALY) averted. The negative national net cost and negative ICER indicate a net savings after factoring in expected offsets to healthcare costs and conventional vector control. Over 10 years, *Wolbachia* deployment is expected to return US$5.61 from a societal perspective for every dollar invested (i.e., benefit-cost ratio of 5.61).

Cali is the city with the most dengue cases. Again over 10 years, in that city, *Wolbachia* would avert 0.0037 DALYs at a deployment and monitoring cost of US$4.36 per person in the target release area for an ICER of

US$-1,343 with a societal benefit-cost ratio of 6.62. Across the 11 cities, the benefit-cost ratios range from 10.60 in Bucaramanga to 1.62 in Cartagena, based primarily on the number of dengue cases per square kilometer in the release area. Counting the economic benefits from averted medical costs and illness avoided, the payback period is 1.43 years (17 months) in Cali and 1.69 years (20 months) nationally. From the more stringent criterion of offsets to healthcare costs alone, over 10 years *Wolbachia* saves sufficient healthcare costs to offset the costs of deployment in 9 of the 11 priority cities.

<u>Discussion</u>

Over 10 years, *Wolbachia* is highly favorable on economic grounds. A negative ICER is even more favorable than just being cost-effective. Over 10 years, *Wolbachia* would be free nationally and in 9 cities individually. Savings in health care costs alone (largely funded by government through mandatory contributions through mandatory premium payments and taxes) would more than offset the costs of *Wolbachia* deployment nationally and in all but two priority cities.

Differences in numbers of dengue cases treated among epidemiological models, macro-costing, RIPS, and SIVIGILA creates uncertainty around the estimated healthcare cost offsets. However, benefit-cost ratios indicate that *Wolbachia* deployment would still be favorable even with smaller cost offsets where the benefit-cost ratio exceeds 2.0 (all cities except Cartagena). *Wolbachia* also presents 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.

Introduction

Dengue, responsible for dengue fever and dengue hemorrhagic fever, is the most widespread vector-borne virus in the southern hemisphere (Castro et al, 2016). Colombia has experienced recent dengue epidemics in 2010, 2013, and 2019 (Guitierrez-Barbosa et al, 2020). The World Mosquito Program (WMP)'s *Wolbachia* program aims to lower the incidence of dengue infections in Colombia as an alternative to traditional vector control methods. A landmark 2021 publication in the *New England Journal of Medicine* reported that *Wolbachia* reduced all virologically confirmed symptomatic dengue cases by 77.1% and hospitalized ones by 86.2% in Yogyakarta, Indonesia (Utarini et al 2021).

The WMP began implementing the *Wolbachia* project in Colombia with pilot releases in 2015 and then city-wide deployments commencing in 2017 in the Aburrá valley (Medellin, Itagui and Bello). Deployment then progressed to Cali, with the first stage in 2020 and the second stage beginning in 2021. The WMP together with the Colombian Ministry of Health is exploring possibilities to extend *Wolbachia* deployments to other dengue endemic areas of Colombia.

Objectives

To inform decision making within Colombia, we conducted an independent economic evaluation of Colombia's WMP *Wolbachia* program. Specifically, this report provides cost-effectiveness and cost-benefit analyses of implementing *Wolbachia* in 11 priority cities in Columbia that accounted for a third of Colombia's reported dengue from 2010 through 2019.

Methods

Framework

We began by estimating the current burden of dengue-related illness in the target 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 study. Next, we examined the cost of implementing *Wolbachia* based on the WMP's latest experience. Finally, the economic analysis related health care gains to costs by city through incremental cost-effectiveness analyses and benefit-cost ratios.

Parameters

The parameters in Table 1 provide the national data for the economic analysis conducted on the*Wolbachia* deployment with monetary amounts in 2020 US dollars (USD).

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	$96,698
(P4)	Cost of *Wolbachia* per km^2 in Aburrá Valley	$92,354
(P5)	Cost of *Wolbachia* per km^2 in other cities	$87,625
(P6)	Year 1, estimated savings in conventional vector control spending	0%
(P7)	Year 2, estimated savings	20%
(P8)	Year 3, estimated savings	30%
(P9)	Year 4, estimated savings	40%
(P10)	Year 5+, estimated savings	50%
(P11)	Efficacy of *Wolbachia* intervention, y1 from date of deployment	37.5%
(P12)	Efficacy, y2 (not used)	75.0%
(P13)	Efficacy, y2 and later	75.0%
(P14)	Overall efficacy 10 years average	71.3%
(P15)	DALY/case (mortality [33%] & morbidity [67%])	0.0476
(P16)	Share of *Wolbachia* deployment cost incurred in first year	100%
(P17)	Share of *Wolbachia* deployment cost needed for long term monitoring, year two onward	1%
(P18)	Annualization factor for 10 years at 3% per year	0.117
(P19)	Factor for cumulative present value over 10 years (inverse of annualization factor)	8.53
(P20)	Colombia GDP/Capita (2020), World Bank, current US$	$5,312
(P21)	Share of dengue cases correctly reported	29%

<u>Number of dengue cases</u>

Global research has found that a substantial share of dengue cases is treated outside the formal health sector, and thus not captured in existing databases (Shepard et al 2016). 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), Carlos Willian Rincon (University Los Andes), and Maria Patricia Arbelaez Montoya (World Mosquito Program, Colombia). Using these proportions, we adjusted for underreporting of dengue cases to SIVIGILA. We adjusted for underreporting in the number of dengue cases using an adjustment factor derived fromel Sistema Nacional de Vigilancia en Salud Pública (SIVIGILA) and Registro Individual de Prestación de Servicios de Salud Municipio de Envigado (RIPS).

<u>Current cost of dengue</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), for reported cases. For numbers of health care services, RIPS provides a national claims system that captures the health care provided tothe insured population by diagnostic codes, care provided and care setting. The data include the number ofconsultations and procedures used, visits to an emergency room, and hospitalizations. Dengue cases were reported as classic dengue and severe dengue. For verification we used the Suficiencia database, which provides the source for calculating the Unidad de Pago por Capitación (UPC) and premium information.

We derived the cost per case through stratification by the severity of dengue and calculated a weighted average based onthe estimated share of dengue cases by severity. To accommodate the number of classical cases that were hospitalized, we stratified by severity and not by treatment setting. To report the cost of a typical denguecase in Colombia from the health system perspective, we adjusted for those treated outside the health care system. To estimate the economic cost, we accounted for both the cost of cases treated outside thehealth care system and direct and indirect household expenditures during a dengue episode.

We adjusted the number of hospitalizations for underreporting of hospitalizations in RIPS data. That adjustment compared the aggregate number of hospitalizations in RIPS data against the estimated number based on national hospital bed capacity using data from the OECD, hospital occupancy, and length of stay. RIPS reported 3,906,350 hospitalizations in 2018 (Table 2). Our derived number was 7,806,386 based on a 3-day overall length of stay and an annual average of 64,162 occupied beds. The ratio of RIPS reported to separately projected numbers was 50% (i.e. 3,906,350 / 7,806,386).

As a supplemental approach, we used the macro-costingapproach, a top-down costing approach that combines national statistics such as health care expenditure,the average length of hospital stay, insurance coverage with a conversion value to estimate the average cost of hospitalization and outpatient visit.

Table 2. Macro costing approach to estimate the average cost of an outpatient visit and hospitalization (monetary amounts in 2020 USD)

	Service	Formula	Parameters	Source
[1]	The population of Colombia in 2018		49,661,048	Worldometer https://www.worldometers.info/world-population/colombia-population/
[2]	Consultations per person (adjusted based on undercounting for hospitalization)		4.62	Derived from RIPS data (average number of consultancies per person)
[3]	Bed-day equivalent factor for consultations		0.32	Shepard et al, 2000
[4]	Bed-day equivalents of average consultations	[2]*[3]	1.4776	
[5]	Hospitalizations derived from RIPS data		0.0787	Derived from RIPS data
[6]	Share of all hospitalizations for all causes adjusted for RIPS		50.0%	OECD (2021), "Hospital beds and occupancy", in Health at a Glance 2021: OECD Indicators, OECD Publishing, Paris. DOI: https://doi.org/10.1787/e5a80353-en
[7]	Estimated mean length of stay		3.00	Derived from Police claims data
[8]	Hospital days (adjusted for RIPs undercount with 3 days LOS)	[7]*[9]/(1-[6])	0.4716	
[9]	Total bed day equivalents	[4]+[8]	1.9492	
[10]	SGSSS amount for 2019		$249.04	https://www.minsalud.gov.co/proteccionsocial/Paginas/cifras-aseguramiento-salud.aspx
[11]	Amount per bed day equivalent	[10]/[9]	$127.77	
[12]	Amount per visit	[3]*[11]	$40.89	
[13]	Amount per average hospitalization	[7]*[11]	$383.30	

We then combined this information with dengue-specific utilization derived from Social Protection Ministry data, RIPS, and expert opinion to estimate the weighted average for a typical dengue case. As presented in Table 3, we derived the proportion of dengue patients hospitalized and the average number of ambulatory services from RIPS data by type of dengue. We estimated the cost of care in the non-medical sector based on the expert panel assessment of the care needed assuming that these cases are mild classic dengue.

Table 3. The health care cost of dengue cases by type of dengue diagnosis and setting (amounts in 2020 USD)

		Formula	Severe dengue	Non-severe dengue*	Non-medical	Sources
[1]	Cost of a hospitalization episode based on macro costing with RIPS volume, US$		$383	$383	$383	Macro costing
[2]	The proportion of dengue patients hospitalized, based on RIPS data		67%	31%	0%	RIPS data
[3]	Cost of hospitalization per patient with any dengue, US$	[1]*[2]	$259	$117	$0	
[4]	The average number of ambulatory visits per dengue patient		3.14	1.91	0.00	RIPS data
[5]	Cost of an ambulatory visit based on macro costing with RIPS volume, US$		$40.89	$40.89	$40.89	Macro costing
[6]	The average cost of ambulatory visits by dengue type, US$	[3]*[4]	$128.55	$78.25	$0.00	Authors' calculation
[7]	Cost of care received outside the medical system, US$		$0.00	$0.00	$1.50	Expert panel
[All]	**Estimated average total cost per dengue case (macro costing), US$**	**[3]+[6]+[7]**	**$387.18**	**$195.72**	**$1.50**	**Authors' calculation**

* Includes non-severe dengue with and without warning signs

To derive the cost of an average dengue case in Colombia, we combined the cost data with dengue epidemiological data. The epidemiological data, based on our panel of epidemiologic experts, estimated that 2% of dengue cases were severe dengue, 58% were non-severe dengue (including those with and without warning signs) treated in the medical sector, and 40% were dengue cases treated in the non-medical sector. Based on these statistics, we estimated the cost of dengue cases from the health system perspective to be $121.01 and $135.33 from the societalperspective (adding household expenditures, derived from Castro et al., 2016, and cost of care in the non-medical sector).

In the second approach, we 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 denguehealth care services based on the care setting: consultations, procedures, emergencies, and hospitalization. One limitation of this dataset is that it provided only aggregate data, which limited our ability to derive consistent information on the cost of care by setting.

Based on this analysis, we estimated the cost of care for a severe case to be $406.37 and for non-severe dengue treated in the medical system to be $188.02. We utilized the same approach used to estimate the cost of an average dengue case in Colombia, where we combined the cost data with dengue epidemiological data, based the estimates that 2% of dengue cases were severe dengue, 58% were non-severe dengue (including those with and without warning signs) treated in the medical sector, and 40% were dengue cases treated in the non-medicalsector. Based on these statistics, we estimated the cost of non-fatal dengue cases from the health system perspective to be $202.11 and $116.90 from the societal perspective (adding household costs for medicalcare including the non-medical sector as well as lost income derived from Castro et al., 2016).

The difference in the cost estimates between the two approaches was small. It 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. Aspirin is contra-indicated for dengue patients. To relieve fever and discomfort, patients might be given paracetamol. However, this long-established generic drug is very inexpensive. Because of its greater detail, in the end, we decided to use the second approach (based on RIPS) as our preferred approach.

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 3 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."

Cost of *Wolbachia*

To estimate the cost of the *Wolbachia* program in 11 priority cities in Columbia, we started by analyzing the program budget for Cali. The budget covered two programmatic phases, each phase divided into three stages: prepare, release, and long-term monitoring (LTM). 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 an indirect cost of 15%. The preparation and release stages span were 6 months, and the LTM stage was 3 months.

Through discussions with the WMP, we learned that their initial plan for implementation of the *Wolbachia* program estimated a timeframe of three years per city. Further discussions, however, suggested that in Colombia, where the program had already begun in Cali, and likely in other countries in a scale-up phase, the program could accelerate the 3-year timeline.

Through these discussions of administrative requirements, timeframes, and staffing requirements, we adjusted the estimated indirect cost of the *Wolbachia* program to 15% of direct costs. This is the maximum global rate allowed to grantees by the Bill & Melinda Gates Foundation, 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 cost of the *Wolbachia* program per square kilometer. To estimate the overall cost of the program in the 11 priority cities, we made the above two adjustments to the budgeted cost of Cali phase 2 deployments to derive an adjusted cost per square kilometer (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 we multiplied by the adjusted cost per km^2 (parameter P5) to estimate the cost of implementation in the rest of Cali and the 10 other priority cities.

The uncertainty in these costs is based on both the size of the deployment needed and the necessary pause in the program due to the COVID-19 pandemic during the Cali deployment. The implementation costs occur primarily during the first and second years of release and short-term monitoring, with an estimated 1% of the initial spending needed annually for long-term monitoring from the second year onward.

<u>Disease burden of dengue per case</u>

This burden summarizes the morbidity and mortality components. The morbidity component comes from (Zeng et al., 2018). 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 and 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:

Discounted remaining life = [1 - (1 + 0.03)^(-50)] / 0.03 = 25.73

<u>Priority cities</u>

In addition to national data, our economic evaluation required a number of city-specific parameters for the priority cities. The information in Table 4 is based on information provided by WMP regarding priority cities for *Wolbachia* deployment.

Table 4. Input data for priority cities

Rank	Municipality	Average notified release area dengue cases	Population 2021 DANE projection (total municipality)	Area km² (municipality)	Cost of regular vector control in full city	% of the population in release areas	% of km² in release areas	Cost of *Wolbachia* deployment
1	Cali	8,018	2,264,748	562	$173,144	97.9%	16.5%	$8,973,571
2	Ibagué	2,999	542,724	1,377	$77,476	92.8%	1.9%	$2,269,484
3	Villavicencio	2,947	549,922	1,286	$101,230	92.0%	2.2%	$2,506,072
4	Cúcuta	2,824	787,891	1,132	$373,402	96.4%	4.4%	$4,363,719
5	Bucaramanga	2,767	614,269	153	$245,927	98.4%	14.8%	$1,989,085
6	Neiva	2,040	367,400	1,269	$51,381	93.4%	1.7%	$1,857,647
7	Barranquilla	1,744	1,297,082	154	$68,153	100.0%	42.9%	$5,783,242
8	Valledupar	1,142	544,134	4,185	$101,230	87.8%	0.6%	$2,234,434
9	Armenia	1,189	308,463	122	$38,484	97.5%	11.7%	$1,253,036
10	Pereira	946	480,803	608	$45,738	84.1%	2.9%	$1,524,673
11	Cartagena	713	1,043,926	595	$374,339	88.8%	7.4%	$3,864,257
All		27,329	8,801,362	11,443	$1,650,504	94.8%	3.6%	$36,619,221

* Cities are ranked in decreasing number of average dengue cases from 2010 through 2019, providing an ordering of cities according to their historical dengue burden.

** Salinas-Lopez et al, 2018

Results

Current cost of dengue

The consultations with project epidemiologists provided the following estimates for the undercount of dengue cases in Colombia:

- 29% of dengue cases are correctly diagnosed and reported to SIVIGILA.
- 11% of dengue cases are diagnosed correctly and are not reported to SIVIGILA.
- 20% of dengue cases are misdiagnosed (e.g.., diagnosed as a non-specific viral fever)
- 40% of dengue cases do not interact with the formal healthcare system (i.e., home treatments)

We estimated that 2% of all dengue cases are severe dengue and are correctly reported to SIVIGILA, 27% of all dengue cases are non-severe dengue (including those with and without warning signs) and correctly reported to SIVIGILA, 11% are non-severe dengue diagnosed but not reported to SIVIGILA due to time and administrative barriers, 20% are non-severe dengue cases that weremisdiagnosed, and 40% of all dengue cases were mild and treated outside the health care system for an estimated cost of $1.50 a case.

Table 5 presents the average cost of a dengue case by severity and the proportion of dengue cases treated by setting. From the health system perspective, we estimated the average cost of a dengue case to be US$116.90. This excludes the costs that occurred outside the health system and household spending. In addition, we estimated the economic cost of a dengue case which accounts for the cost to the health system, the costs outside of the health system, and household spending, to be $131.22 per case.

Table 5. Cost of dengue case by dengue type (Tarifa SOAT for reported), US$ 2019

	Severe dengue	Non-severe dengue*	Non-medical	Non-medical and HH expenditures**
Cost per case per setting	$406.37	$188.02	$1.50	$22.86
Proportion of reported dengue cases	2%	27%	0%	29%
Proportion of unreported dengue cases	0%	11%	0%	11%
Proportion of misdiagnosed dengue cases	0%	20%	0%	20%
Proportion of dengue cases treated outside the medical system	0%	0%	40%	0%

* Includes non-severe dengue with and without warning signs
**HH denotes household. Applies for severe and non-severe dengue

<u>Disease burden of dengue per case</u>
Based on the calculation provided for Discounted Remaining Life, the Years of Life Lost (YLL) and Years Lived with Disability (YLD) 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 Disability-Adjusted Life Years.

<u>Analytical results in priority cities</u>
Table 6 displays the analytic results for Cali, ten other priority cities, and the national level. Rounding the results from the Indonesian trial (Utarini et al., 2021), we assume the *Wolbachia* program in Colombia will result in a 75% reduction in dengue cases once *Wolbachia* is stably established in the mosquito population, assumed to be from the second year of implementation onwards. Therefore, we assumed a 37.5% reduction in dengue cases in the first year of implementation.

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%. The vector control offset was calculated through the percentages of cost savings of vector control estimated in Table 1. The medical cost offset comprises the estimated reduction of cases over the ten-year time horizon. The net costs are then divided by the DALYs to calculate the final Incremental Cost-Effectiveness Ratio (ICER) across all cities. The benefit-cost ratio (BCR) was then derived from the calculated total economic benefits (including the economic value of good health) divided by the cost of the deployment. Where the BCR is above 1.0, *Wolbachia* is considered as a favorable economic investment.

Table 6. Ranked results table for priority cities (monetary amounts in US$)

Rank	Municipality	Adjusted Population in Release area	Adjusted release area dengue cases (including unreported)	Initial *Wolbachia* deployment cost	PV *Wolbachia* program [a]	PV Vector control offset	PV Medical cost offset	Net cost	DALYs	ICER	ICER/per capita	Benefit-Cost ratio
1	Cali	2,217,961	27,649	$8,973,571	$9,672,263	$563,261	$20,086,318	-$10,977,315	8,174	-$1,343	-$0.25	$6.62
2	Ibagué	503,745	10,342	$2,269,484	$2,446,189	$238,873	$7,512,810	-$5,305,494	3,057	-$1,735	-$0.33	$9.81
3	Villavicencio	506,145	10,161	$2,506,072	$2,701,197	$309,493	$7,381,782	-$4,990,078	3,004	-$1,661	-$0.31	$8.76
4	Cúcuta	759,395	9,739	$4,363,719	$4,703,483	$1,195,491	$7,075,123	-$3,567,131	2,879	-$1,239	-$0.23	$5.01
5	Bucaramanga	604,186	9,540	$1,989,085	$2,143,957	$803,501	$6,930,606	-$5,590,150	2,821	-$1,982	-$0.37	$10.60
6	Neiva	343,194	7,035	$1,857,647	$2,002,286	$159,430	$5,110,385	-$3,267,529	2,080	-$1,571	-$0.30	$8.15
7	Barranquilla	1,296,471	6,015	$5,783,242	$6,233,532	$226,281	$4,370,044	$1,637,207	1,778	$921	$0.17	$2.25
8	Valledupar	477,763	3,937	$2,234,434	$2,408,410	$295,246	$2,860,029	-$746,866	1,164	-$642	-$0.12	$3.88
9	Armenia	300,785	4,100	$1,253,036	$1,350,598	$124,653	$2,978,651	-$1,752,705	1,212	-$1,446	-$0.27	$7.07
10	Pereira	404,270	3,262	$1,524,673	$1,643,386	$127,747	$2,369,401	-$853,762	964	-$885	-$0.17	$4.64
11	Cartagena	926,747	2,460	$3,864,257	$4,165,132	$1,103,887	$1,786,889	$1,274,356	727	$1,752	$0.33	$1.62
All	National	8,340,662	94,239	$36,619,221	$39,470,433	$5,147,863	$68,462,037	-$34,139,468	27,862	-$1,225	-$0.23	$5.61

[a] 10 years present values

PV denotes present value; DALYs denotes disability adjusted life years.

Figure 1 provides a visual representation of the costs and medical and vector offsets of the *Wolbachia* program in Cali at both the five-year, ten-year, fifteen-year, and twenty-year time horizons. In Cali, comparing the multiple time horizons, the bulk of the *Wolbachia* costs are accumulated within the first five years. The medical and vector offsets, along with health benefits and overall benefits, continue to increase with the longer time horizons, contributing to negative ICERs of increasing magnitudes (Figure 2).

Figure 1. Cali net cost analysis by time horizon (with cumulative amounts for 10 and 20 years)

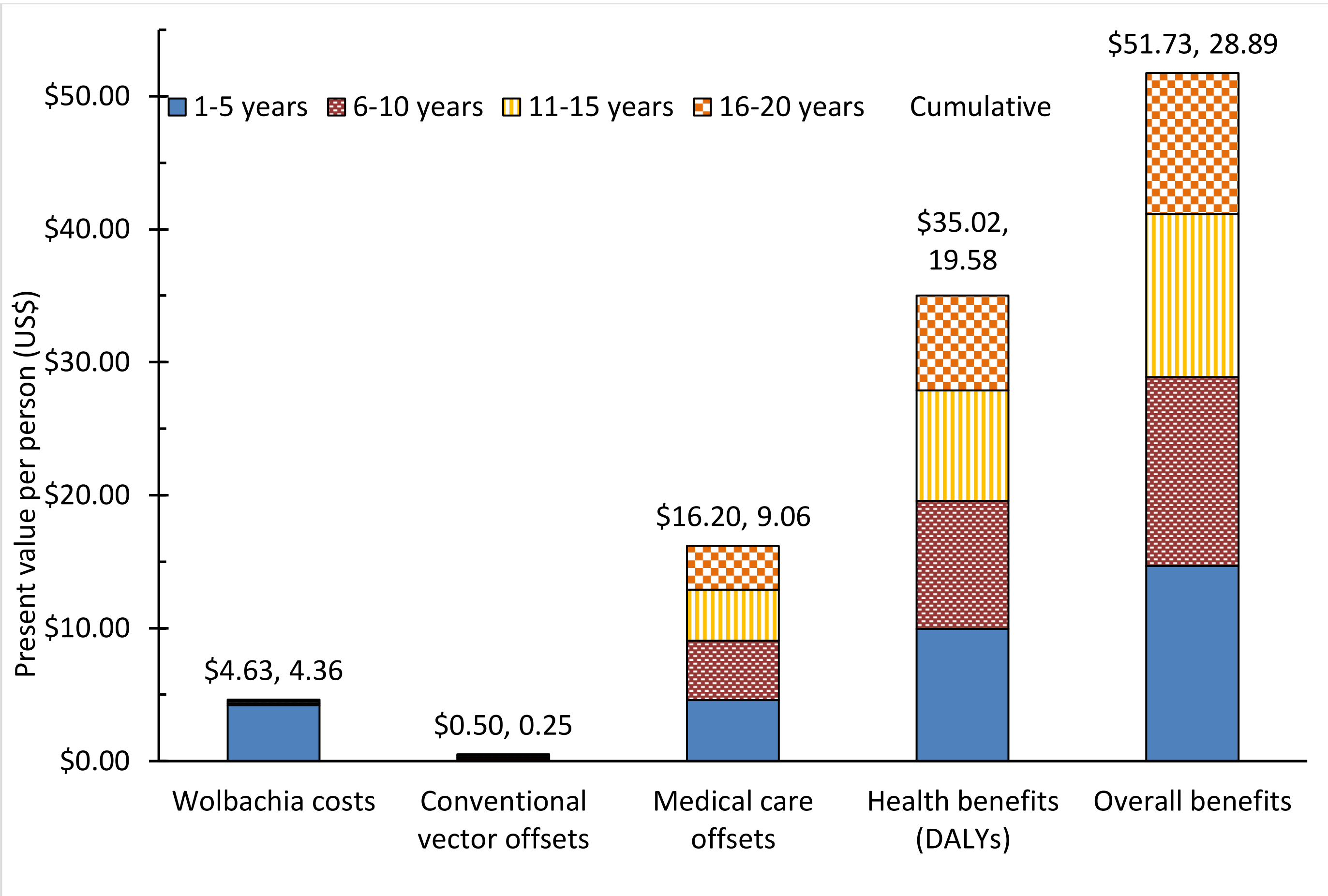
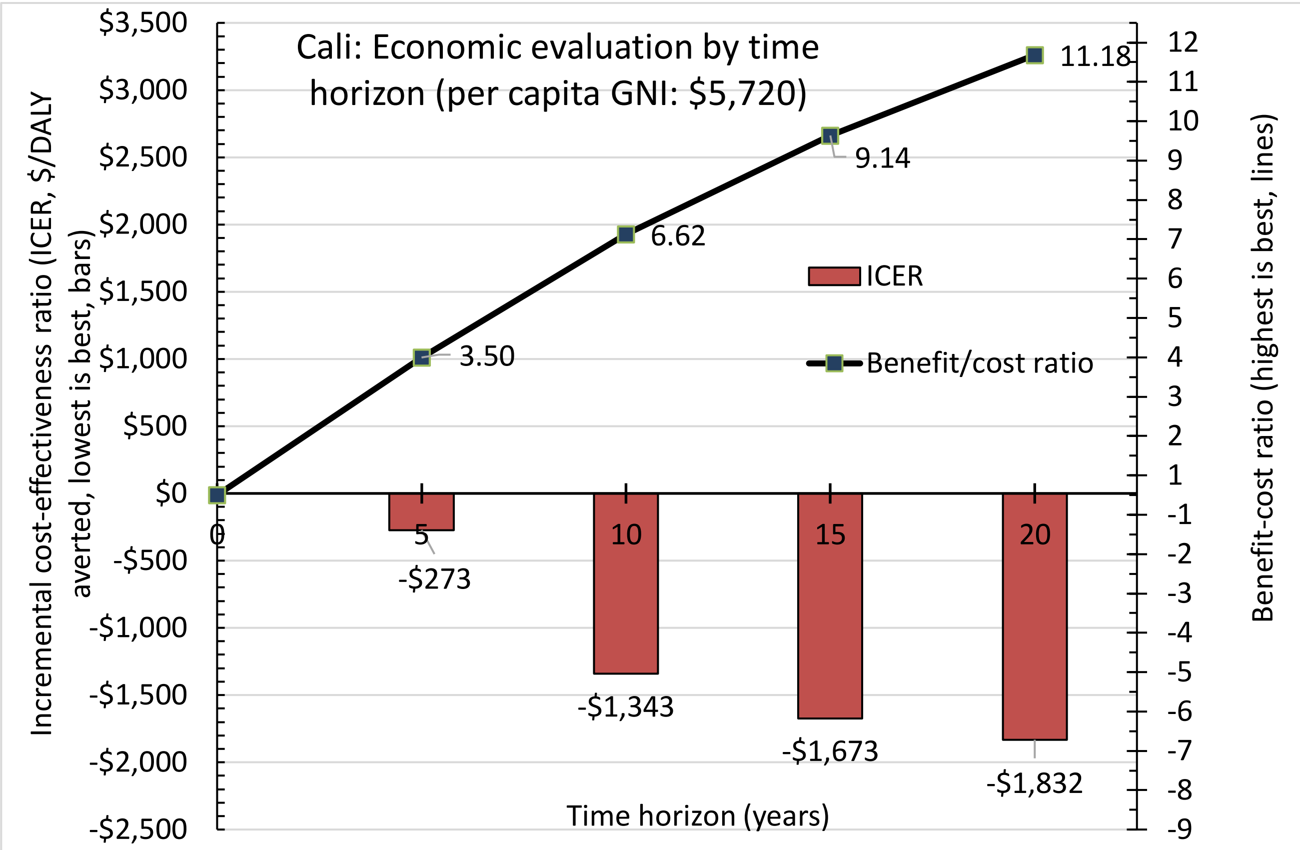


Figure 2. Cali economic evaluation by time horizon



The national trends mirror the finding in Cali. As the time horizon increases, so does the benefit-cost ratio, while the negative ICER gets larger in magnitude (Figures 3 and 4). Over 10 years in present value terms per person in the release area, *Wolbachia* deployment costs US$4.73, offsets $0.62 in conventional vector control costs and $8.21 in medical costs for total offsets of $8.83 and negative net costs ($-4.10).

Figure 3. National cost-projections by time horizon

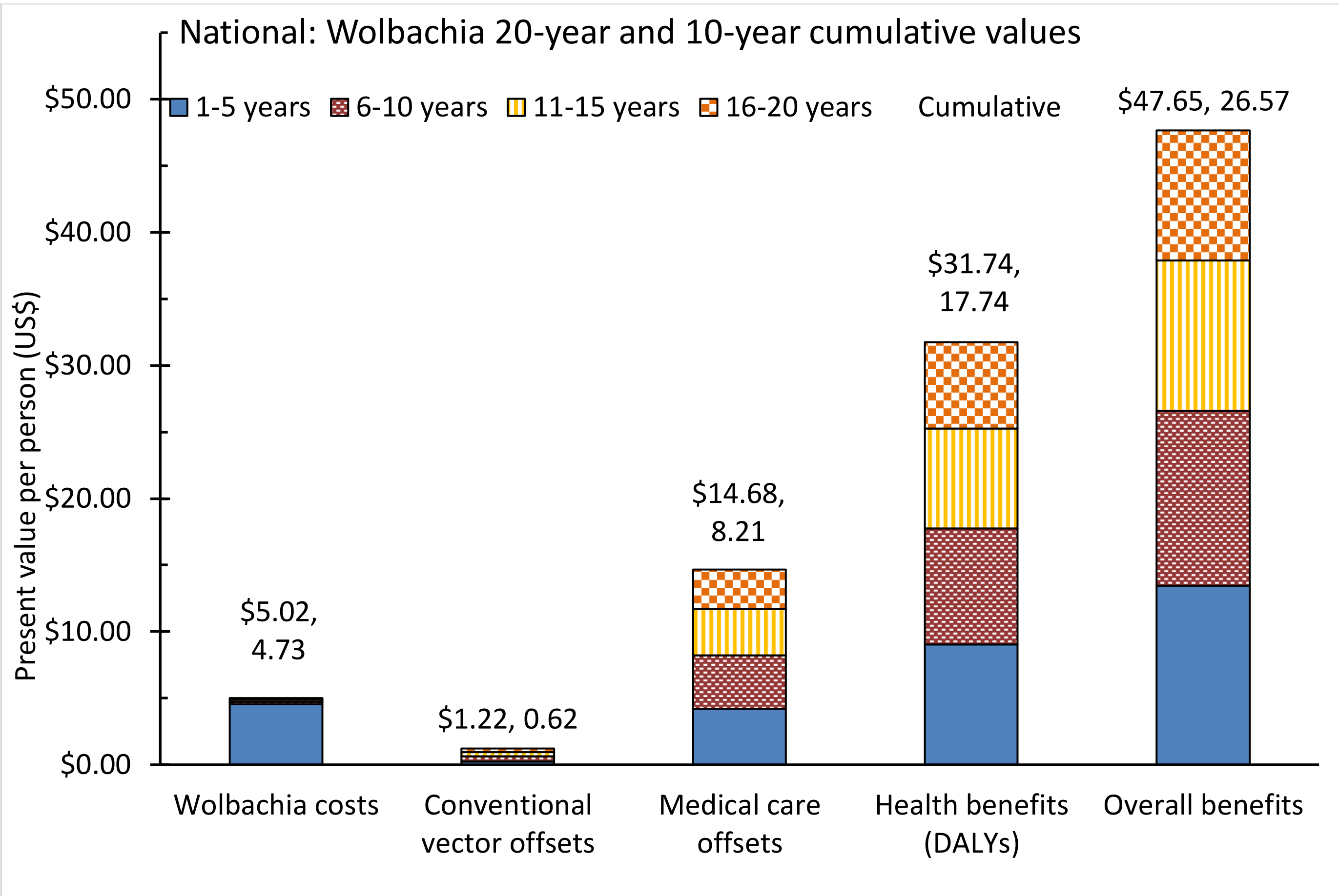
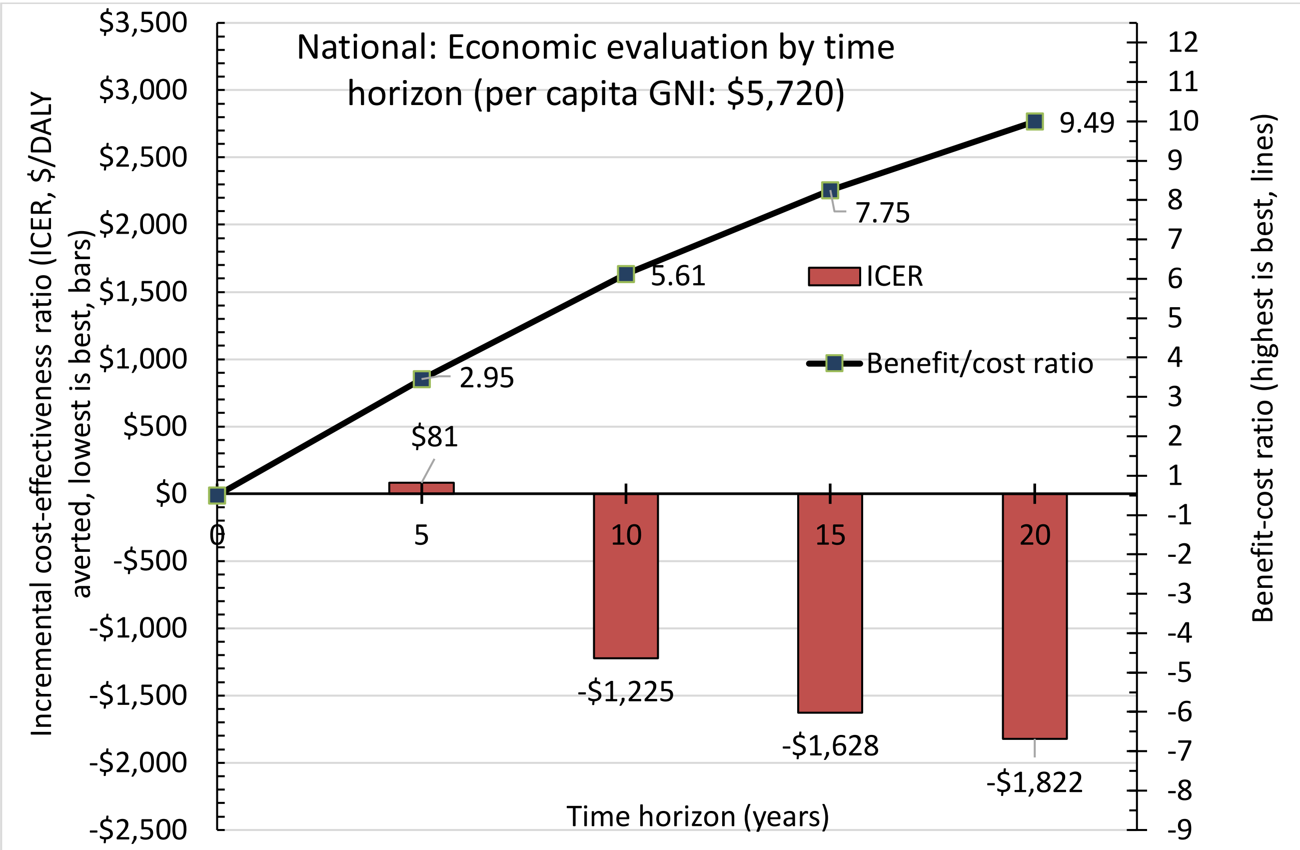


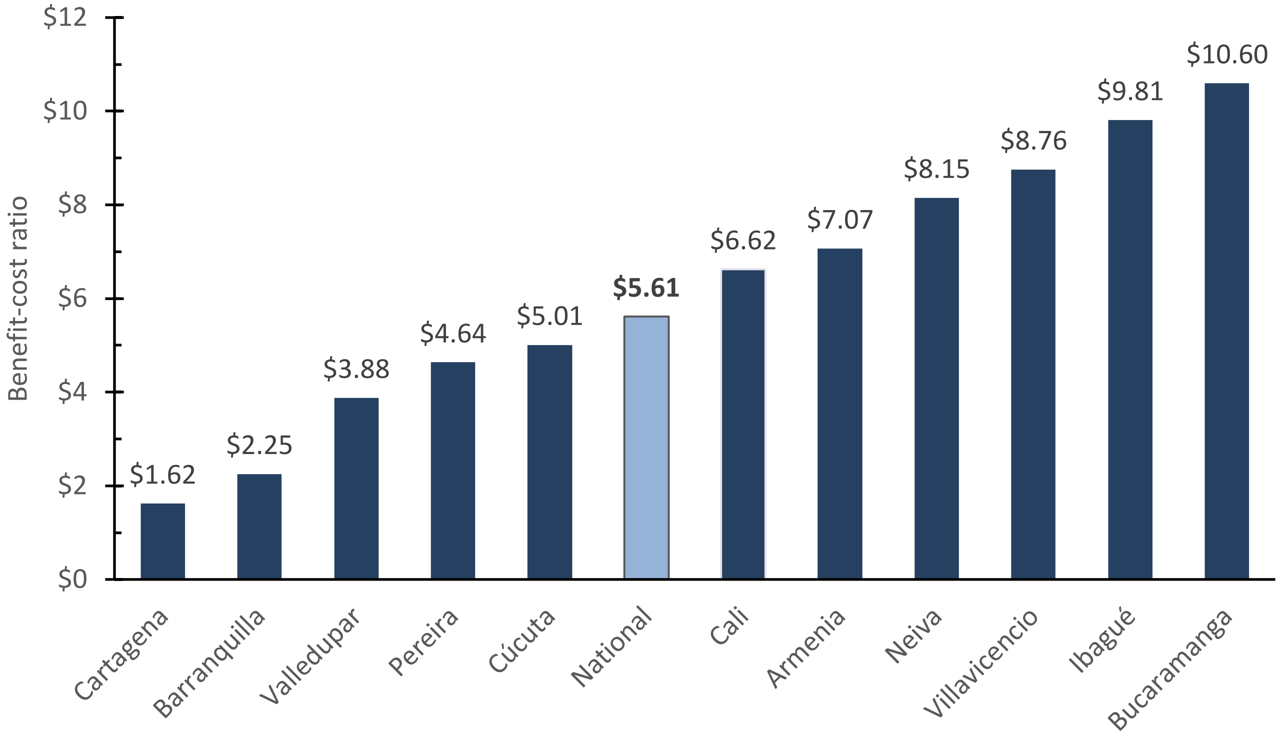
Figure 4. The benefits and cost of *Wolbachia* nationally



The benefit-cost ratio at 10 years for Cali (6.62) and nationally (5.61) mean that even within that short time horizon, the economic benefits would exceed the costs. 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.

Extending these results nationally, Figure 5 presents the cost-effectiveness ratios for all priority cities based on the 10-year horizon. Please refer to the Supplementary Data for graphs of all ten remaining cities to complement the earlier graphs on Cali.

Figure 5. Estimated benefit-cost ratios by city with a 10-year horizon



Discussion

This report shows that the ICER and BCR results generally favor the *Wolbachia* program. If implemented with efficacy mirroring that from the Utarini et al. (2021) study, *Wolbachia* will substantially mitigate dengue incidence in the priority cities in Colombia. As shown in Table 6, the initial investment costs of the *Wolbachia* program are recouped in many of the priority cities within 10 years through the offset in direct medical costs alone.

Colombia is hyperendemic with dengue (Guitierrez-Barbosa et al, 2020). This study aimed to capture a fuller picture of the disease burden of dengue in a heavily affected country to provide deeper insight into the cost-effectiveness of the *Wolbachia* intervention. Through the expertise of the epidemiologic panel, we incorporated best estimates of dengue cases that may have been mis-diagnosed, not reported, or did not interact with the formal healthcare system.

The summary data shows that *Wolbachia* is highly cost-effective in all cities in that all cost-effectiveness ratios are less than one times the GDP per capita, and in fact negative in 9 of 11 cities. Similarly, all the benefit-cost ratios exceed 1.00, indicating that the economic value generated exceeds the costs. In many cities, such as Cali, the benefit-cost ratio exceeds 5.0, being extremely favorable. With longer time horizons, the results are even more favorable. For example, the national benefit-cost ratio grows from 5.61 at 10 years to 9.49 at 20 years.

This study did have several limitations. The number of dengue cases varies across the RIPS and Suficiencia databases, pointing to inconsistencies and 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 US $116.90 (based on Table 1, P2) and the macro costing adds $4.12 or 3.5% of the SOAT tariff for a total of $121.01 per episode. This difference may arise 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 highly cost-effective by the criterion of comparing the ICER to Colombia's GDP per capita. 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. (2019) studied the impact of a screen-and-vaccinate strategy against dengue in Colombia. From the perspective of the formal healthcare system, the median ICER was equivalent to 42% of the GDP per capita, with the ICER decreasing as the percentage of nine-year old seropositive individuals in the population increased. When comparing the corresponding ICERs in the 11 municipalities, the *Wolbachia* intervention ICERs are negative (highly favorable) in all but two municipalities (Barranquilla and Cartagena), and while positive, a smaller percentage of the GDP per capita in that one city (0.33) than the screen-and-vaccinate Therefore, in all of the municipalities targeted by the *Wolbachia* program, it is even more cost-effective than the Sanofi vaccine (Denvaxia). *Wolbachia* also avoids the risk of adverse effects from vaccinating sero-negatives. In August 2022, a second dengue vaccine manufactured by Takeda was licensed in Indonesia. Published clinical results have not shown the risk associated with the Sanofi dengue vaccine.

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. Other strategies, including vaccination, may be preferable for less densely populated locations.

Two important vaccines provide instructive examples of considerable public health initiatives that do not address dengue. Aponte-Gonzalez et al. (2013) conducted a cost-effectiveness analysis of both available Human Papillomavirus vaccines from in Colombia, focusing on the societal perspective. The author found an ICER greater than three times the 2013 GDP per capita, making it less cost-effective than the *Wolbachia* program. We are not aware whether other economic appraisals were done, but Colombia introduced HPV vaccination into its national vaccination program in 2012 (PAHO, 2012).

More recently, Morales-Zamora et al. (2022) assessed the cost-effectiveness of high-prioritization and no prioritization strategies for COVID-19 vaccination campaigns in Colombia for 2023. The high-prioritization strategy focused on the population at the highest risk. The ICER of US$3,339 for a high-prioritization strategy and the ICER of US$5,224 for a no-prioritization strategy remain less favorable than the ratios for all of the 11 municipalities and the combined cities ratio of US$3,689 for the *Wolbachia* intervention. Thus, while COVID-19 vaccination is reasonably cost-effective and addresses a pressing health problem, *Wolbachia* appears substantially more favorable.

Wolbachia also presents 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.

Acknowledgments
The authors thank Ivan Velez and Patricia Arbelaez Montoya from the WMP Colombia and Reynold Dias and Katie Anders from the global WMP (Australia) for valuable advice.

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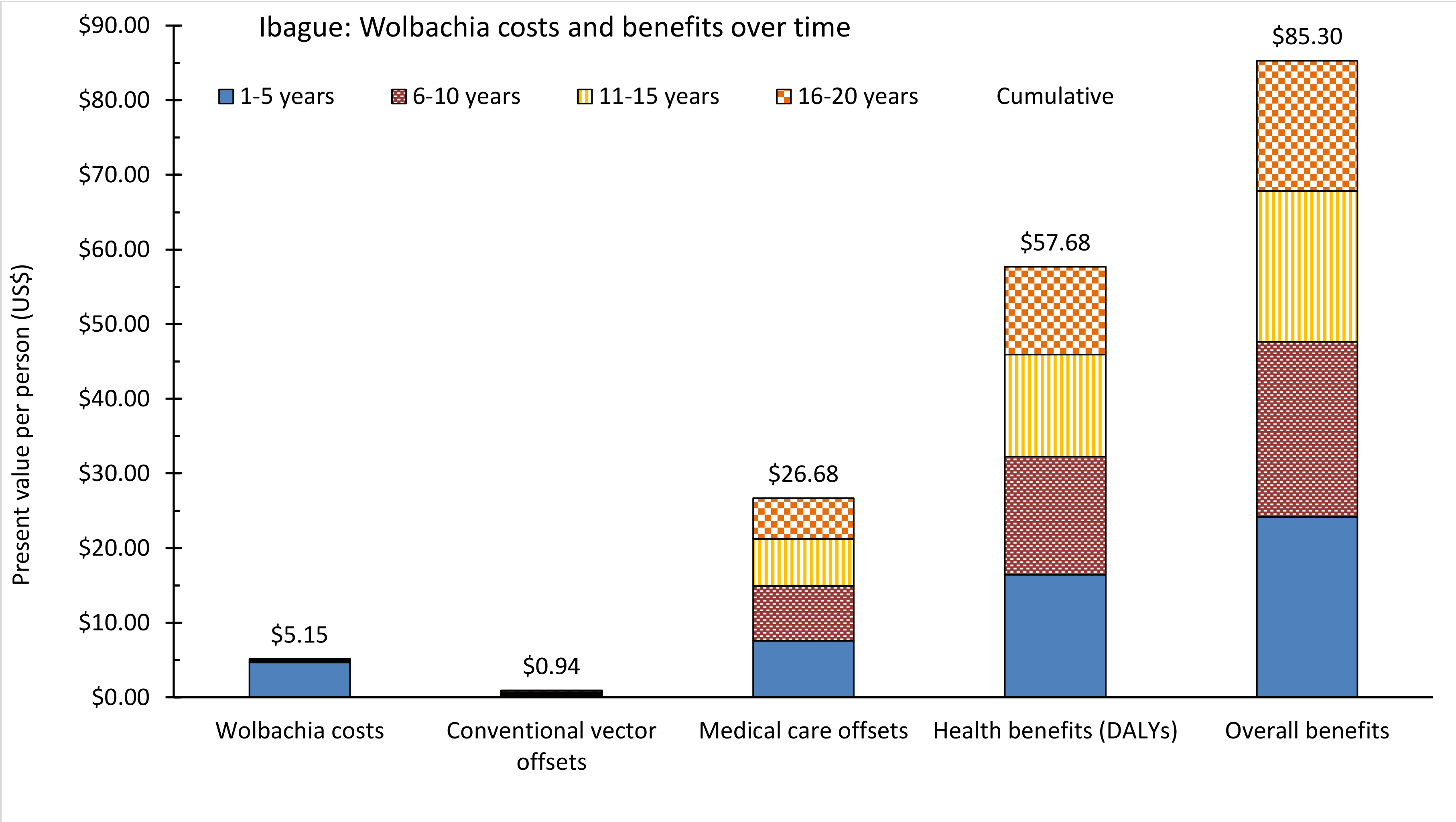
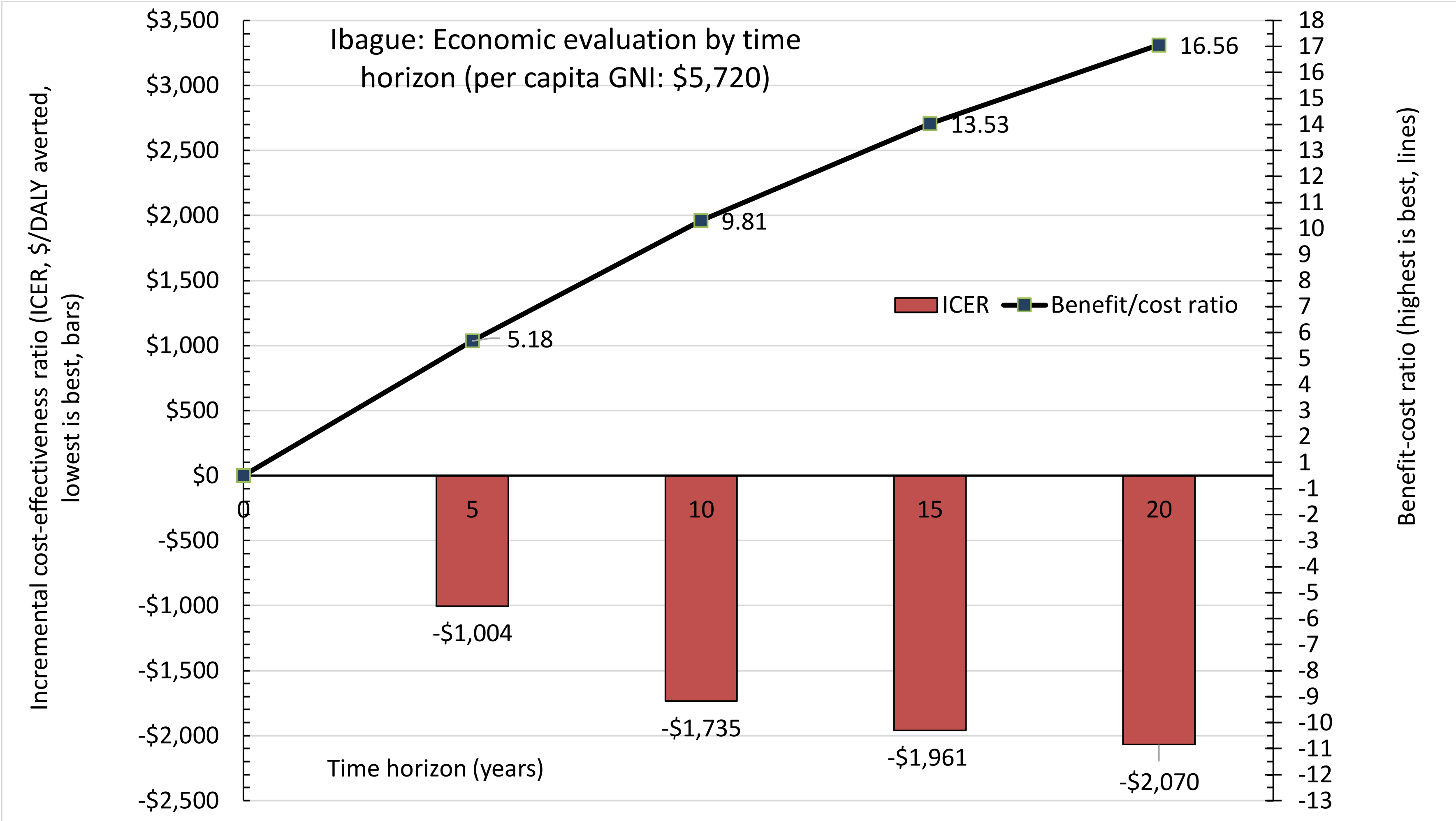
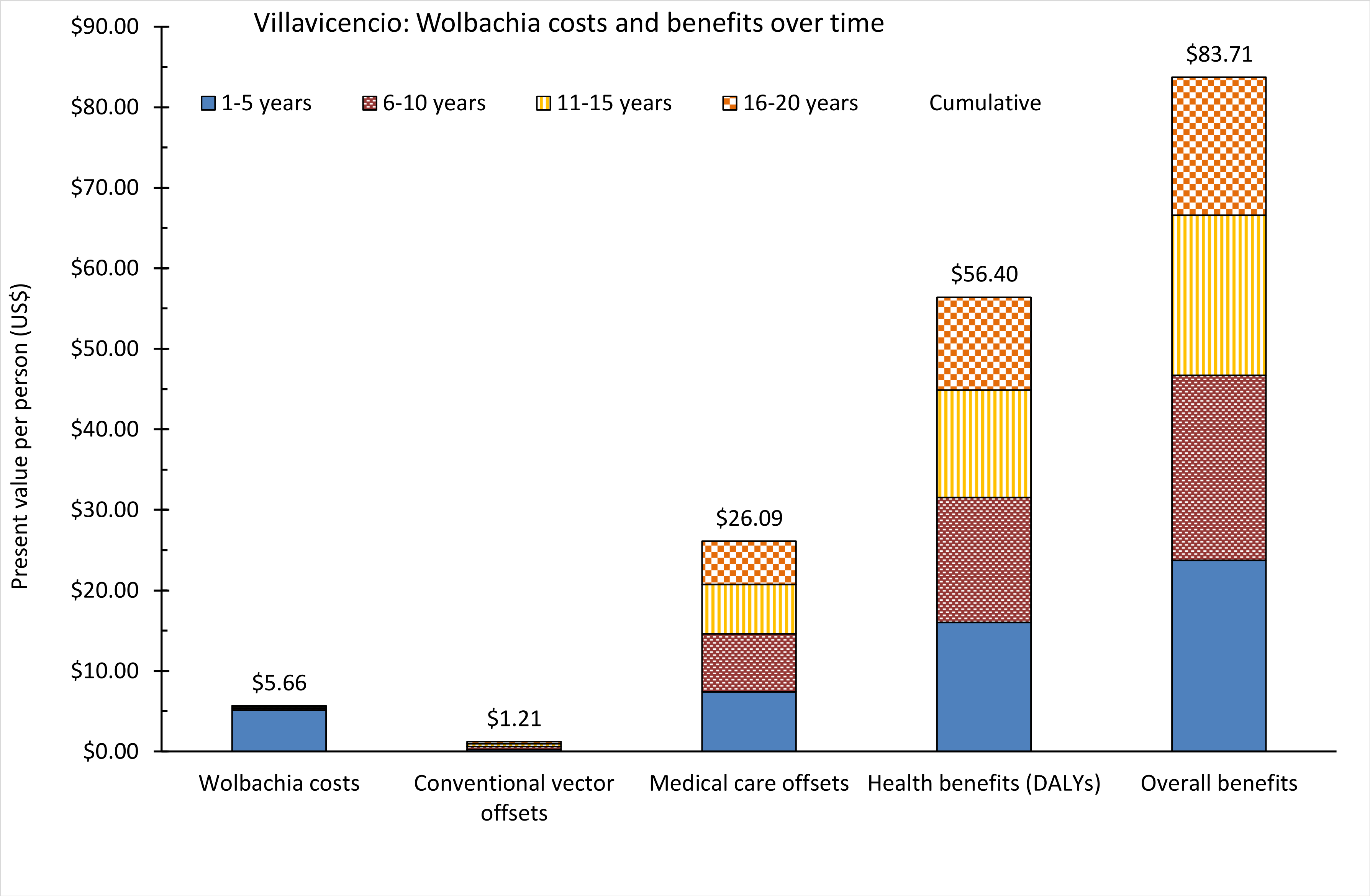
Supplementary data: cost-effectiveness by city showing cumulative 20-year values

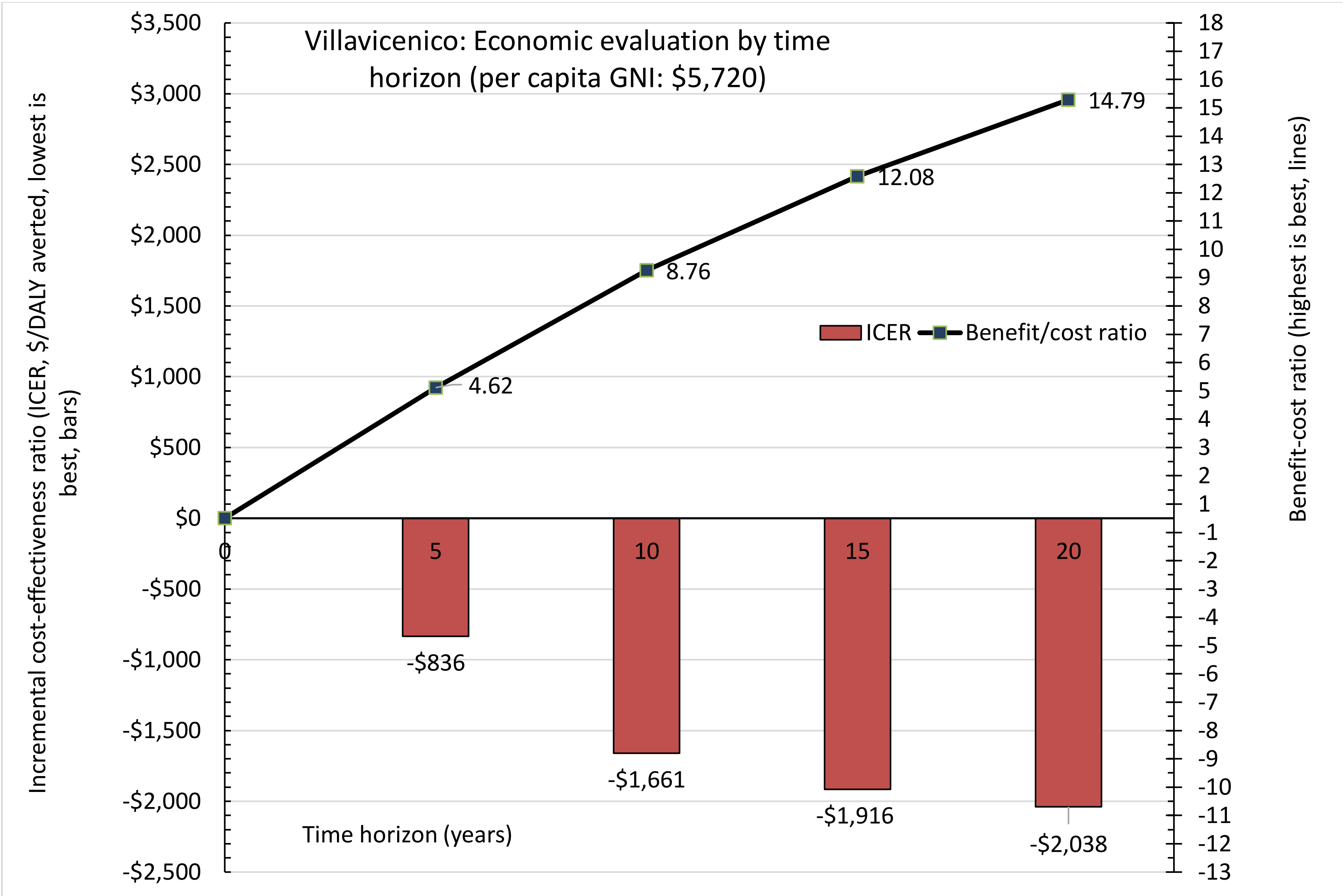
Supplement S1. Ibague *Wolbachia* Economics



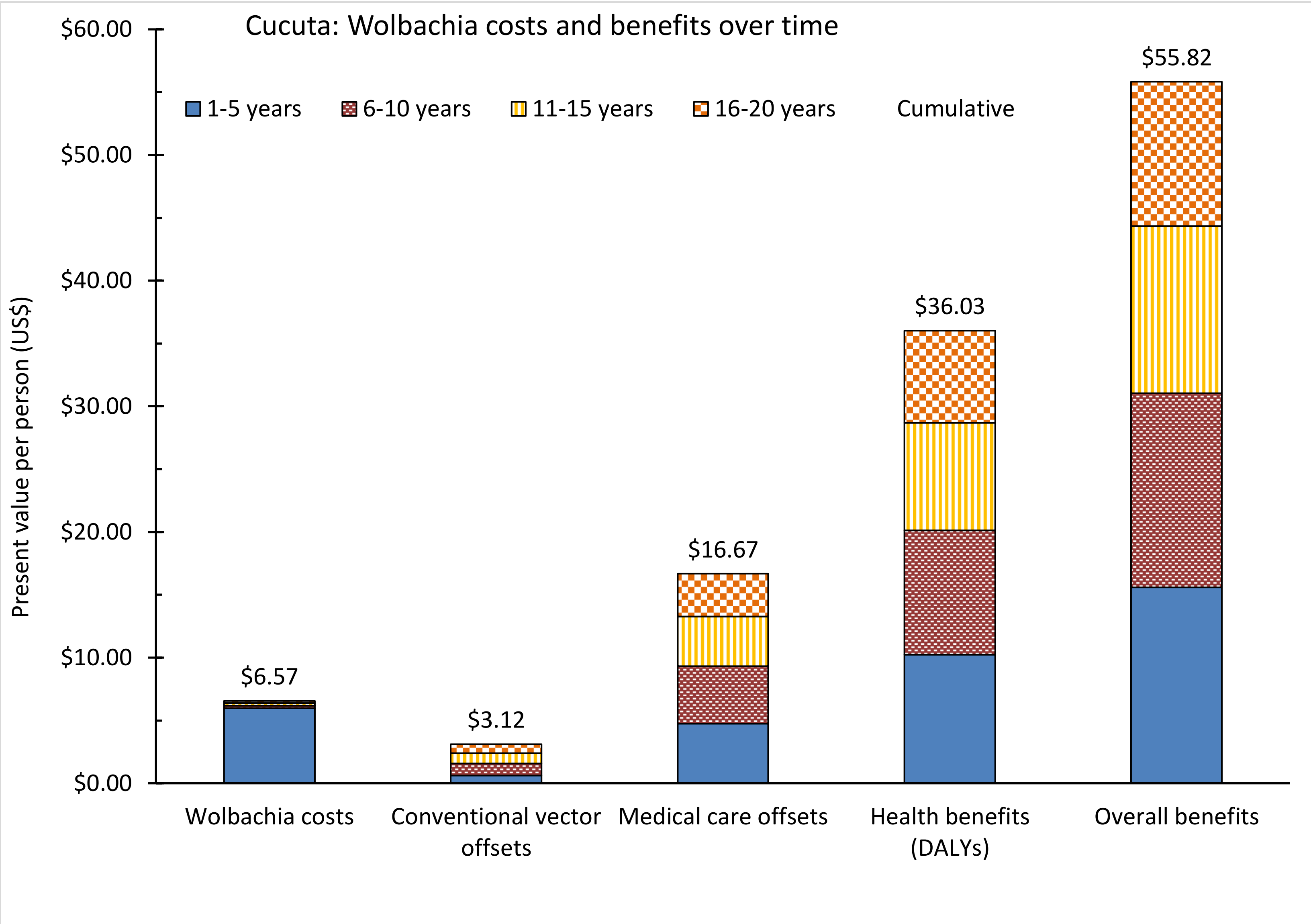


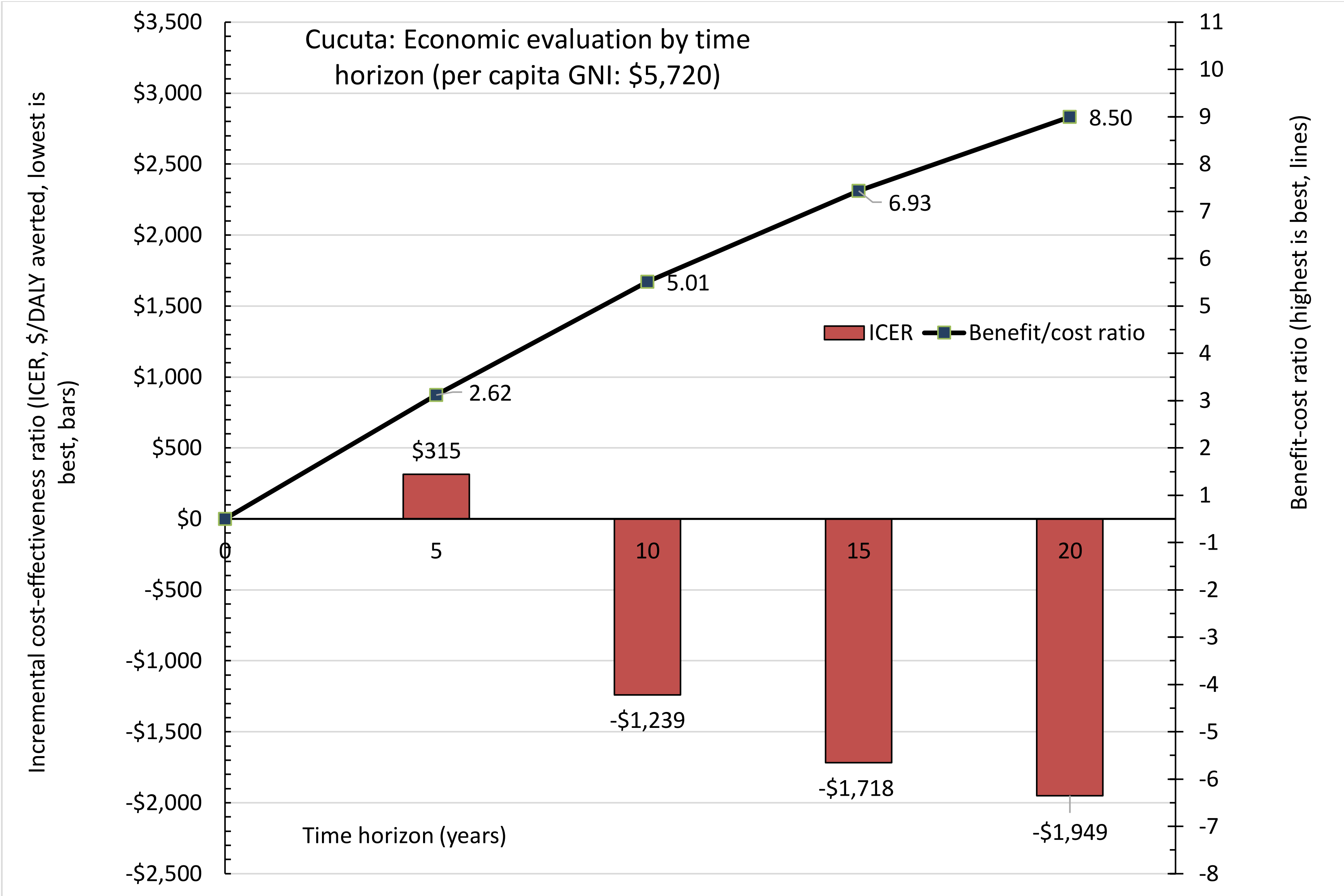
Ibague: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
Time horizon (years)
ICER
Benefit/cost ratio
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
-12
-13
0
5
10
15
20
5.18
9.81
13.53
16.56
-$1,004
-$1,735
-$1,961
-$2,070

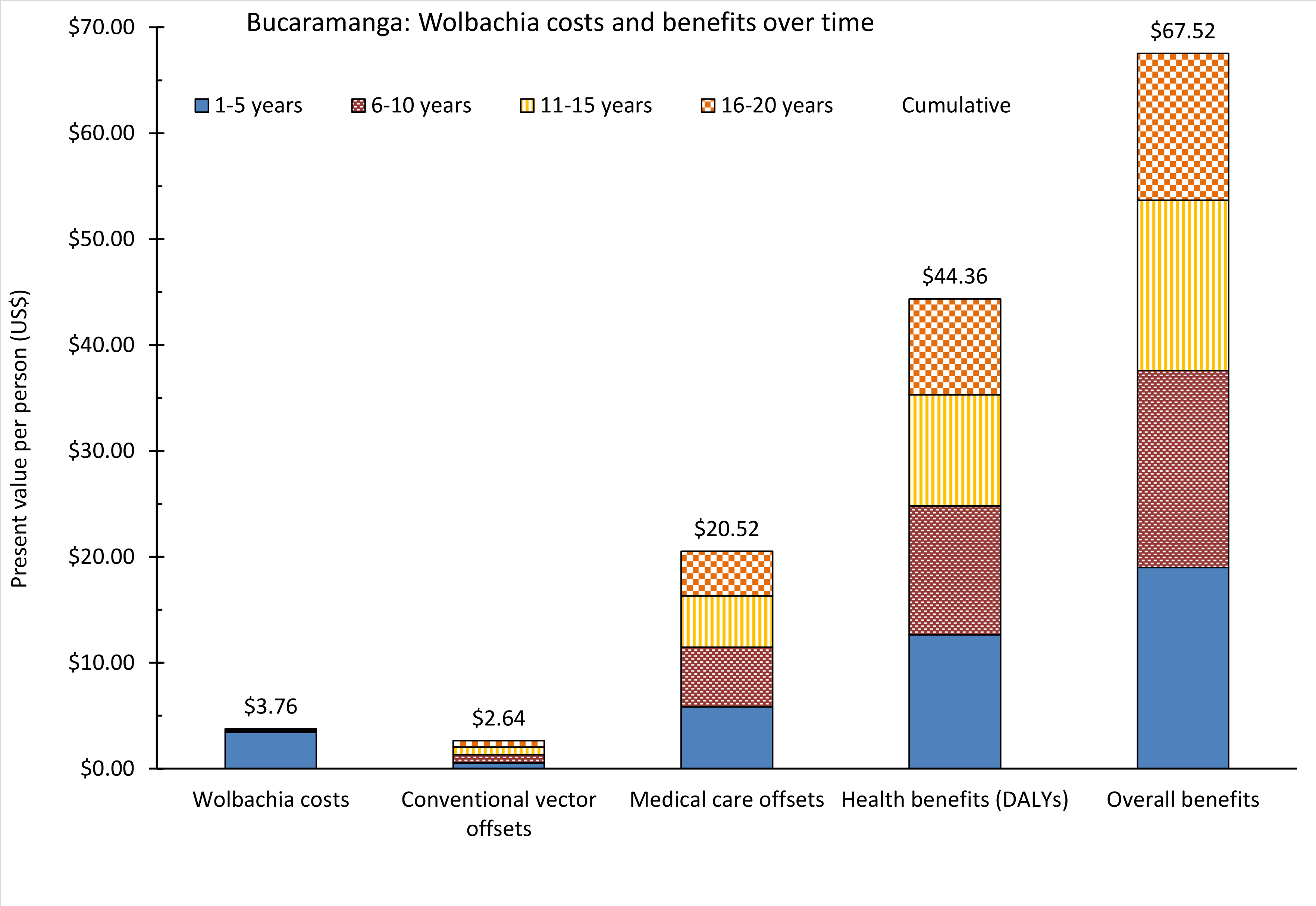

Villavicencio: Wolbachia costs and benefits over time
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
Present value per person (US$)
$90.00
$80.00
$70.00
$60.00
$50.00
$40.00
$30.00
$20.00
$10.00
$0.00
$5.66
$1.21
$26.09
$56.40
$83.71
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits

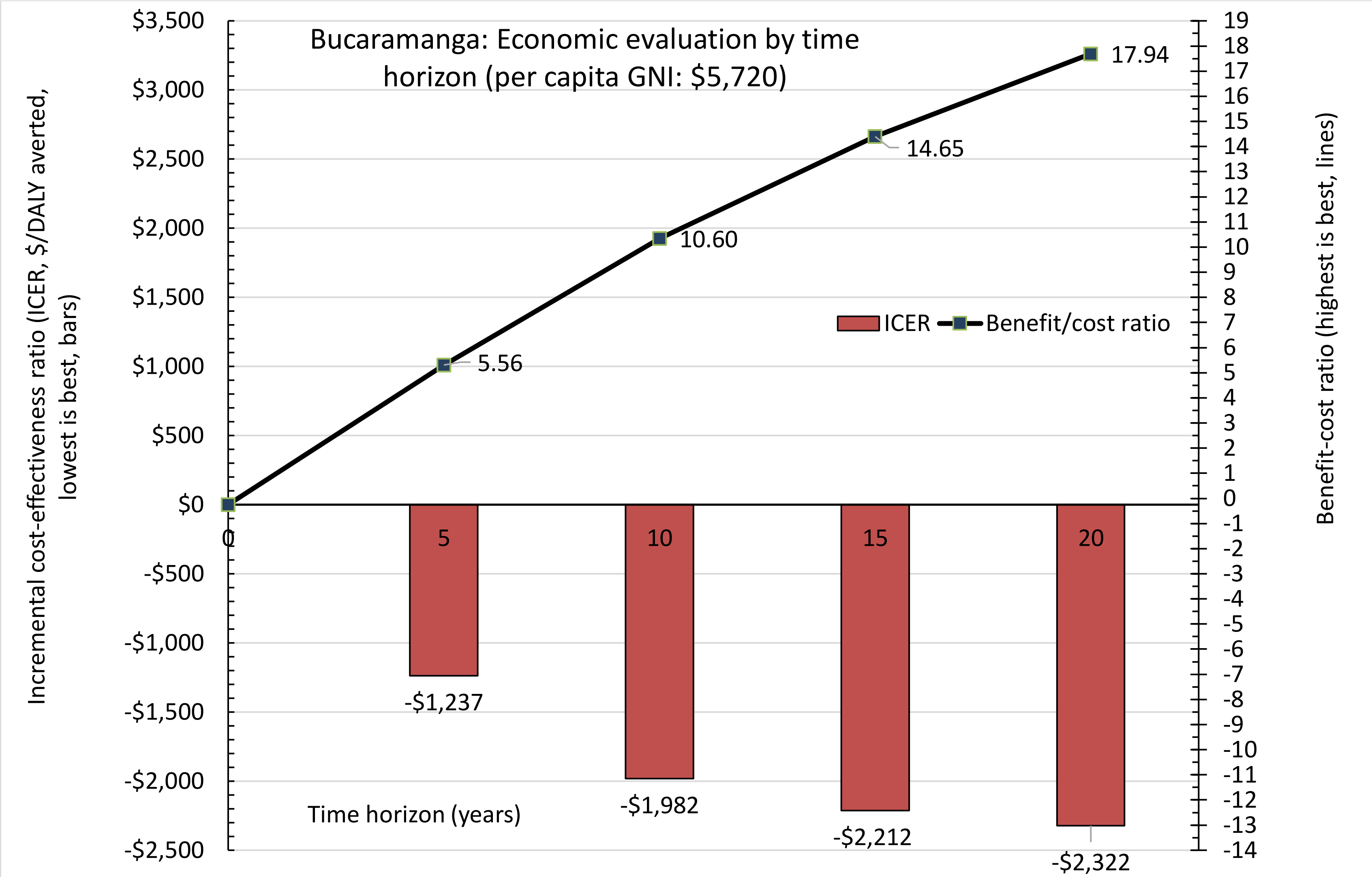


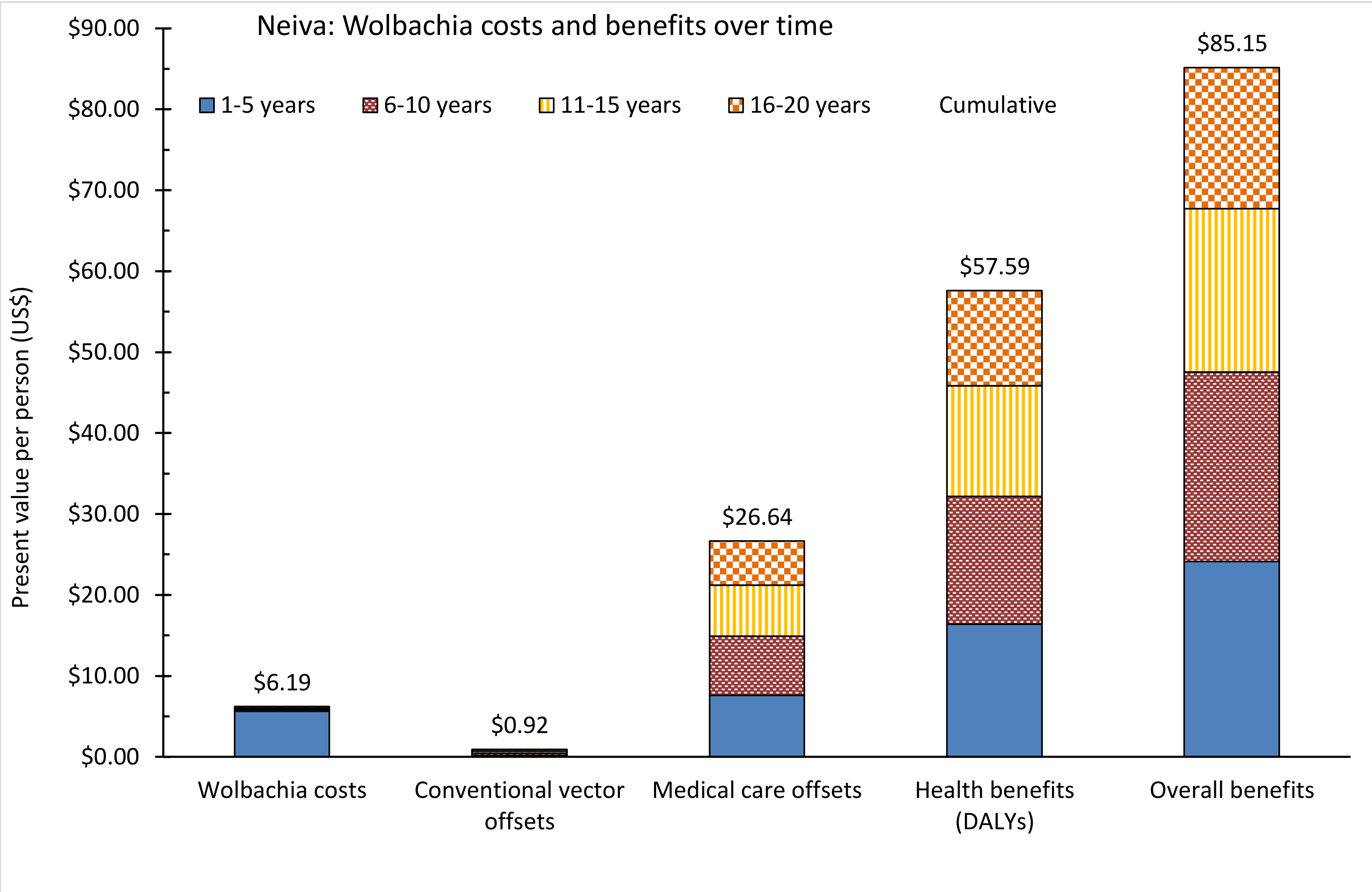
Villavicenico: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
ICER
Benefit/cost ratio
Time horizon (years)
0
5
10
15
20
4.62
8.76
12.08
14.79
-$836
-$1,661
-$1,916
-$2,038
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500

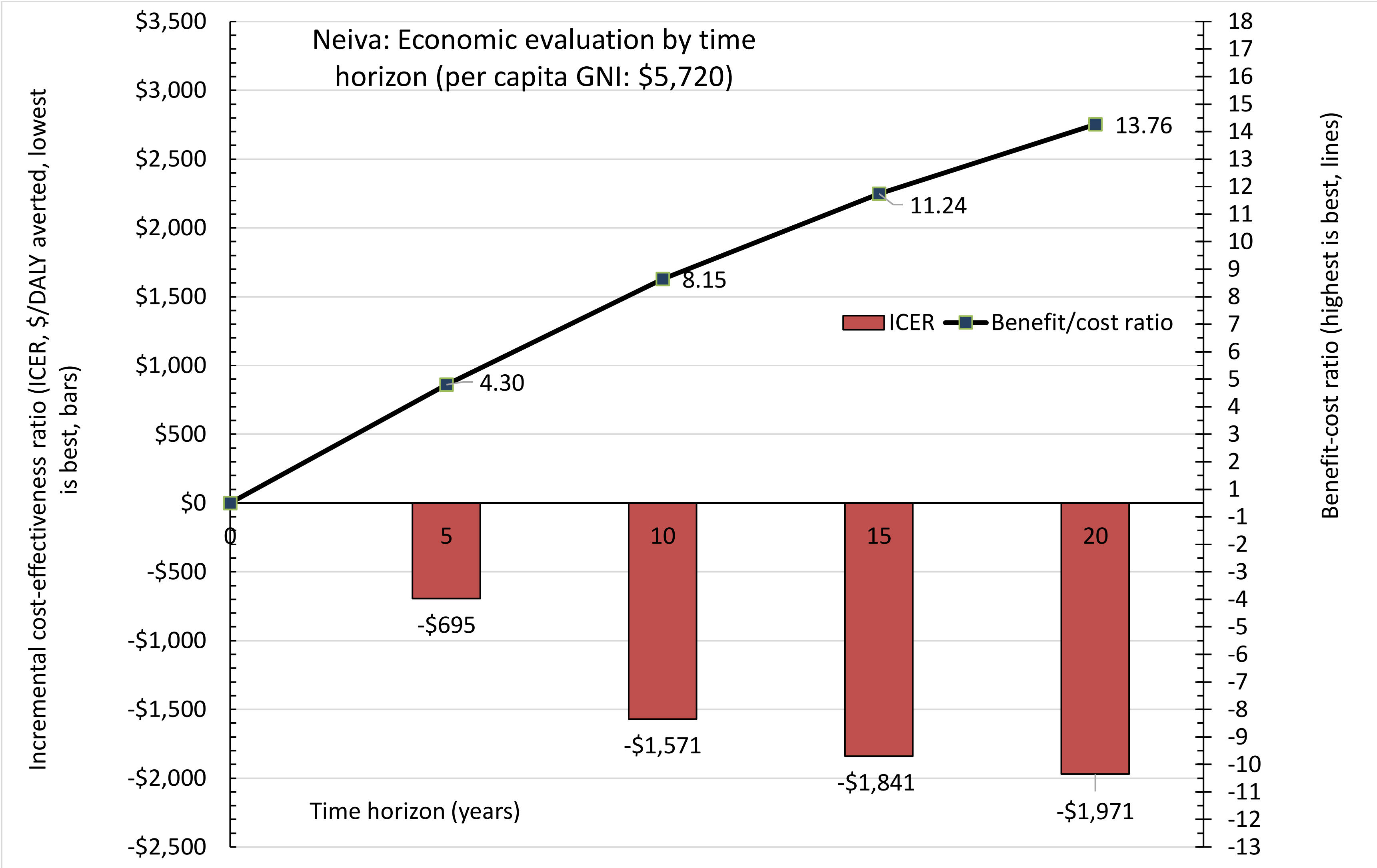

Cucuta: Wolbachia costs and benefits over time
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
Present value per person (US$)
$60.00
$50.00
$40.00
$30.00
$20.00
$10.00
$0.00
$6.57
$3.12
$16.67
$36.03
$55.82
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits

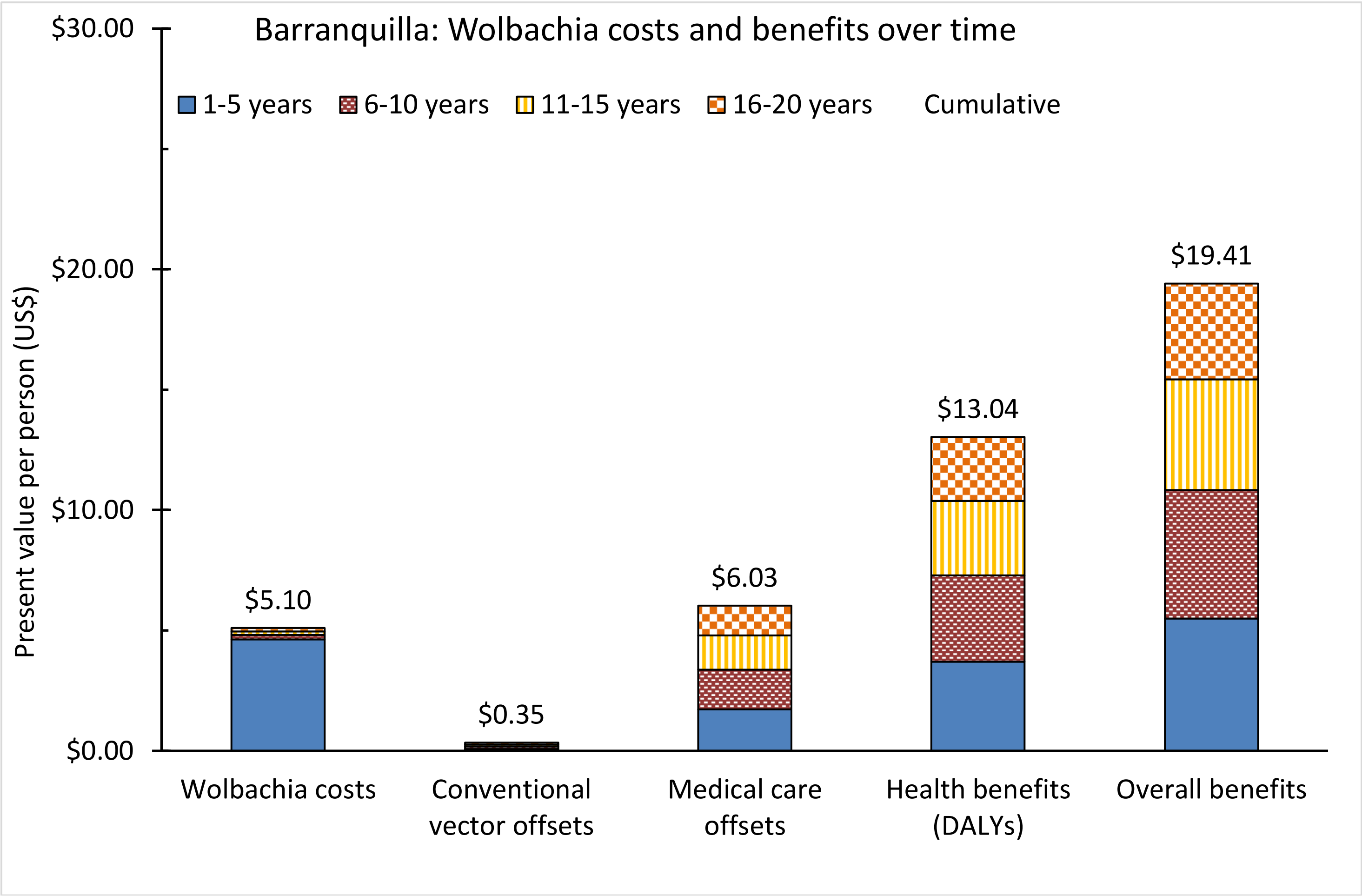

Cucuta: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500
11
10
9
8
7
6
5
4
3
2
1
-1
-2
-3
-4
-5
-6
-7
-8
0
5
10
15
20
ICER
Benefit/cost ratio
2.62
5.01
6.93
8.50
$315
-$1,239
-$1,718
-$1,949
Time horizon (years)

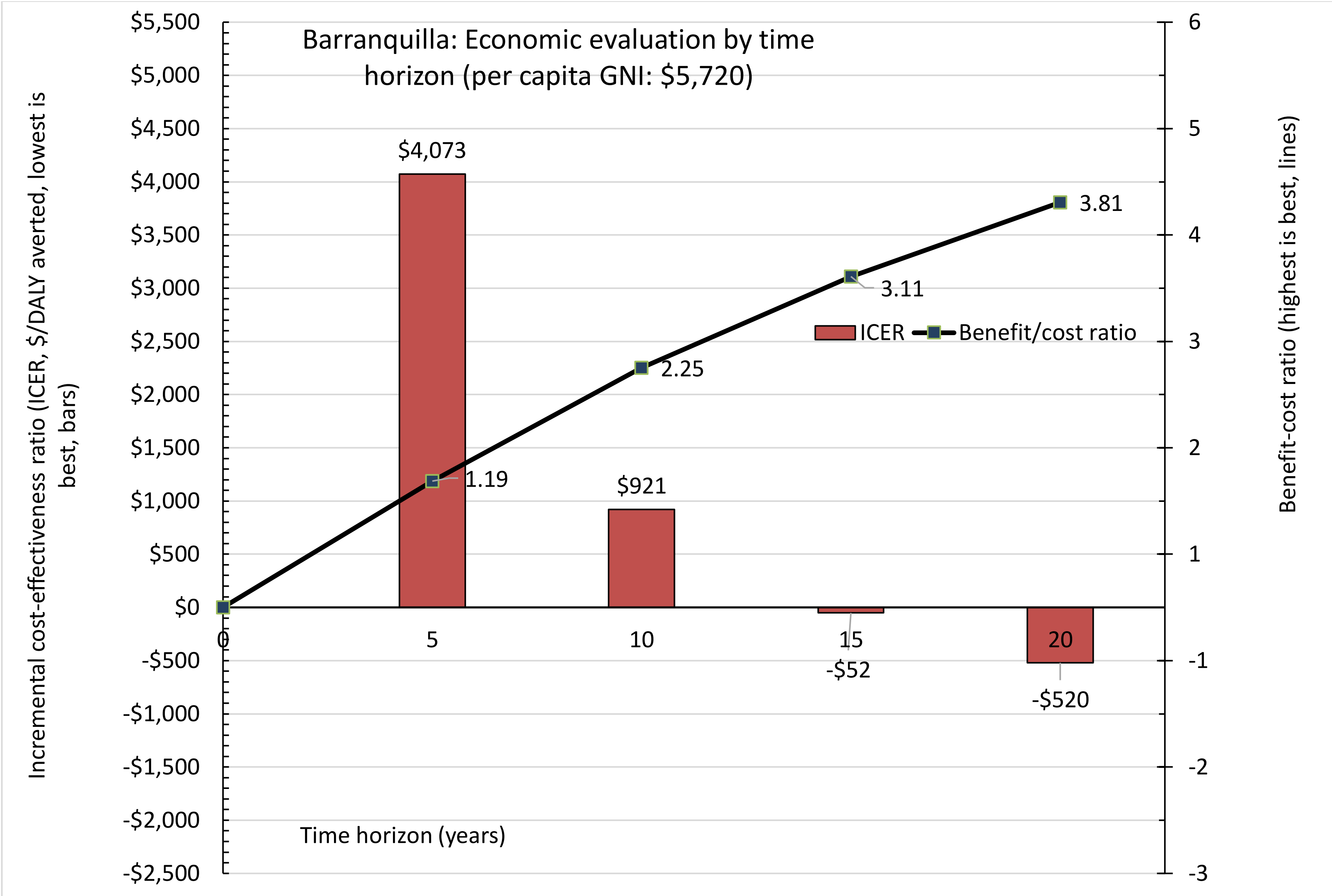

Bucaramanga: Wolbachia costs and benefits over time
$70.00
$60.00
$50.00
$40.00
$30.00
$20.00
$10.00
$0.00
Present value per person (US$)
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
$3.76
$2.64
$20.52
$44.36
$67.52
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits

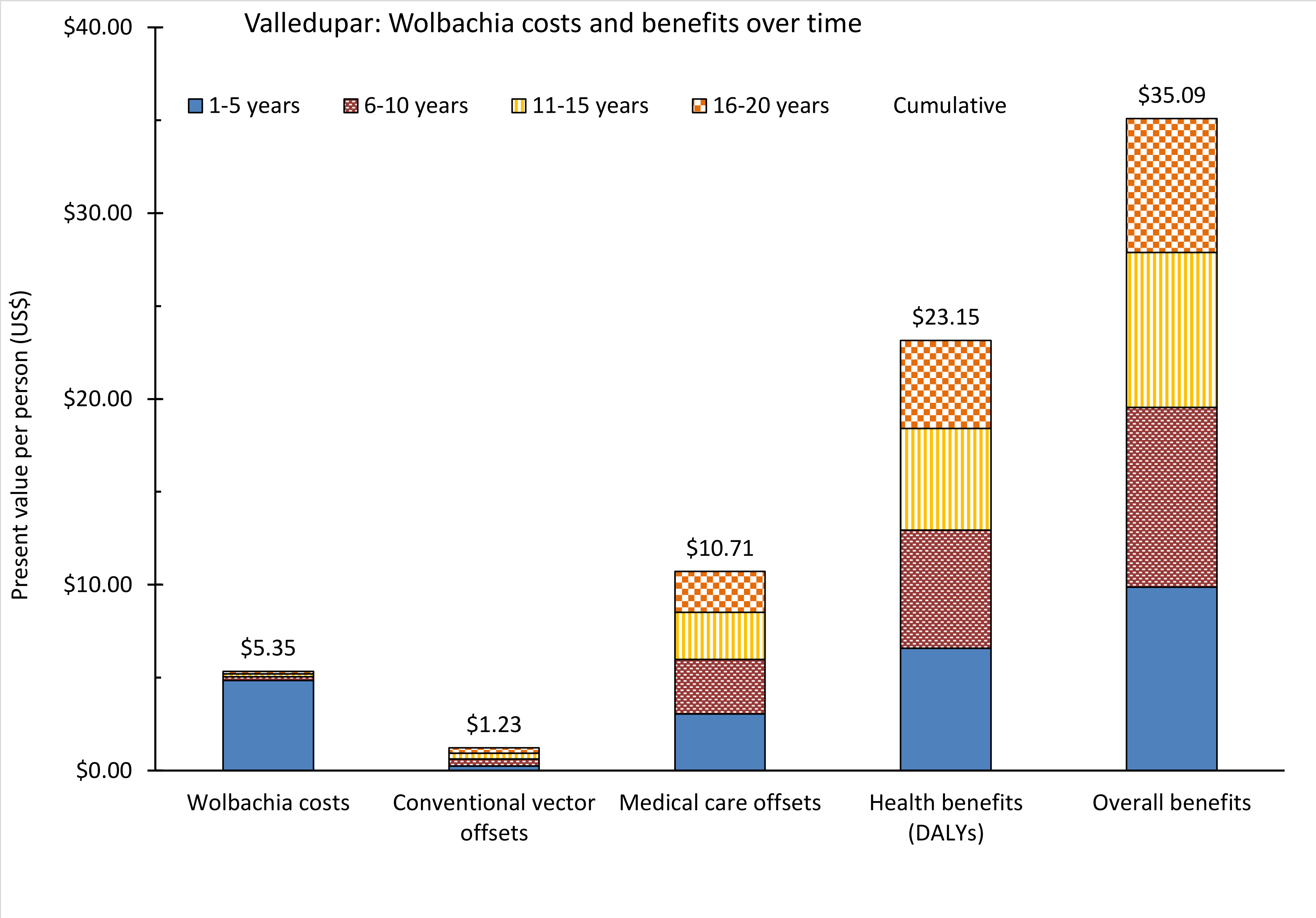

Bucaramanga: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
Time horizon (years)
ICER
Benefit/cost ratio
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500
0
5
10
15
20
5.56
10.60
14.65
17.94
-$1,237
-$1,982
-$2,212
-$2,322

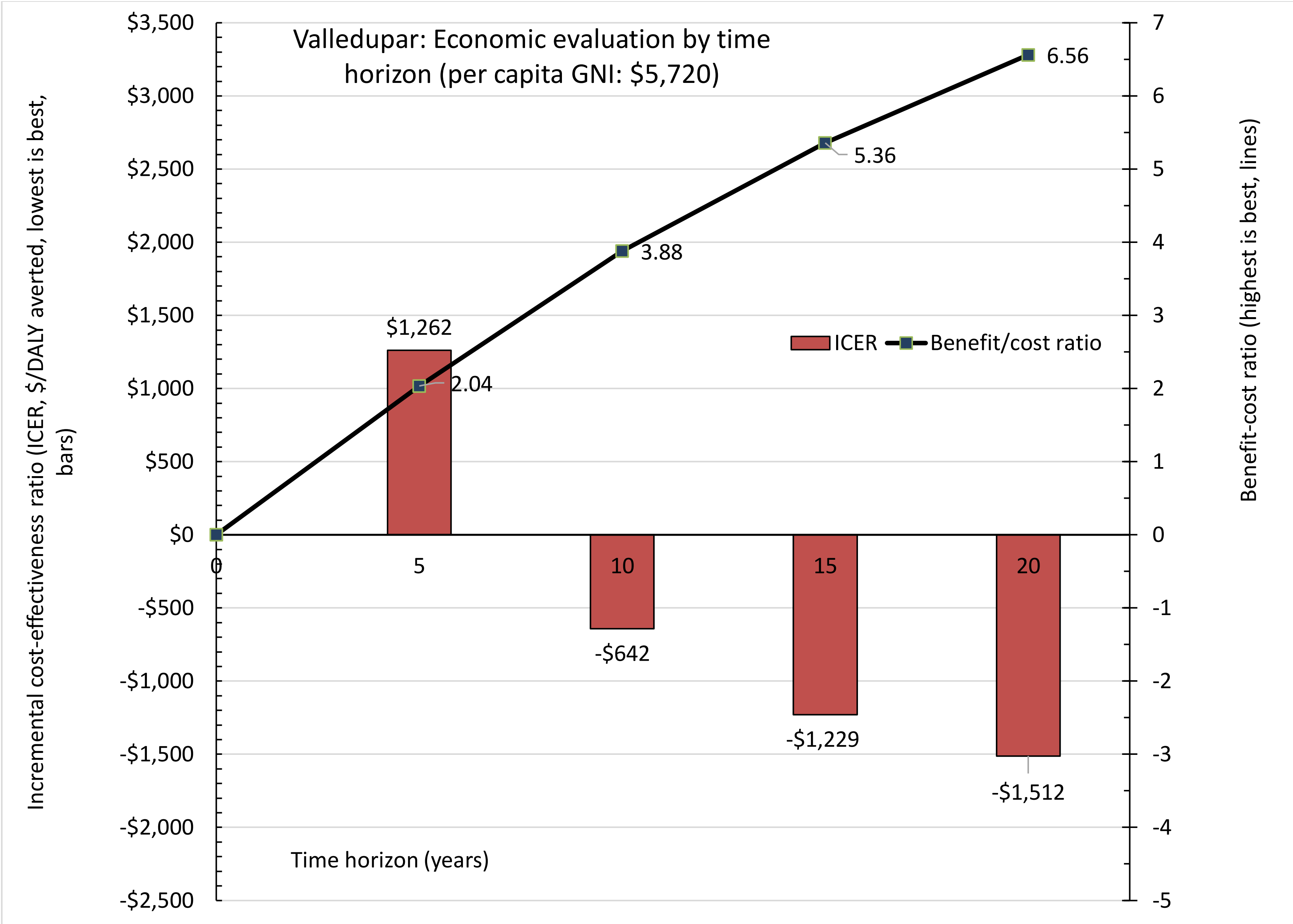

Neiva: Wolbachia costs and benefits over time
Present value per person (US$)
$90.00
$80.00
$70.00
$60.00
$50.00
$40.00
$30.00
$20.00
$10.00
$0.00
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
$6.19
$0.92
$26.64
$57.59
$85.15
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits

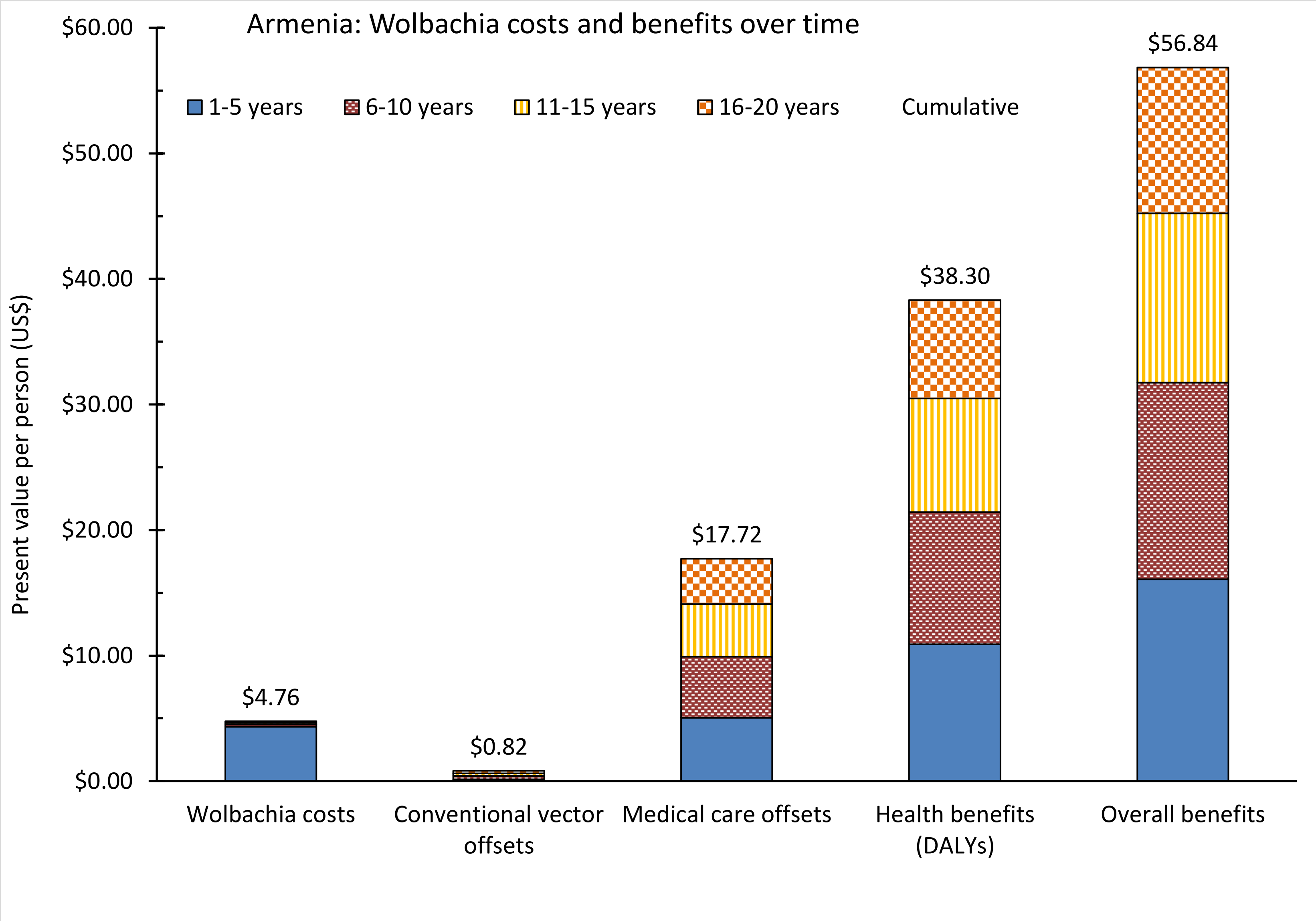

Neiva: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
ICER
Benefit/cost ratio
Time horizon (years)
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
-12
-13
0
5
10
15
20
4.30
8.15
11.24
13.76
-$695
-$1,571
-$1,841
-$1,971

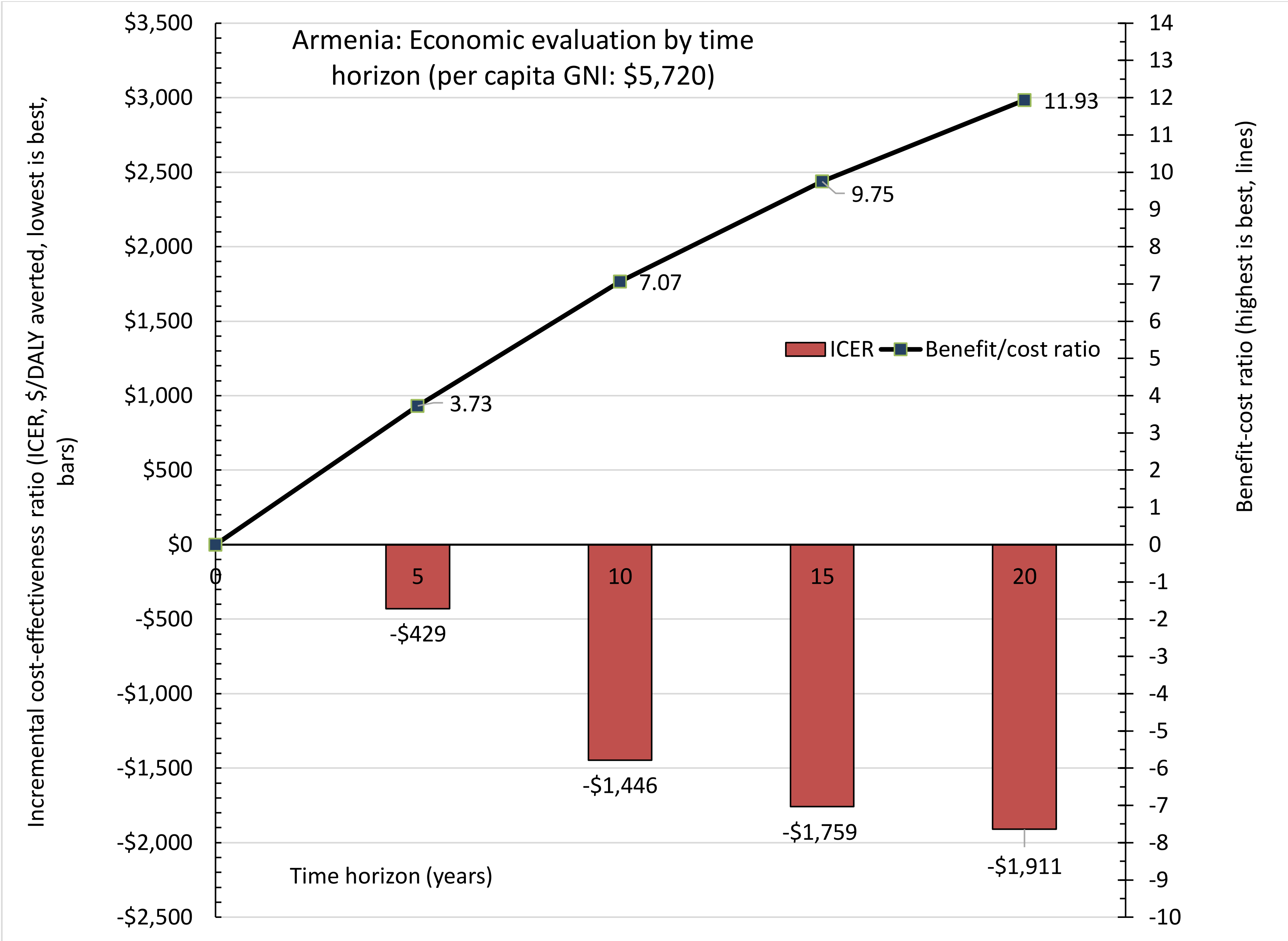

Barranquilla: Wolbachia costs and benefits over time
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
Present value per person (US$)
$30.00
$20.00
$10.00
$0.00
$5.10
$0.35
$6.03
$13.04
$19.41
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits


Barranquilla: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
$5,500
$5,000
$4,500
$4,000
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500
6
5
4
3
2
1
-1
-2
-3
$4,073
$921
-$52
-$520
1.19
2.25
3.11
3.81
0
5
10
15
20
ICER
Benefit/cost ratio
Time horizon (years)

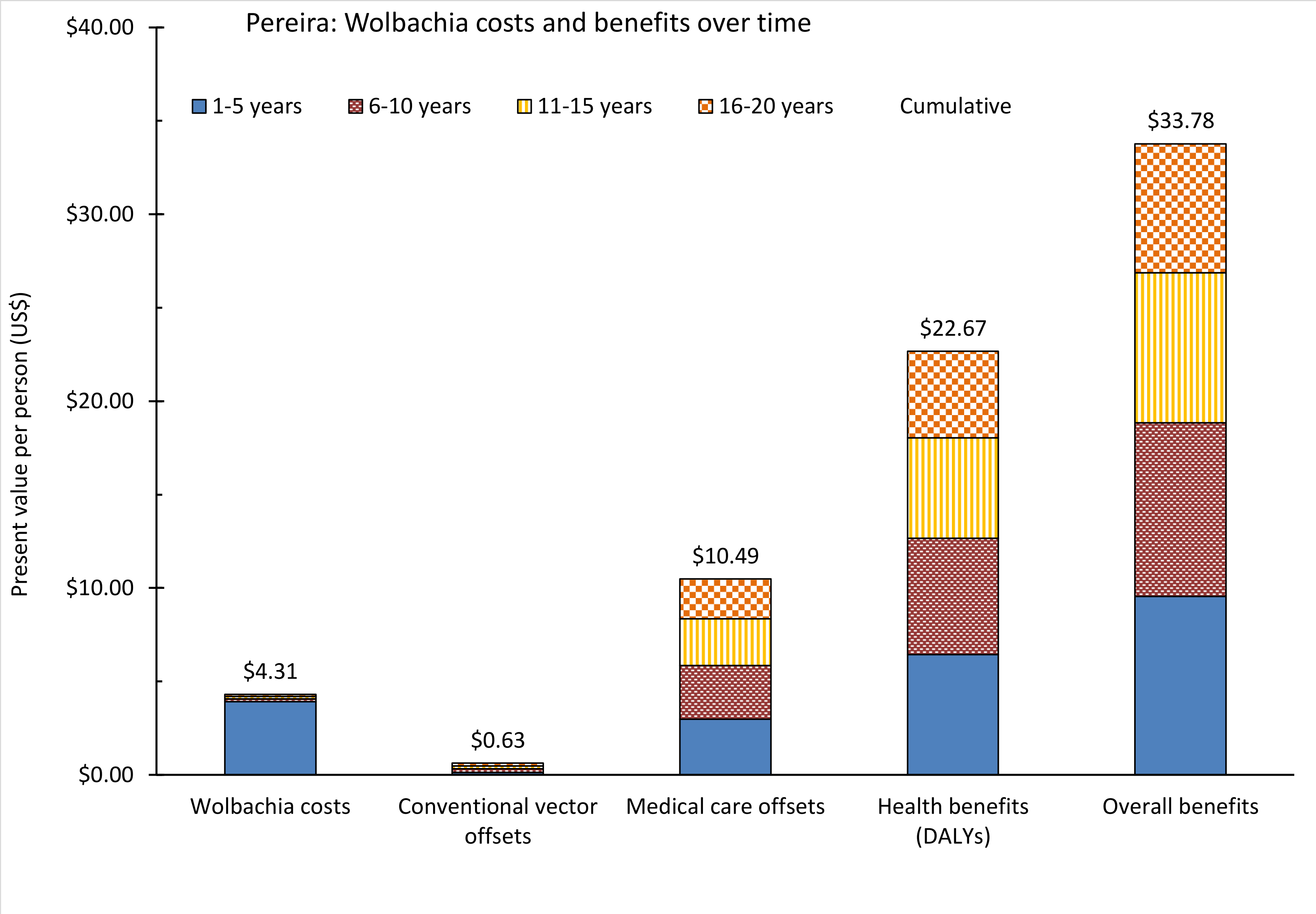

Valledupar: Wolbachia costs and benefits over time
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
Present value per person (US$)
$40.00
$30.00
$20.00
$10.00
$0.00
$5.35
$1.23
$10.71
$23.15
$35.09
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits

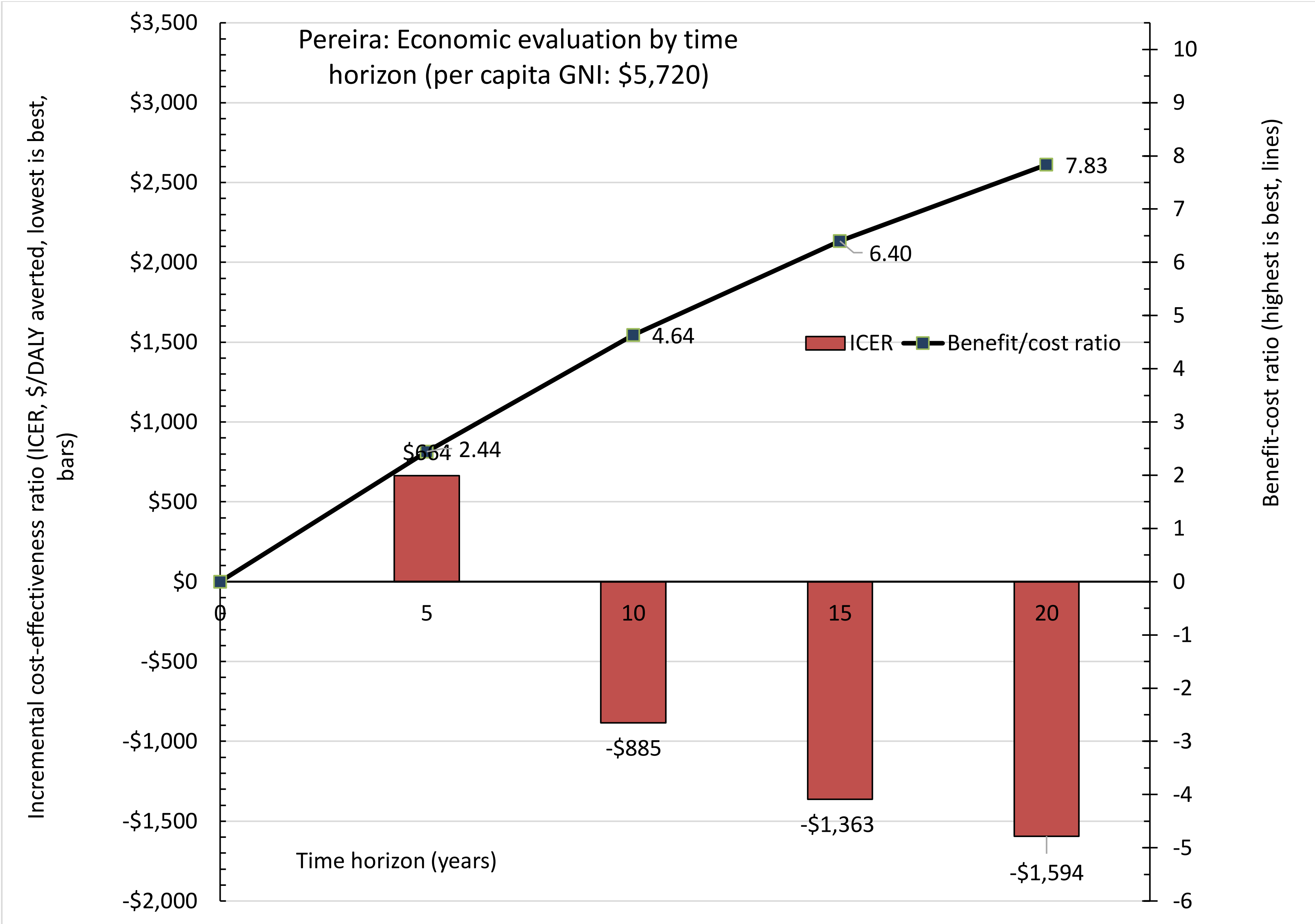

Valledupar: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
0
5
10
15
20
$1,262
-$642
-$1,229
-$1,512
2.04
3.88
5.36
6.56
ICER
Benefit/cost ratio
Time horizon (years)


Armenia: Wolbachia costs and benefits over time
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
Present value per person (US$)
$60.00
$50.00
$40.00
$30.00
$20.00
$10.00
$0.00
$4.76
$0.82
$17.72
$38.30
$56.84
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits



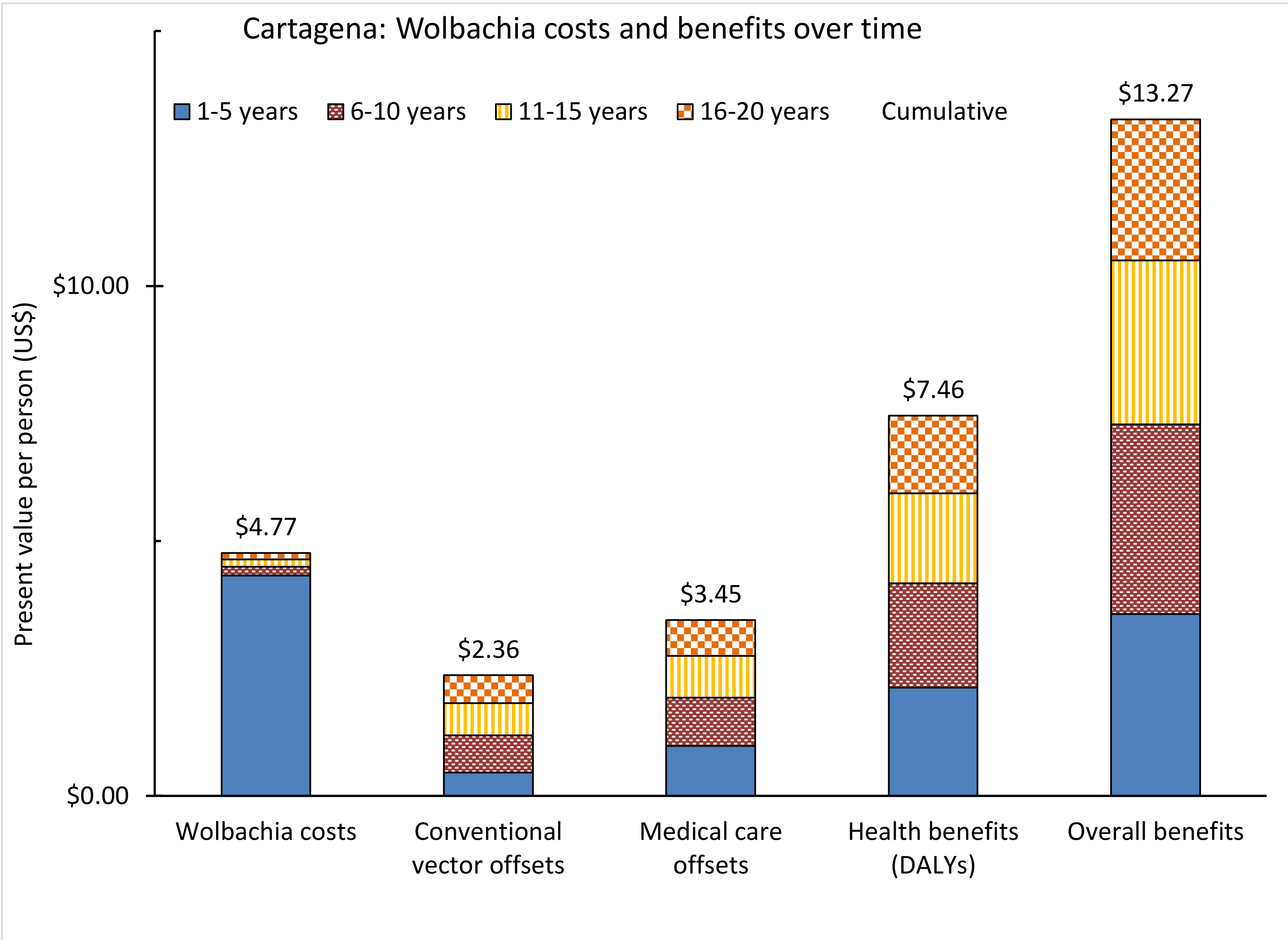
Armenia: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
Time horizon (years)
ICER
Benefit/cost ratio
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
-$2,500
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
0
5
10
15
20
3.73
7.07
9.75
11.93
-$429
-$1,446
-$1,759
-$1,911

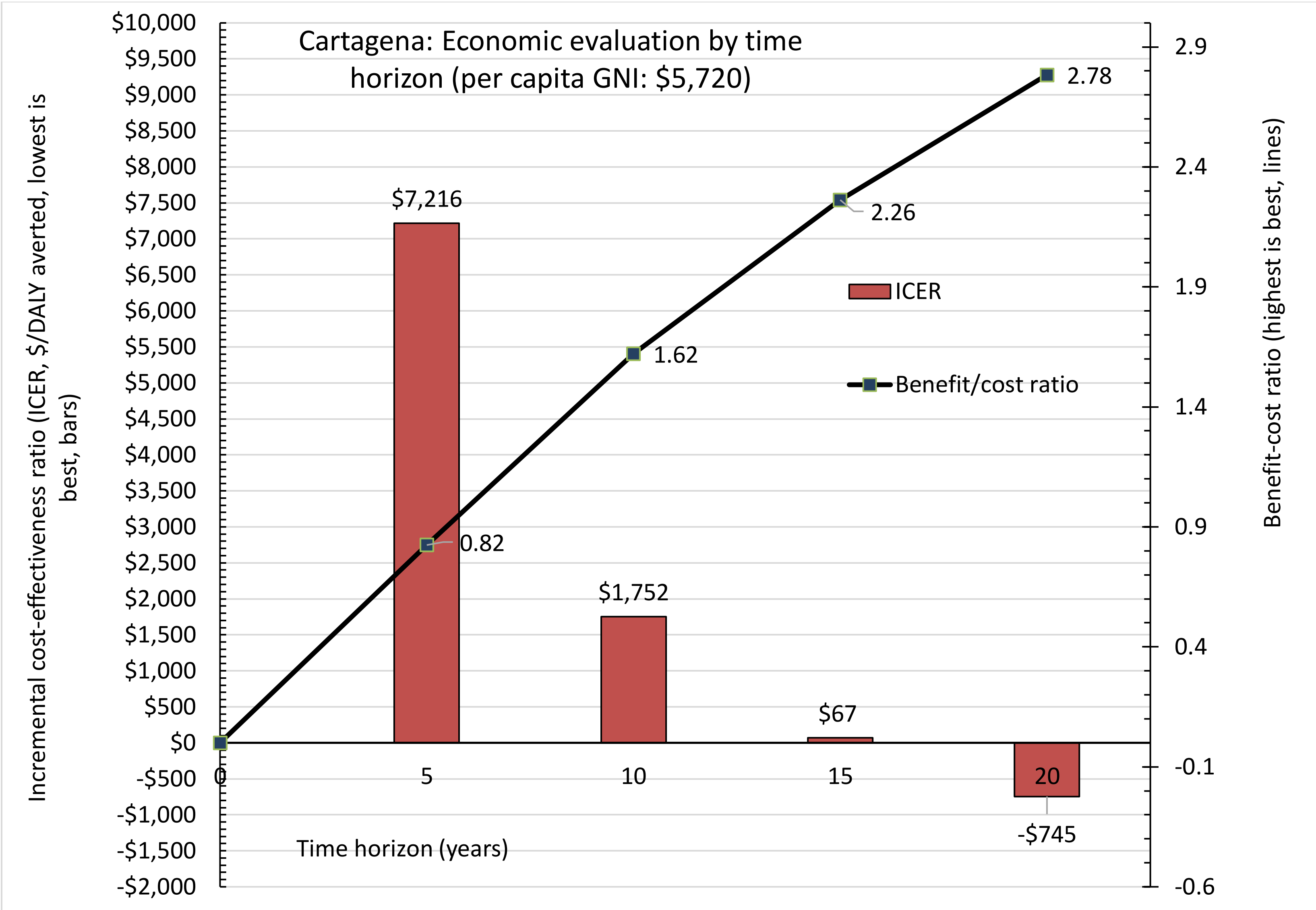

Pereira: Wolbachia costs and benefits over time
1-5 years
6-10 years
11-15 years
16-20 years
Cumulative
Present value per person (US$)
$40.00
$30.00
$20.00
$10.00
$0.00
$4.31
$0.63
$10.49
$22.67
$33.78
Wolbachia costs
Conventional vector offsets
Medical care offsets
Health benefits (DALYs)
Overall benefits



Pereira: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
0
5
10
15
20
Time horizon (years)
ICER
Benefit/cost ratio
$664
2.44
4.64
6.40
7.83
-$885
-$1,363
-$1,594

Supplement S10. Cartagena *Wolbachia* Economics




Cartagena: Economic evaluation by time horizon (per capita GNI: $5,720)
Incremental cost-effectiveness ratio (ICER, $/DALY averted, lowest is best, bars)
Benefit-cost ratio (highest is best, lines)
$10,000
$9,500
$9,000
$8,500
$8,000
$7,500
$7,000
$6,500
$6,000
$5,500
$5,000
$4,500
$4,000
$3,500
$3,000
$2,500
$2,000
$1,500
$1,000
$500
$0
-$500
-$1,000
-$1,500
-$2,000
2.9
2.4
1.9
1.4
0.9
0.4
-0.1
-0.6
0
5
10
15
20
Time horizon (years)
$7,216
$1,752
$67
-$745
0.82
1.62
2.26
2.78
ICER
Benefit/cost ratio