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What Is the Value of Different Zika Vaccination Strategies to Prevent and Mitigate Zika Outbreaks?

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(See the Editorial commentary by Clapham et al, on pages 917–9.)

Background. While the 2015–2016 Zika epidemics prompted accelerated vaccine development, decision makers need to know the potential economic value of vaccination strategies.

Methods. We developed models of Honduras, Brazil, and Puerto Rico, simulated targeting different populations for Zika vaccination (women of childbearing age, school-aged children, young adults, and everyone) and then introduced various Zika outbreaks. Sensitivity analyses varied vaccine characteristics.

Results. With a 2% attack rate ($5 vaccination), compared to no vaccination, vaccinating women of childbearing age cost $314–$1664 per case averted ($790–$4221/disability-adjusted life-year [DALY] averted) in Honduras, and saved $847–$1644/case averted in Brazil, and $3648–$4177/case averted in Puerto Rico, varying with vaccination coverage and efficacy (societal perspective). Vaccinating school-aged children cost $718–$1849/case averted (≤$5002/DALY averted) in Honduras, saved $819–$1609/case averted in Brazil, and saved $3823–$4360/case averted in Puerto Rico. Vaccinating young adults cost $310–$1666/case averted ($731–$4017/DALY averted) in Honduras, saved $953–$1703/case averted in Brazil, and saved $3857–$4372/case averted in Puerto Rico. Vaccinating everyone averted more cases but cost more, decreasing cost savings per case averted. Vaccination resulted in more cost savings and better outcomes at higher attack rates.

Conclusions. When considering transmission, while vaccinating everyone naturally averted the most cases, specifically targeting women of childbearing age or young adults was the most cost-effective.

Keywords. Zika; cost-effectiveness; vaccine.

The 2015–2016 Zika epidemics prompted accelerated development of a Zika vaccine as one potential strategy to prevent and mitigate future outbreaks [1–3]. Decision makers need to know the potential value of different vaccination strategies. Given limited resources, there is a balance between various mitigation strategies to prevent morbidity and costs associated with Zika-related complications, and the difficulty and cost of implementation. For vaccination strategies, possibilities range from vaccinating everyone to specific target populations. Previous studies have shown the potential cost of a Zika epidemic [4, 5]. Knowing the value of vaccination prior to rollout of the vaccine can help policy makers decide on vaccination as a prevention strategy, whom to vaccinate, and guide program planning. Since multiple candidates are currently being developed and it is unclear which vaccines will reach the market, it is also important to understand how these decisions may change based on differing

vaccine characteristics, such as cost and efficacy [6]. Therefore, we developed a model of Honduras, Brazil, and Puerto Rico, represented various vaccination approaches, and simulated different Zika outbreaks to determine the resulting economic value of vaccination to prevent and mitigate outbreaks.

METHODS

We developed a Zika clinical and economic outcomes model coupled with a transmission model that translated the number of Zika infections into clinical and health outcomes and their associated costs from the healthcare system and societal perspectives. We evaluated Zika vaccination scenarios in Brazil, Honduras, and Puerto Rico, as these countries were significantly affected by the 2015–2016 Zika epidemic [7, 8] and are representative of other Latin American countries based on income group (defined by the World Bank [9, 10]) and country characteristics (eg, life expectancy, population age distribution, mortality rate).

Model Structure

We used a previously described transmission model [11] to quantify the number of people infected under various scenarios. Supplementary Appendix Figure 1 outlines the model. In brief, this model represents individuals aged 0–99 years and includes population demographics, age-specific fertility, and

mortality. Mosquito vectors could be susceptible, exposed, or Zika-infected, where vector population prevalence was modeled with a seasonally varying carrying capacity defined according to country-specific female mosquito indices [12–14], to reflect seasonal variation in mosquito populations. Humans could be susceptible, exposed, infected, recovered, or vaccinated. Human infectiousness to vectors lasted 4–7 days [15] and was assumed to confer lifelong immunity [16]. Transmission between humans and vectors was frequency-dependent with a constant daily vector biting rate (which varied indirectly with seasonal carrying capacity). Transmission was based on the force of infection, which accounts for the transmission rate (ie, mosquito to humans and humans to mosquitos), the biting rate, and the proportion of infections in the population. To calibrate the model to specific attack rates, we ran the model for each country over 5 years with no vaccination, while varying the vector transmission rate, and computed the population fraction infected for each rate. We then recorded the transmission rate corresponding to each attack rate scenario.

The number of infected persons over the course of the outbreak and the number of vaccinated persons were input to the economic model (adapted from our previously published model [4]). Each Zika infection had a probability of developing symptoms, with a corresponding probability of seeking care. Those with Zika infection (symptomatic and asymptomatic) had a probability of developing Guillain-Barré syndrome (GBS). All GBS cases were hospitalized and had a probability of mortality. GBS patients had probabilities of developing mild, moderate, or severe motor deficits, each associated with a given duration of symptoms and disability. To determine the number of congenital Zika infections, we multiplied the number of live births to Zika-infected women by the probability of congenital infection given a live birth.

The healthcare system perspective included direct costs (ie, outpatient visits and hospitalization), while the societal perspective included direct and indirect costs (ie, productivity losses for absenteeism and mortality). Hospitalization costs were calculated as the bed-day cost for each hospitalization day. Productivity losses were estimated using the gross national income (GNI) per capita as a proxy for daily wages. We assumed symptomatic Zika cases only accrued losses if they sought ambulatory care. GBS cases accrued losses for the duration of their hospitalization or motor impairment, whichever was longer. Those with microcephaly accrued productivity losses attenuated by the disability weight for severe intellectual disability for the duration of their lifetime. Death resulted in the accrual of lifetime productivity losses using the median age of the population and discounted GNI over the remainder of the person's life expectancy.

For each scenario, the following formula determined the incremental cost-effectiveness ratio (ICER):

$$= \left(\text{Cost}_{\text{No vaccination}} - \text{Cost}_{\text{Vaccination}} \right)$$
$$/ \left(\text{Health Effects}_{\text{Vaccination}} - \text{Health Effects}_{\text{No vaccination}} \right),$$

where health effects were measured in disability-adjusted life-years (DALYs), cases, and deaths. DALYs equaled the sum of the years lived with disability (YLD) and the years of life lost (YLL) due to premature mortality, calculated as:

$$\text{YLD} = \text{Number of Incident Cases} \times \text{Disability Weight}$$
$$\times \text{Average Duration of Disability in Years}$$
$$\text{YLL} = \text{Number of Deaths} \times \text{Life Expectancy}$$
$$\text{at Age of Death in Years}$$

ICERs were considered highly cost-effective if they were less than or equal to the gross domestic product (GDP) per capita, cost-effective if between 1 and 3 times the GDP per capita, and not cost-effective if >3 times the GDP per capita. The 2017 GDP per capita of Puerto Rico, Brazil, and Honduras was $32 307, $8910, and $2432, respectively. Vaccination strategies were economically dominant if they saved costs and provided health benefits (ie, averted DALYs) compared to no vaccination. All future costs and DALYs were discounted to net present value using a 3% discount rate.

Data Sources

Supplementary Appendix Table 1 summarizes the models' input parameters, values, and sources. All inputs were country-specific when available. Population demographics, age-specific fertility, and age-specific mortality came from the United Nations [17]. We utilized care-seeking rates for fever of all causes as a proxy for care-seeking rates for symptomatic Zika infection. Cost of outpatient and hospital beds came from the World Health Organization's Choosing Interventions That Are Cost Effective initiative (WHO-CHOICE) [18]. The direct lifetime medical and nonmedical cost for microcephaly came from a study using congenital cytomegalovirus as a proxy for Zika-associated microcephaly [19] and converted this cost for each country. GNI per capita emanated from the World Bank and life expectancy from the WHO's Global Health Observatory [10, 20]. Disability weights came from the Global Burden of Disease Study [21] and assumed acute, mild episode of an infectious disease, motor impairment (mild, moderate, and severe), and severe intellectual disability as proxies for Zika infection, GBS, and congenital Zika infection, respectively. All costs were discounted to 2017 US dollars using a 3% rate.

Modeled Scenarios and Sensitivity Analyses

Our baseline scenario simulated the course of a Zika outbreak with no vaccination. Vaccination scenarios evaluated the impact of immunization of different target populations: women of childbearing age (women 15–49 years old), school-aged children (5–14 years old), young adults (15–20 years old), and everyone. We implemented large-scale vaccination of the target population at the start of the simulation (ie, year 1) followed by annual coverage of the youngest age in the target group in subsequent years. We choose these target populations as they are

ideal to prevent congenital Zika infection (ie, women of child-bearing age, young adults), to easily reach for heavy vaccination campaigns (ie, school-aged children), and to represent large campaigns to show the full impact of vaccination (ie, everyone).

Monte Carlo simulation (ie, probabilistic sensitivity analysis) consisted of 1000 trials and varied each parameter in the economic model throughout the ranges listed in Supplementary Appendix Table 1. Sensitivity analysis varied the vaccination cost per vaccinee ($5–$50), vaccine efficacy (25%–75%), vaccination coverage of the target population (25%–75%), lag time between vaccination and outbreak onset (1–5 years), and Zika attack rate (2%–50%, at 5 years). Additional scenarios evaluated the use of a booster (after the vaccine protection duration elapsed, varied from 1 to 5 years) to maintain the specified coverage level over the duration of the simulation. For each scenario, we estimated costs and health effects for the entire duration of the outbreak compared to no vaccination (as simulated in the transmission model).

RESULTS

No Vaccination

Tables 1–4 and Supplementary Appendix Tables 2–13 show the epidemiologic (ie, number of symptomatic cases and deaths) and economic (ie, direct costs, productivity losses, and total societal costs) outcomes of Zika outbreaks with attack rates of 2% and 20% occurring in year 6. An outbreak with a 50% attack rate resulted in $347.8 million in total societal costs in Honduras (551 841 symptomatic cases; 215 493 DALYs), $11.8 billion in Brazil (16.0 million cases; 775 213 DALYs), and $1.2 billion in Puerto Rico (294 573 cases; 82 833 DALYs).

Vaccinating Women of Childbearing Age

Table 1 and Supplementary Appendix Tables 2–4 show the impact of vaccinating women of childbearing age on the resulting clinical and economic outcomes for each country when an outbreak occurred 5 years after vaccination start (ie, year 6). In some circumstances, the additional vaccination costs outweighed the cost savings generated by averted cases, resulting in higher overall costs. For example, in Honduras the cost of vaccination increased direct costs by at least an additional $2.5 million, but only saved as much as $2.5 million in productivity losses ($5 vaccination, 2% attack rate; Table 1). However, total cost savings were generated in many scenarios and could save thousands of dollars per case averted (Table 1). Vaccination resulted in even higher cost savings with a 50% attack rate (not shown).

Figure 1 shows the ICER compared to no vaccination and how it changes with various vaccine characteristics under different Zika outbreak scenarios (an ICER of 0 indicates the strategy would be economically dominant, ie, saves cost and provides health benefits). Increases in both coverage and efficacy tended to have a linear effect on the ICER, while increasing vaccination costs had a nonlinear effect. Additionally, changes in vaccination

coverage had a larger impact than efficacy changes. These trends also held for higher outbreak attack rates. In Honduras, a $5 vaccination would be cost-effective (ICERs: $790–$5270/DALY averted from both perspectives) compared to no vaccination with a 2% attack rate. For an outbreak with a ≥20% attack rate in Brazil, a ≤$50 vaccination was dominant, except with a vaccine efficacy of 25% from the healthcare system perspective (ICERs: $255–$390/DALY averted), while in Puerto Rico vaccination was dominant from both perspectives.

The tables can be used to determine the marginal cost of changing vaccine characteristics, especially for economically dominant scenarios. For example, in Puerto Rico a $5, 50% efficacious vaccination would be dominant for coverage rates of 25% and 50%, saving $2.6 and $3.4 million in total direct costs, respectively (Supplementary Appendix Table 6). It cost a marginal $1.3 million to increase coverage from 25% to 50% but would avert 472 more DALYs.

Figure 2 shows how the ICER changes when using a booster following various durations of vaccine protection. In many circumstances, an annual booster would not be cost-effective. However, $5 vaccination given every 5 years was cost-effective and even dominant compared to no vaccination under many conditions.

When the outbreak occurred 1 year after the start of vaccination (ie, in year 2; data not shown), vaccinating women of childbearing age resulted in more cost savings and better outcomes, as more cases would be averted over the course of the outbreak. Vaccination saved $636–$684 per case averted in Honduras ($5 vaccination, 20% attack rate) and $1642–$2169 per case averted in Brazil ($5 vaccination, 2% attack rate, varying with efficacy and coverage).

Vaccinating School-Aged Children

Vaccinating school-aged children resulted in a similar epidemiologic impact as vaccinating women of childbearing age and therefore resulted in similar clinical outcomes and costs (Table 2 and Supplementary Appendix Tables 5–7). In Honduras, vaccination resulted in higher total direct and societal costs compared to no vaccination with an attack rate <20%. However, with a ≥20% attack rate, vaccination generated total direct cost savings with a $5 vaccination and societal cost savings with a ≤$25 vaccination. In Brazil, the averted productivity losses were always enough to overcome the higher total direct costs due to vaccination (saving ≤$15.3 billion in total costs for attack rates ≤50%), except with a ≥$25 vaccination and 2% attack rate (Supplementary Appendix Table 6). Total cost savings in Puerto Rico exceeded $1.1 million (≤$0.5 billion) for outbreaks with attack rates ≤50%.

Cost-effectiveness trends followed a similar pattern to that of vaccinating women of childbearing age (Figures 1 and 2) and under some conditions vaccinating school-aged children was more cost-effective (eg, $50 vaccination in Puerto Rico;

Table 1. Epidemiologic, Clinical, and Economic Outcomes for Zika Vaccination When Vaccinating Women of Childbearing Age 5 Years Before the Start of an Outbreak With a 2% Attack Rate

Country and Model	Total Vaccinated[a], Millions	Symptomatic Zika Cases, No.	DALYs, Median (95% UI)	Vaccination Costs	Total Direct Costs, Median (95% UI)	Total Societal Costs, Median (95% UI)	Cost per Case Averted[b]
Honduras							
No vaccine[c]	…	9229	3535 (1074–8208)	…	2.0 (1.4–3.5)	5.8 (3.1–11.1)	
$5 vaccine							
25% efficacy							
25% coverage[c]	0.7	7359	2757 (790–6630)	3.5	5.0 (4.5–6.3)	8.0 (5.9–11.8)	1171
75% coverage[d]	2.1	4844	1806 (510–4354)	10.3	11.2 (10.9–12)	13.1 (11.7–15.6)	1664
75% efficacy							
25% coverage[d]	0.7	5724	2141 (610–5152)	3.5	4.6 (4.2–5.6)	6.9 (5.3–9.8)	314
75% coverage[e]	2.1	3009	1112 (308–2695)	10.3	10.7 (10.6–11.2)	11.9 (11.0–13.5)	979
$25 vaccine							
25% efficacy							
25% coverage[c]	0.7	7359	2812 (851–6539)	23.7	19.0 (18.5–20.2)	22.0 (19.9–26.3)	8671
75% coverage[d]	2.1	4844	1840 (551–4296)	70.7	52.5 (52.3–53.2)	54.5 (53.1–57.3)	11 102
75% efficacy							
25% coverage[d]	0.7	5724	2182 (657–5083)	23.7	18.6 (18.2–19.5)	20.9 (19.3–24.2)	4315
75% coverage[e]	2.1	3009	1133 (334–2661)	70.7	52.0 (51.9–52.5)	53.3 (52.4–55)	7630
Brazil							
No vaccine	…	346 206	106 455 (32 764–257 059)	…	193.9 (130.8–264.9)	732.7 (366.0–1441.8)	…
$5 vaccine							
25% efficacy							
25% coverage	17.8	261 055	81 754 (23 135–193 630)	86.5	222.7 (177.9–278.7)	634.6 (356.9–1195.1)	−1152
75% coverage	52.7	156 680	48 932 (13 710–116 041)	256.4	324.2 (302.1–354.7)	572.2 (405.4–907.8)	−847
75% efficacy							
25% coverage	17.8	184 802	57 803 (16 278–136 974)	86.5	174.9 (145.9–212.5)	467.3 (270.6–863.6)	−1644
75% coverage[d]	52.7	83 413	25 914 (7135–61 617)	256.4	279.4 (271.9–294.6)	411.8 (320.3–591.3)	−1221
$25 vaccine							
25% efficacy							
25% coverage	17.8	261 055	80 168 (24 629–193 713)	23.7	570.0 (525.0–622.0)	978.5 (702.5–1513.4)	2886
75% coverage	52.7	156 680	47 980 (14 663–116 074)	70.7	1350.6 (1328.2–1379.1)	1596.1 (1430.1–1914.9)	4555
75% efficacy							
25% coverage	17.8	184 802	56 667 (17 367–137 023)	23.7	521.8 (492.8–556.3)	811.6 (615.9–1190.2)	489
75% coverage[d]	52.7	83 413	25 418 (7695–61 620)	70.7	1305.3 (1297.7–1318.2)	1436.2 (1348.6–1607.0)	2677
Puerto Rico							
No vaccine	…	7860	2337 (656–5390)	…	9.2 (6.1–26.3)	35.3 (16.2–70.9)	…
$5 vaccine							
25% efficacy							
25% coverage	0.3	5792	1723 (460–3971)	1.4	8.0 (5.6–19.7)	27.5 (13.2–53.7)	−3769
75% coverage	0.8	3392	1007 (267–2324)	4.1	7.5 (6.2–14.4)	19.0 (10.6–34.3)	−3648
75% efficacy							
25% coverage	0.3	3936	1170 (311–2698)	1.4	5.6 (4.1–13.5)	18.9 (9.2–36.7)	−4177
75% coverage[d]	0.8	1667	493 (130–1140)	4.1	5.3 (4.8–8.7)	11.0 (6.9–18.7)	−3921
$25 vaccine							
25% efficacy							
25% coverage	0.3	5792	1721 (481–3970)	23.7	13.4 (11.2–25.9)	32.7 (18.6–59.0)	−1249
75% coverage	0.8	3392	1005 (279–2323)	70.7	23.7 (22.6–31.0)	35.1 (26.9–50.6)	−42
75% efficacy							
25% coverage	0.3	3936	1168 (325–2697)	23.7	11.0 (9.6–19.5)	24.2 (14.6–42.2)	−2829
75% coverage[d]	0.8	1667	491 (134–1139)	70.7	21.6 (21.2–25.2)	27.2 (23.2–34.9)	−1304

Costs are shown as million 2017 US dollars. Simulated outbreak occurs 5 years after the start of vaccination; all outbreaks lasted 5 years unless otherwise noted.

Abbreviations: DALY, disability-adjusted life-year; GBS, Guillain-Barré syndrome; UI, uncertainty interval.

[a]Transmission model result.

[b]From the societal perspective; US dollars; negative values imply savings.

[c]Outbreak duration 4 years.

[d]Outbreak duration 3 years.
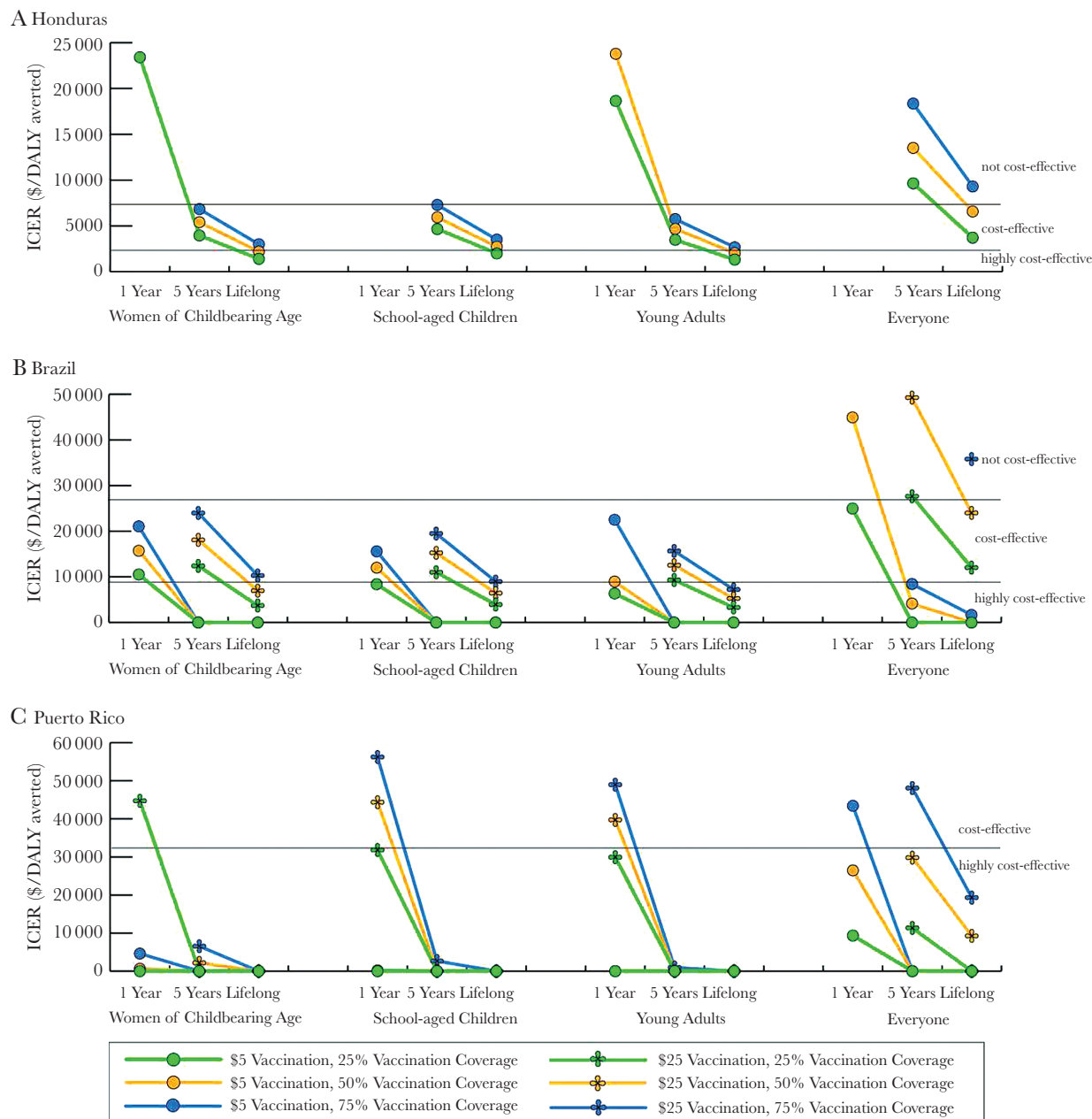
[e]Outbreak duration 2 years.

Figure 1. Impact of varying vaccine characteristics on the incremental cost-effectiveness ratio (ICER) from the healthcare system perspective when vaccinating each target population (women of childbearing age, school-aged children, young adults, and everyone) for a Zika outbreak starting 5 years after vaccination in Honduras with a 20% attack rate (*A*), Brazil with a 2% attack rate (*B*), and Puerto Rico with a 2% attack rate (*C*). An ICER of 0 indicates the strategy would be economically dominant (provides cost savings and health benefits). ICERs greater than $50 000 per disability-adjusted life-year (DALY) averted and $35 000 per DALY averted are not shown for Brazil and Puerto Rico, respectively.

Figure 1C). For a 2% outbreak, a $5 vaccination was cost-effective in Honduras (ICERs: $1210–$6052/DALY averted from both perspectives). In Brazil, vaccination was dominant compared to no vaccination for attack rates ≥20%, except for a $50 vaccination and 20% attack rate, but vaccination remained highly cost-effective. Although an annual booster was not cost-effective compared to no vaccination in Honduras (Figure 2A), it was cost-effective in Brazil (Figure 2B), and was dominant in Puerto Rico (Figure 2C). Supplementary Appendix Tables 5–7

can be used to calculate the marginal cost of increasing various vaccine characteristics. When the outbreak occurred 1 year after vaccine availability, vaccination resulted in more cost savings and better outcomes (results not shown).

Vaccinating Young Adults

Vaccinating young adults resulted in a similar epidemiologic impact as vaccinating women of childbearing age and school-aged children, thus yielding similar clinical outcomes and costs
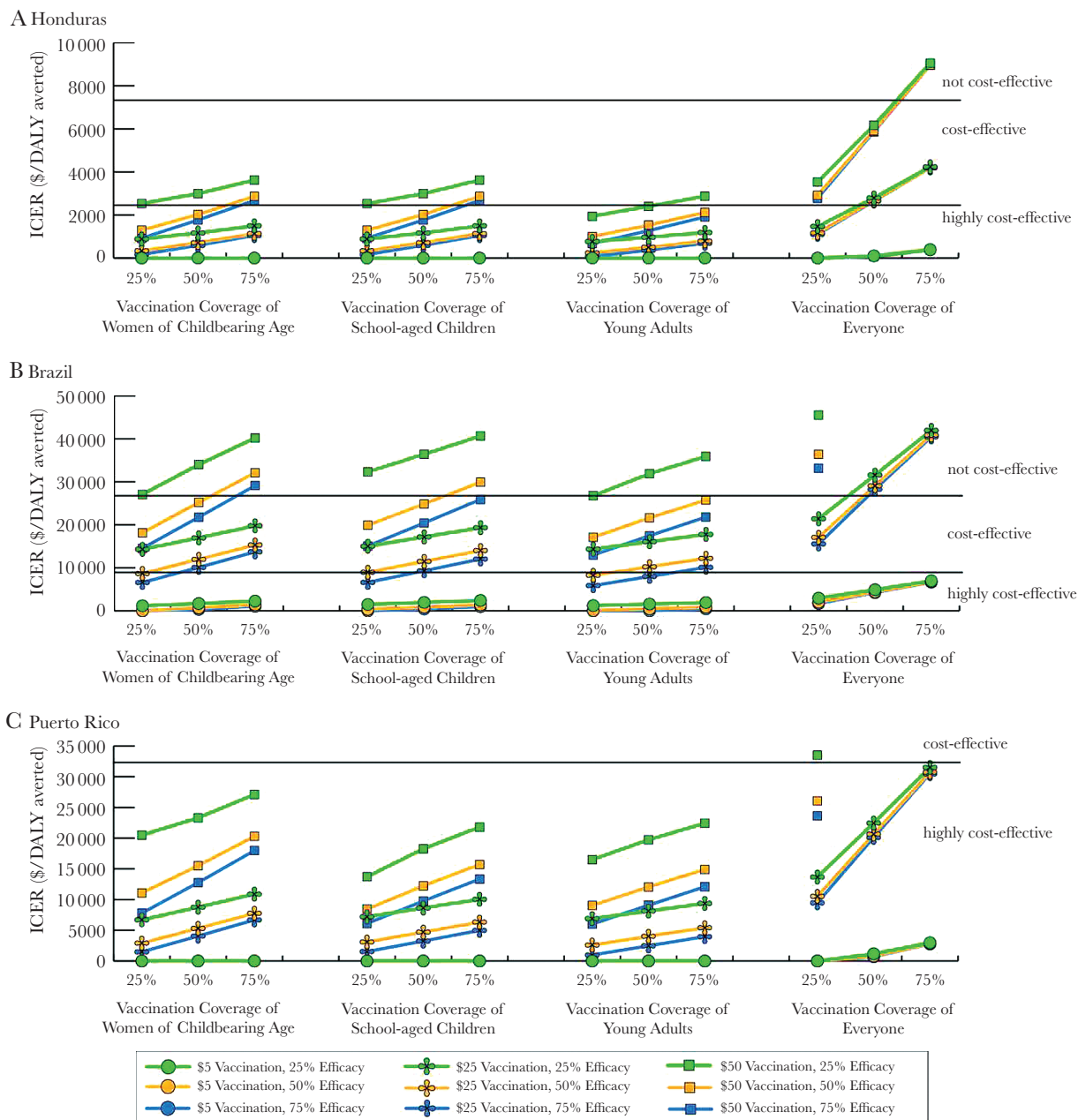
Figure 2. Impact of using a booster with varying vaccine characteristics on the incremental cost-effectiveness ratio (ICER) from the societal perspective when vaccinating women of childbearing age, school-aged children, young adults, and everyone for a Zika outbreak starting 5 years after vaccination in Honduras (*A*), Brazil (*B*), and Puerto Rico (*C*) with a 2% attack rate. An ICER of 0 indicates the strategy would be economically dominant (provides cost savings and health benefits). Vaccine efficacy held at 50%. ICERs greater than $25 000 per disability-adjusted life-year (DALY) averted, $50 000 per DALY averted, and $60 000 per DALY averted are not shown for Honduras, Brazil, and Puerto Rico, respectively.

(Table 3 and Supplementary Appendix Tables 8–10). While vaccinating young adults averted thousands of Zika cases in Honduras and Puerto Rico and millions in Brazil (for an outbreak occurring 5 years after vaccine availability), overall cost savings were not always generated due to the additional vaccination cost (eg, in Honduras the vaccination cost increased direct costs by an additional $2.4–$80.5 million, and societal costs by an additional $0.9–$78.1 million with a 2% attack rate; Supplementary Appendix Table 8). However, vaccination

garnered cost savings of ≤$214.0 million, ≤$13.3 billion, and ≤$471.7 million in Honduras, Brazil, and Puerto Rico, respectively, from the societal perspective (attack rates ≤50%).

ICERs showed similar trends as when vaccinating women of childbearing age (Figures 1 and 2). Vaccination was not cost-effective in Honduras with a 2% attack rate and ≥$25 vaccination, 25% efficacious, ≥50% coverage. In Puerto Rico, vaccination was dominant compared to no vaccination under all conditions tested, except at a 2% attack rate (Figure 1C). Even a vaccine

Table 2. Epidemiologic, Clinical, and Economic Outcomes for Zika Vaccination When Vaccinating School-Aged Children 5 Years Before the Start of an Outbreak With a 2% Attack Rate

Country and Model	Total Vaccinated[a], Millions	Symptomatic Zika Cases	DALYs, Median (95% UI)	Vaccination Costs	Total Direct Costs, Median (95% UI)	Total Societal Costs, Median (95% UI)	Cost per Case Averted[b]
Honduras							
No vaccine[c]	…	9229	3552 (1050–8461)	…	2.1 (1.4–3.5)	5.8 (3.1–10.8)	…
$5 vaccine							
25% efficacy							
25% coverage[c]	0.6	7785	2861 (834–6971)	2.8	4.5 (4.0–5.9)	7.6 (5.5–11.9)	1237
75% coverage[d]	1.8	5747	2108 (611–5141)	8.2	9.3 (9.0–10.3)	11.6 (10.0–14.8)	1666
75% efficacy							
25% coverage[d]	0.6	6375	2341 (681–5706)	2.8	4.2 (3.8–5.3)	6.7 (5.0–10.3)	310
75% coverage[e]	1.8	3799	1390 (400–3394)	8.2	8.9 (8.7–9.5)	10.4 (9.3–12.5)	836
$25 vaccine							
25% efficacy							
25% coverage[c]	0.6	7785	2994 (883–7135)	23.7	15.9 (15.3–17)	19.0 (16.7–23.2)	9138
75% coverage[d]	1.8	5747	2206 (647–5263)	70.7	42.0 (41.6–42.9)	44.4 (42.7–47.5)	11 066
75% efficacy							
25% coverage[d]	0.6	6375	2449 (721–5841)	23.7	15.5 (15.0–16.5)	18.1 (16.2–21.6)	4301
75% coverage[e]	1.8	3799	1454 (423–3475)	70.7	41.6 (41.3–42.1)	43.1 (42.0–45.2)	6860
Brazil							
No vaccine	…	538 546	159 241 (49 707–395 540)	…	308.2 (207.3–421.9)	1106.5 (550.1–2270.3)	…
$5 vaccine							
25% efficacy							
25% coverage	12.5	291 471	92 864 (26 468–226 681)	57.6	214.4 (166.6–275.7)	686.5 (364.2–1341.7)	−1133
75% coverage	36.3	215 403	68 531 (19 454–167 444)	166.7	274.6 (241.6–317.2)	623.9 (386.1–1109.1)	−953
75% efficacy							
25% coverage	12.5	232 027	73 863 (21 002–180 401)	57.6	177.4 (140.8–224.4)	554.1 (296.9–1076.2)	−1703
75% coverage[c]	36.2	131 899	41 853 (11 789–102 442)	166.6	223.5 (206.1–248.6)	437.4 (291.8–738)	−1452
$25 vaccine							
25% efficacy							
25% coverage	12.5	291 471	93 652 (24 903–217 176)	23.7	445.2 (392.5–502.7)	914.2 (573.9–1524.1)	3027
75% coverage	36.3	215 403	69 133 (18 341–160 432)	70.7	941.3 (905.1–981.4)	1288 (1037.3–1739.5)	4124
75% efficacy							
25% coverage	12.5	232 027	74 503 (19 784–172 842)	23.7	407.9 (367.8–451.8)	781.7 (511.2–1268.1)	291
75% coverage[c]	36.2	131 899	42 241 (11 157–98 164)	70.7	889.8 (870.8–912.4)	110.02 (949.9–1 378.7)	1649
Puerto Rico							
No vaccine	…	7860	2388 (686–5865)	…	9.5 (6.2–25.4)	35.6 (16.8–75.4)	…
$5 vaccine							
25% efficacy							
25% coverage	0.2	6581	1959 (512–4527)	0.9	8.6 (5.9–20.5)	30.3 (15.0–60.8)	−4204
75% coverage	0.6	4837	1439 (375–3327)	2.5	8.0 (6.1–16.7)	24.0 (12.7–46.5)	−3857
75% efficacy							
25% coverage	0.2	5138	1529 (399–3534)	0.9	6.7 (4.7–16.0)	23.7 (11.8–47.6)	−4372
75% coverage[d]	0.6	2838	843 (218–1951)	2.5	5.4 (4.4–10.5)	14.9 (8.2–28.1)	−4139
$25 vaccine							
25% efficacy							
25% coverage	0.2	6581	1999 (574–4910)	23.7	12.1 (9.4–25.4)	34.1 (18.4–67.4)	−1231
75% coverage	0.6	4837	1468 (421–3608)	70.7	18.1 (16.2–27.9)	34.2 (22.7–58.8)	−469
75% efficacy							
25% coverage	0.2	5138	1560 (448–3833)	23.7	10.3 (8.2–20.7)	27.4 (15.2–53.6)	−3019
75% coverage[d]	0.6	2838	860 (246–2115)	70.7	15.5 (14.5–21.3)	25.0 (18.3–39.5)	−2114

Costs are shown as million 2017 US dollars. Simulated outbreak occurs 5 years after the start of vaccination; all outbreaks lasted 5 years unless otherwise noted.

Abbreviations: DALY, disability-adjusted life-year; GBS, Guillain-Barré syndrome; UI, uncertainty interval.

[a]Transmission model result.

[b]From the societal perspective; US dollars; negative values imply savings.

[c]Outbreak duration 4 years.

[d]Outbreak duration 3 years.

[e]Outbreak duration 2 years.

Table 3. Epidemiologic, Clinical, and Economic Outcomes for Zika Vaccination When Vaccinating Young Adults 5 Years Before the Start of an Outbreak With a 2% Attack Rate

Country and Model	Total Vaccinated[a], Millions	Symptomatic Zika Cases	DALYs, Median (95% UI)	Vaccination Costs	Total Direct Costs, Median (95% UI)	Total Societal Costs, Median (95% UI)	Cost per Case Averted[b]
Honduras							
No vaccine[c]	…	9229	3506 (1015–7703)	…	2.1 (1.4–3.4)	5.8 (3.2–10.4)	…
$5 vaccine							
25% efficacy							
25% coverage[c]	0.8	7398	2873 (818–6432)	3.6	5.2 (4.7–6.2)	8.3 (6.0–12.4)	1381
75% coverage[d]	2.2	4968	1931 (551–4322)	10.4	11.6 (11.2–12.2)	13.6 (12.1–16.4)	1849
75% efficacy							
25% coverage[d]	0.8	5779	2246 (640–5026)	3.6	4.9 (4.5–5.7)	7.3 (5.5–10.5)	442
75% coverage[d]	2.2	3110	1211 (347–2707)	10.4	11.2 (10.9–11.6)	12.5 (11.5–14.2)	1097
$25 vaccine							
25% efficacy							
25% coverage[c]	0.8	7398	2812 (815–6176)	23.7	19.6 (19.0–20.7)	22.6 (20.5–26.3)	9172
75% coverage[d]	2.2	4968	1891 (550–4150)	70.7	53.4 (53.0–54.1)	55.3 (53.9–57.9)	11 637
75% efficacy							
25% coverage[d]	0.8	5779	2198 (638–4826)	23.7	19.2 (18.8–20.1)	21.6 (19.9–24.5)	4579
75% coverage[d]	2.2	3110	1185 (346–2600)	70.7	52.9 (52.7–53.4)	54.2 (53.3–55.8)	7915
Brazil							
No vaccine	…	346 206	107 296 (28 385–255 941)	…	193.4 (132.4–266.2)	737.5 (357.0–1443.0)	…
$5 vaccine							
25% efficacy							
25% coverage	14.8	279 544	85 716 (27 720–204 492)	69.3	225.4 (176.2–282.9)	663.1 (358.2–1252.4)	−1115
75% coverage	43.2	191 468	58 716 (18 994–140 072)	202.5	310.3 (276.2–350.0)	610.7 (401.5–1014.9)	−819
75% efficacy							
25% coverage	14.8	212 635	65 206 (21 093–155 556)	69.3	188.8 (151.1–233.1)	522.5 (290.2–971.6)	−1609
75% coverage[c]	43.2	109 844	33 692 (10 905–80 368)	202.4	265.1 (245.3–288.1)	437.9 (317.8–670.2)	−1268
$25 vaccine							
25% efficacy							
25% coverage	14.8	279 544	86 644 (22 925–206 669)	23.7	503.5 (454–562.6)	943.5 (635.8–1514.2)	3090
75% coverage	43.2	191 468	59 355 (15 708–141 564)	70.7	1120.6 (1086.5–1161.3)	1 422.6 (1211.4–1814.4)	4427
75% efficacy							
25% coverage	14.8	212 635	65 915 (17 444–157 212)	23.7	466.7 (428.8–511.9)	802.0 (567.6–1237.2)	483
75% coverage[c]	43.2	109 844	34 061 (9018–81 225)	70.7	1075.1 (1055.2–1098.4)	1248.6 (1127.3–1474.1)	2163
Puerto Rico							
No vaccine	…	7860	2421 (701–5659)	…	9.4 (6.2–23.1)	36.5 (17.3–71.7)	…
$5 vaccine							
25% efficacy							
25% coverage	0.2	6369	1881 (549–4504)	1.0	8.8 (6.1–21.5)	30.2 (15.0–61.4)	−4180
75% coverage	0.6	4407	1302 (380–3117)	2.9	8.4 (6.5–17.2)	23.3 (12.7–44.9)	−3823
75% efficacy							
25% coverage	0.2	4787	1414 (413–3386)	1.0	6.9 (4.9–16.5)	23.1 (11.6–46.6)	−4360
75% coverage[c]	0.6	2435	720 (210–1722)	2.9	6.0 (5.0–10.9)	14.3 (8.4–26.2)	−4093
$25 vaccine							
25% efficacy							
25% coverage	0.2	6369	1962 (568–4585)	23.7	12.7 (10.1–23.8)	34.7 (19.1–63.3)	−1195
75% coverage	0.6	4407	1358 (393–3173)	70.7	20.1 (18.3–27.8)	35.3 (24.5–55.2)	−327
75% efficacy							
25% coverage	0.2	4787	1475 (427–3447)	23.7	10.9 (8.9–19.2)	27.4 (15.7–49.0)	−2944
75% coverage[c]	0.6	2435	751 (218–1753)	70.7	17.8 (16.7–22.0)	26.2 (20.2–37.2)	−1894

Costs are shown as million 2017 US dollars. Simulated outbreak occurs 5 years after the start of vaccination; all outbreaks lasted 5 years unless otherwise noted.

Abbreviations: DALY, disability-adjusted life-year; GBS, Guillain-Barré syndrome; UI, uncertainty interval.

[a]Transmission model result.

[b]From the societal perspective; US dollars; negative values imply savings.

[c]Outbreak duration 4 years.

[d]Outbreak duration 3 years.

that required an annual booster (ie, 1-year protection duration) was highly cost-effective under many circumstances (Figure 2). Again, the tables can be used to determine the marginal cost of increasing various vaccine characteristics.

When the outbreak occurred 1 year after the start of vaccination (ie, in year 2), vaccinating young adults resulted in more cost savings and better outcomes (results not shown). The cost per case averted, while still resulting in savings, was less than it was when vaccinating women of childbearing age. For example, in Honduras it saved $13–$38 less (20% attack rate) and in Brazil, vaccination saved $1482–$1912 per case averted ($5 vaccination, 2% attack rate, varying with efficacy and coverage).

Vaccinating Everyone
Vaccinating the entire population averted ≤5.7 million cases and ≤38 158 GBS deaths (Table 4 and Supplementary Appendix Tables 11–13). While vaccinating everyone averted direct healthcare costs and productivity losses, vaccination costs were higher, and vaccination did not result in overall cost savings in Honduras or Brazil (except with a $5 vaccination, ≤50% coverage) for a 2% attack rate (Supplementary Appendix Tables 11 and 12). However, a $5 vaccination saved $29.7–$46.1 million in societal costs (all coverages) in Honduras and $0.4–$2.7 billion in direct costs and $3.6–$11.7 billion in societal costs in Brazil for a 20% attack rate. Vaccination usually generated cost savings in Puerto Rico (Supplementary Appendix Table 13), saving $0.1–$126.2 million in direct costs and $1.5–$499.5 million in societal costs, depending on vaccine characteristics. Vaccinating everyone decreased the cost savings per case averted (Table 4 and Supplementary Appendix Tables 11–13).

Increases in coverage resulted in larger increases in ICER values compared to the other target populations (Figures 1 and 2). Vaccination was cost-effective compared to no vaccination, except with a 2% attack rate in Honduras (>$5 vaccination, ≥75% coverage, ≤75% efficacious from both perspectives) and some conditions in Brazil (Figure 1B). In Puerto Rico, vaccinating everyone was dominant compared to no vaccination under all conditions tested, except when the attack rate was 2% (Figure 1C) and 20% with a ≥$50 vaccine and ≥75% coverage (ICERs: $429–$459/DALY averted, healthcare system perspective). Use of a booster was highly cost-effective under many conditions (Figure 2C). Supplementary Appendix Tables 11–13 can be used to determine the marginal cost to change vaccine characteristics. When the outbreak occurred in year 2, vaccinating everyone resulted in fewer cases, yielding higher cost savings.

DISCUSSION

Vaccinating different target populations to mitigate Zika outbreaks provided economic value in a wide range of epidemiologic and economic conditions. Our results show that vaccinating women of childbearing age, school-aged children, young adults, and everyone would result in cost savings (≥$1.0 million in total direct costs and ≥$1.8 million in productivity losses) under many conditions. Vaccination was cost-effective at high costs ($50 per vaccinee) and fairly low efficacies (25%) and Zika attack rates (2%). Assuming that the cost of vaccine delivery and administration is less than the cost savings generated from cases averted, Zika vaccination could actually pay for itself.

Cost-effectiveness varied the most with increasing vaccine coverage. Thus, there is a trade-off between the additional reduction in cases and increased vaccination costs, which is more prominent for lower attack rates. Our study can help guide decisions on coverage level needed, given this trade-off.

Our results show that women of childbearing age or young adults would be an ideal target group for vaccination. While vaccinating the entire population had the largest impact on mitigating an outbreak, it cost more. Short of vaccinating everyone, vaccinating women of childbearing age prevented the largest number of negative outcomes, while vaccinating young adults typically resulted in the greatest cost savings per case averted. Benefits of vaccinating these populations varied with outbreak timing and vaccine coverage. While vaccinating women averted more Zika cases, as young adults are a smaller population and include a part of the key vaccination target (ie, young women of childbearing age) similar gains were accrued for vaccinating fewer individuals. Thus, if vaccine availability was limited, women of childbearing age and young adults provided the best overall benefits (cases and deaths averted, while providing economic gains).

Better understanding the potential economic value of Zika vaccination in the context of preventing and mitigating a Zika outbreak can assist public health officials and other decision makers. Our results can aid in program planning, guide decisions on target populations for vaccination, and determine necessary coverage levels given different vaccine characteristics. Our results also show that under many conditions, third-party payers can save costs; therefore, they should consider providing coverage and reimbursements for such a vaccine. Considerable benefits of Zika vaccine in the event of a future outbreak support further investment into its development. One potential area of future work is to develop a tool for decision makers to generate other result comparisons and to evaluate vaccination in other countries and under different epidemiologic, economic, and vaccination conditions and other target groups to aid in policy decisions.

We attempted to be conservative in our analysis. We did not include any costs associated with additional testing or prenatal care for Zika-infected pregnant women. Nor did we include any potential costs or health effects associated with prenatal infection (eg, abortion or fetal death). Inclusion of these costs would further increase the value of vaccinating women of childbearing age. We did not include sexual transmission of the Zika virus,

Table 4. Epidemiologic, Clinical, and Economic Outcomes for Zika Vaccination When Vaccinating Everyone 5 Years Before the Start of an Outbreak With a 2% Attack Rate

Country and Model	Total Vaccinated[a], Millions	Symptomatic Zika Cases	DALYs, Median (95% UI)	Vaccination Costs	Total Direct Costs, Median (95% UI)	Total Societal Costs, Median (95% UI)	Cost per Case Averted[b]
Honduras							
No vaccine[c]	…	9229	3395 (956–8158)	…	2.0 (1.4–3.8)	5.7 (3.1–11.0)	…
$5 vaccine							
25% efficacy							
25% coverage[d]	2.4	4473	1672 (474–3778)	11.6	12.6 (12.3–13.4)	14.4 (13.1–17.1)	1828
75% coverage[e]	7.1	905	339 (96–765)	34.6	34.8 (34.8–35.0)	35.2 (34.9–35.7)	3542
75% efficacy							
25% coverage[e]	2.4	2725	1019 (289–2302)	11.6	12.3 (12.1–12.7)	13.3 (12.6–15.0)	1171
75% coverage[f]	7.1	536	200 (57–453)	34.6	34.8 (34.7–34.8)	35.0 (34.8–35.3)	3365
$25 vaccine							
25% efficacy							
25% coverage[d]	2.4	4473	1645 (463–3954)	58.2	59.2 (58.9–60.0)	61.0 (59.7–63.5)	11 618
75% coverage[e]	7.1	905	333 (94–801)	173.2	173.4 (173.3–173.5)	173.7 (173.5–174.2)	20 184
75% efficacy							
25% coverage[e]	2.4	2725	1002 (282–2409)	58.2	58.8 (58.6–59.3)	59.9 (59.1–61.4)	8329
75% coverage[f]	7.1	536	197 (56–474)	173.2	173.3 (173.2–173.4)	173.5 (173.3–173.8)	19 301
Brazil							
No vaccine	…	346 206	105 830 (29 821–258 523)	…	191.5 (129.8–261.7)	728.8 (368.1–1462.4)	…
$5 vaccine							
25% efficacy							
25% coverage	58.6	142 928	45 350 (12 796–102 918)	288.4	369.0 (342.7–399.6)	599.7 (440.6–879.6)	−635
75% coverage[d]	174.7	24 829	7879 (2224–17 879)	859.8	873.9 (869.3–879.3)	914.1 (886.4–962.8)	577
75% efficacy							
25% coverage[d]	58.6	74 466	23 630 (6669–53 622)	288.4	330.6 (316.8–346.5)	450.9 (367.9–597.1)	−1022
75% coverage[f]	174.7	13 524	4292 (1212–9739)	859.8	867.6 (865.0–870.5)	889.4 (874.3–916.0)	483
$25 vaccine							
25% efficacy							
25% coverage	58.6	142 928	43 697 (12 319–106 735)	1441.9	1521.5 (1495.8–1550.7)	1744.2 (1594.8–2048.4)	4995
75% coverage[d]	174.7	24 829	7592 (2141–18 542)	4299.2	4313.1 (4308.6–4318.2)	4351.9 (4325.9–4404.8)	11 274
75% efficacy							
25% coverage[d]	58.6	74 466	22 768 (6421–55 611)	1441.9	1483.5 (1470.1–1498.8)	1599.7 (1521.7–1758.5)	3205
75% coverage[f]	174.7	13 524	4 135 (1167–10 100)	4299.2	4306.8 (4304.4–4309.6)	4327.9 (4313.7–4356.7)	10 819
Puerto Rico							
No vaccine	…	7860	2224 (700–5648)	…	9.3 (6.0–25.5)	34.7 (16.9–71.4)	…
$5 vaccine							
25% efficacy							
25% coverage[c]	1.0	2892	886 (244–2017)	5.0	8.5 (7.3–15.5)	18.5 (11.4–32.0)	−3262
75% coverage[e]	3.0	456	140 (39–318)	15.0	15.5 (15.3–16.6)	17.1 (16.0–19.2)	−2381
75% efficacy							
25% coverage[d]	1.0	1367	419 (116–954)	5.0	6.7 (6.1–10.0)	11.4 (8.0–17.8)	−3590
75% coverage[f]	3.0	237	73 (20–165)	15.0	15.2 (15.1–15.8)	16.1 (15.5–17.2)	−2447
$25 vaccine							
25% efficacy							
25% coverage[c]	1.0	2892	818 (258–2078)	25.1	28.5 (27.3–34.5)	37.9 (31.3–51.5)	646
75% coverage[e]	3.0	456	129 (41–328)	74.8	75.3 (75.1–76.3)	76.8 (75.8–79.0)	5684
75% efficacy							
25% coverage[d]	1.0	1367	387 (122–982)	25.1	26.7 (26.1–29.5)	31.2 (28.0–37.6)	−549
75% coverage[f]	3.0	237	67 (21–170)	74.8	75.0 (74.9–75.5)	75.8 (75.3–76.9)	5392

Costs are shown as million 2017 US dollars. Simulated outbreak occurs 5 years after the start of vaccination; all outbreaks lasted 5 years unless otherwise noted.

Abbreviations: DALY, disability-adjusted life-year; GBS, Guillain-Barré syndrome; UI, uncertainty interval.

[a]Transmission model result.

[b]From the societal perspective; US dollars; negative values imply savings.

[c]Outbreak duration 4 years.

[d]Outbreak duration 3 years.

[e]Outbreak duration 2 years.

[f]Outbreak duration 1 year.

which would increase the number of women with infection, thereby increasing the number of perinatal infections; thus, we may underestimate the number of congenital Zika infection cases and subsequently their costs. We evaluated a 25% vaccine efficacy to show the range of possibilities, as a less efficacious vaccine may be better than no vaccination. Additionally, some vaccines have low efficacies, for example, the influenza vaccine has a variable efficacy of 19%–60% over the past 10 years [22], the BCG vaccine has a low efficacy (10%–66%) against pulmonary tuberculosis [23, 24], and the RTS,S vaccine for malaria has an efficacy of approximately 30% for first episodes and wanes to <10% over time [25–28]. We also used the disability weight for severe intellectual disability for congenital Zika infection, rather than profound disability, which may underestimate the burden.

There are limitations to this study. By definition, models are simplifications that aim to distill systems down to the most pertinent relationships and key factors without including extraneous detail. We assumed equal mixing between humans and vectors [29], when in reality, transmission is heterogeneous and driven by local neighborhood-level factors [30]. We assumed that Zika infection confers lifelong immunity, but this has not yet been established. Should recovered individuals be susceptible to reinfection, our results may underestimate vaccination's benefit. While our data-driven analyses drew from a variety of sources and locations, the current literature on Zika is limited and new data continue to emerge. For instance, there are discrepancies in the reported microcephaly risk. The exact duration and impact of GBS may vary from person to person and have differing impacts on productivity losses; additionally, some patients may experience further productivity losses beyond the duration of hospitalization.

While vaccinating everyone will naturally avert the most cases, specifically vaccinating women of childbearing age or young adults garnered the highest economic value, often resulting in cost savings, even when considering transmission.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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