Supplementary Materials

Input Parameters for the Decision Tree Model

The number of women served, contraception use stratified by method type before and after the Z-CAN intervention, and cost of the Z-CAN intervention were derived from actual Z-CAN program data. Other parameters, including contraception failure rates, distribution of outcomes of unintended pregnancies, costs of prenatal care, delivery, birth outcomes, and Zika-associated costs were derived from the previous CEA.

Contraception Use Before and After the Z-CAN Intervention

Contraception use and method mix before and after the Z-CAN intervention were the key input parameters in the decision tree model to calculate the effectiveness of Z-CAN. They were derived from Z-CAN program record (9). Contraception method mix among participants shifted after the Z-CAN intervention towards use of more effective methods. **Among Z-CAN participants,** LARC use increased from 3.7% before Z-CAN to 69.8% after Z-CAN; pills, patch, ring, injection increased from 20.3% before Z-CAN to 23.2% after Z-CAN; condoms only decreased from 29.7% before Z-CAN to 2.8% after Z-CAN; and no method decreased from 45.3% before Z-CAN to 4.2% after Z-CAN (Appendix Table 1) (9).

Cost of Z-CAN

Actual Z-CAN intervention costs were obtained from the CDC Foundation and included costs associated with programmatic activities (including training, training materials and program supplies, proctoring, administrative costs, and a health communication campaign) and the provision of contraceptive services (including provision of the full range of reversible contraceptive methods, client-centered contraceptive counseling, IUD and implant insertion and removal reimbursement). (Appendix Table 2).

Training costs included the development and facilitation of 8 one-day evidence-based trainings for 177 physicians and 259 staff, and 5 one-day staff-only trainings for 129 staff, and support for staff salary and travel time to Puerto Rico from the continental United States for the training organizations. Training materials and program supplies included the production of documents provided to each Z-CAN training participant.

Proctoring costs included stipend and travel to Puerto Rico for 12 obstetrician/gynecologists to conduct clinic visits with all trained Z-CAN physicians. Proctoring included direct observation of contraceptive counseling, at least one insertion of an intrauterine device, and staff interaction with patients; review of data collection, inventory tracking, and billing procedures; and a clinic audit to ensure appropriate supplies, space, and equipment.

Administrative costs included funding for CDC Foundation staff (2.5 FTE) and travel, Z-CAN Puerto Rico program staff (13 FTE) and local expenses, Z-CAN Puerto Rico office (rent), and local implementation partner (contract support). Health communication campaign costs included funding for formative research and the development and implementation of the health communication campaign.

The cost of contraception and associated service costs was based on unit cost of the contraception (25) and services during Z-CAN (2017 US dollars) and number of women receiving them in the scenarios with and without the intervention. For the contraceptive services costs, client-centered contraceptive counseling and a bundled insertion and removal reimbursement fees commensurate with Medicaid reimbursement fee schedules in the continental United States were provided to Z-CAN physicians. For each woman who participated in Z-CAN, client-centered contraceptive counseling was provided. For women that chose a non-LARC method or no-method, the reimbursement fee was $30. For women who chose an IUD or implant, at the time of the insertion visit, a bundled reimbursement fee was IUD ($135) or implant ($207) for insertion and removal (Appendix Table 2).

Other Epidemiological and Cost Parameters

Supplementary Table 1 presents the epidemiological and cost parameters used in the model. Point estimates represented the most likely sets of parameters used for the base-case analysis, and ranges of values reflecting the uncertainty of the input parameters were used for sensitivity analyses. As previously described, method-specific annual pregnancy rates were calculated by applying failure rates of contraception methods under typical use (19). The proportions of unintended pregnancies that result in live birth, spontaneous abortion/fetal deaths, and induced abortions in the first trimester were calculated for women with data from the Caribbean region (including Puerto Rico) or Puerto Rico (20-21), assuming ZIKV infection or the Z-CAN intervention did not change the distribution of these pregnancy outcomes.

For adverse outcomes associated with ZIKV infection during pregnancy, we only considered microcephaly with prenatal diagnosis of ZAM after the start of the second trimester. For ZAM impacted pregnancies, outcomes included live births and pregnancy losses (miscarriage at >13 weeks, stillbirths and elective terminations). For simplicity of modeling we assumed that second trimester pregnancies without ZAM diagnosis all resulted in live birth; a very small number of losses occur in second trimester pregnancies in the absence of ZAM diagnosis. Data published since the initial cost effectiveness analysis indicate that ZIKV infection during pregnancy is not associated with neural tube defects (1). Additionally, while ZIKV infection during pregnancy is associated with brain defects other than microcephaly, information on the prevalence and cost of these conditions were unavailable; therefore, these birth defects were not included in the model. For the prevalence of ZIKV-associated birth defects, we used 4.7/1,000 live births. This was estimated by multiplying 5.6/1,000 (prevalence of birth defects potentially related to ZIKV from population-based surveillance in Puerto Rico and the US Virgin Islands in January to March 2017) by 83.7% (proportion of ZIKV-associated birth defects with brain abnormalities and/or microcephaly) (17). Conceptions for most infants born during this time period corresponded to the time period April to June 2016, when women had started to participate in Z-CAN (May 2016). We varied this pamameter as a uniform distribution with a range of 3.4/1,000-7/1,000 in the sensitivity analyses.

A pregnancy loss rate of 8% among ZIKV-exposed fetuses who survived the first trimester was assumed based on data from the US Zika Pregnancy Registry which included any pregnancy loss (spontaneous, elective, stillbirth) in a pregnant woman with laboratory evidence of ZIKV infection (24). Given the nature of this surveillance, pregnancy losses were more likely to occur in the 2nd trimester although no information on when they occurred was collected (24).

A 30% prevalence of ZIKV among women of reproductive age was assumed based on 31% positive ZIKV testing among participants from a study conducted in Puerto Rico (22). This assumption is further supported by a study in Puerto Rico which reported 30% prevalence of positive testing for Chikungunya, which is transmitted by the same vector, *Aedes aegypti* (23). This parameter was only used to calculate how many women potentially had to be monitored and tested due to being Zika positive. The assumption applied to the whole Z-CAN implementation period.

The analysis was performed using a health sector perspective that includes direct medically related costs regardless of the payers. Medical costs associated with pregnancy, delivery and postpartum care, as well as treatment for ZAM were from the nationwide IBM® MarketScan® Commercial claims database. These data were used given Medicaid reimbursements might underestimate the true cost of providing healthcare services (33).

ZIKV-related costs avoided included ZIKV testing and monitoring for ZIKV-exposed pregnancies and infants assuming a 30% infection rate, and for cases of ZIKV-associated microcephaly. The lifetime cost of a case of ZIKV-associated birth defects was estimated at $3.8 million per infant at a discount rate of 3% per year; the sum of undiscounted costs for children who survive to adulthood was $10 million. The estimates for non-ZIKV-related medical costs associated with a live birth, including pregnancy, delivery and postpartum care were derived from an analysis of MarketScan Commercial health plan expenditures (25). Costs of spontaneous and induced abortion were calculated by the author (Grosse) as the mean 7-

day cost for all claims associated with induced abortion procedure codes using 2014 MarketScan commercial claims data.

One-way sensitivity analysis parameters

We conducted sensitivity analysis to test the impact of the key parameters on the cost-effectiveness of Z-CAN, including prevalence of ZAM among second trimester pregnancies, pregnancy loss rate for second trimester pregnancies with ZAM, and the cost of ZAM. Since LARC devices can last up to 3-10 years, a sensitivity analysis was conducted using annualized LARC device cost. To account for differences in healthcare costs between the continental U.S. and Puerto Rico, the costs for testing and monitoring ZIKV-affected pregnancies and for treatment and supportive care for cases of ZIKV-associated birth defects were adjusted to prices in Puerto Rico by multiplying by the U.S. mainland cost estimates used in the base-case scenario by the ratios of healthcare spending per capita and wages of nurse assistants between the United States and Puerto Rico. We also estimated the medical cost avoided only from unwanted pregnancies as opposed to mistimed pregnancies which might result in delayed costs occurring later as in the previous CEA (11). Roughly 60% of unintended pregnancies are classified as mistimed and 40% as unwanted (34).

Supplementary Table 1. Estimates of input parameters used in a model to assess cost-effectiveness of the Zika Contraception Access Network (Z-CAN) *

Parameter	Value in main scenario (range)	Distribution[&]	Source
Epidemiologic parameters			
Number of women participated in Z-CAN	29,221	n/a	Z-CAN program data
% of women receiving contraceptive services at baseline			Z-CAN program data
No contraception users	45.8% (44.7%-45.8%)	Beta	
Less-effective method users§	30.0% (29.2%-30.2%)	Beta	
Moderately effective method users§	20.5% (19.8%-20.7%)	Beta	
Highly effective method users§	3.7% (3.5%-3.9%)	Beta	
% of women receiving contraceptive services with intervention			Z-CAN program data
No contraception users	4.2% (4.0%-4.5%)	Beta	
Least-effective method users§	2.8% (2.6%-3.0%)	Beta	
Moderately effective method users§	23.2% (22.7%-23.7%)	Beta	
Highly effective method users§	69.8% (69.2%-70.3%)	Beta	
Contraceptive failure rate over 1 year			Sundaram al. 2017 (19), National Survey of Family Growth
No method	85% (68%–100%)	Triangular	
Less-effective methods	13% (10%–14.8%)	Beta	
Moderately effective methods	7% (6%–8.5%)	Beta	
Highly effective methods	1.4% (0%–2.7%)	Beta	
Distribution of outcomes of unintended pregnancies			
Induced abortion in first trimester pregnancies	28%		Calculated based on Sedgh et al. 2011 (20), review of abortion statistics from the countries and regions
Spontaneous abortion/fetal death in first trimester pregnancies	14%		Singh et al. 2010 (21), nationally representative and small-scale surveys of the countries
Live birth in first trimester pregnancies	58%		Calculated from the above two sources
Prevalence of Zika virus infection	30% (10%–70%)	Uniform	Lozier et al. (22) and Bloch et al. (23)
Prevalence of ZAM** among mid-trimester pregnancies#	4.7/1,000 (3.4/1,000–7/1,000)	Uniform	Smoots et al. 2020 (17), household-based cluster investigations data and population-based surveillance data. Population-based surveillance for birth defects
Pregnancy loss with ZAM***	8% (8%–35%)	Uniform	Reynolds et al. 2017 (24), U.S. Zika Pregnancy Registry
Cost parameters (in 2019 U.S. dollars)			
Prenatal, delivery and postpartum care for mother and neonatal care for infant (not Zika virus–related)††,‡‡‡	$23,531 ($18,825–$28,237)	Triangular	Weighted average of vaginal and C-section, Truven Analytics, 2013 (25) MarketScan claims data
Prenatal care	$3,739		
Delivery and postpartum care	$11,688		
Neonatal care	$8,104		
Induced abortion††	$1,173 ($938–$1,408)	Triangular	Derived by author (Grosse SD) from 2014 MarketScan Commercial Claims database
Spontaneous abortion††	$1,173 ($938–$1,408)	Triangular	Assumed same as for induced abortion
Zika virus–associated cost			
Cost of Zika-associated testing and monitoring of women during pregnancy††,§§§	$548 ($438–$657)	Triangular	Derived by author (Grosse SD) from 2014 MarketScan commercial claims database
Cost of Zika-associated testing among live-born infants with Zika-infected mothers††,¶¶¶	$269 ($215–$323)	Triangular	Derived by author (Grosse SD) from MarketScan commercial claims database, 2009–2014
Cost of testing for fetus with ZAM††,###	$352 ($282–$422)	Triangular	Derived by author (Grosse SD) from MarketScan commercial claims database, 2009–2014
Cost of pregnancy loss with ZAM††,****	$5,871 ($4,169–$7,045)	Triangular	Grosse et al. 2008 (26) and Biggio et al. 2004 (27) Truven 2013 (25)
Cost of live-born infant with ZAM††,‡‡‡‡	$24,348 ($19,478–$29,217)	Triangular	Truven, 2013 (25)

Lifetime discounted direct cost of live-born infants with ZAM§§§§	$4,040,425 ($3,232,340–$4,872,041)	Triangular	Derived in part by author (Grosse SD) from MarketScan commercial claims database, 2009–2014

* All costs are adjusted to 2019 U.S. dollars.
&: uniform distribution assumes equal probability of the values within the range; triangular distribution assumes a continuous probability distribution with a probability density shaped like a triangle bounded by the range of the parameter and with the highest density at the point estimate; beta distribution assumes a family of continuous probability distribution bounded on the interval [0,1].
§ Least-effective methods include condoms, spermicides, fertility awareness methods, withdrawal, sponge, and diaphragm. Moderately effective methods include oral contraceptive pills, patches, vaginal rings, and injectable contraceptives. Highly effective methods include levonorgestrel (LNG) intrauterine device (IUD), copper IUD and implant. Contraceptive methods provided by Z-CAN included IUDs, implants, injectables, pills, patch, ring, and male condoms.
** ZAM, Zika virus–associated microcephaly.
# It was estimated by multiplying 5.6/1,000 (prevalence of birth defects potentially related to Zika from population-based surveillance in Puerto Rico and the US Virgin Islands in early 2017) by 83.7% (proportion of Zika-associated birth defects with brain abnormalities and/or microcephaly).
*** Among all second trimester pregnancies with ZAM. Pregnancy loss included still birth and termination of fetus due to ZAM. The pregnancy loss rate was based on pregnancy loss among pregnancies in the U.S. Zika Pregnancy Registry.
††A range of the main value ±20% was used to create upper and lower bounds used in sensitivity analyses.
‡‡‡Weighted average for vaginal and C-section delivery, including prenatal care, delivery, postpartum, and neonatal cost at delivery and in the first 3 months.
§§§Assumes additional costs related to repeated Zika virus testing by IgM (1–2 tests) for all pregnant women, 4 extra detailed ultrasound examinations, and 25% of women getting amniocentesis during all Zika-positive pregnancies (25% infection rate at baseline, range 10%–70%) , based on Oduyebo et al. source: Oduyebo T, Petersen EE, Rasmussen SA, Mead PS, Meaney-Delman D, Renquist CM, et al. Update: interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible Zika virus exposure—United States, 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:122–7.
¶¶¶Assumes 2 Zika virus tests (IgM and PCR) for serum and placenta, cranial ultrasound, and eye examination for all infants born to Zika virus–positive mothers based on Fleming-Dutra et al. Source: Fleming-Dutra KE, Nelson JM, Fischer M, Staples JE, Karwowski MP, Mead P, et al. Update: interim guidelines for health care providers caring for infants and children with possible Zika virus infection—United States, February 2016. MMWR Morb Mortal Wkly Rep. 2016; 65:182–7.
###Three PCR tests for Zika virus using placenta, cord, and brain tissues of the fetus based on Martines et al. Source: Martines RB, Bhatnagar J, Keating MK, Silva-Flannery L, Muehlenbachs A, Gary J, et al. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses—Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016; 65:159–60.
**** pregnancy losses included miscarriage at >13 weeks, stillbirths and elective terminations after the start of the second trimester attributable to prenatal diagnosis of ZAM. The cost is the average of still birth and fetus termination with ZAM. To calculate cost of still birth with ZAM, assuming all prenatal care cost, including extra cost of Zika virus–associated testing and monitoring during pregnancy and extra cost for Zika virus–associated testing for fetus. To calculate cost of fetus termination for fetus with ZAM, assuming half of the prenatal care cost, including extra cost of Zika virus–associated testing and monitoring during pregnancy and extra cost for Zika virus–associated testing for fetus.
‡‡‡‡Cost of prenatal care and delivery and extra cost of Zika virus–associated testing and monitoring during pregnancy and testing of infants for Zika virus.
§§§§Present value of cumulative medical and supportive care cost for infant with ZAM, discounted at 3% annually and taking into account mortality. Expenditures by employer-sponsored health plans for privately insured children with combined diagnoses of microcephaly and congenital cytomegalovirus enrolled during the first 4 years of life were used to project medical costs for cases of ZAM.

Supplementary Table 2. Direct Cost of the Zika Contraception Access Network (Z-CAN)*

Cost categories	Unit costs (nominal 2017 US $)	# of participants	Total costs (2019 US $)	costs per participant (2019 US $)
Programmatic activities		29,221	**4,900,567**	168
Training fees†			267,026	9
Training materials and program supplies‡			224,010	8
Proctoring §			78,836	3
Administrative costs**			2,810,378	96
Health communication campaign††			1,520,318	52
Contraception Method‡‡			**17,419,538**	
Least-effective contraception §§	34.75	816	30,239	
Moderately effective contraception***		6,788	3,251,231	
Injectable	240.02	1,236	316,364	
Pills	370.34	4,358	1,721,109	
Patch	982.41	251	262,958	
Ring	945.49	943	950,800	

Highly effective contraception†††		20381	14,138,068
LNG-IUD	659.41	9,316	6,550,968
Copper IUD	598.00	2,960	1,887,615
Implant	659.42	8,105	5,699,485
Contraception associated services‡‡‡			**3,773,603**
IUD insertion/removal bundle	135	12,276	1,767,303
Implant insertion/removal bundle	207	8,105	1,789,138
Non-LARC§§§ method provided or no method provided	30	6,788	217,162
Total cost of Z-CAN			**26,093,708**

*The cost data was obtained from the CDC Foundation who administered and managed the Z-CAN program. All the contraceptives were donated or provided at a nominal fee, but the cost estimates were based on what they could cost from the manufacturer if not donated.

†Training fees are for 8 one-day evidence-based trainings for 177 physicians and 259 staff, and five staff-only trainings for 129 staff.

‡Training materials and program supplies are for the production of documents provided to each Z-CAN training participant and used throughout the Z-CAN program, including Z-CAN toolkit (i.e., Z-CAN Policy and Procedure Manual, Z-CAN product ordering, consent, and data collection forms, Z-CAN Inventory Tracking Logs, CDC Zika resources, CDC evidence-based contraceptive guidelines)

§Proctoring costs are for 12 OB/GYN's stipends and travel to Puerto Rico to conduct visits with all trained Z-CAN physicians.

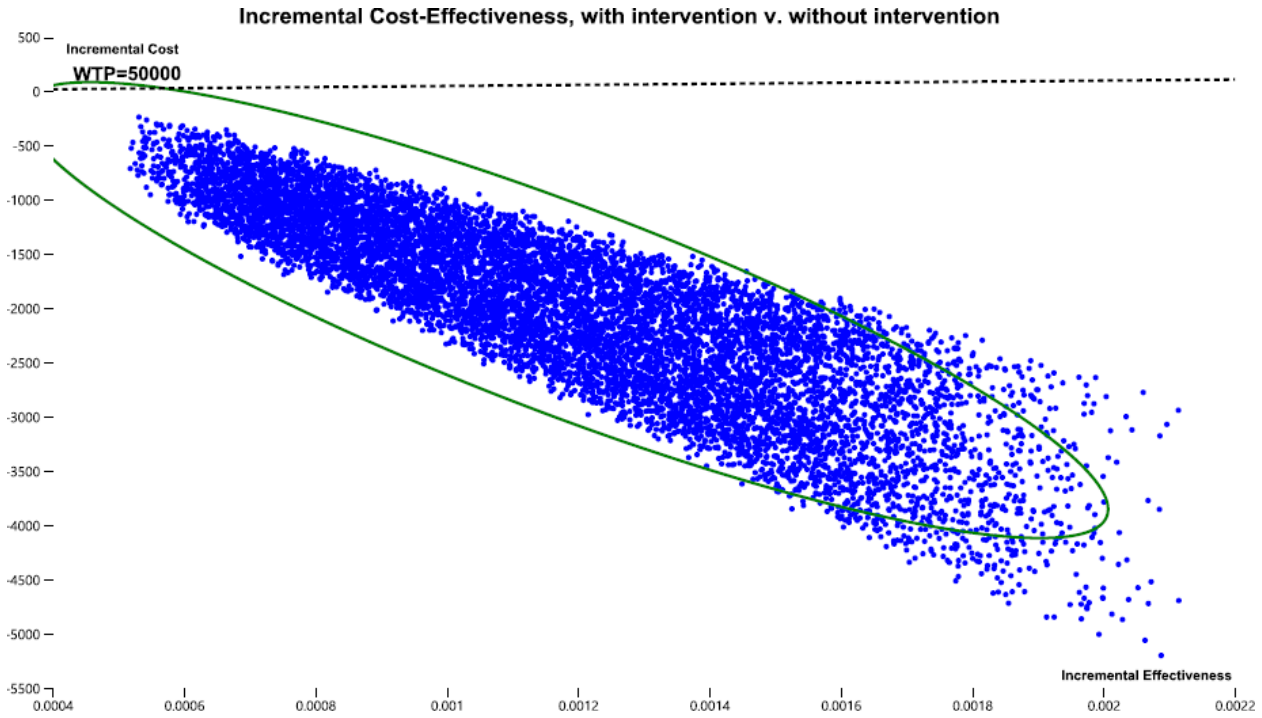
**Administrative costs are for CDC Foundation staff (2.5 FTE) and travel, Z-CAN Puerto Rico program staff (13 FTE) and local expenses, Z-CAN Puerto Rico office (rent), local implementation partner (contract support).

††Health communication campaign costs are for formative research and the development and implementation of the health communication campaign. Formative research included conducting ten focus groups with women and men, aged 18 to 49 years, in Puerto Rico to assess contraception awareness, use, and decision making during the Zika outbreak, and culturally appropriate messaging and outreach strategies. The health communication campaign, Ante La Duda, Pregunta [When in Doubt, Ask], was used to promote awareness of Z-CAN services and included a website, social media marketing (Facebook page), video and radio public service announcements (PSAs), digital and non-digital advertisements, community engagement events, influencer partnerships and print materials.

‡‡Contraceptive methods provided by Z-CAN included intrauterine devices, implants, injectables, pills, patch, ring, and male condoms.

§§Least effective contraceptive methods include male condoms. ***Moderately effective contraceptive methods include oral contraceptive pills, patches, vaginal rings, and injectable contraceptives.

†††Highly effective contraceptive methods include levonorgestrel (LNG) intrauterine device (IUD), copper IUD and implant.
‡‡‡All contraception associated services included cost for client-centered contraceptive counseling, applicable insertion or removal fees, and supplies.
§§§Long acting reversible contraception (LARC) include IUDs and implants. Non-LARC methods provided by Z-CAN included injectables, pills, patch, ring, and male condoms.



Supplementary Figure 1: Sensitivity analysis indicating the effect of changes of assumptions on the number of ZAM cases prevented in Z-CAN during the Zika virus outbreak, Puerto Rico, 2016.

WTP: willingness to pay

Each of the dots in the graph indicates the incremental cost-effectiveness ratio of the scenario with Zika-Contraception Access Network (Z-CAN) compared to the scenario without Z-CAN. The X-axis of the dot represents the risk reduction of Zika Associated Microcephaly under the scenario with Z-CAN compared to the scenario without Z-CAN for a representative women; the Y-axis of the dot represents the cost difference between the scenario with Z-CAN compared to the scenario without Z-CAN for a representative women; negative costs means the scenario with Z-CAN is cost-saving.