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Bridging the Gap Between Pilot and Scale-Up: A Model of Antenatal Testing for Curable Sexually Transmitted Infections From Botswana

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Background: *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) are common sexually transmitted infections (STIs) associated with adverse outcomes, yet most countries do not test and conduct syndromic management, which lacks sensitivity and specificity. Innovations allow for expanded STI testing; however, cost is a barrier.

Methods: Using inputs from a pilot program in Botswana, we developed a model among a hypothetical population of 50,000 pregnant women to compare 1-year costs and outcomes associated with 3 antenatal STI testing strategies: (1) point-of-care, (2) centralized laboratory, and (3) a mixed approach (point of care at high-volume sites, and hubs elsewhere), and syndromic management.

Results: Syndromic management had the lowest delivery cost but was associated with the most infections at delivery, untreated women treated, CT/NG-related low-birth-weight infants, disability-adjusted life years, and low birth weight hospitalization costs. Point-of-care CT/NG testing would treat and cure the most infections but had the highest delivery cost. Among the testing scenarios, the mixed scenario had the most favorable cost per woman treated and cured (\$534/cure). Compared with syndromic management, the mixed approach resulted in a mean incremental cost-effectiveness ratio of \$953 per disability-adjusted life years averted, which is cost-effective under World Health Organization's one-time per-capita gross domestic product willingness-to-pay threshold.

Conclusions: As countries consider new technologies to strengthen health services, there is an opportunity to determine how to best deploy resources. Compared with point-of-care, centralized laboratory, and syndromic management, the mixed approach offered the lowest cost per infection averted and is cost-effective if policy makers' willingness to pay is informed by the World Health Organization's gross domestic product/capita threshold.

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Chlamydia trachomatis (CT) and *Neisseria gonorrhoeae* (NG) are the most common curable sexually transmitted infections (STIs) worldwide.¹ Among women and neonates, CT and NG infections are associated with an increased risk of adverse health outcomes, including preterm birth and low birth weight,^{2,3} which were the leading causes of mortality among children younger than 5 years (17.8%; uncertainty range, 15.4%–19.0%) in 2015.⁴

Despite the health risks associated with antenatal CT and NG infections, few countries recommend routine STI testing in pregnant women.⁵ The World Health Organization (WHO) has no specific guidelines for antenatal STIs beyond syndromic management.⁶ Thus, the syndromic approach is the standard of care for STI management in most countries. Through this approach, patients are treated with standardized drug regimens based only on symptoms and clinical signs.⁷ However, syndromic management has low sensitivity because many infections are asymptomatic,^{8–10} and it lacks specificity because symptoms may be due to other causes, thereby exposing women to unnecessary antibiotics.^{8,9} Etiological testing is not offered in lower-resource health systems largely because of limited resources.¹¹ However, developments in technology have introduced the possibility of testing with highly sensitive, easy-to-use, rapid tests for CT and NG infections. Several studies have shown that an etiological approach to CT and NG testing during antenatal care is acceptable to patients and can achieve high treatment rates.¹² Furthermore, integration of routine CT and NG testing into antenatal care could identify more true CT and NG infections among pregnant women, which may reduce the risks for adverse outcomes such as low birth weight.

Given the many options for designing and implementing a CT and NG testing program, policy makers face decisions about how to keep costs low while maximizing benefits. For example, research on other infections has found that point-of-care testing

increases the proportion of infections treated compared with other testing options,^{13,14} but at a higher cost.¹⁵ Therefore, this study modeled the trade-offs between costs and outcomes of 3 approaches for national scale-up of antenatal CT and NG testing, compared with syndromic management. Such models and their results can help inform policy makers on the most effective strategies for expanding CT and NG testing if national management guidelines are updated to include routine antenatal testing.

METHODS

Overview

This study considers 3 CT and NG antenatal testing approaches: (1) sample processing at the point-of-care with same-day results and treatment (point-of-care scenario), (2) sample processing in centralized laboratory hubs with delayed results and treatment (centralized laboratory scenario), and (3) a hub-and-spoke approach (mixed scenario) that offers point-of-care testing at high-volume sites that act as centralized laboratory hubs for lower-volume sites (spokes) in their regions. We also compared those modeled costs and outcomes with similar estimations for the standard of care (syndromic management) in Botswana. Costs were collected and cleaned in Microsoft Excel and analyzed in MATLAB. Analyses were based on a hypothetical cohort of 50,000 women attending their first antenatal care visit using the analytic horizon of 1 year. Table 1 provides the variables and sampling distributions used to parameterize our model. Model assumptions and parameters were derived primarily from a CT and NG testing and treatment pilot program. The pilot program has been previously described.¹⁶ In summary, we enrolled 400 pregnant women in Gaborone, Botswana, for CT, NG, and *Trichomonas vaginalis* testing and treatment using the GeneXpert. We found that the prevalence of CT was 7.8%, and that of NG was 1.3%. If results were provided on the same day, more than 95% received treatment. However, if women received delayed results, 67% were treated.

Data Sources and Assumptions

Setting

The Botswana Health Statistics Report¹⁷ provided the volume of antenatal visits at each hospital and regional volumes for lower-level health facilities (e.g., clinics and health posts). Thus, we averaged the regional clinic and health post volume. We assumed that women who tested positive for CT would receive one oral stat dose of 1000 mg azithromycin, those testing positive for NG would receive dual therapy (1000 mg azithromycin and 500 mg intramuscular injection of ceftriaxone), and those who tested positive for either infection would be asked to return for a test of cure at their regularly scheduled appointment after 4 weeks.¹⁸ In the syndromic management scenario, per Botswana guidelines, pregnant women with STI-related symptoms were assumed to receive 1000 mg azithromycin, 500 mg intramuscular injection of ceftriaxone, and 2000 mg of oral metronidazole, and asked to return for a nonroutine visit to the antenatal clinic after 3 to 7 days. Women and infants with uncomplicated deliveries spend 24 hours in the postnatal ward with vital checks and services provided by nurse midwives. Women with infants born between 1800 and 900 g are admitted to the neonatal ward.

Scale-Up Scenarios

For the *point-of-care scenario*, we allocated at least one Xpert machine (with 4 modules, which is the smallest system currently available in the region) to all clinics and hospitals that provided antenatal care in Botswana. Health posts were not included

in this scenario because of a lack of trained personnel and infrastructure for point-of-care testing. The size (and cost) of point-of-care machines was determined based on summed patient volume at each facility.

For the *centralized laboratory scenario*, at least one 4-module Xpert was placed in “hub hospitals” across the country where Xperts are housed for tuberculosis testing (located at health facilities in all but 1 of Botswana's 27 health districts). We assumed samples would be processed by a laboratory technician. Samples collected in hospitals, clinics, and health posts would be stored on-site in sample collection tubes and shipped twice per month to these Xperts in each hub hospital. The size (and cost) of each centralized machine placed in each hub hospital was determined based on summed patient volume across each of the health districts.

For the mixed scenario, the centralized Xperts were used to provide point-of-care testing on site and served as a central laboratory hub for samples from smaller facilities in that district, including health posts.

We compared the testing scenarios described previously with Botswana's standard of care, syndromic management, where women are treated based on the presence of symptoms or clinical signs.

Model Probabilities

Probabilities of CT and NG testing were obtained from the pilot program and the literature (Table 1). The probability of attending a syndromic management follow-up visit was derived from an STI testing study in South Africa.¹⁹ The probabilities of low birth weight associated with untreated maternal CT or NG infection were found in the literature.^{3,20} As found in prior research, we assumed that women who tested positive for CT and/or NG during pregnancy and were treated, had the same risk of delivering a low-birth-weight infant as those who were uninfected.^{21s,22s} The probabilities of having a current sex partner and partner treatment receipt were included for calculating costs in all scenarios, but did not influence reinfection probabilities.

Costs

We took a health system perspective and did not incorporate potential costs to patients (e.g., transportation or childcare) or society (e.g., loss of productivity). Costs included capital, personnel, and supplies and are presented in 2018 US dollars (USD). All costs that were collected in Botswana Pula were converted to USD using the average exchange rate between July 2015 and May 2016.^{23s}

We assumed the Xpert 4-module system could run 4 CT/NG tests every 90 minutes. Assuming an 8-hour working day, up to 21 tests per day (4620/year assuming 220 working days/year) could be processed with a 4-module system. An additional 4-module system was added when the daily volume (including initial test, test of cure, and errors) exceeded 21 tests. For the point-of-care scenario, we assumed all samples were processed on the day of testing. For the laboratory scenario, we assumed samples would be shipped bimonthly and would be run over the course of 2 weeks. For the mixed scenario, we assumed samples collected onsite at the hub hospital would be processed on the same day and samples from other facilities would be run over 2 weeks. Capital cost of the Xpert system was obtained based on high-burden, low-income country negotiated prices.^{24s} The acquisition costs were converted to annual costs, based on a useful life of 5 years and a discount rate of 3%, which resulted in an annualization factor of 4.58.¹⁵ Furthermore, to ensure the 2-year warranty, the system must be calibrated at a cost of \$450 after the first year. The costs of temperature-controlled storage and shipping were added and were estimated to be 5% of the cost of the CT/NG testing cartridges, which was based on a cost analysis from South Africa.¹⁵

TABLE 1. Variables Used to Parameterize Antenatal CT and NG Testing Scale-Up Models

Parameter	Mean Sampled Value (5%–95% Quantiles)	Sampling Distribution	Source
Epidemiology			
Prevalence of CT	0.085 (0.063 to 0.102)	β (35.648, 410.552)	16
Prevalence of NG	0.017 (0.007 to 0.026)	β (5.147, 315.823)	16
Current sex partner	0.705 (0.649 to 0.735)	β (219.407, 85.936)	16
Partner treatment	0.594 (0.561 to 0.633)	β (159.949, 111.456)	16
Costs			
CT/NG treatment			
CT treatment: azithromycin (1 g) and gloves	\$0.65 (\$0.53 to \$0.75)	Uniform range, \$0.53 to \$0.88	5,42s
NG treatment: azithromycin (1 g), ceftriaxone (250 mg vial), syringe, needle, and gloves	\$1.38 (\$1.15 to \$1.79)	Uniform range, \$1.13 to \$1.88	5,25s,42s
CT/NG testing			
Testing supplies: CT/NG cartridges, sample collection tubes, and gloves*	\$17.86 (\$13.24 to \$24.36)	Uniform range, \$12.17 to \$24.70	24s
Annual GeneXpert IV (4) cost	\$4108 (\$3509 to \$4841)	Uniform range, \$3017 to \$5029	
CT/NG personnel			
Testing (laboratory)	\$2.05 (\$1.64 to \$2.56)	Uniform range, \$1.58 to \$2.63	
Test of cure (laboratory)	\$1.628 (\$1.27 to \$2.95)	Uniform range, \$1.20 to \$2.0	
Testing (POC)	\$1.51 (\$1.20 to \$1.64)	Uniform range, \$1.01 to \$1.68	
Test of cure (POC)	\$0.84 (\$0.65 to \$1.05)	Uniform range, \$0.63 to \$1.05	
CT treatment	\$1.38 (\$1.05 to \$1.71)	Uniform range, \$1.03 to \$1.72	
NG treatment	\$2.21 (\$1.69 to \$2.73)	Uniform range, \$1.658 to \$2.76	
Added cost of physician in clinic	\$0.10 (\$0.09 to \$0.13)	Uniform range, \$0.08 to \$0.13	
Partner CT treatment	\$1.78 (\$1.52 to \$2.40)	Uniform range, \$1.50 to \$2.50	
Partner NG treatment	\$2.70 (\$2.19 to \$3.54)	Uniform range, \$2.13 to \$3.55	
Syndromic management			
Personnel			
SM treatment	\$3.30 (\$1.42 to \$5.19)	Uniform range, \$1.32 to \$5.28	
Partner treatment	\$4.09 (\$1.76 to \$6.42)	Uniform range, \$1.635 to \$6.54	
Treatment supplies	\$2.66 (\$1.14 to \$4.16)	Uniform range, \$1.06 to \$4.24	
Follow-up visit			
Health center (no beds)	\$18.76 (\$9.94 to \$33.02)	Uniform range, \$8.76 to \$35	
Health center with beds (additional)	\$5.60 (\$2.19 to \$7.47)	Uniform range, \$2.06 to \$8	
Primary level hospital (additional)	\$8.44 (\$3.88 to \$13.86)	Uniform range, \$3.57 to \$14	
Secondary-level hospital (additional)	\$10.98 (\$4.30 to \$15.87)	Uniform range, \$4.08 to \$16	
Average LBW hospitalization cost*	\$3954 (\$3173 to \$4827)	Uniform range, \$3010 to \$5018	
Probabilities			
CT/NG testing			
Testing uptake	0.88 (0.82 to 0.93)	β (104.410, 13.911)	16
Xpert sensitivity CT	0.97 (0.938 to 0.987)	β (61.219, 1.793)	43s
Xpert sensitivity NG	0.998 (0.994 to 0.999)	β (271.311, 1.003)	43s
Xpert specificity CT	0.99 (0.991 to 0.997)	β (2430.76, 15.667)	43s
Xpert specificity NG	0.998 (0.996 to 0.999)	β (1304.29, 2.305)	43s
Xpert error rate (laboratory)	0.11 (0.030 to 0.293)	β (1.580, 17.484)	15
Xpert error rate (clinic)	0.142 (0.014 to 0.326)	β (1.488, 7.693)	15
Treatment (if same day)	0.94 (0.898 to 0.982)	β (36.703, 2.879)	16
Treatment (if delayed)	0.63 (0.43 to 0.867)	β (17.149, 8.954)	16
Test for cure	0.71 (0.409 to 0.929)	β (6.463, 2.92)	16
Proportion cured at test of cure/follow-up	0.798 (0.72 to 0.966)	Uniform range, (0.68 to 0.999)	16
Syndromic management			
Assessed for symptoms	0.832 (0.675 to 0.997)	β (4.772, 1.199)	8
Sensitivity	0.409 (0.122 to 0.606)	β (4.984, 5.864)	8
Specificity	0.661 (0.391 to 0.917)	β (4.7424, 2.681)	8
Treatment	0.777 (0.464 to 0.946)	β (4.471, 1.386)	8
Partner treatment	0.501 (0.222 to 0.775)	β (4.852, 3.677)	8
Attend follow-up visit	0.699 (0.356 to 0.876)	β (4.607, 1.902)	19
Health outcomes			
Probability of low birth weight from maternal CT	0.10 (0.03 to 0.26)	β (2.0633, 21.202)	20
Probability of low birth weight from maternal NG	0.17 (0.005 to 0.624)	β (1, 5.699)	3

*LBW hospitalization calculated with WHO-CHOICE average inpatient night cost for Botswana and additional length of stay associated with LBW. Per cartridge freight, customs tax is 5% of the cartridge cost.

CT indicates *Chlamydia trachomatis*; LBW, low birth weight; NG, *Neisseria gonorrhoeae*; POC, point of care.

Estimates of personnel time and supplies were identified through time-and-motion studies conducted on a random sample of testing days. Personnel costs were adjusted as we assumed that medical auxiliary staff and nurses were available at all sites, and

that doctors were not available except at health posts. Staff salaries were found in Botswana Ministry of Health employment announcements. Supply costs were derived from invoices from the pilot program invoices and WHO costing tools.^{24s,25s} For the

TABLE 2. Estimated 1-Year Costs of 3 Scale-Up Strategies for Antenatal *C. trachomatis* (CT) and *N. gonorrhoeae* (NG) Testing and Treatment (2018 USD), Mean and 2.5% to 97.5% Quantiles

	Capital/Start-Up	Shipping	Personnel	Supplies
Point-of-care scenario				
Total 1-y costs: \$2,110,963 (\$1,661,949–\$2,569,751)	\$1,263,594 (\$962,282–\$1,563,040)	\$0	\$50,335 (\$38,448–\$62,345)	\$737,085 (\$499,850–\$978,670)
Testing			\$5390 (\$3573–\$7643)	\$2977 (\$1951–\$4325)
Partner management			\$2085 (\$4615–\$4483)	\$1260 (\$811–\$1847)
Test of cure			\$2029 (\$950–\$3345)	\$44,340 (\$20,014–\$76,347)
Laboratory scenario				
Total 1-y costs: \$1,201,700 (\$879,300–\$1,557,200)	\$119,230 (\$90,883–\$148,350)	\$41,442 (\$30,654–\$54,065)	\$93,699 (\$71,478–\$116,110)	\$893,840 (\$591,150–\$1,233,200)
Testing			\$4565 (\$2669–\$6852)	\$2520 (\$1467–\$3856)
Partner management			\$2,724 (\$1,584–\$4,193)	\$1,068 (\$616–\$1,655)
Test of cure		\$1744 (\$780–\$2980)	\$3270 (\$1469–\$5608)	\$37,592 (\$16,030–\$67,202)
Mixed scenario				
Total 1-y costs: \$1,207,100 (\$883,100–\$1,556,500)	\$119,670 (\$91,244–\$148,710)	\$41,142 (\$30,567–\$53,256)	\$90,625 (\$70,453–\$110,940)	\$900,370 (\$597,890–\$1,233,200)
Testing			\$4745 (\$2861–\$7009)	\$2615 (\$1563–\$3949)
Partner management			\$2830 (\$1698–\$4285)	\$1107 (\$656–\$1694)
Test of cure		\$1810 (\$827–\$3062)	\$3193 (\$1459–\$5404)	\$39,008 (\$16,925–\$69,080)
Syndromic management				
Total 1-y costs: \$658,050 (\$174,880–\$1,482,700)	\$497,580 (\$105,490–\$1,221,400)		\$0	\$0
Assessment			\$60,374 (\$14,958–\$134,720)	\$48,126 (\$12,057–\$109,730)
No symptoms or signs			\$31,627 (\$7,876–\$71,238)	\$20,335 (\$4,995–\$46,612)
STI-related syndrome				
Partner management				
Follow-up (7 d)				

Results represent the mean sampled values and 5% to 95% quantiles derived from the probabilistic uncertainty analysis. Capital/start-up includes the Xpert system. Shipping is a 5% increase on cartridge costs. Personnel include medical auxiliary staff, nurses, pharmacists, and physicians, and the laboratory scenario includes a laboratory technician. Supplies include treatment, CT/NG cartridges, and consumables. Rows: Testing includes the activities and supplies involved in explaining sample collection, processing the sample (e.g., cartridges), providing results for uninfected patients, and completing paperwork. CT/NG management include providing results, counseling, and treatment for infected patients. Partner management includes providing counseling and treatment for partners. Test of cure includes testing and providing results for a test of cure.

syndromic management scenario, personnel time was also informed by interviews with 5 clinic staff members, and recurrent costs were categorized into assessment, treating index patients based on symptoms, treating partners, and follow-up visit for those with symptoms. This methodology isolated the costs of STI treatment from the costs associated with the general antenatal examination. The cost of a follow-up visit for those treated syndromically and the cost per bed per day at a public-level hospital came from the WHO's CHOICE tool.^{26s}

Outcomes

We also estimated the numbers of CT and NG infections treated, CT and NG infections at delivery, low-birth-weight infants, and disability-adjusted life years (DALYs; associated with low birth weight) for each scenario. Disability-adjusted life years were estimated following the methods outlined by Fox-Rushby et al.^{27s} and Terris-Prestholt et al.^{28s} using disability and death averted due to preventing low birth weight. We estimated health savings associated with averting low birth weight by multiplying the average per bed per day hospital costs by the median length of hospital stay of mothers and low-birth-weight infants, including those who died, minus the 1 day spent by mothers and infants born with normal weight. Statistics on length of stay were derived from a previously conducted chart review of 140 infants admitted to the neonatal ward in Princess Marina Hospital between 2015 and 2017 (Balebanye Tlhaodi, unpublished data, 2020).

Uncertainty Analysis

Because of parameter uncertainty, we performed a probabilistic uncertainty analysis where parameters were randomly sampled from probabilistic distributions (Table 1) to generate 10,000 parameter sets. For each parameter set, the model was run and outputs (e.g., costs and CT-associated low-birth-weight infants) were generated, which resulted in a distribution of outcomes. We provided the mean and 2.5% and 97.5% quantiles for each cost and health outcome. We also calculated mean incremental cost-effectiveness ratios (ICERs; \$/DALY averted, mean incremental costs divided by the mean incremental DALYs for each intervention compared with its next least costly nondominated comparator) compared with syndromic management, assessing cost-effectiveness under a willingness-to-pay threshold informed by the WHO's gross domestic product/capita threshold, which was \$8258 (2018 USD).^{29s}

Sensitivity Analysis

We also performed numerous 1-way sensitivity analyses to test the robustness of the ICER between the testing scenarios with the lowest cost per DALY averted compared with syndromic management. Most parameters were either halved or doubled for these sensitivity tests, but for some parameters, we used high and low ranges of published confidence intervals. For the Xpert modules, the low-range parameter represents a high-efficiency scenario where the STI testing program would only need to pay for additional modules in machines that are currently being used by the national tuberculosis program. Finally, we conducted an analysis of covariance to understand the relative effect of different parameters in terms of their contribution to overall uncertainty in estimating the incremental cost per DALY averted. Included parameters were those found to have the largest influence in 1-way sensitivity analyses.

Ethics Statement

The institutional review boards at the University of Botswana, the Botswana Ministry of Health, Health Research Development

Committee; and Princess Marina Hospital approved the study protocol for the pilot study. The University of California, San Diego, approved these secondary analyses using de-identified data.

RESULTS

The modeled annual delivery costs of scaling up antenatal CT and NG testing according to the point-of-care, centralized laboratory, and mixed scenarios compared with syndromic management are outlined in Table 2. The point-of-care scenario was the most expensive to deliver because of the large capital costs (314 four-module Xperts placed at every hospital and clinic serving antenatal patients), followed by the supplies required for testing, which were largely composed of the cost of the CT/NG cartridges. The laboratory and mixed scenarios had similar costs (29 four-module Xperts placed in health districts across the country), although the mixed scenario saved money on shipping and laboratory personnel. In each of the testing scenarios, activities and supplies for testing made up more than 95% of the cost, whereas less than 5% of the total cost was for treatment and partner management. Syndromic management had the lowest overall delivery cost. Because assessment of symptoms and clinical signs takes place during the routine antenatal physical examination, this process had no cost. Treatment costs were higher because patients receive metronidazole in addition to azithromycin and ceftriaxone treatment. Costs of the follow-up visits were high (mean, \$497,580 [95% confidence interval, \$105,490–\$1,221,400]) because all women with symptoms (not just infected) were included.

Table 3 shows the estimated programmatic and health outcomes per scenario. Although syndromic management had the lowest delivery cost, it was associated with the fewest CT/NG infections treated (mean CT, 1124 [95% confidence interval, 313–2322]; mean NG, 225 [95% confidence interval, 41–585]) and cured (mean CT, 941 [95% confidence interval, 259–2,020]; mean NG, 188 [95% confidence interval, 34–498]), and the most infections at delivery (mean CT, 3073 [95% confidence interval, 1872–4459]; mean NG, 615 [95% confidence interval, 194–1285]), low-birth-weight infants (mean CT and NG, 363 [95% confidence interval, 73–887]), and DALYs due to low birth weight (mean, 1727 [95% confidence interval, 347–4220]). This scenario was also associated with the most uninfected women (mean, 16,872 [95% confidence interval, 5103–31,289]) and partners (mean, 7150 [95% confidence interval, 2188–13,479]) treated, and the highest medical costs associated with low-birth-weight infant hospitalizations (mean, \$1.5 million [95% confidence interval, 276,130–3,678,700]). Among the testing scenarios, the mixed scenario had the lowest cost per woman tested (mean, \$26 [95% confidence interval, \$19–\$35]) and cost per cure (mean, \$534 [95% confidence interval, \$306–\$888]).

We also compared the costs and DALYs associated with syndromic management and the mixed and point-of-care testing scenarios (Table 4). The laboratory scenario was not included because it was dominated by the mixed scenario. Comparing the mixed scenario with syndromic management, the mixed scenario resulted in incremental costs of \$549,050 (95% confidence interval, –\$361,361 to \$1,188,690) and incremental DALYs averted of 576 (95% confidence interval, 3 to 1730), resulting in a mean ICER of \$953 per DALY averted. Ninety-six percent of the simulations fell below the willingness-to-pay threshold informed by the WHO's gross domestic product/capita threshold (\$8258; USD 2018 in Botswana). The point-of-care scenario was the most costly, resulting in incremental costs of \$903,863 (95% confidence interval, \$592,928 to \$1,217,341) compared with the mixed scenario, but also averting of 166 (95% confidence interval, –118 to 652) additional DALYs, generating a mean ICER of \$5445

TABLE 3. Estimated Programmatic and Health Outcomes by Antenatal STI Management Strategy, Mean and 2.5% to 97.5% Quantiles

Outcome	Point-of-Care	Laboratory	Mixed	Syndromic
Programmatic				
Women with CT infection [†]	4005 (2838–5357)	4014 (2818–5398)	4011 (2823–5388)	4014 (2818–5398)
Women with NG infection [†]	807 (276–1604)	804 (268–1622)	815 (268–1627)	803 (267–1622)
Women tested/assessed	37,960 (36,609–39,310)	44,311 (41,186–46,873)	44,311 (41,186–46,873)	40,229 (22,034–49,717)
CT infections treated	2690 (1880–3665)	2274 (1406–3302)	2359 (1505–3376)	1124 (313–2322)
NG infections treated	555 (186–1112)	475 (149–993)	492 (155–1020)	225 (41–585)
Partners treated	1486 (1055–2008)	1259 (1826–1902)	1307 (846–1860)	767 (262–1377)
Uninfected women treated for CT	205 (116–321)	173 (91–288)	179 (96–295)	—
Uninfected women treated for NG	60 (9–156)	51 (7–139)	52 (7–143)	—
Uninfected treated for CT, NG, and TV	—	—	—	16,872 (5103–31,289)
Partners of uninfected women treated	110 (93–126)	94 (41–183)	98 (43–186)	7150 (2188–13,479)
Missed CT infections	1315 (888–1857)	1748 (1020–2701)	1652 (971–2536)	2542 (1291–3979)
Missed NG infections	251 (84–512)	339 (105–744)	324 (100–698)	508 (148–1109)
Women cured of CT	2252 (1456–3260)	1902 (1105–2907)	1973 (1183–2976)	941 (259–2020)
Women cured of NG	465 (154–952)	2435	412 (126–876)	188 (34–498)
CT infections at delivery*	1753 (1071–2594)	2109 (1246–3171)	2038 (1206–3060)	3073 (1872–4459)
NG infections at delivery*	341 (109–716)	419 (127–893)	404 (122–862)	615 (194–1285)
Health				
LBW infants related to CT	156 (20–430)	188 (23–537)	182 (23–519)	272 (36–739)
LBW infants related to NG	50 (1–192)	63 (1–252)	61 (1–235)	91 (2–352)
LBW infants total	207 (41–514)	252 (49–635)	242 (47–609)	363 (73–887)
DALY due to LBW	985 (195–2445)	1199 (233–3021)	1151 (224–2897)	1727 (347–4220)
Cost and outcome comparisons				
Cost per test/assessment	\$57 (\$45–69)	\$27 (\$20–35)	\$26 (\$19–35)	\$18 (\$4–51)
Cost per cure	\$812 (\$512–\$1242)	\$554 (\$313–\$940)	\$534 (\$306–\$888)	\$748 (\$153–\$2418)
LBW hospitalization costs	\$835,720	\$1,012,000	\$977,250	\$1,459,500
	(\$162,740–\$2,128,200)	(\$190,980–\$261,960)	(\$184,390–\$253,830)	(\$276,130–\$3,678,700)

Results represent the mean sampled values and 2.5% to 97.5% quantiles derived from the probabilistic uncertainty analysis.

*Includes, untested, untreated, not cured, and re-infected between ToC and delivery.

[†]Includes total ANC volume and women who tested/assessed and those who were not.

ANC indicates antenatal care; CT, *Chlamydia trachomatis*; DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; LBW, low birth weight; NG, *Neisseria gonorrhoeae*; STI, sexually transmitted infection; ToC, test of cure.

per DALY averted compared with the mixed scenario. A figure displaying the distribution of the incremental costs and DALYs averted can be found in Supplementary Digital Content (<http://links.lww.com/OLQ/A718>).

In the univariate sensitivity analyses, which assessed the impact of varying model parameters on the ICER between the mixed approach and syndromic management, the most influential parameters were as follows: syndromic management sensitivity, probability of treatment among those diagnosed with CT/NG infections, and the probability of low birth weight due to CT infection (Fig. 1). Finally, in our analysis of covariance analysis, we found that the uncertainty in sensitivity of syndromic management ($F = 6.05$, $P = 0.01$) and the probability of treatment if etiologically diagnosed ($F = 3.94$, $P = 0.05$) contributed the majority of uncertainty to the ICER.

DISCUSSION

As many countries are considering implementing antenatal CT/NG infection testing, there are essential implementation questions. Among the testing strategies, we found that the mixed scenario, which combined point-of-care and centralized testing, had the most favorable cost per woman tested and cured and was cost-effective compared with syndromic management. Point-of-care testing had the largest total delivery cost, had the highest cost per outcomes, and may not be a feasible strategy to implement nationally because of its high cost. However, it could be considered for high-volume regions as part of a hub-and-spoke model. A large proportion of point-of-care testing cost comes from the capital costs involved in placing a GeneXpert machine at each testing site. Thus, as STI testing platforms continue to improve^{30s} and

TABLE 4. Comparison of Costs and Disability-Adjusted Life Years (DALYs) Associated With the Syndromic Management and the Mixed and Point-of-Care Testing Scenarios

Scenario	Total Cost	Δ Total Cost	DALYs Averted	Δ DALYs Averted	ICER
Syndromic management	\$658,050 (\$174,880 to \$1,482,700)	—	1727 (347 to 4220)	—	—
Mixed	\$1,207,100 (\$883,100 to \$1,556,500)	\$549,050 (-\$361,361 to \$1,188,690)	1151 (224 to 2897)	576 (3 to 1730)	\$953
Point-of-care	\$2,110,963 (\$1,661,949 to \$2,569,751)	\$903,863 (\$592,928 to \$1,217,341)	985 (195 to 2445)	166 (-118 to 652)	\$5445

DALYs associated with low-birth-weight infants averted. The laboratory scenario was removed from this table because it was more expensive and less effective than the mixed scenario and thus dominated. The total cost and DALYs averted are the means and 2.5% to 97.5% intervals derived from the probabilistic uncertainty analysis. The change in total cost and DALYs averted represents the distributions of the differences between the 10,000 parameter sets. The ICERs represent the mean incremental costs divided by the mean incremental DALYs averted.

ICER indicates incremental cost-effectiveness ratio.



Notes: Parameters were varied based on the 5% and 95% quantiles of their sampling distribution (Table 1).
SM=Syndromic Management, CT=Chlamydia trachomatis, NG=Neisseria gonorrhoeae, LBW=low birth weight

Figure 1. Tornado diagram of the ICER comparing the mixed testing scenario with syndromic management using key parameters (Base ICER = \$953). Parameters were varied based on the 5% and 95% quantiles of their sampling distribution (Table 1). CT, *Chlamydia trachomatis*; ICER, incremental cost-effectiveness ratio; LBW, low birth weight; NG, *Neisseria gonorrhoeae*; SM, syndromic management.

potentially reduce in cost, more widespread adoption will be more economically feasible for low-income countries. Syndromic management had the lowest total delivery cost and allowed for point-of-care treatment, but it was estimated to overtreat many uninfected women and partners and miss infections, which resulted in higher estimated numbers of low-birth-weight infants and DALYs. When we compared syndromic management with the mixed approach, we found that the mean ICER per DALY averted would be considered cost-effective using the WHO willingness-to-pay threshold. The mixed scenario continued to be cost-effective in our 1-way sensitivity analysis where we varied syndromic management sensitivity, mixed-scenario treatment probability, GeneXpert cost, CT/NG cartridge cost, syndromic management follow-up cost, CT and NG prevalence, and CT-related low-birth-weight risk. Furthermore, the mixed scenario was estimated to contribute to significant savings in terms of reducing hospitalizations associated with low birth weight compared with syndromic management.

Modeling studies are intended to provide evidence when large randomized controlled trials are not feasible.^{31s} Previous studies have found that policy makers and planners have integrated evidence from decision-making modeling with primary research to develop recommendations and update guidelines related to heart disease and HIV treatment.^{31s–33s} This study provides a methodology to translate findings from pilot research to estimate impacts at scale. As issues facing policy makers become increasingly complex, models can help ensure that policies are evidence based by providing a way to systematically explore trade-offs between competing strategies. As policy makers update STI management guidelines, they should consider intervention impacts reported by primary studies in specific locations and estimations of costs and outcomes at scale.

Our analysis has several limitations. First, many parameter estimates were based on data from a single pilot study and may not reflect variation across facilities. However, we compared our parameter estimates with antenatal syphilis testing research and found the personnel time and supply estimations were similar.^{28s} For example, compared with an antenatal syphilis costing study conducted in Tanzania, we both found that pretest counseling took 1 minute on average and providing negative results took 1 minute in our study and 0.5 minutes in the syphilis study.^{28s} The results also may have limited generalizability outside Botswana, but because many sub-Saharan African countries have an antenatal care

attendance rate of 70% or higher and deliver opt-out antenatal HIV testing, this could provide a framework for integrating CT and NG testing.^{34s,35s} The primary cost drivers in the model (Xpert modules and cartridges) were based on high-burden low-income country prices, so they would be similar across the region. Furthermore, our results were similar to a point-of-care STI costing study conducted in South Africa, which found that testing was between \$37 and \$50 per patient.^{36s} In addition, although we had facility-specific antenatal volume for hospitals, we could not disaggregate antenatal volume statistics to the clinics or health post level and instead averaged the volume at health posts and clinics in each region. If a large number of clinics did not offer antenatal care services, then our point-of-care delivery cost would be an overestimation. In addition, the results should not be used to make decisions about implementing testing at individual facilities.

Furthermore, a key assumption that undergirds these simulated scenarios is that testing could reach scale immediately. The model does not consider the political advocacy, leadership, and training that would be required to implement expanded testing. This might affect both time/delay in attaining at-scale implementation and possible costs (e.g., training, lobbying, communications, etc.).^{37s} In addition, we were also not able to estimate the full costs of syndromic management. Even though 80% of women in Botswana have more than one antenatal care visit, we were not able to estimate the costs of syndromic management at all visits because the probabilities of symptoms over time are unknown. Thus, our cost estimations for syndromic management are likely lower than the real-world costs.

Finally, although quasi-experimental studies have identified an association between maternal NG infection and low birth weight, there is a lack of evidence demonstrating the benefits of testing and treatment. Thus, we assumed wide uncertainty intervals. Furthermore, our estimate of an increased risk of low birth weight associated with maternal CT infection is from a study in the United States, and this relationship may be different in low-resource settings.

This study also has a number of strengths. It was based on primary data collection in Botswana. Also, it is in line with the World Health Assembly's global strategy on STIs 2016–2021, which recognizes that efforts are needed to rapidly scale up effective interventions and services to reach the goal of a 90% reduction in curable STIs by 2030.^{38s} According to the WHO, there is

limited practical guidance on how to implement scale-up, and many successful health service innovation pilot programs have failed to expand beyond the pilot stage.^{37s}

Our findings and limitations suggest the need for additional research. The syndromic management scenario was associated with large numbers of uninfected women and partners treated for STIs. Although STI treatments are low cost, more research is needed to assess excess adverse events associated with overtreatment such as emotional stress, relationship strain, intimate partner violence, changes to the microbiome, and antimicrobial resistance. Furthermore, we know that CT/NG infections are associated with adverse outcomes; however, there is a lack of research evaluating the impact of etiologic testing on health outcomes. Randomized controlled trials are needed to estimate the impact of testing on a range of infant and maternal health outcomes beyond low birth weight.

Next, future analyses could consider the cost savings associated with integrating STI testing with other testing programs.^{39s} For example, Xpert capacity can be used for many other infections, such as early detection of HIV, and viral load testing and diagnosis of human papilloma virus, *T. vaginalis*, or multidrug-resistant tuberculosis. Multi-indication use would have important clinical and public health implications and would spread costs across multiple diseases. Viral load testing is critical for provision of antiretroviral therapy, but access to testing is limited in many countries because of equipment costs and personnel needs.^{40s}

Finally, our study involves a closed population modeled in just 1 cycle, and we know that infectious disease dynamics are more complex. Therefore, dynamic infectious disease transmission models are needed over a longer time horizon to develop a more robust understanding of how transmission, disease progression, cure, and reinfection are impacted by STI testing in a population over time.

In conclusion, our model showed that among the testing and treatment scenarios, the mixed scenario had the lowest average cost per woman tested and cured and would be cost-effective if using the WHO benchmark (the ICER is less than one times the per capita gross domestic product). Although syndromic management had lower costs than testing, it was associated with suboptimal care, including a large number of inappropriately treated infections, missed infections, and adverse birth outcomes. As countries move away from syndromic management, there is an opportunity to determine how to best deploy resources. This study demonstrates that a mix of point-of-care and centralized testing should be considered based on costs as well as regional and facility volume.

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For further references, please see “Supplemental References,” <http://links.lww.com/OLQ/A719>.