WORKING
PAPER

A Technical Supplement: Reducing the Burden of Sexually Transmitted Infections and HIV/AIDS in Resource-Poor Countries

The Role of Improved Diagnostics for Gonorrhoea and Chlamydia

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RAND HEALTH

PREFACE

This paper contains technical material supporting the article by Aledort et. al. "Reducing the burden of sexually transmitted infections in resource-limited settings: the role of improved diagnostics." *Nature*. S1 59-72 (2006). It is intended to be read in conjunction with that article. This supplement includes additional material referred to in the published article as well as supplemental analyses and tables that were not included in the published paper. Although this technical supplement in its current form has not been formally peer-reviewed, an earlier version of this paper, which also contained material that appears in the corresponding *Nature* paper, was reviewed by an outside expert and was revised in response to the reviewer's comments.

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A. OVERVIEW

Curable bacterial sexually transmitted infections (STIs) such as gonorrhoea and chlamydia exact a heavy toll in terms of morbidity and mortality in the developing world, the long-term complications of which are disproportionately borne by women. In

particular, women with multiple sexual contacts, such as commercial sex workers (CSWs), and those whose partners have visited CSWs, are at substantial risk of infection.

Despite the recognized need for early diagnosis and treatment of gonorrhoea and chlamydia, detection strategies are currently limited in low-resource countries. We developed a model to quantify the potential health benefits of new gonorrhoea and chlamydia diagnostic tests for symptomatic and asymptomatic CSWs in sub-Saharan Africa, China and southeast Asia, three regions that account for the majority of incident infections. The analysis considers test-performance characteristics and access requirements associated with a new diagnostic, and incorporates downstream gonorrhoea, chlamydia and HIV infections averted.

A.1. Selection of Priority Intervention Points for Improved STI Diagnostics

At the first meeting of the Global Health Diagnostics Forum of the Bill & Melinda Gates Foundation in September 2004, experts assigned to the HIV/STI Expert Panel identified gonorrhoea and chlamydia as primary areas of interest because of their high prevalence of infection in resource-poor countries and high rates of associated morbidity and curability.

The experts then identified several areas for which new diagnostics could improve outcomes associated with gonorrhoea and chlamydia. There was immediate consensus that the benefit of improved diagnosis and treatment of gonorrhoea and chlamydia was twofold: reductions in individual gonorrhoea and chlamydia morbidity and interruption of gonorrhoea, chlamydia and HIV transmission in the community. Initially, three separate analyses were proposed for study, reflecting the relative importance of different sub-populations: (1) Gonorrhoea and chlamydia screening in CSWs who attend STI clinics; (2) gonorrhoea and chlamydia screening in 'low-risk' asymptomatic women, e.g., women who attend family planning and antenatal clinics, and; (3) gonorrhoea and

chlamydia diagnosis in women presenting with symptoms, i.e., women presenting with vaginal discharge syndrome and/or lower abdominal pain.

RAND surveyed the experts in mid-April 2005 to narrow the scope of the HIV/STI modeling efforts. Of the three analyses identified by the group, the CSW model emerged as a clear priority because of the increased prevalence of gonorrhoea and chlamydia among highly sexually active women and their disproportionate contribution to transmission of gonorrhoea, chlamydia and potentially HIV through multiple partners. The experts also agreed that it would be important to consider both asymptomatic and symptomatic infections. Moreover, the experts agreed that the gonorrhoea and chlamydia analysis should focus on sub Saharan Africa, China and Southeast Asia since those regions account for nearly 75 percent of gonorrhoea and chlamydia disease burden in women.[1]

B. METHODS

B.1 Modeling Health Outcomes

Because morbidity (rather than mortality) is the primary health outcome of interest for gonorrhoea and chlamydia infections, we report outcomes such as disability adjusted life years (DALYs). DALYs combine length of life with quality of life into a single measurement, and allow comparison across multiple health benefits. Given the infectious nature of gonorrhoea and chlamydia, CSWs may acquire infection and also transmit infection to their sexual partners. To capture the individual and population effect of gonorrhoea and chlamydia diagnosis and treatment in CSWs, we model total DALYs saved as a composite measure that incorporates both DALYs saved from treating the gonorrhoea and/or chlamydia source case and DALYs saved from preventing subsequent cases due to downstream transmission. We therefore account for the probability that treating individual infections in a highly sexually active population interrupts transmission and prevents future infections in the community. Since there is evidence that gonorrhoea and chlamydia may facilitate the transmission of HIV, we also report as a

secondary outcome, the number of HIV infections that could be averted with appropriate gonorrhoea and chlamydia diagnosis and treatment. The following sections review how we calculated individual, population and total DALYs saved as well as downstream HIV cases averted.

B.2 Estimating Incremental DALYs Saved with a New Diagnostic

To quantify the DALYs that we attribute to a test result that is true positive, false positive, false negative and true negative, we first defined four quantities denoted by *TP*, *FP*, *FN* and *TN*, respectively. These are defined using both screening and treatment outcomes. A woman is counted as a true positive only when she receives appropriate treatment for gonorrhoea and chlamydia. For instance, a woman who tests positive with a laboratory test, but fails to receive treatment, is counted as a false negative. Similarly, a women self-treating with an inappropriate drug and who does not receive effective treatment, is also counted as a false negative. The total health outcome, H, is then computed as follows:

$$H=N_{tp}TP+N_{fp}FP+N_{fn}FN+N_{tn}TN$$

where N_{tp}, N_{fp}, N_{fn}, and N_{tn} are the number of women in each test outcome category.

To derive the incremental total DALYs saved associated with the introduction of a new diagnostic for gonorrhoea and chlamydial infections (compared to the status quo), we calculated the total DALYs lost for both the status quo and the new diagnostic models and then computed the difference between DALYs lost with a new diagnostic and DALYs lost under the status quo. The incremental health benefit of a new diagnostic compared to the status quo is expressed in terms of total DALYs not lost, or *saved*. Details of calculating DALYs saved with the introduction of a new diagnostic are given below. We first outline the individual components of adjusted DALYs lost for each region and then provide the methods for calculating DALYs saved with the introduction of a new diagnostic.

B.3. Estimating Individual DALYs Lost

We estimated individual DALYs lost per treated and untreated gonorrhoea and chlamydia infection in each region to allow for differences in regional characteristics, such as access to care that may impact the severity and course of disease. First, we calculated the total number of gonorrhoea and chlamydia cases in the population by region, by multiplying gonorrhoea and chlamydia prevalence by the population of interest. Based on expert opinion, and the published literature, we assumed a uniform gonorrhoea and chlamydia prevalence of 1.5 percent among the general female population aged 15-44 (the general population includes women with a high number of sexual partners as well as women in the general population).[2] At a prevalence of 1.5 percent, the total number of gonorrhoea and chlamydia cases among women age 15-44 in sub Saharan Africa, for example, is 2.355 million (this includes both *treated* and *untreated* cases, Table 1). By focusing on gonorrhoea and chlamydia cases in the general population, we implicitly assume that our eventual estimates of DALYs lost per treated and untreated gonorrhoea and chlamydia case are independent of risk behavior. Specifically, we assume that CSWs and women in the general population who are infected with gonorrhoea and chlamydia face the same per-case disease burden.

After estimating the total number of gonorrhoea and chlamydia cases for our regions of interest, we distributed the DALY burden among treated and untreated cases using the DALY burden given by the 2005 Global Burden of Disease (GBD) study[3]. Table 1 presents key estimates that were utilized to derive DALYs lost per treated gonorrhoea and chlamydia case. Note that although Aledort and colleagues defined the primary regions of interest as sub-Saharan Africa, China and southeast Asia[4], the GBD study uses slightly different regional definitions. Therefore Table 1 corresponds to the GBD-defined regions of southeast Asia, Western Pacific and Africa.

Table 1. Estimates and Calculations Utilized in the Derivation of DALYs Lost Per Treated Gonorrhoea and Chlamydia Case

	southeast Asia	**Western Pacific**	**Africa**
Population of women 15-44*[1] (million)	385	420	157
General population prevalence of gonorrhoea and chlamydia[2]	1.5%	1.5%	1.5%
Total gonorrhoea and chlamydia cases among women 15-44 (million)†	5.775	6.3	2.355
Total DALYs lost to gonorrhoea and chlamydia for women 15-44 [D_{total}] (million)[1]‡	1.735	.352	1.055
Proportion of cases treated in the status quo§	31.1%	31.1%	7.90%
Number of cases treated [$N_{treated}$] || (million)	1.796	1.960	0.186
Number of cases untreated [$N_{untreated}$] || (million)	3.979	4.340	2.169
Average DALYs lost for a treated case of gonorrhoea and chlamydia|| [$D_{treated}$]	0.098	0.018	0.119
Average DALYs lost for an untreated case of gonorrhoea and chlamydia|| [$D_{untreated}$]	0.392	0.730	0.476
Difference in DALYs lost per treated and untreated case of gonorrhoea and chlamydia treated|| [$D_{individual}$]	0.294	0.054	0.357

* For this calculation, we downward adjusted our target population of women aged 15-49 to women aged 15-44 to better align our estimates with the most relevant age group reported by the Global Burden of Disease study.

† This is a product of the first two rows.

‡ Estimates of DALYs lost are taken from the 2005 projections of the GBD and can be found at http://www.who.int/healthinfo/statistics/bodprojections2030/en/index.html

§ The proportion of cases treated are projections, or outputs, of the status quo model described in Aledort et al. [4].

|| This is a calculation based on the estimates in the table. The methods are described in the text below.

The status quo model described in Aledort et al.[4]projected that that in sub-Saharan Africa, on average, about 8 percent of all CSWs receive appropriate treatment for gonorrhoea and chlamydia. Applying this 8 percent treatment rate to the 2.355 million cases in the general sub Saharan population, for example, generates the following numbers of treated and untreated cases:

$$N_{treated} = 0.186 \text{ million}$$

$$N_{untreated} = 2.169 \text{ million}$$

Let $D_{treated}$ be the DALYs lost for each treated case of gonorrhoea and chlamydia. This number is greater than zero because a small proportion of women treated for gonorrhoea and chlamydia will still progress to pelvic inflammatory disease (PID).[5-7] Let $D_{untreated}$ be the DALYs lost for each untreated case of gonorrhoea and chlamydia. Then we can specify the total individual DALYs lost as follows:

$$\text{Total DALYs lost} = D_{total} = N_{untreated} * D_{untreated} + N_{treated} * D_{treated}$$

Based on expert opinion and estimates of the risk of PID among treated and untreated cases of gonorrhoea and chlamydia, we assume that the DALYs lost for each untreated case are four times those lost for each treated case. Because PID is the largest contributor to DALYs lost for gonorrhoea and chlamydia, we applied the 4:1 ratio to the total DALY burden for treated and untreated women. Thus,

$$D_{untreated} = 4 * D_{treated}$$

Given the estimates in Table 1 for D_{total}, $N_{treated}$ and $N_{untreated}$ for each region, we calculated $D_{treated}$ as follows:

$$D_{total} = N_{untreated} * 4 * D_{treated} + N_{treated} * D_{treated}$$

$$\Rightarrow D_{treated} = \frac{D_{total}}{4 * N_{untreated} + N_{treated}}$$

Once we established $D_{treated}$ for each region, we could also estimate $D_{untreated}$. Combined with the estimates of total DALYs for treated gonorrhoea and chlamydia in Table 1, we calculated 0.119 DALYs lost for each treated case of gonorrhoea and chlamydia and 0.476 DALYs lost for each untreated case in sub Saharan Africa. For southeast Asia, we

estimated 0.098 and 0.392 DALYs lost for each treated and untreated case of gonorrhoea and chlamydia, respectively, and for the Western Pacific region, we estimated 0.018 and 0.730 DALYs lost for each treated and untreated case of gonorrhoea and chlamydia.

To estimate the effect of treating an additional woman for gonorrhoea and chlamydia, we calculated the difference in DALYs lost per treated and untreated case. Specifically,

$$D_{individual} = D_{untreated} - D_{treated}.$$

$D_{individual}$ is the individual DALY lost for each CSW that is infected and remains untreated.

B.4. Estimating Downstream Gonorrhoea, Chlamydia and HIV Cases Saved per Infection Treated

In the absence of treatment, a highly sexually active woman with gonorrhoea and chlamydia will contribute directly to downstream gonorrhoea and chlamydia cases in the community through her sex partners. Subsequently, for every additional woman appropriately treated with the introduction of a new diagnostic that improves upon the status quo, some number of downstream gonorrhoea and chlamydial infections are averted. In addition, non-ulcerative STIs are thought to increase the risk of sexual transmission of HIV.[8-12] For example, there is some evidence that STIs increase the infectiousness of HIV from men to women.[12] Although debate persists about the strength of the correlation between the spread of non-ulcerative STIs and HIV transmission, and more research is required to clarify our understanding about the nature of the interaction, the control of STIs (including gonorrhoea and chlamydia) is widely recognized as an important component in HIV prevention efforts.[12-14] Because we did not want to overlook the potential benefit of gonorrhoea and chlamydia control on the incidence of HIV, we also estimated the transmission effects of treated and untreated gonorrhoea and chlamydia on downstream HIV infections. Following the methods outlined above in section B.2, we estimated downstream gonorrhoea, chlamydia and HIV cases averted as the difference between downstream gonorrhoea and chlamydia cases in the status quo and downstream cases following the introduction of a new diagnostic.

To estimate the downstream number of cases averted per treated case of gonorrhoea and chlamydia, we capitalized on previous research by Vickerman and colleagues that used a dynamic deterministic mathematical model to estimate the impact of interventions targeted to two CSW populations[15, 16]. Vickerman and colleagues developed a mathematical model that utilized behavioral and epidemiological data from two sub-Saharan Africa sites to explore the impact of new diagnostics for the diagnosis and treatment of gonorrhoeae and chlamydia in female CSWs. The analysis focused on two settings: Cotonou in Benin, and Hillbrow in Johannesburg, South Africa. These settings differed in many ways, including prevalence of HIV and STIs, and different patterns of sexual behavior and condom use, but both settings had established CSW focused interventions.[16, 17] Specifically, Vickerman and colleagues fit their mathematical model to available gonorrhoea, chlamydia and HIV and prevalence data from different population sub-groups in Cotonou and Hillbrow, over a wide range of model input parameters (behavioral, epidemiological and biological parameters),.

Working with RAND, Vickerman and colleagues then used model outputs from their analyses to estimate the impact of a new diagnostic for gonorrhoea and chlamydia over a range of test sensitivities (0%, 40%, 45%, 67%, 85%, 100%), compared to the current syndromic algorithm (status quo), in terms of downstream gonorrhoea and chlamydia and HIV cases averted per treated gonorrhoea and chlamydia case in CSWs, their clients and the general population. This analysis did not examine specificity since only the sensitivity of the test determines the number of gonorrhoea and chlamydia infections that are treated. Test specificity, on the other hand, determines the amount of overtreatment. Estimates were also derived for the expected number of gonorrhoea and chlamydia and HIV infections per untreated case of gonorrhoea and chlamydia. We derived our estimates from Vickerman's analysis of Hillbrow, South Africa.

The impact of the test was simulated over 4 years to obtain an estimate of the chain of infections that can be averted from treating one infection. The number of infections averted per infection treated was obtained by dividing the model's projections of the

infections averted over four years by the number of CSWs tested and treated. All CSWs that tested positive were assumed to be treated appropriately. The different model fits produced different estimates for the impact of each rapid test, and these were used to obtain a mean and uncertainty range for the model's impact projections. The estimated number of gonorrhoea and chlamydia and HIV cases averted per treated case of gonorrhoea and chlamydia for varying sensitivities of a new diagnostic are reported in Table 2.

Table 2. Model Projections of the Number of Gonorrhoea, Chlamydia and HIV Infections Averted per Treated CSW Over Four Years. (*Uncertainty ranges are in brackets*)

	Sensitivity of a New Diagnostic for Gonorrhoea and Chlamydia				
	40%	45%	67%	85%	100%
Gonorrhoea and chlamydial infections averted per treated case	10.8 (8.3-12.9)	10.7 (8.3-12.8)	10.6 (8.2-12.6)	10.5 (8.1-12.5)	10.5 (8.1-12.4)
HIV cases averted per treated gonorrhoea and chlamydial infection	0.135 (0.089-0.215)	0.135 (0.089-0.214)	0.135 (0.089-0.213)	0.134 (0.089-0.212)	0.134 (0.089-0.211)

Results from this analysis indicate that estimates vary only slightly over the range of sensitivities explored. The Hillbrow population is transitory, and the epidemic there is fueled by populations with a high HIV and STI prevalence, thus mitigating the effect of STI treatment on transmission in the community. Since these estimates vary only slightly over the range of sensitivities explored, we assumed constant transmission multipliers of 10.55 and 0.135 for gonorrhoea and chlamydia and HIV cases averted, respectively.

B.5 Combining DALYs Lost due to Individual Infection and Downstream Transmission

Because interrupting transmission is an important component of testing and treating

gonorrhoea and chlamydia among CSWs, we incorporated the above-described estimate of 10.5 downstream cases gonorrhoea and chlamydia cases averted into our derivation of DALYs saved for each CSW treated for gonorrhoea and chlamydia. We assumed that each time a CSW is treated, benefits in terms of DALYs accrue from two sources: (1) $D_{individual}$ DALYs are saved when progression of disease is interrupted in the individual patient, and (2) DALYs are saved when the 10.5 downstream cases of gonorrhoea and chlamydia are prevented . The details of this second DALY benefit are outlined below.

Building on the calculations presented in section B.2., we estimated *average* DALYs lost per case of gonorrhoea and chlamydia for each region as a weighted average of DALYs lost per treated and untreated case. Specifically,

$$D_{average} = \frac{N_{treated} * D_{treated} + N_{untreated} * D_{untreated}}{N_{treated} + N_{untreated}}$$

Using the above formula and the values presented in Table 1, we derived the following values for $D_{average}$ in each region.

Table 3. Calculating DALYs Lost Per Treated Gonorrhoea and Chlamydia Case

	southeast Asia	**Western Pacific**	**Africa**
Number of cases treated [$N_{treated}$] (million)	1.796	1.960	0.186
Number of cases untreated [$N_{untreated}$] (million)	3.979	4.340	2.169
Average DALYs lost for a treated case of gonorrhoea and chlamydia [$D_{treated}$]	0.098	0.018	0.119
Average DALYs lost for an untreated case of gonorrhoea and chlamydia [$D_{untreated}$]	0.392	0.073	0.476
Difference in DALYs lost per treated and untreated case of gonorrhoea and chlamydia treated [$D_{individual}$]	0.294	0.054	0.357
Average DALYs lost per case of gonorrhoea and chlamydia [$D_{average}$]	0.301	0.056	0.448
Total DALYs lost per untreated CSW [D_{FN}]	3.56755	0.663	5.20
DALYs saved per treated gonorrhoea and Chlamydia case [$D_{FN} - D_{TP}$]	3.46	0.64	5.08

To combine DALYs lost for each untreated CSW in each region, we performed the following calculation:

$$DALYs\ Lost\ per\ Untreated\ CSW = D_{FN} = D_{untreated} + 10.55 * D_{average}$$

D_{FN} is the primary outcome used to evaluate the model. In the above calculation we assume that effective treatment prevents all transmission. This relies on the early detection and treatment of CSWs and represents the upper bound in terms of DALY savings possible through treatment and detection. Because the transmission multipliers from Vickerman et al. are for a four year period and provide little information about the distribution of infections over this four year period, we do not discount DALYs lost due to these downstream cases.

Note further that, because we assume that treatment prevents all transmission, the DALYs lost for each treated case of gonorrhoea and chlamydia are simply those lost by the index patient. In other words, $D_{TP} = D_{treated}$

B.6. Estimating DALYs Lost due to Harm of Treatment

When a woman receives treatment for gonorrhoea and chlamydia, either appropriate or inappropriate, we assumed some harm, or penalty, associated with treatment. Sources of harm may include adverse events associated with treatment, the development of antibiotic resistance, and/or stigma. For example, if a pathogen develops resistance to an antibiotic agent, at some point in the future, individuals with a resistant strain of infection may not respond to treatment, thus causing adverse health outcomes. In addition, once resistance occurs, new therapeutic agents must be developed, leading to additional costs, and consuming resources which may have been put to better use. Each time we treat inappropriately with antibiotics we utilize scarce resources that may have been otherwise used to treat patients in need.

We quantified the harm of treatment with a single number *C*, which represent the DALYs lost, at some point in the future, as a result of treating one woman with antibiotics. We refer to the total DALYs lost due to harm of treatment as "future DALYs lost". The total number of future DALYs lost is computed as follows:

$$D_{\text{future}} = C\left(N_{tp} + N_{fp}\right)$$

We estimated a range for *C* using the methods described in Girosi et al.[18] Conceptually, if a test for NG/Ct is widely accepted and adopted by the medical community, then using the test must be better than the alternative of treating everybody or treating no one. We maintain that this is sufficient information to estimate the approximate weight assigned by the medical community to specificity relative to sensitivity. We then translated this revealed preference into an estimate of the harm of treatment, *C*. The bound on *C* has the following form:

$$\frac{p \cdot (1 - sens) \cdot (D_{FN} - D_{TP})}{p \cdot (1 - sens) + (1 - p) \cdot spec} \leq C \leq \frac{p \cdot sens \cdot (D_{FN} - D_{TP})}{p \cdot sens + (1 - p) \cdot (1 - spec)}$$

where *p* is the prevalence of NG/Ct in our population of interest, *sens* and *spec* are the sensitivity and specificity of a laboratory test combined with clinical evaluation, and D_{FN} and D_{TP} are as described above in section B.4. The bounds above are most informative when the test characteristics are poor. In other words, while it is always preferable to use a test that is perfectly sensitive and specific, this preference does not reveal much about the relative harm of treatment. Because prevalence and, more importantly, D_{FN} and D_{TP}, vary by region, we calculated a range for C for each region of interest. The method described in Girosi et al. does not tell us how to choose a value of C within the given bounds.[18] Based on expert opinion, for each region we selected the point estimate for C to be the minimum of the range estimated for that region. To account for the uncertainty surrounding this parameter we varied it extensively in sensitivity analysis.

To interpret estimates of C, recall that each time one CSW is treated for gonorrhoea and chlamydia, *C* future DALYs are lost, or, for every 1/*C* CSW treated, one future DALY is lost. Consider the point estimate for *C* of 0.96 for sub-Saharan Africa reported in Table 2

in Aledort et al.[4] This implies that for approximately every 1 (~1/0.96) high risk woman treated for gonorrhoea and chlamydia we lose one DALY. If we think of a healthy year of life as one DALY then, for every 1 treatment, we lose one year of life. For the average female life expectancy in sub-Saharan Africa of 47.5 years, this means that for approximately every 48 treatments given we lose one healthy life. (The Global Burden of Disease reports a life expectancy at birth of 46.5 for males and 48.4 for females in 2002 in the African Region.)[1]

B.7. Estimating Adjusted DALYs Saved

'Adjusted' DALYs lost includes in the composite DALY measure described above a penalty, or harm, associated with treatment. Specifically, this additional DALY adjustment incorporates the relative weight of sensitivity and specificity through the inclusion of the harm of treatment, C, and subsequent future DALYs lost. The total DALYs lost for a single region is calculated as follows:

$$\begin{aligned} \textit{Adjusted DALYs Lost} = D &= D_{TP} + D_{FN} + D_{future} \\ &= D_{TP}N_{tp} + D_{FN}N_{fn} + C(N_{tp} + N_{fp}) \\ &= (D_{TP} + C)N_{tp} + D_{FN}N_{fn} + CN_{fp} \end{aligned}$$

Incremental adjusted DALYs saved are the primary measure of attributable benefit of a new diagnostic (i.e. the difference in adjusted DALYs between the new diagnostic and the status quo). The model only selects a new diagnostic for use when it results in fewer adjusted DALYs lost (or a positive number of adjusted lives *saved*). More formally, for each region and access category, the number of adjusted DALYs saved when the new diagnostic is introduced is expressed as follows:

$$\Delta Adjusted\ DALYs_{\ Access\ Category\ i}$$
$$= Adjusted\ DALYs\ Lost\ in\ Status\ Quo_{\ Access\ Category\ i}$$
$$- Adjusted\ DALYs\ Lost\ with\ New\ Diagnostic_{\ Access\ Category\ i}$$
$$= (D_{TP} + C)N_{tp}^{SQ} + D_{FN}N_{fn}^{SQ} + CN_{fp}^{SQ} - \left((D_{TP} + C)N_{tp}^{NewDx} + D_{FN}N_{fn}^{NewDx} + CN_{fp}^{NewDx}\right)$$
$$= (D_{TP} + C)\Delta N_{tp} + D_{FN}\Delta N_{fn} + C\Delta N_{fp}$$

where Δ is the difference between health outcomes in the status quo and health outcomes with the new diagnostic. In our model, for any given access level, the new diagnostic can improve upon the status quo standard of care either through an increase in sensitivity or specificity. Improvements in specificity will reduce the number of false positives, such that $\Delta N_{fp} < 0$. Improvements in sensitivity will both increase the number of true positives and decrease the number of false negatives, making $\Delta N_{tp} < 0$ and $\Delta N_{fn} > 0$. For a given region, adjusted DALYs saved with the introduction of a new diagnostic is the sum of adjusted DALYs saved for each access category.

C. Additional Model Assumptions and Limitations

There are several important limitations to our analysis, in addition to the ones reported in Aledort et al.[4]First, we did not explicitly consider the effect of antimicrobial resistance on the efficacy of treatment. Antimicrobial resistance to *Chlamydia trachomatis* is generally not considered to be clinically significant, but *N. Gonorrhoeae* is an example of widespread resistance that has forced the use of newer, more expensive antibiotics as primary treatment. Quinolone antibiotics such as ciprofloxacin have been used extensively for treatment of gonorrhoea worldwide since the mid-1980s, particularly in developing countries where ciprofloxacin is the least expensive of the highly effective drugs available. [19, 20] Nonetheless, clinical quinolone-resistance to *N. gonorrhoeae* was documented almost immediately,[21] and over the last few decades it has become well-established in several areas.[19, 20, 22-30] Currently, broad-spectrum cephalosporins such as cefixime and ceftriaxone are the only agents to which *N. gonorrhoeae* remains fully susceptible. Although we did not explicitly consider the effect of antimicrobial resistance

on the efficacy of treatment, our estimation of *C*, the harm associated with treatment, accounts for potential downstream loss of efficacy.

Second, there are some important limitations to our approach of estimating downstream NG/Ct and HIV infections averted from Vickerman et al. First, contrary to our static decision tree model, in which we assume a treatment rate of 80 percent, Vickerman et al. assume all women who test positive will receive treatment. However, varying this assumption is equivalent to varying sensitivity, so Vickerman and colleagues adequately capture our base case assumption. Second, although the authors estimated outcomes for a fairly concentrated HIV epidemic in Benin and a more generalized HIV epidemic in Hillbrow, in our model, we elected to use the more conservative estimates from Hillbrow, where NG/Ct treatment has less affect on transmission. Third, for lack of better information, we made the simplifying assumption that outcomes attributed to CSWs in Hillbrow applied uniformly to our population of high-risk women in sub Saharan Africa, China and Southeast Asia, even though the HIV epidemic in China and Southeast Asia may not approximate the epidemic characterized by Vickerman and colleagues. Finally, since Vickerman et al. estimated downstream cases of NG/Ct and HIV averted over a four year time horizon, the multipliers we used in our model may underestimate the potential effect on NG/Ct and HIV incidence over a longer time period.

Finally, we did not explicitly distinguish between symptomatic and asymptomatic infections in the model. However, in determining the proportion of high risk women attending a clinic, the HIV/STI experts recognized that the majority of women who present to a clinic do so because of genitourinary symptoms including vaginal discharge and lower abdominal pain. A minority will present to a clinic due to partner contact referral. Because the majority of women who present to a clinic do so because of genitourinary symptoms, it is also reasonable to assume that the proportion receiving clinical evaluation upon arrival is substantial. Although it stands to reason that women with symptoms have a higher probability of testing positive, we assumed that prevalence of disease was independent of symptoms.

D. SUPPLEMENTARY ANALYSES

Tables 4, 5 and 6 present the incremental health benefits of a hypothetical new diagnostic for gonorrhoea and chlamydia screening in CSWs relative to the current diagnostic standard of care (status quo). Here we present separate regional results for sub-Saharan Africa, China and Southeast Asia, our three areas of interest. We report incremental outcomes relative to the status quo in terms of in terms of disability-adjusted life years (DALYs) saved by treating the source case and by preventing downstream cases due to transmission. DALYs saved are also further adjusted to account for the harm of treatment. Finally, we report the number of HIV infections that could be averted with appropriate gonorrhoea and chlamydia diagnosis and treatment as a secondary outcome.

In the tables, each row corresponds to a particular potential new diagnostic defined by infrastructure requirements (moderate, minimal and no infrastructure), sensitivity, and specificity. The level of infrastructure determines the probability that a woman has access to the new test, and this differs across regions. For example, in Africa, a test which requires moderate to advanced infrastructure (e.g., requires refrigeration/electricity, water, nurses or well-trained technicians) would be available only to 28.4% of women. However, if the test only requires minimal infrastructure an additional 47.3% of the people would have access to it, for a total of 75.5%. In both China and Southeast Asia, 87% of women have access to a test requiring moderate infrastructure.

For each level of infrastructure we present several combinations of sensitivity and specificity for the new diagnostic. The first two rows replicate the estimated sensitivity and specificity of clinical evaluation alone and clinical evaluation combined with a lab test, respectively. We then consider several improvements over these base-case performance characteristics.

Table 4. Incremental Gonorrhoea, Chlamydia and HIV Cases Averted and Adjusted DALYs Saved in Sub-Saharan Africa with a Hypothetical New Diagnostic Relative to Status Quo Tests

	Test	Sensitivity	Specificity	Adjusted DALYs Saved* *(SD)*	Gonorrhoea and Chlamydia Cases Averted *(SD)*	HIV Cases Averted *(SD)*	Proportion of Adjusted DALYs Saved†
Advanced/Moderate Infrastructure‡							
1	Clinical Evaluation	45%	70%	130,519	506,182	6,453	3%
				(68,394)	*(180,412)*	*(2,703)*	
2	Lab + Clinical Evaluation	67%	61%	333,507	1,174,220	14,970	8%
				(253,354)	*(618,646)*	*(8,572)*	
3	More Specific Test§	67%	75%	427,063	1,174,220	14,970	10%
				(276,304)	*(510,928)*	*(7,879)*	
4	More Sensitive Test‖	85%	70%	614,981	1,740,744	22,192	15%
				(231,282)	*(610,235)*	*(8,822)*	
5	Overall Better Test1	85%	90%	748,631	1,740,744	22,192	18%
				(192,391)	*(591,760)*	*(8,860)*	
6	Overall Better Test2¶	96%	98%	937,349	2,086,953	26,606	23%
				(267,347)	*(529,724)*	*(7,921)*	
7	Perfect Test	100%	100%	999,899	2,212,848	28,211	25%
				(242,804)	*(435,326)*	*(5,885)*	
Minimal Infrastructure‡							
8	Clinical Evaluation	45%	70%	689,033	2,701,575	34,442	17%
				(450,164)	*(999,360)*	*(13,401)*	
9	Lab + Clinical Evaluation	67%	61%	1,242,395	4,522,831	57,661	31%
				(1,015,999)	*(1,843,651)*	*(16,519)*	
10	More Specific Test§	67%	75%	1,491,767	4,522,831	57,661	37%
				(598,418)	*(1,812,329)*	*(25,769)*	
11	More Sensitive Test‖	85%	70%	1,992,661	6,032,898	76,912	49%
				(726,628)	*(1,766,776)*	*(22,291)*	
12	Overall Better Test1	85%	90%	2,348,906	6,032,898	76,912	58%
				(901,658)	*(1,676,896)*	*(25,810)*	
13	Overall Better Test2¶	96%	98%	2,851,933	6,955,717	88,677	70%
				(693,171)	*(1,442,332)*	*(17,758)*	
14	Perfect Test	100%	100%	3,018,659	7,291,288	92,955	74%
				(981,138)	*(1,622,465)*	*(15,071)*	

Table 4. Continued

	Test	New Diagnostic Sensitivity	New Diagnostic Specificity	Adjusted DALYs Saved* *(st.dev.)*	Gonorrhoea and Chlamydia Cases Averted *(SD)*	HIV Cases Averted *(st. dev.)*	Proportion of Adjusted DALYs Saved†
No infrastructure *(Universal Access)*							
15	Clinical Evaluation	45%	70%	990,944	3,913,419	49,891	24%
				(397,387)	*(685,373)*	*(13,291)*	
16	Lab + Clinical Evaluation	67%	61%	1,724,308	6,327,132	80,663	42%
				(819,143)	*(1,280,158)*	*(19,424)*	
17	More Specific Test§	67%	75%	2,053,729	6,327,132	80,663	50%
				(748,979)	*(1,631,228)*	*(16,086)*	
18	More Sensitive Test‖	85%	70%	2,715,412	8,321,937	106,095	67%
				(1,006,116)	*(2,534,632)*	*(39,887)*	
19	Overall Better Test1	85%	90%	3,186,013	8,321,937	106,095	78%
				(1,295,185)	*(3,132,638)*	*(54,032)*	
20	Overall Better Test2¶	96%	98%	3,850,513	9,540,984	121,636	95%
				(747,239)	*(1,861,189)*	*(24,590)*	
21	Perfect Test	100%	100%	4,070,758	9,984,274	127,288	100%
				(1,207,455)	*(915,428)*	*(29,234)*	

*Adjusted DALYs saved includes those saved from appropriate treatment of the index case, and those saved from preventing transmission and subsequent downstream cases. This measure also includes an adjustment to capture the harm associated with treatment. HIV transmission is not included in this primary outcome measure, but instead is reported separately. †The proportion of adjusted DALYs saved is calculated by dividing the adjusted DALYs saved with any given individual test by the adjusted DALYs saved by a test that is 100% sensitive, 100% specific and universally accessible (test 21). ‡A test can be performed in a setting with advanced/moderate infrastructure if electricity and water are available, and a laboratory is at least minimally equipped (for example, in African hospitals). Staff requirements include nurses, a physician and a technician with minimal training. A test can be performed in a setting with minimal infrastructure if is does not require water or electricity and can be performed at a clinic with minimal training. See Girosi et al.[18] for more detailed information on calculating the percentage of people with access to a new diagnostic requiring moderate, minimal or no infrastructure. §Relative to laboratory test + clinical evaluation. ‖Relative to clinical evaluation. ¶In terms of sensitivity and specificity, this overall better test is an approximation of currently available NAAT test technology in the developed world that requires the equivalent of advanced infrastructure in resource-limited settings. DALYs, disability-adjusted life years; HIV, human immunodeficiency virus; NAAT, nucleic-acid amplification tests; SD, standard deviation.

Table 5. Incremental Gonorrhoea, Chlamydia and HIV Cases Averted and Adjusted DALYs Saved in China with a Hypothetical New Diagnostic Relative to Status Quo Tests

	Test	Sensitivity	Specificity	Adjusted DALYs Saved* *(SD)*	Gonorrhoea and Chlamydia Cases Averted *(SD)*	HIV Cases Averted *(SD)*	Proportion of Adjusted DALYs Saved†
Advanced/Moderate Infrastructure‡							
1	Clinical Evaluation	45%	70%	15,585 *(30,059)*	220,588 *(517,904)*	2,812 *(8,284)*	3%
2	Lab + Clinical Evaluation	67%	61%	79,939 *(111,501)*	2,017,971 *(1,491,680)*	25,727 *(20,022)*	14%
3	More Specific Test§	67%	75%	112,770 *(91,803)*	2,017,971 *(1,091,356)*	25,727 *(12,007)*	19%
4	More Sensitive Test‖	85%	70%	179,360 *(106,163)*	3,723,852 *(1,749,514)*	47,475 *(19,907)*	31%
5	Overall Better Test1	85%	90%	226,261 *(122,703)*	3,723,852 *(1,941,214)*	47,475 *(19,575)*	39%
6	Overall Better Test2¶	96%	98%	292,881 *(140,236)*	4,766,334 *(2,392,863)*	60,765 *(33,589)*	50%
7	Perfect Test	100%	100%	314,974 *(82,910)*	5,145,419 *(1,624,179)*	65,598 *(30,391)*	54%
Minimal Infrastructure‡							
8	Clinical Evaluation	45%	70%	40,695 *(38,469)*	575,980 *(693,040)*	7,343 *(9,306)*	7%
9	Lab + Clinical Evaluation	67%	61%	142,355 *(80,328)*	3,415,846 *(3,482,712)*	43,548 *(47,463)*	24%
10	More Specific Test§	67%	75%	191,601 *(84,744)*	3,415,846 *(955,610)*	43,548 *(22,371)*	33%
11	More Sensitive Test‖	85%	70%	291,486 *(191,174)*	5,974,666 *(3,219,359)*	76,170 *(46,371)*	50%
12	Overall Better Test1	85%	90%	361,838 *(118,655)*	5,974,666 *(2,242,128)*	76,170 *(34,223)*	62%
13	Overall Better Test2¶	96%	98%	461,767 *(217,511)*	7,538,390 *(2,663,632)*	96,106 *(40,006)*	79%
14	Perfect Test	100%	100%	494,907 *(216,669)*	8,107,017 *(3,508,148)*	103,355 *(40,863)*	84%

Table 5. Continued

	Test	New Diagnostic Sensitivity	New Diagnostic Specificity	Adjusted DALYs Saved* *(st.dev.)*	Gonorrhoea and Chlamydia Cases Averted *(SD)*	HIV Cases Averted *(st. dev.)*	Proportion of Adjusted DALYs Saved†
No infrastructure *(Universal Access)*							
15	Clinical Evaluation	45%	70%	63,623	1,286,763	16,405	11%
				(41,834)	*(880,036)*	*(13,196)*	
16	Lab + Clinical Evaluation	67%	61%	182,007	4,593,949	58,567	31%
				(218,573)	*(4,306,745)*	*(79,329)*	
17	More Specific Test§	67%	75%	238,611	4,593,949	58,567	41%
				(139,051)	*(1,986,742)*	*(30,972)*	
18	More Sensitive Test‖	85%	70%	353,422	7,535,122	96,064	60%
				(224,903)	*(2,603,768)*	*(42,657)*	
19	Overall Better Test1	85%	90%	434,285	7,535,122	96,064	74%
				(167,271)	*(2,822,100)*	*(49,541)*	
20	Overall Better Test2¶	96%	98%	549,147	9,332,505	118,978	94%
				(172,222)	*(3,163,056)*	*(41,738)*	
21	Perfect Test	100%	100%	587,239	9,986,099	127,311	100%
				(223,560)	*(3,903,492)*	*(59,242)*	

*Adjusted DALYs saved includes those saved from appropriate treatment of the index case, and those saved from preventing transmission and subsequent downstream cases. This measure also includes an adjustment to capture the harm associated with treatment. HIV transmission is not included in this primary outcome measure, but instead is reported separately. †The proportion of adjusted DALYs saved is calculated by dividing the adjusted DALYs saved with any given individual test by the adjusted DALYs saved by a test that is 100% sensitive, 100% specific and universally accessible (test 21). ‡A test can be performed in a setting with advanced/moderate infrastructure if electricity and water are available, and a laboratory is at least minimally equipped. Staff requirements include nurses, a physician and a technician with minimal training. A test can be performed in a setting with minimal infrastructure if is does not require water or electricity and can be performed at a clinic with minimal training. See Girosi et al.[18] for more detailed information on calculating the percentage of people with access to a new diagnostic requiring moderate, minimal or no infrastructure. §Relative to laboratory test + clinical evaluation. ‖Relative to clinical evaluation. ¶In terms of sensitivity and specificity, this overall better test is an approximation of currently available NAAT test technology in the developed world that requires the equivalent of advanced infrastructure in resource-limited settings. DALYs, disability-adjusted life years; HIV, human immunodeficiency virus; NAAT, nucleic-acid amplification tests; SD, standard deviation.

Table 6. Incremental Gonorrhoea, Chlamydia and HIV Cases Averted and Adjusted DALYs Saved in Southeast Asia with a Hypothetical New Diagnostic Relative to Status Quo Tests

	Test	New Diagnostic Sensitivity	New Diagnostic Specificity	Adjusted DALYs Saved* *(st.dev.)*	Gonorrhoea and Chlamydia Cases Averted *(SD)*	HIV Cases Averted *(st. dev.)*	Proportion of Adjusted DALYs Saved†
Advanced/Moderate Infrastructure ‡							
1	Clinical Evaluation	45%	70%	11,669 *(11,761)*	24,307 *(26,956)*	310 *(334)*	3%
2	Lab + Clinical Evaluation	67%	61%	59,161 *(55,262)*	222,362 *(146,106)*	2,835 *(1,784)*	13%
3	More Specific Test§	67%	75%	84,106 *(51,772)*	222,362 *(147,982)*	2,835 *(2,066)*	19%
4	More Sensitive Test‖	85%	70%	133,368 *(45,940)*	410,334 *(95,343)*	5,231 *(2,315)*	30%
5	Overall Better Test1	85%	90%	169,002 *(38,767)*	410,334 *(101,313)*	5,231 *(1,262)*	39%
6	Overall Better Test2¶	96%	98%	218,805 *(34,039)*	525,205 *(92,787)*	6,696 *(2,351)*	50%
7	Perfect Test	100%	100%	235,296 *(46,138)*	566,977 *(62,069)*	7,228 *(1,598)*	54%
Minimal Infrastructure ‡							
8	Clinical Evaluation	45%	70%	30,470 *(22,195)*	63,468 *(55,017)*	809 *(842)*	7%
9	Lab + Clinical Evaluation	67%	61%	105,493 *(92,087)*	376,394 *(239,292)*	4,799 *(3,100)*	24%
10	More Specific Test§	67%	75%	142,909 *(79,340)*	376,394 *(306,189)*	4,799 *(3,267)*	33%
11	More Sensitive Test‖	85%	70%	216,803 *(66,956)*	658,352 *(220,298)*	8,393 *(2,100)*	49%
12	Overall Better Test1	85%	90%	270,255 *(118,843)*	658,352 *(257,698)*	8,393 *(3,477)*	62%
13	Overall Better Test2¶	96%	98%	344,959 *(85,146)*	830,660 *(147,209)*	10,590 *(3,348)*	79%
14	Perfect Test	100%	100%	369,694 *(101,282)*	893,317 *(133,731)*	11,389 *(3,243)*	84%

Table 6. Continued

	Test	New Diagnostic Sensitivity	New Diagnostic Specificity	Adjusted DALYs Saved* *(st.dev.)*	Gonorrhoea and Chlamydia Cases Averted *(SD)*	HIV Cases Averted *(st. dev.)*	Proportion of Adjusted DALYs Saved†
No infrastructure *(Universal Access)*							
15	Clinical Evaluation	45%	70%	47,335	141,789	1,808	11%
				(33,998)	*(97,594)*	*(1,217)*	
16	Lab + Clinical Evaluation	67%	61%	134,700	506,210	6,454	31%
				(66,606)	*(227,288)*	*(3,085)*	
17	More Specific Test§	67%	75%	177,707	506,210	6,454	41%
				(52,701)	*(118,774)*	*(924)*	
18	More Sensitive Test‖	85%	70%	262,642	830,300	10,585	60%
				(161,770)	*(302,356)*	*(5,433)*	
19	Overall Better Test1	85%	90%	324,081	830,300	10,585	74%
				(120,623)	*(245,663)*	*(2,934)*	
20	Overall Better Test2¶	96%	98%	409,948	1,028,355	13,110	94%
				(74,632)	*(166,130)*	*(3,528)*	
21	Perfect Test	100%	100%	438,380	1,100,375	14,028	100%
				(138,732)	*(217,545)*	*(5,145)*	

*Adjusted DALYs saved includes those saved from appropriate treatment of the index case, and those saved from preventing transmission and subsequent downstream cases. This measure also includes an adjustment to capture the harm associated with treatment. HIV transmission is not included in this primary outcome measure, but instead is reported separately. †The proportion of adjusted DALYs saved is calculated by dividing the adjusted DALYs saved with any given individual test by the adjusted DALYs saved by a test that is 100% sensitive, 100% specific and universally accessible (test 21). ‡A test can be performed in a setting with advanced/moderate infrastructure if electricity and water are available, and a laboratory is at least minimally equipped. Staff requirements include nurses, a physician and a technician with minimal training. A test can be performed in a setting with minimal infrastructure if is does not require water or electricity and can be performed at a clinic with minimal training. See Girosi et al.[18] for more detailed information on calculating the percentage of people with access to a new diagnostic requiring moderate, minimal or no infrastructure. §Relative to laboratory test + clinical evaluation. ‖Relative to clinical evaluation. ¶In terms of sensitivity and specificity, this overall better test is an approximation of currently available NAAT test technology in the developed world that requires the equivalent of advanced infrastructure in resource-limited settings. DALYs, disability-adjusted life years; HIV, human immunodeficiency virus; NAAT, nucleic-acid amplification tests; SD, standard deviation.

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