Technical Appendix

An illustration of the potential health and economic benefits of combating antibiotic resistant gonorrhea

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Overview of equation used to estimate the impact of emerging resistance on gonorrhea incidence

We used the following equation to calculate the gonorrhea incidence rate for each year over a ten-year period (Year 1 to Year 10):

$$G_t = \text{Constant} + \beta_1 G_{t-1} + \beta_2 R_t,$$

where G_t is the log of the gonorrhea incidence rate in year t and R_t is the percentage of *N. gonorrhoeae* infections resistant to treatment in year t. This equation is based on the regression equation that was used in a published analysis of historical gonorrhea surveillance data (reported gonorrhea case rates) and ciprofloxacin antimicrobial resistance data from the Gonococcal Isolate Surveillance Project (GISP) in the US.[1]

Description of regression equation used in published analysis of gonorrhea case rates and ciprofloxacin resistance on which our equation is based

The published analysis of historic gonorrhea case rate data and ciprofloxacin resistance used the following regression equation:

$$G_{i,t} = \alpha + \beta_1 G_{i,t-1} + \beta_2 R_{i,t} + \gamma X_{i,t} + C_i + Y_t + \varepsilon_{i,t},$$

where $G_{i,t}$ is the log of the gonorrhea case rate in city *i* in year *t*; α is a constant term; $R_{i,t}$ is the percentage of isolates resistant to ciprofloxacin in the GISP clinic(s) of city *i* in year *t*; $X_{i,t}$ is a vector of sociodemographic variables (percent of population black, percent of population aged 15 to 29 years, unemployment rate, per-capita income, and the robbery rate); C and Y denote city and year dummy variables, respectively; and the error term is denoted by ε.[1]

Our adaptation of published equation

In our adaptation of the regression analysis from the published study, we applied the equation to the nation as a whole, thereby deleting the need for city subscripts (i). To focus on the potential influence of antimicrobial resistance on gonorrhea incidence in a scenario when all other factors were held constant, we assumed that the national gonorrhea incidence rate was at an equilibrium and would be constant over time in the absence of changes to the percentage of *N. gonorrhoeae* infections resistant to treatment. Whereas the original regression model included city dummy variables, year dummy

variables, and demographic variables, in our application of the model we assumed these factors would be fixed over time and could be therefore be subsumed into the constant term.

We combined the city, year and demographic factors (the γX terms) and the original constant term α to yield the new constant term. That is, by setting Constant = α + γX + Ω, where γX reflects the average demographic factors in a given year and Ω represents the average city and trend effects in a given year (C and Y, respectively), , the original regression equation was reduced to the simpler form of the equation we applied: $G_t = \text{Constant} + \beta_1 G_{t-1} + \beta_2 R_t$.

Values for β_1 and β_2 in the published study were 0.553 and 0.710, respectively. We assumed that in the absence of emerging resistance, there would be 820,000 incident *N. gonorrhoeae* infections annually[2] and that the percentage of *N. gonorrhoeae* infections resistant to treatment would be 2%. The 820,000 value we applied reflects the estimated actual annual incidence of gonorrhea (reported plus unreported cases), not just reported cases.[2] Assuming a population size of about 318.86 million, the 820,000 incident *N. gonorrhoeae* infections would correspond to a rate of 257.17 per 100,000. The value of Constant was thus calculated as 2.47, by rearranging the equation above to Constant = $G_t - \beta_1 G_{t-1} - \beta_2 R_t$, assuming a fixed value of 0.02 for R_t, and assuming that the gonorrhea incidence rate would be 257.17 per 100,000 if R_t were held fixed at 0.02 for all years.

Example of calculations: Scenario of no emerging resistance

In Year 0, the gonorrhea incidence rate was assumed to be 257.17 per 100,000, and the natural log of the gonorrhea rate was thus 5.55. For Year 1, the log of the gonorrhea incidence rate (G_1) was calculated as $G_1 = \text{Constant} + \beta_1 G_0 + \beta_2 R_t$, or $G_1 = 2.47 + (0.553)(5.55) + (0.710)*(0.02)$, or $G_1 = 5.55$. For Year 2, the log of the gonorrhea incidence rate (G1) was calculated as $G_2 = \text{Constant} + \beta_1 G_1 + \beta_2 R_2$, or $G_2 = 2.47 + (0.553)(5.55) + (0.710)*(0.02)$, or G1 = 5.55. An analogous process was used for the remaining years (Year 3 through Year 10), and in each year the natural log of the gonorrhea incidence rate was 5.55, which corresponds to a gonorrhea incidence rate of 257 per 100,000.

Example of calculations: Scenario of emerging resistance

In the scenario of emerging resistance, the percentage of *N. gonorrhoeae* infections resistant to treatment in year t (R_t) was assumed to increase linearly from 2% in Year 0 to 15% in Year 6, and to remain at 15% through Year 10. Thus, R_t was calculated as 4.17% in Year 1, 6.33% in Year 2, 8.50% in Year 3, 10.67% in Year 4, 12.83% in Year 5.

As in the scenario of no emerging resistance, for Year 0, the gonorrhea incidence rate was assumed to be 257.17 per 100,000, and the natural log of the gonorrhea rate was thus 5.55.

For Year 1, the natural log of the gonorrhea incidence rate (G1) was calculated as $G_1 = \text{Constant} + \beta_1 G_0 + \beta_2 R_t$, or $G_1 = 2.47 + (0.553)(5.55) + (0.710)*(0.0417)$, or G1 = 5.569. The value of 5.569 for the log corresponds to a value of 262.1 for the gonorrhea incidence rate, which corresponds to 835,627 *N. gonorrhoeae* infections.

For Year 2, the log of the gonorrhea incidence rate (G_2) was calculated as $G_2 = \text{Constant} + \beta_1 G_1 + \beta_2 R_2$, or $G_2 = 2.47 + (0.553)(5.569) + (0.710)*(0.0633)$, or $G_2 = 5.594$. The value of 5.594 for the log corresponds to a value of 268.9 for the gonorrhea incidence rate, which corresponds to 857,463 *N. gonorrhoeae* infections.

An analogous process was used for the remaining years (Year 3 through Year 10),

Lifetime medical cost estimates

Lifetime medical costs per *N. gonorrhoeae* infection

The discounted lifetime cost per *N. gonorrhoeae* infection that we applied represents the average lifetime cost per new infection, discounted to the time of infection. It accounts for the fact that many infections are asymptomatic and remain untreated, and includes the possibility of sequelae costs in the future among those not treated or not effectively treated.[3] We applied $86 and $383 for the lifetime medical costs per infection in males and females, respectively.[3] These values were obtained from Owusu-Edusei and colleagues, who estimated the lifetime cost per infection at $79 and $354 for males and females, respectively, in 2010 dollars.[3]

In calculating the costs of emerging resistance, we assumed that 57% of infections would occur in males.[2]

Lifetime medical costs per HIV infection

The discounted lifetime cost per HIV infection that we applied represents the average lifetime cost per new infection, discounted to the time of infection. We obtained these estimates from a published study of the lifetime cost of HIV by Farnham and colleagues,[4] which accounted for factors such as the average time from infection to treatment, the average CD4 count at diagnosis, treatment uptake and adherence, treatment costs, survival probabilities, and the cost of AIDS-related opportunistic infections.

We applied $351,000 as the lifetime medical cost per new HIV infection (range: $269,000 to $427,000). Farnham and colleagues provided lifetime cost estimates based on CD4 count (cells/mL) at the time of diagnosis.[4] The base case value we applied was obtained from their weighted average of these estimates ($330,000 in 2011 dollars). The lower bound value we applied was obtained from their estimate of $253,000 (in 2011 dollars) for CD4 count ≤ 200 at time of diagnosis. The upper bound value we applied was obtained from their estimate of $402,000 (in 2011 dollars) for CD4 count > 500 at time of diagnosis.

The antiretroviral regimens than Farnham and collegues included in their source analysis[5] on which the above estimates were based were: (1) efavirenz/tenofovir/emtricitabine; (2) atazanavir/ritonavir + abacavir/lamivudine; (3) raltegravir + tenofovir/emtricitabine; and (4) salvage therapy.

Discounting

The published lifetime cost estimates we applied represent the expected lifetime medical costs per new infection, discounted to the time of infection. We multiplied the number of outcomes averted in year t by the estimated, discounted lifetime medical cost. This yielded the lifetime medical costs of the outcomes that occurred in year t, discounted to year t. In order to discount these averted medical costs to Year 1, we discounted these costs by an additional t- 1 years.

Gonorrhea-attributable HIV infections

The average number of gonorrhea-attributable HIV infections per each new *N. gonorrhoeae* infection has been estimated at 0.0007.[6] However, It has been recommended that those who apply this estimate in assessing the benefits of preventing gonorrhea should adjust the estimate downward to account for a range of factors that might otherwise result in overestimation, such as partner overlap, reductions in the probability of HIV transmission due to antiretroviral therapy among those with HIV and pre-exposure prophylaxis among those at risk for HIV, and the possibility that an estimated HIV infection averted might actually be delayed rather than permanently averted.[7] Specific adjustment factors of 75% and 12.5% have been suggested for heterosexuals and MSM, respectively.[7] For this exercise, we used the average of these two adjustment factors, or 43.75%. When multiplied by 43.75% and rounded to the nearest multiple of 0.0005, the resulting estimated number of gonorrhea-attributable HIV infections per new *N. gonorrhoeae* infection is 0.0005.

Probabilistic sensitivity analyses

In addition to the one-way sensitivity analyses, we also performed a probabilistic sensitivity analysis in which all seven parameters (Table 1 in the main text) were varied simultaneously. Specifically, we ran the model 10,000 times, each time selecting a random value for each of the seven parameters according to the following assumptions.

For the 3 lifetime cost parameters (lifetime cost per *N. gonorrhoeae* infection in men, lifetime cost per *N. gonorrhoeae* infection in women, and lifetime cost per HIV infection), we used the lognormal distribution. The use of the lognormal distribution for cost parameters is a common practice in health economic studies because cost estimates cannot be negative and cost estimates are typically right-skewed.[8] Following the methods described elsewhere,[8] the parameters of the lognormal distribution we applied (μ and σ, respectively) were (4.42, 0.25) for the cost of gonorrhea in males, (5.92, 0.25) for the cost of gonorrhea in females, and (12.75, 0.12) for the cost of HIV.

Due to a lack of evidence to inform the distribution assumptions for the remaining 4 parameters (annual number of *N. gonorrhoeae* infections, peak percentage of *N. gonorrhoeae* infections resistant to ceftriaxone in the scenario of emerging resistance, and the probability of a gonorrhea-attributable HIV infection), we assumed that each of these parameters was distributed uniformly between its lower and upper bound value.

References

1. Chesson HW, Kirkcaldy RD, Gift TL, Owusu-Edusei K, Jr., Weinstock HS. Ciprofloxacin resistance and gonorrhea incidence rates in 17 cities, United States, 1991-2006. *Emerg Infect Dis.* 2014;20(4):612-619.
2. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections smong US women and men: prevalence and incidence estimates, 2008. *Sex Transm Dis.* 2013;40(3):187-193.
3. Owusu-Edusei K, Jr., Chesson HW, Gift TL, et al. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. *Sex Transm Dis.* 2013;40(3):197-201.
4. Farnham PG, Holtgrave DR, Gopalappa C, Hutchinson AB, Sansom SL. Lifetime costs and quality-adjusted life years saved from HIV prevention in the test and treat era. *J Acquir Immune Defic Syndr.* 2013;64(2):e15-e18.
5. Farnham PG, Gopalappa C, Sansom SL, et al. Updates of lifetime costs of care and quality-of-life estimates for HIV-infected persons in the United States: late versus early diagnosis and entry into care. *J Acquir Immune Defic Syndr.* 2013;64(2):183-189.
6. Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. *J Acquir Immune Defic Syndr.* 2000;24(1):48-56.
7. Chesson HW, Collins D, Koski K. Formulas for estimating the costs averted by sexually transmitted infection (STI) prevention programs in the United States. *Cost Eff Resour Alloc.* 2008;6:10.
8. Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. *Vaccine.* 2010;28(42):6858-6867.