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# An Illustration of the Potential Health and Economic Benefits of Combating Antibiotic-Resistant Gonorrhea

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## Abstract

Preventing the emergence of ceftriaxone-resistant *Neisseria gonorrhoeae* can potentially avert hundreds of millions of dollars in direct medical costs of gonorrhea and gonorrhea-attributable HIV infections. In the illustrative scenario we examined, emerging ceftriaxone resistance could lead to 1.2 million additional *N. gonorrhoeae* infections within 10 years, costing $378.2 million.

Gonococcal resistance to treatment may increase gonorrhea incidence rates through factors such as increased duration of infection.[1–3] One of the targets of the National Strategy for Combating Antibiotic-Resistant Bacteria is to maintain the prevalence of ceftriaxone resistance at less than 2% of *Neisseria gonorrhoeae* infections.[4] Achieving this target could yield substantial health and economic benefits by preventing increases in the incidence of gonorrhea. To provide a plausible example of these potential benefits, we performed a modeling exercise of an illustrative scenario of increased gonorrhea incidence in the United States caused by emerging cephalosporin resistance. We focused on the potential benefits of preventing emerging resistance, not on the cost-effectiveness (costs and benefits) of activities to prevent emerging resistance.

We estimated the increased health and economic burden of ceftriaxone-resistant *N. gonorrhoeae* in a scenario in which the emergence of ceftriaxone resistance was assumed to have an impact on gonorrhea incidence consistent with the impact estimated for the emergence of ciprofloxacin resistance during the late 1990s and 2000s. In our approach, the gonorrhea incidence rate in a given year was calculated based on (1) the percentage of *N. gonorrhoeae* infections resistant to treatment in the given year and (2) the gonorrhea incidence rate in the previous year. To focus on the potential influence of antimicrobial resistance on gonorrhea incidence, we assumed that the national gonorrhea incidence rate would be constant over time in the absence of changes to the percentage of *N. gonorrhoeae* infections resistant to treatment. Specifically, we used the following equation:

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

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 recent analysis of historical gonorrhea surveillance data and ciprofloxacin antimicrobial resistance data in the United States.[1] The values 0.553 and 0.71 were applied for $\beta_1$ and $\beta_2$ (Table 1), respectively, based the previous analysis from which we obtained the model equation.[1] Although the original regression model included a range of demographic variables as well as city and year variables, in our application of the model, we assumed that these factors would be fixed over time and could be therefore be subsumed into the CONSTANT term. The CONSTANT term was assigned a value of 2.47 so that our equation would yield a steady gonorrhea incidence rate over time in the scenario of no emerging resistance (see Appendix, http://links.lww.com/OLQ/A201).

We assumed that the annual number of *N. gonorrhoeae* infections (reported cases plus unreported infections) in the absence of emerging resistance would be 820,000 for the entire United States, based on a published estimate of annual incidence.[5] The lower bound (395,000) reflects the approximate number of reported gonorrhea cases in 2015,[10] and the upper bound (1,245,000) was calculated such that the base case would be the midpoint of the lower and upper bounds.

We estimated gonorrhea incidence during a 10-year period, for 2 scenarios. We assumed that prevalence of resistance would be at 2% of *N. gonorrhoeae* infections at the start of each scenario, for clarity and ease of interpretation of the results in terms of the benefits of maintaining prevalence of resistance at 2% or lower. In scenario 1, the prevalence of resistance was assumed to remain at 2% of *N. gonorrhoeae* infections and the annual incidence of *N. gonorrhoeae* infections was 820,000 for all years (year 1 through year 10). In scenario 2 (the “emerging resistance” scenario), the prevalence of resistance was assumed to increase linearly from 2% in year 0 to 15% in year 6 and remain at 15% through year 10. This assumption of the increase in resistance in years 1 to 6 is consistent with historical data on the emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the 1990s.[11]

We calculated the costs of scenario 2 compared with scenario 1. We included the direct lifetime medical costs (2016 US dollars) of *N. gonorrhoeae* infections and gonorrhea-attributable HIV infections. The discounted lifetime cost per gonococcal infection was $86 for male individuals and $383 for female individuals. These lifetime cost estimates per infection account for the possibility that the infection might not be treated and include potential sequelae costs (Table 1).[6] We assumed that male individuals account for 57% of *N. gonorrhoeae* infections.[5] We also assumed that each *N. gonorrhoeae* infection would have a 0.0005 probability of resulting in a gonorrhea-attributable HIV infection.[8,9] We applied a lifetime cost per HIV infection of $351,000, which accounts for factors such as the average time from infection to initiation of treatment, the average CD4 count at diagnosis, and treatment uptake and cost.[7]

We conducted 1-way sensitivity analyses in which the 7 key parameters listed in Table 1 were varied one at a time, from their lower-bound value to their upper-bound value, while holding all other parameters at their base case values. The lower- and upper-bound values we applied are listed in the "range" column of Table 1. We also performed a probabilistic sensitivity analysis in which all 7 parameters were varied simultaneously. Specifically, we ran the model 10,000 times, each time selecting a random value for each of the 7 parameters (see Appendix, http://links.lww.com/OLQ/A201).

Compared with a scenario in which the prevalence of ceftriaxone resistance is maintained at 2% of *N. gonorrhoeae* infections (scenario 1), gonorrhea rates in the scenario of emerging resistance (scenario 2) were estimated to be 2% higher in year 1, 14% higher in year 5, and 22% higher in year 10. During a 10-year period, there would be a total of 1.2 million additional *N. gonorrhoeae* infections (at a cost of $207.7 million) and 579 gonorrhea-attributable HIV infections (at a cost of $170.5 million), for a total cost of $378.2 million (Table 2).

In the 1-way sensitivity analyses, the cumulative number of additional *N. gonorrhoeae* infections within 10 years ranged from 250,300 to 1,879,300 and the cumulative, additional costs ranged from $81.9 million to $613.7 million (Table 3). The lower values were obtained when applying the lower-bound value of 5% for peak ceftriaxone resistance, and the higher values were obtained when applying the upper-bound value of the $\beta_2$ parameter, which reflects the impact of resistance on gonorrhea incidence. The cumulative number of additional HIV infections ranged from 58 to 1157, when applying the lower- and upper-bound values, respectively, of the probability of gonorrhea-attributable HIV infection. In the multiway probabilistic sensitivity analysis, the 5th and 95th percentiles of results of the 10,000 simulations ranged from 172,300 to 2,558,000 for the cumulative number of additional *N. gonorrhoeae* infections, 20 to 2160 for the cumulative number of additional gonorrhea-attributable HIV infections, and $41 million to $1099 million for the cumulative additional costs (Table 3).

Substantial health and economic losses can be averted by maintaining the prevalence of ceftriaxone-resistant *N. gonorrhoeae* lower than 2%, particularly if ceftriaxone resistance emerges at a rate similar to the rate of ciprofloxacin resistance, if emerging resistance contributes to increased gonorrhea incidence, and if gonorrhea facilitates HIV acquisition and transmission to the extent that we assumed. The possibility of increased gonorrhea incidence due to emerging resistance has been illustrated by complex mathematical models[2,3] as well as a recent ecological analysis of historical gonorrhea incidence and ciprofloxacin resistance data[1] on which our model is based.

Our estimates are subject to considerable uncertainty. We illustrated the possible health and economic burden of emerging resistance in a scenario in which the impact of emerging cephalosporin resistance was assumed to be similar to the impact estimated for emerging ciprofloxacin resistance in the 1990s and 2000s. The main benefit of this simple approach is that we could estimate the cost and health effects of emerging cephalosporin resistance by using a published, ecological analysis of the association between emerging ciprofloxacin resistance and increased gonorrhea incidence. This approach precludes the need for a

dynamic transmission model and associated assumptions regarding the effect of cephalosporin resistance on factors such as treatment efficacy and duration of infection. The main limitation of this simple approach is that ciprofloxacin resistance and cephalosporin resistance might differ in many ways (including the rate at which resistance increases), and the potential effect of cephalosporin resistance on gonorrhea incidence rates might differ substantially from that of ciprofloxacin resistance.[1,12] Even if ciprofloxacin resistance and cephalosporin resistance do not differ, our approach is based on data from the 1990s and does not account for changes in sexual risk behavior, testing frequencies, awareness of antimicrobial resistance, and other factors. Given this considerable uncertainty, we note that the health and economic burden of emerging resistance could be substantially higher or lower than suggested by the particular scenario we examined. Furthermore, because the lower- and upper-bound values we applied in the sensitivity analyses for an influential model parameter (the impact of resistance on gonorrhea incidence; $\beta_2$) were based on the ciprofloxacin study, the range of results generated in our sensitivity analyses likely underestimates the true degree of uncertainty in the potential effects of emerging resistance. Another limitation is that the regression equation in the ciprofloxacin study on which our model is based included demographic and other factors, whereas we assumed that any influence of these factors on gonorrhea incidence rates would be constant over time and thus did not explicitly include these factors in our model.

Other model assumptions are subject to uncertainty as well, particularly the estimate of the probability of a gonorrhea-attributable HIV infection per *N. gonorrhoeae* infection. The estimate we applied is based on a simple and dated approximation,[8] whereas a dynamic transmission model with both HIV and gonorrhea would be needed to generate more reliable estimates of the number of gonorrhea-attributable HIV infections. Furthermore, more information on the current effect of gonorrhea on HIV acquisition and transmission is needed, given that the probability of gonorrhea-attributable HIV infection may have decreased over time with the availability of antiretroviral therapy for those with HIV and preexposure prophylaxis for those at risk for acquiring HIV.[13,14] For these reasons, we included in Table 2 the “cost of additional *N. gonorrhoeae* infections” and the “cost of additional gonorrhea-attributable HIV infections” so that readers can see these 2 cost components separately. We also note that we did not include the possibility that the average treatment cost per case of gonorrhea might increase over time in a scenario of emerging resistance, perhaps due to more intensive treatment regimens. Another important clarification is that our analysis is not a cost-effectiveness analysis, because we assessed only the benefits and not the costs of preventing the emerging of resistance. The costs to develop, implement, and maintain programs to keep the prevalence of ceftriaxone resistance at less than 2% of *N. gonorrhoeae* infections were not included in this study.

Despite these limitations, our model provides a useful illustration of the possible health and economic costs of ceftriaxone-resistant *N. gonorrhoeae*. Future studies could address the cost-effectiveness of efforts to prevent emerging resistance, which would require estimates of the costs and benefits of such activities. However, whatever the costs might be to combat antibiotic-resistant gonorrhea, our results illustrate the possibility that these costs can be offset, at least in part, by averting the costs of emerging resistance. Complex mathematical models of gonorrhea have been developed to help understand the development and spread of

antibiotic resistance, and these models can be valuable tools to inform strategies to combat resistance.[2,15–17] Preventing the emergence of ceftriaxone-resistant *N. gonorrhoeae* in accordance with the National Strategy for Combating Antibiotic-Resistant Bacteria targets can potentially avert hundreds of millions of dollars in direct medical costs of gonorrhea and gonorrhea-attributable HIV infections.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1.**

Model Parameters and Cost Assumptions: Base Case Value and Range

| Parameter | Base Case Value | Range |
|---|---|---|
| No. *N. gonorrhoeae* infections annually, year 0[5] | 820,000 | 395,000–1,245,000 |
| Peak % of *N. gonorrhoeae* infections resistant to ceftriaxone (assumption) | 15% | 5%–20% |
| Model input ($\beta_2$) for the impact of resistance on gonorrhea incidence[1] | 0.71 | 0.32–1.1 |
| Average lifetime cost per *N. gonorrhoeae* infection in male individuals[6] | $86 | $43–$129 |
| Average lifetime cost per *N. gonorrhoeae* infection in female individuals[6] | $383 | $192–$575 |
| Average lifetime cost per HIV infection (both sexes)[7] | $351,000 | $269,000–$427,000 |
| Probability of gonorrhea-attributable HIV infection[8,9] | 0.0005 | 0.00005–0.001 |

Costs were updated to 2016 US dollars using the health care component of the personal consumption expenditures index. For the number of *N. gonorrhoeae* infections annually, the lower bound reflects the approximate number of cases reported in 2015,[10] the base case reflects estimated incidence (all incident infections, not just reported cases) in 2008,[5] and the upper bound was calculated such that the base case would be the midpoint of the lower and upper bounds. The lifetime cost estimates per infection that we applied for gonorrhea account for the possibility an infection might not be treated, include the costs of treatment (medication cost and physician cost) among those who are treated, and include the possibility of sequelae costs in the future. The average lifetime cost per N. gonorrhoeae infection was calculated assuming that 57% of infections occur in male individuals.[5] For the model equation $G_t = \text{CONSTANT} + \beta_1 G_{t-1} + \beta_2 R_t$, the value of $\beta_1$ was 0.553[1] and the value of CONSTANT was 2.47. The 2.47 value for CONSTANT was calculated so that $G_t$ would be constant over time if $R_t$ was set to 0.02, assuming a population size of approximately 318 million (see Appendix, http://links.lww.com/OLQ/A201).

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**Table 2.**

Base Case Results: Estimated Number of Additional *N. Gonorrhoeae* Infections and Gonorrhea-Attributable HIV Infections, and Estimated Additional Costs in a Scenario of Emerging Ceftriaxone Resistance

| Year | Additional Number of *N. gonorrhoeae* Infections | Cost of Additional *N. gonorrhoeae* Infections, $ Million | Additional Number of Gonorrhea-Attributable HIV Infections | Cost of Additional Gonorrhea-Attributable HIV Infections, $ Million | Total Additional Costs, $ Million |
|---|---|---|---|---|---|
| Year 1 | 12,700 | 2.7 | 6 | 2.2 | 4.9 |
| Year 2 | 32,800 | 6.8 | 16 | 5.6 | 12.4 |
| Year 3 | 57,600 | 11.6 | 29 | 9.5 | 21.1 |
| Year 4 | 85,400 | 16.7 | 43 | 13.7 | 30.4 |
| Year 5 | 115,400 | 21.9 | 58 | 18.0 | 39.9 |
| Year 6 | 147,200 | 27.1 | 74 | 22.3 | 49.4 |
| Year 7 | 165,300 | 29.6 | 83 | 24.3 | 53.9 |
| Year 8 | 175,400 | 30.5 | 88 | 25.0 | 55.5 |
| Year 9 | 181,000 | 30.5 | 91 | 25.1 | 55.6 |
| Year 10 | 184,200 | 30.2 | 92 | 24.8 | 54.9 |
| Total | 1,157,100 | 207.7 | 579 | 170.5 | 378.2 |

Future costs were discounted to year 1 at 3% annually. Costs are expressed in 2016 US dollars. The additional number of *N. gonorrhoeae* infections was calculated by subtracting the number of *N. gonorrhoeae* infections in scenario 1 (in which the prevalence of resistance was assumed to remain at 2% of *N. gonorrhoeae* infections and the annual incidence of *N. gonorrhoeae* infections was 820,000 for year 1 through year 10) from the number of *N. gonorrhoeae* infections in scenario 2 (the “emerging resistance” scenario in which the prevalence of resistance was assumed to increase linearly from 2% in year 0 to 15% in year 6 and remain at 15% through year 10). For example, in year 1, there would be an estimated 820,000 *N. gonorrhoeae* infections in scenario 1 and 832,700 (820,000 plus the additional 12,700 due to emerging resistance) in scenario 2. The column “Cost of additional *N. gonorrhoeae* infections” includes only the direct medical costs associated with gonorrhea and does not include any HIV-related costs. The costs of gonorrhea-attributable HIV infections are shown in the column “Cost of additional gonorrhea-attributable HIV infections.”

**Table 3.**

One-Way and Multiway Sensitivity Analyses: Summary of Results Within 10 Years (Cumulative Additional *N. gonorrhoeae* and HIV Infections, and Estimated Additional Costs in a Scenario of Emerging Ceftriaxone Resistance) When Varying One or More Parameter Values at a Time

| Parameter Varied (Range of Parameter Values) | Cumulative Additional *N. gonorrhoeae* Infections Within 10 y | Cumulative Additional HIV Infections Within 10 y | Cumulative Additional Costs Within 10 y, $ Million |
|---|---|---|---|
| None (base case results) One-way sensitivity analyses | 1,157,100 | 579 | 378.2 |
| No. *N. gonorrhoeae* infections, year 0 (395,000–1,245,000) | 557,400–1,756,800 | 279–878 | 182.2–574.2 |
| Peak % of *N. gonorrhoeae* infections resistant to ceftriaxone (5%–20%) | 250,300–1,655,800 | 125–828 | 81.9–540.8 |
| Impact of resistance on gonorrhea incidence, $\beta_2$ (0.32–1.1) | 497,900–1,879,300 | 249–940 | 162.9–613.7 |
| Average lifetime cost per *N. gonorrhoeae* infection, male individuals ($43–$129) | 1,157,100 | 579 | 354.4–402.0 |
| Average lifetime cost per *N. gonorrhoeae* infection, female individuals ($192–$575) | 1,157,100 | 579 | 298.4–458.4 |
| Average lifetime cost per HIV infection ($269,000–$427,000) | 1,157,100 | 579 | 338.4–415.1 |
| Probability of gonorrhea-attributable HIV infection (0.00005–0.001) | 1,157,100 | 58–1157 | 224.7–548.7 |
| Multiway sensitivity analyses | | | |
| All parameters varied (5th–95th percentile of 10,000 simulations) | 172,300–2,558,000 | 20–2160 | 41–1099 |

Costs are expressed in 2016 US dollars. The additional number of *N. gonorrhoeae* infections was calculated by subtracting the number of *N. gonorrhoeae* infections in scenario 1 (in which the prevalence of resistance was assumed to remain at 2% of *N. gonorrhoeae* infections and the annual incidence of *N. gonorrhoeae* infections was 820,000 for year 1 through year 10) from the number of *N. gonorrhoeae* infections in scenario 2 (the “emerging resistance” scenario in which the prevalence of resistance was assumed to increase linearly from 2% in year 0 to 15% in year 6 and remain at 15% through year 10).