Association between city-level sociodemographic and health factors and the prevalence of antimicrobial-resistant gonorrhea in the US, 2000–2019: a spatial–temporal modeling study

Jingwen Li,[a,b] Rachel E. Murray-Watson,[a,b] Sancta B. St Cyr,[c] Yonatan H. Grad,[d,e] Joshua L. Warren,[b,f,g] and Reza Yaesoubi[a,b,g,*]

[a]Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA
[b]Public Health Modeling Unit, Yale School of Public Health, New Haven, CT, USA
[c]Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA
[d]Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, MA, USA
[e]Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[f]Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA

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Summary

Background Evidence from the surveillance systems of antimicrobial-resistant (AMR) gonorrhea suggests substantial variation in the prevalence of AMR gonorrhea across populations. However, little is known about the extent to which the population-level demographic, socioeconomic, and health factors (e.g., population density, poverty level, or the prevalence of other sexually-transmitted diseases) are associated with the burden of AMR gonorrhea. We developed a hierarchical Bayesian spatial–temporal logistic regression model to investigate the association between multiple spatially- and temporally-varying predictors and the proportion of isolates with resistance to each one of ciprofloxacin, penicillin, and tetracycline between 2000 and 2019 in the United States (US).

Methods The model was informed by data from the Gonococcal Isolate Surveillance Project (GISP), a sentinel surveillance system to monitor trends in the AMR gonorrhea in the US. During our study period, GISP included 112,487 isolates from the first 25 symptomatic men who have been diagnosed with urethral gonorrhea each month after attending participating sexually-transmitted disease clinics in one of about 30 select cities.

Findings Among 112,487 isolates collected between 2000 and 2019, 16.5%, 13.7%, and 22.2% were resistance to ciprofloxacin, penicillin, and tetracycline. Denser populations were associated with higher prevalence of ciprofloxacin and penicillin resistance (odd ratio (OR): 1.5, 95% with credible interval: [1.29, 1.74] and 1.36 [1.22, 1.52], respectively); West was associated with higher prevalence of ciprofloxacin resistance (OR with respect to Midwest: 14.42 [2.02, 59.27]) and Southeast was associated with higher prevalence of ciprofloxacin and penicillin resistance (OR with respect to Midwest: 6.66 [1.59, 18.20] and 7.59 [2.3, 22.94]); higher prevalence of HIV was associated with higher prevalence of ciprofloxacin and tetracycline resistance (OR: 1.18 [1.01, 1.37] and 1.14 [1.02, 1.28]); and higher incidence of gonorrhea was associated with higher prevalence of tetracycline resistance (OR: 1.08 [1.05, 1.11]).

Interpretation Geographic location and certain population-level characteristics including population density and HIV prevalence could provide insight about the population-level risk of AMR gonorrhea at a county-level. These results could guide the expansion of AMR surveillance systems or access to drug susceptibility testing in areas with characteristics associated with increased prevalence of AMR gonorrhea.

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Keywords: Gonorrhea; Antimicrobial resistance; Spatial; Temporal; Logistic regression; Gonococcal isolate surveillance project

*Corresponding author. Department of Health Policy and Management, Yale School of Public Health, 350 George Street, Room 308, New Haven, CT, 06510, USA.
E-mail address: reza.yaesoubi@yale.edu (R. Yaesoubi).
[g]These authors are joint senior authors on this work.

Research in context

Evidence before this study

Trends in the prevalence of antimicrobial-resistant (AMR) gonorrhea are monitored through national surveillance systems, which usually consist of a limited number of surveillance sites. For example, the Gonococcal Isolate Surveillance Project (GISP), a sentinel surveillance system to monitor trends in antimicrobial susceptibilities of gonococcal strains in the United States (US), includes only 25–35 surveillance sites annually throughout the US each year. Therefore, for most areas, there is no information about the burden of AMR gonorrhea. One approach to mitigate this limitation is to identify population-level socioeconomic and health factors (e.g., population density, poverty level, or the prevalence of other sexually-transmitted diseases) that are associated with the burden of AMR gonorrhea. Identifying these factors would allow local policymakers to better assess the risk of AMR gonorrhea in the absence of local surveillance data. To find studies identifying population-level factors that are associated with AMR gonorrhea, we searched PubMed in English on July 15, 2023, using terms ("gonorrhea" OR "gonorrhoeae" OR "gonococcal") AND (resist*) AND ("associate*" OR "predict*") AND ("regression" OR "model") with no date restrictions. We found 124 abstracts, among which 15 identified various individual-level factors (such as gender, HIV-positivity, sexual orientation, and prior antibiotic use) and three assessed the association between the population-level antibiotic consumption and the burden of AMR gonorrhea. No study evaluated the association between population-level socioeconomic and public health factors and the risk of AMR gonorrhea.

Added value of this study

Using a hierarchical Bayesian spatial–temporal logistic regression model, we investigated the association between multiple spatially- and temporally-varying predictors and the proportion of isolates with resistance to each of ciprofloxacin, penicillin, and tetracycline among GISP isolates over 2000–2019. We found that an increase of 1000/km^2 in population density was associated with 50% [95% credible interval: 29%–74%] and 36% [22%–52%] increase in the odds of a sampled isolate having resistance to ciprofloxacin and penicillin; an increase of 500 per 100,000 population in the prevalence of HIV was associated with 18% [1%–37%] and 14% [2%–28%] increase in the odds of a sampled isolate having resistance to ciprofloxacin and tetracycline, respectively. To our knowledge, this is the first study to evaluate the association between population-level demographic, socioeconomic, and health factors and the burden of AMR gonorrhea.

Implications of all the available evidence

Gonococcal infections in cities in the Southeast/West regions or cities with high density or high HIV prevalence are more likely to have resistance to antibiotics. This suggests that additional efforts are needed to ensure the effective treatment of patients with gonorrhea in these cities. This could include 1) expanding GISP to collect isolates from these cities to estimate the prevalence of antimicrobial resistance more accurately and to revise the treatment guidelines more promptly in response to rises in prevalanece of antimicrobial resistance for these cities, and/or 2) conducting the test of cure for patients with gonorrhea in these cities to ascertain the successful treatment with the first-line antibiotic.

Introduction

Neisseria gonorrhoeae, the bacterial pathogen that causes gonorrhoea, has developed resistance to all antibiotics that have been used to treat it, and the emergence of gonococcal infections with resistance to multiple first-line antibiotics poses a major public health threat.[1,2] Evidence from surveillance systems of antimicrobial resistant (AMR) gonorrhoea indicates substantial variability in the trend and prevalence of AMR gonorrhoea across different geographic regions, suggesting that some areas are at higher risk for the emergence and spread of resistant strains of *N. gonorrhoeae*.[3–5]

Efforts to control the spread of AMR gonorrhoea should ideally be informed by its local epidemiology. However, information related to the local prevalence of AMR gonorrhoea is not commonly available as surveillance systems often collect samples from only a select number of locations. For example, the Gonococcal Isolate Surveillance Project (GISP), a sentinel surveillance system to monitor trends in antimicrobial susceptibilities of gonococcal strains in the United States (US),[3,6] includes only about 25–35 surveillance sites annually throughout the US each year.[7] Although GISP is considered to be nationally representative, for a substantial portion of US,[8] there is no or limited information about the prevalence of AMR gonorrhoea.

Studies using data from surveillance systems of AMR gonorrhoea in the US,[4,5,9–11] England and Wales,[12–16] and other European countries[17–22] have demonstrated that specific individual-level characteristics such as age, sexual orientation, geographic location, and the anatomical site of infection, are associated with the risk of AMR gonococcal infection. These risk factors are helpful to identify individuals at risk of AMR gonococcal infection. However, there is no straightforward approach to use these individual-level predictors to assess the burden of AMR gonorrhoea at the population level.

In this study, we developed a spatial–temporal model of AMR gonorrhoea in the US to identify population-level factors (e.g., population density, unemployment rate, or prevalence of other sexually-transmitted diseases) that are associated with the prevalence of resistance to three antibiotics (ciprofloxacin, penicillin, and tetracycline) between 2000 and 2019. Knowing these population-level risk factors would be beneficial in guiding local-level strategies to mitigate the burden of AMR gonorrhoea. For example, policymakers might consider expanding the antimirobial resistance surveillance systems or the access to drug susceptibility testing in areas with characteristics associated with increased prevalence of AMR gonorrhoea to more accurately monitor the prevalence and trends in AMR gonorrhoea and to ensure the effective treatment of AMR gonorrhoea.

Methods

Study setting and data sources

We examined data from the GISP, which is the sentinel surveillance system of AMR gonorrhoea in the US. GISP is designed to provide reliable estimates for the prevalence and trends in AMR gonorrhea.[9] It includes isolates from the first 25 symptomatic men who have been diagnosed with urethral gonorrhoea each month attending participating sexually-transmitted disease (STD) clinics in one of about 30 select cities (Table S1).[9,23,24] As urethral infections in men are more likely to be symptomatic, which prompts seeking health care, GISP included only urethral samples from men as an efficient approach to monitor AMR gonorrhoea; furthermore, the consistent sampling is meant to minimize the potential confounding induced by changes in screening and testing practices.[9] Clinical and demographic data were abstracted from medical records, and isolates were tested to determine minimum inhibitory concentrations of different antibiotics including penicillin, tetracycline, ceftriaxone, cefixime, ciprofloxacin, and azithromycin. Our dataset includes 112,487 isolates, from 42 sentinel sites over the period 2000–2019. GISP uses the criteria established by the Clinical & Laboratory Standards Institute (CLSI) to define resistance to each one of these antibiotics (Table S2).

In our analyses, we only considered isolates with the resistance to ciprofloxacin, penicillin, and tetracycline and excluded azithromycin, cefixime, and ceftriaxone since the percentage of isolates with resistance to any of these antibiotics was low during 2000–2019 (1.35%, 0.034%, and 0.002%, respectively, of 112,487 isolates tested during this period).

To identify factors that are associated with the prevalence of AMR gonorrhoea, we considered variables describing different characteristics of surveillance sites. This includes information related to:

1) Population size, density, geographic region (West, Midwest, Northwest, Southeast, and Southwest, defined in Table S3), and age distribution as proxies for sexual behaviour, local sexual networks, and access to health care;
2) The percentage of the male population who have sex with men (MSM), who have historically been at higher risk of infection with AMR gonorrhea;[16,18,25–28]
3) The percentage of the adult population from historically marginalized races (i.e., Black and American Indian or Alaska Native) to capture inadequate access to health care, inadequate treatment, and mistrust in health systems;[29,30]
4) Socioeconomic data such as education, income, unemployment, and health insurance coverage, as proxies for risk- and care-seeking behaviour and access to health care;
5) Connectivity with other cities, characterized by the distance to a major airport, the volume of passengers served by the nearest commercial service airports, and percentage of population who worked outside the city of residence to account for the potential importation of AMR gonococcal infections;
6) Burden of STDs (including reported cases of HIV, gonorrhoea, chlamydia, and syphilis) as proxies for local sexual networks, and public health policies to control STDs and
7) Outpatient antibiotic prescriptions, to account for the selective pressure of different antibiotics.

We used various sources to inform the value of these variables for each surveillance site over the period 2000–2019, including American Community Surveys from the US Census Bureau,[31] the CDC AtlasPlus,[32] the outpatient antibiotic prescriptions reported by CDC,[33] and studies to estimate the size of MSM population in the US.[34] The details of these data sources and the approach to handling missing observations are provided in Table S4.

This study utilized publicly available data, as described in the manuscript and provided in the Supplement. The dataset does not contain personally identifiable information or sensitive data requiring special protection. Given that this study involved secondary analysis of publicly available data, no direct interaction with human participants was required, and no new data was collected. Therefore, this study did not require prior ethical approval.

Descriptive analysis

To evaluate whether certain surveillance sites have continuously reported higher or lower prevalence of AMR gonorrhoea, we visualized the *comparative* percentage of isolates resistant to penicillin, ciprofloxacin, or tetracycline between 2000 and 2019, which we defined as follows. For surveillance site i, the

comparative percentage of isolates resistant to antibiotic a in year t is defined as

$$D_{i,t,a} = \left(\frac{R_{i,t,a}}{N_{i,t}} - \frac{R_{t,a}}{N_t}\right) \times 100\%,$$

where $R_{i,t,a}$ is the number of isolates resistant to antibiotic a (ciprofloxacin, penicillin, and tetracycline) in surveillance site i (42 sites in total) in year t (2000–2019), and $N_{i,t}$ is the number of isolates tested in surveillance site i in year t, $R_{t,a}$ is the total number of isolates collected from all surveillance sites to antibiotic a in year t (i.e., $R_{t,a} = \sum_{i=1}^{42} R_{i,t,a}$), and N_t is the total number of isolates evaluated from all surveillance sites in year t (i.e., $N_t = \sum_{i=1}^{42} N_{i,t}$).

We also applied the above method to calculate the comparative percentage of isolates resistant to each antibiotic reported by surveillance sites in each region (West, Midwest, Northwest, Southeast, and Southwest) such as

$$D'_{r,t,a} = \left(\frac{R'_{r,t,a}}{N'_{r,t}} - \frac{R_{t,a}}{N_t}\right) \times 100\%,$$

where $R'_{r,t,a}$ is the number of isolates with resistance to antibiotic a reported by surveillance sites in region r in year t, and $N'_{r,t}$ is the total number of isolates tested by surveillance sites in region r.

These metrics allow us to visualize and evaluate the trend in the prevalence of resistance for each surveillance site and region with respect to the national-level prevalence of resistance for each antibiotic.

Spatial–temporal logistic regression model

We developed a hierarchical Bayesian logistic regression model to investigate the association between multiple spatially- and temporally-varying predictors and the proportion of isolates resistant to each one of ciprofloxacin, penicillin, and tetracycline among isolates from each sentinel site over 2000–2019 (i.e., a separate model for each antibiotic). The model included a categorical predictor for year of study (year 2000 set as the reference category) to account for large-scale temporal trends that may impact all spatial sites simultaneously, and 13 demographic, socioeconomic, and public health covariates as listed in Table S4. To avoid model fitting issues related to multicollinearity, we used the correlation between variables to decide which demographic, socioeconomic, and public health covariates to exclude from the model (Fig. S3). Among related covariates (e.g., "Percentage of adult population who completed high school or equivalency" and "Percentage of adult population who got bachelor's degree or higher", both of which relate to education), we included the covariate that had the least correlation with other predictors in the model. The pairwise correlations between the set of covariates included in the final model were each lower than 0.7 in absolute value (Fig. S3 and Table S5).

To account for repeatedly measured data in a site over time as well as spatial correlation between sites, the model also included spatially structured, site-specific random effect parameters. Specifically, the model is given as

$R_{i,t,a}|p_{i,t,a} \sim \text{Binomial}(N_{i,t}, p_{i,t,a})$, for $i = 1, 2, \ldots, 42$ and $t = 2000, 2001, \ldots, 2019$

$$\ln\left(\frac{p_{i,t,a}}{1-p_{i,t,a}}\right) = \beta_0 + \sum_{j=2001}^{2019} 1(t=j)\eta_j + \mathbf{x}_{it}^{\mathrm{T}}\boldsymbol{\gamma} + \phi_i$$

where $R_{i,t,a}$ and $N_{i,t}$ were previously described and $p_{i,t,a}$ is the probability that an isolate from site i collected in year t is resistant to antibiotic a. We modelled $p_{i,t,a}$ on the logit scale as a function of fixed effects and site-specific random effects, ϕ_i.[35] The fixed effect predictors are represented by the $\mathbf{x}_{it}$ vector and include the variables listed in Table S5. The year of data collection variables are defined using the indicator function, 1(.), which is equal to one if the input statement is true and is equal to zero otherwise. To improve model fitting properties without loss of generality, we standardized each predictor by subtracting the mean from recorded values and dividing by the standard deviation of recorded values (Table S5).

We also evaluated the potential for residual spatial correlation in the data that may be present even after adjusting for the fixed effects. For example, the proportion of the resistant isolates from one site might be correlated between sites that are nearby due to the easier transmission of the AMR *N. gonorrhoeae* between these locations. To account for this correlation, we modelled the ϕ_i parameters using the Leroux version[36] of a conditional autoregressive (CAR) model such that

$$\phi_i|\boldsymbol{\phi}_{-i}, \tau^2, \rho \sim \mathrm{N}\left(\frac{\rho\sum_{j=1}^{n} w_{ij}\phi_j}{\rho\sum_{j=1}^{n} w_{ij} + 1 - \rho}, \frac{\tau^2}{\rho\sum_{j=1}^{n} w_{ij} + 1 - \rho}\right)$$

Here, $\boldsymbol{\phi}_{-i}$ is the vector of random effect parameters excluding ϕ_i, and w_{ij} represents the inverse distance between the centroids of sites i and j, with $w_{ii} = 0$ by convention. The centroids were obtained based on the cartographic boundary data of 42 sentinel sites from the US Census Bureau.[37] This model suggests that a priori, a random effect value from a specific site is more similar to the values from locations nearby (i.e., those with larger w_{ij} values). The parameter $\rho \in (0, 1)$ describes the strength of spatial correlation among the random effects; when $\rho = 0$, the random effect values are independent and when $\rho = 1$, the impact of surrounding values plays a more important role. Finally, τ^2 describes the variability in the ϕ_i parameters. These site-specific random effect parameters also serve to account for correlation due to repeated

measures, as the same site receives the same value in each year, resulting in within-site correlation.

To complete the model specification, we assigned weakly informative prior distributions to all model parameters: τ^2 is assigned an inverse-gamma prior distribution such that $\tau^2 \sim$ Inverse-Gamma (1.00, 0.01). The intercept and fixed effect regression parameters are assigned independent Gaussian distributions centred at zero with a standard deviation of 100. After model fitting, we also analysed the posterior distributions of the random effects for each antibiotic to create maps that display the spatial structure of the variation in the data that was not fully explained by the covariates included in our model.

We used the S. CARmultilevel() function in the CARBayes package[35] for model fitting using Markov chain Monte Carlo (MCMC) posterior sampling techniques. To ensure convergence of the model and that we collected an adequate number of posterior samples to conduct accurate statistical inference, we let the MCMC algorithms run for 1.1 million iterations, discarding the first 100 k samples prior to convergence of the model, and thinning the remaining samples by a factor of 100 to reduce posterior autocorrelation. Convergence of the models was assessed using Geweke's diagnostic[38] along with visual inspection of individual parameter trace plots. We used the collected posterior samples to make inference for all included covariates on the odds ratio (OR) scale. Posterior means and 95% quantile based equal tailed credible intervals (CrIs) are used to summarize the marginal posterior distributions.

For the main analysis, we present results from main models that included all 14 predictors (one categorical variable representing the geographic region and 13 continuous variables listed in Table S5). To evaluate whether excluding certain predictors would impact the conclusions provided by the main models (due to collinearity among variables, for example), we also present results from more parsimonious models for each antibiotic. These models are built by sequentially dropping predictors based on estimated ORs and CrIs (Table S6). Furthermore, for our main analysis, we did not include the consumption of antibiotics as a covariate since county-level data on the consumption of antibiotics were not available and the state-level data in catchment areas of GISP surveillance sites were highly correlated with geographic region and the percentage of Black American and Native American in adult populations (Fig. S3). In a sensitivity analysis, however, we investigated whether including the state-level consumption for antibiotics would impact our conclusions. All data visualizations and analysis of this model were performed using R 4.2.1.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study, and all authors had final responsibility for the decision to submit for publication.

Results

During 2000–2019, 112,487 isolates were tested for antibiotic susceptibility, among which 14.49% demonstrated resistance to ciprofloxacin, 12.16% to penicillin, and 20.45% to tetracycline. Surveillance sites in the West and Northeast collected, respectively, the largest and the smallest number of isolates (30.5% versus 11.8% of 112,487 isolates) between 2000 and 2019 (Table 1). Surveillance sites in the West (mainly, Honolulu, San Diego, San Francisco, Orange County, and Seattle) reported the highest prevalence of resistance to any of three antibiotics between 2000 and 2019 (Fig. 1 and Fig. S2).

The model included 14 covariates presented in Table 2. The importance of each predictor was relatively consistent between the three models developed for each antibiotic (Table 2). Denser populations were associated with higher prevalence of antimicobial resistance for ciprofloxacin and penicillin. An increase of 1000/km^2 in population density was associated with 50% [95% CrI: 29%, 74%] and 36% [95% CrI: 22%, 52%] increase in the odds of a sampled isolate presenting resistance to ciprofloxacin and penicillin, respectively. A higher prevalence of HIV was associated with higher prevalence of antimicobial resistance for ciprofloxacin and tetracycline. An increase of 500 per 100,000 population in the prevalence of HIV was associated with 18% [95% CrI: 1%, 37%] and 14% [95% CrI: 2%, 28%] increase in the odds of a sampled isolate presenting resistance to ciprofloxacin and tetracycline.

Compared to Midwest, residing in the Southeast was associated with 6.7 and 7.6-fold increase in the odds of a sampled isolate presenting resistance to ciprofloxacin and penicillin (with [95% CrI: 1.6, 18.2] and [95% CrI: 2.3, 22.9], respectively). Residing in the West was associated with a 14.4-fold increase [95% CrI: 2.0, 59.3] in the odds of a sampled isolate presenting resistance to ciprofloxacin.

Region	Total	% of total isolates reported by this region	% of isolates resistant to		
			Ciprofloxacin	Penicillin	Tetracycline
Midwest	28,467	25.3	8.5	7.6	15.2
Northeast	13,269	11.8	15.9	16.2	19.0
Southeast	19,756	17.6	10.8	12.3	20.0
Southwest	16,734	14.9	10.2	8.8	19.7
West	34,261	30.5	23.1	15.9	26.0
Total	112,487		14.5	12.2	20.4

Table 1: **Susceptibility of isolates collected from different US regions.**

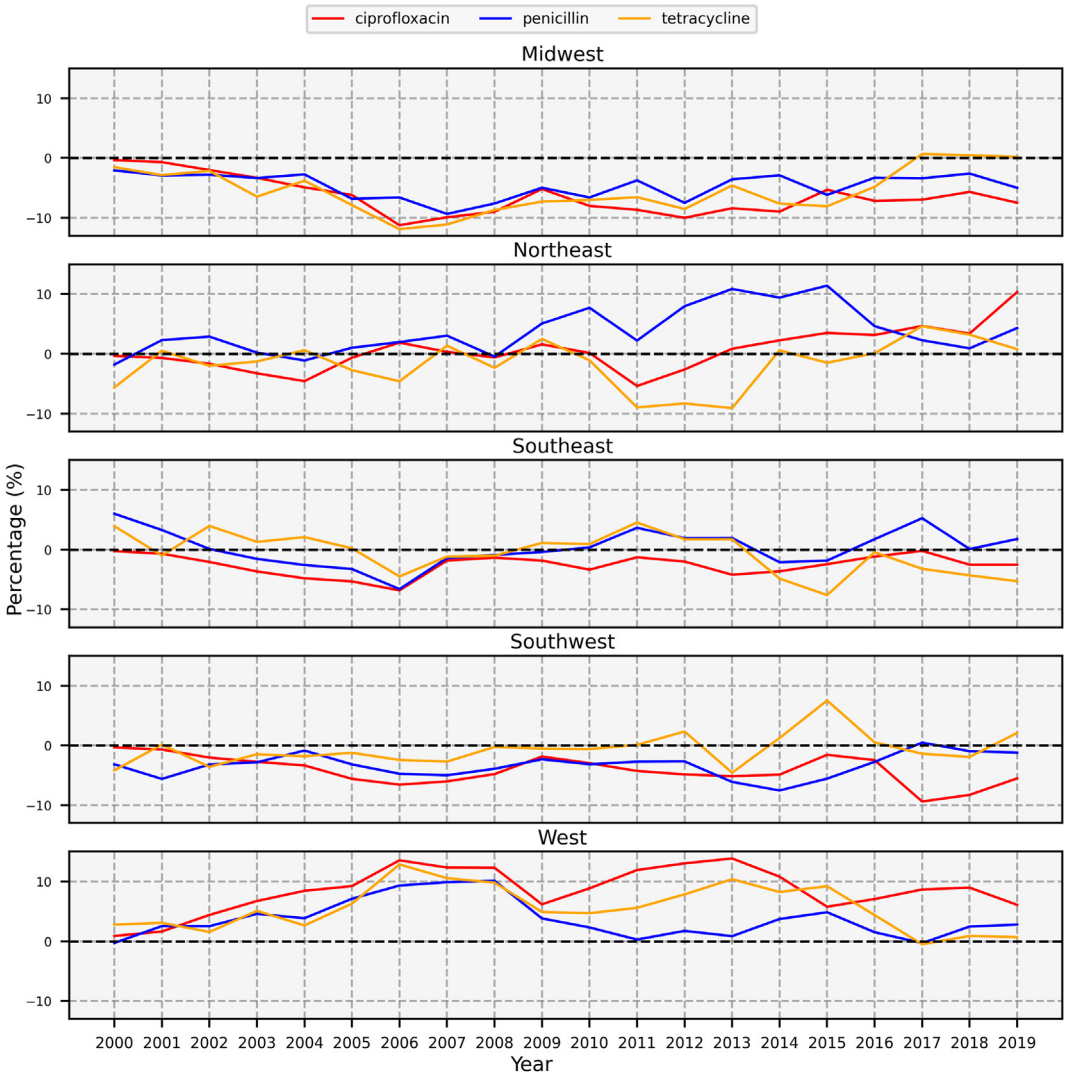

Fig. 1: **Comparative prevalence of resistance to different antibiotics in each region relative to the overall prevalence of resistance.**

Among demographic and socioeconomic factors considered here, the percentage of adult population that are Black American or American Indian or Alaska Native, unemployment rate, and the adult population with at least college degree were inversely associated with the odds of a sampled isolates presenting resistance. An increase of 25% in the percentage of adult population that are Black American, or American Indian, or Alaska Native was associated with 57% [95% CrI: 34%, 74%] and 23% [95% CrI: 5%, 38%] reduction in the odds of a sample isolate presenting resistance to penicillin and tetracycline. An increase of 10% in the percentage of adults with at least college degree was associated with 62% [95% CrI: 52%, 71%] and 53% [95% CrI: 41%, 63%] reduction in the odds of a sample isolate presenting resistance to ciprofloxacin and penicillin.

The association of the percentage of adult population with health insurance and incidence rate of gonorrhoea with the prevalence of AMR gonorrhoea was mixed for ciprofloxacin, penicillin, and tetracycline. An increase of 5% in health insurance coverage was associated with an 8% [95% CrI: 2%–15%] increase in the odds of a sampled isolate presenting resistance to penicillin but the same increase in health insurance coverage was associated with a reduction in the odds of a sample presenting resistance to ciprofloxacin and tetracycline. While an increase of 100 per 100,000 population in the reported gonorrhoea cases was associated with 8% [95% CrI: 5%–11%] increase in the odds of a sampled isolate presenting resistance to tetracycline, the same increase in the rate of reported gonorrhea cases was associated with a 26% [95% CrI: 21–30%] decrease in the odds for resistance to ciprofloxacin (Table 2).

Predictors[a]	Ciprofloxacin			Penicillin			Tetracycline		
	OR	95%	CrI	OR	95%	CrI	OR	95%	CrI
Population density (1000/km^2)	**1.50**	**1.29**	**1.74**	**1.36**	**1.22**	**1.52**	1.02	0.95	1.09
% of population aged 65 and over (1%)	0.97	0.91	1.03	*0.89*	*0.85*	*0.94*	0.99	0.96	1.03
% Black American or American Indian or Alaska Native among adult population (25%)	0.96	0.59	1.49	*0.43*	*0.26*	*0.66*	*0.77*	*0.62*	*0.95*
% MSM population among adult male population (1%)	1.03	0.89	1.22	0.98	0.87	1.09	1.02	0.95	1.09
% of population aged 18–64 with health insurance coverage (5%)	*0.76*	*0.70*	*0.82*	**1.08**	**1.02**	**1.15**	*0.89*	*0.85*	*0.93*
% of population aged 18–64 years who were unemployed in the past 12 months (1%)	*0.92*	*0.90*	*0.94*	*0.95*	*0.93*	*0.98*	*0.94*	*0.93*	*0.96*
% of adult population with at least college degree (10%)	*0.38*	*0.29*	*0.48*	*0.47*	*0.37*	*0.59*	*0.95*	*0.82*	1.09
% population over 16 years old who worked outside the city of residence (15%)	*0.94*	*0.73*	1.19	*0.82*	*0.66*	*0.98*	1.00	0.88	1.12
Connectivity-(1/distance) × (passenger volume) (1 million)	*0.87*	*0.75*	*0.98*	*0.95*	*0.83*	1.06	*0.90*	*0.82*	*0.99*
Prevalence rates of individuals living with HIV per 100,000 population (500)	**1.18**	**1.01**	**1.37**	1.06	0.93	1.21	**1.14**	**1.02**	**1.28**
Rate of reported gonorrhea cases per 100,000 population (100)	*0.74*	*0.70*	*0.79*	1.00	0.97	1.03	**1.08**	**1.05**	**1.11**
Rate of reported chlamydia cases per 100,000 population (200)	1.04	0.99	1.09	1.00	0.96	1.05	0.99	0.96	1.02
Rate of reported syphilis cases per 100,000 population (10)	0.99	0.95	1.03	*0.89*	*0.86*	*0.93*	0.98	0.95	1.01
Geographic region (with Midwest as reference)									
Northeast region	1.41	0.21	4.53	1.44	0.42	3.09	1.43	0.92	2.22
Southeast region	**6.66**	**1.59**	**18.20**	**7.59**	**2.30**	**22.94**	1.29	0.78	2.01
Southwest region	2.99	0.40	11.25	0.69	0.14	2.00	0.76	0.38	1.32
West region	**14.43**	**2.02**	**59.27**	1.35	0.42	3.10	1.28	0.74	1.95

The font of cells with credible interval entirely above one is bold and the cells with credible interval entirely below one is italic (see Supplementary Information for the results from more parsimonious models described in Table S6). [a]The numbers in parentheses represent the amount of change in each variable for which the odds ratios are calculated. For example, an increase of 1000/km^2 in the population density is associated with 50% increase in the odds of a sampled isolates having resistance to ciprofloxacin.

Table 2: **Posterior means of odds ratios (OR) and their 95% quantile-based equal-tailed credible intervals (CrI).**

The most parsimonious model we considered for each antibiotic included nine variables with predictors related to connectivity, percentage of MSM population among the adult male, and the rate of reported chlamydia and syphilis cases excluded (Table S9). The OR estimates and credible intervals provided by these more parsimonious models are consistent with those obtained from the main models that included all 14 variables (comparing Table 2 with Table S9). Moreover, including the state-level consumption of antibiotics as a covariate did not change the relative importance of covariates in our main model (comparing Table 2 with Table S10).

The absolute values of the estimated spatial random effects for the models of penicillin and tetracycline were relatively low across surveillance sites (Fig. 2b and c). For penicillin, only 2 sites (Miami and New York City) and for tetracycline no sites had absolute values greater than 1.5. In contrast, for ciprofloxacin, 6 sites (Boston, Las Vegas, Miami, Minneapolis, New York City, and Seattle) had absolute values greater than 1.5 (see Fig. S4 for other thresholds). The relatively low values for penicillin and tetracycline suggest that the spatial variability in prevalence of resistance to penicillin and tetracycline could largely be explained by the covariates included in our analysis, while more unexplained spatial variation remained for resistance to ciprofloxacin.

Discussion

GISP, the sentinel surveillance system of AMR gonorrhoea in the US, provides important information regarding the prevalence and trends in the spread of AMR gonorrhoea. However, GISP includes isolates only from select 25 to 35 surveillance sites annually and hence, for many cities no information is available about the risk for AMR gonorrhoea. In this study, we investigated the population-level demographic, socioeconomic and health factors (e.g., population density, poverty level, and the prevalence of other STDs) that could be associated with the prevalence of AMR gonorrhoea. We developed a hierarchical Bayesian spatial–temporal logistic regression model using the data provided by GISP related to the number of isolates not susceptible to ciprofloxacin, penicillin, and tetracycline between 2000 and 2019. Among 14 population characteristics we considered here, population density, HIV prevalence, and residence in the Southeast and West regions were positively associated with higher odds of antimicobial resistance.

The data we used to inform the predictors in our model are readily and freely available through existing surveys and surveillance systems, such as the US Census Bureau, the American Community Surveys, and AtlasPlus (Table S4). Therefore, our findings, as summarized in Table 2, could provide insight into the risk of AMR gonorrhoea in cities not included as surveillance sites in GISP. Obviously, this does not remove the need for surveillance systems of AMR gonorrhoea, but given the high cost of expanding and maintaining the surveillance sites, the results presented here could be helpful to identify cities that are expected to have a high prevalence of AMR gonorrhoea.

Fig. 2: **Bubble maps for the mean and the standard deviations (SD) of spatial random effects across 42 surveillance sites from the spatial temporal models. Low (close to zero) means and SDs suggest that the prevalence of resistance to the antibiotic during 2000–2019 could largely be explained by the covariates included in the model (e.g., in Panels b and c). For ciprofloxacin (Panel a), however, several surveillance sites present high mean of random effect (e.g., Minneapolis, MN and Miami, FL) indicating that included covariates were not adequately describing the prevalence of resistance to ciprofloxacin in these areas. See Supplementary Information for the results from more parsimonious models described in** Table S6.

Several prior studies have identified individual-level risk factors including age, sexual orientation, geographic location, prior diagnosis of gonorrhoea, and the anatomical site of infection that were associated with the risk for AMR gonorrhea.[4,5,9–16,18,21,25–28,39–43] While many of these studies suggested that MSM are at higher risk of infection with AMR gonorrhea,[16,18,25–28] our analysis indicated that the percentage of MSM in a population was not an important factor for describing the prevalence of AMR gonorrhoea. This could be because our models account for burden of other STDs including HIV and gonorrhoea, and the impact of individual-level sexual behaviour is most likely reflected in these covariates.

There were marked differences in the prevalence and trend in resistance to ciprofloxacin, penicillin, and tetracycline across GISP sites (Fig. S1). Despite heterogeneous antimicobial resistance trajectories across antibiotics and sites, our analysis suggested positive association between three covariates (namely, population density, HIV prevalence, and residence in Southeast or West) and the prevalence of resistance to each of ciprofloxacin, penicillin, and tetracycline (Table 2). In contrast, the association between certain covariates and resistance to ciprofloxacin, penicillin, and tetracycline was less consistent. For example, an increase in population-level health insurance coverage was associated with an increased odds of an isolate presenting resistance to penicillin but was negatively associated with resistance to ciprofloxacin and tetracycline; or an increase in reported gonorrhoea cases was associated with an increased odds of an isolate presenting resistance to tetracycline but had insignificant association with resistance to penicillin and a negative association with resistance to ciprofloxacin (Table 2). Future studies based on the latest GISP data could resolve or justify these inconsistent associations across antibiotics.

Our study has several limitations. First, our model may not be fully specified due to the omission of other relevant predictors including those related to particular features of the local sexual network and

sexually-transmitted infections (such as the rate of partner change or the rates of reinfection versus new infection) and ecological factors (such as trade and migration) that are shown to be associated with antimicrobial resistance.[44] These covariates are not routinely collected and available in cities participating in GISP and hence, we could not include them in our analysis. As such, our study is not designed to identify the population-level "drivers" of AMR gonorrhoea but instead, to identify the factors that are associated with the prevalence of antimicobial resistance. Second, as county-level data on the consumption of antibiotics were not available, we used state-level data as estimates for the consumption of antibiotics in catchment areas of GISP surveillance sites. However, since this variable was highly correlated with geographic region and the percentage of Black American and Native American in adult populations, our main model excluded the consumption of antibiotics (Fig. S3). Our sensitivity analysis, however, suggested that adding the state-level antibiotic consumption as a covariate in the model did not change our conclusions.

Third, we used a simple measure of connectivity between GISP sites based on the product of the inverse distance to a major airport and the volume of air travel in that airport but also included the geographic region of GISP sites as covariate. While new resistant strains of *N. gonorrhoeae* are often imported to the US from overseas,[39,45–47] it appears that connectivity is not a strong predictor for the burden of AMR gonorrhoea (Table 2). However, we found that being in Southeast region was a strong predictor for the prevalence of resistance to ciprofloxacin and penicillin and being in West was strong predictor for the prevalence of resistance to ciprofloxacin. Fourth, our model did not include the time-lagged association between covariates and the prevalence of AMR gonorrhoea. However, covariates considered here had relatively stable values over time, which mitigate the impact of this limitation. Fifth, most covariates considered in our analysis were informed by American Community Surveys (ACS) and AtlasPlus (Table S4). ACS and AtlasPlus did not report data on some covariates during certain periods (e.g., county population sizes were not reported for years 2001–2009). Since we did not find any evidence that suggests the trend in variables informed by ACS and AtlasPlus changed markedly during our study period, we used linear interpolation to estimate missing values for our covariates. However, since the missingness may not have occurred at random, estimates provided by interpolation approaches could be biased; for example, if there was a sudden and substantial temporal change in any of the variables.

Finally, our analysis of mean and variance for the estimated spatial random effects suggested that the included covariates were not adequately describing the prevalence of resistance to ciprofloxacin in some areas (Fig. 2c). However, note that the predicted values by all three models were reasonably close to the prevalence of resistance observed between 2000 and 2019 (Fig. S5), indicating acceptable ability of these models to describe the prevalence of resistance to ciprofloxacin, penicillin, and tetracycline during this period.

Our analysis suggests that the percentage of adult population that are 1) Black American or American Indian or Alaska Native, 2) unemployed, and 3) with at least college degree were inversely associated with the odds of a sampled isolates presenting resistance (Table 2). Nevertheless, additional research is required to confirm whether the prevalence of antimicobial resistance is in fact lower in communities with higher Black American or American Indian or Alaska Native population, unemployment rate, and adult population with at least college degree.

Since 2020, the CDC has recommended a single drug therapy with ceftriaxone for the empiric treatment of gonorrhea.[48] As the prevalence of resistance to ceftriaxone is still extremely low (<0.002% among GISP isolates collected between 2000 and 2019), we did not include ceftriaxone in our analysis. Hence, our results may not be generalizable to describe the prevalence of resistance to ceftriaxone in the future. However, the method we described here could be used to identify the population-level risk factors that are associated with the prevalence of ceftriaxone-resistance gonorrhoea in the future when the resistance to this antibiotic starts to spread more widely.

In summary, we demonstrated that data from surveillance systems of AMR gonorrhoea could be used to identify population-level socioeconomic and health factors that are associated with the prevalence of AMR gonorrhoea. Since surveillance systems do not provide information about the prevalence of AMR gonorrhoea in every city or county, the identification of population-level risk factors could provide valuable information to detect areas where the prevalence of antimicobial resistance is expected to be high. While our analysis does not replace the need for antimicobial resistance surveillance systems, it could be used to guide the expansion of antimicobial resistance surveillance systems or access to drug susceptibility testing in areas with characteristics associated with increased prevalence of AMR gonorrhoea.

Contributors

Jingwen Li: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing–Original Draft, Writing–Review & Editing, Visualization.

Rachel E. Murray-Watson: Conceptualization, Investigation, Data Curation, Writing–Review & Editing, **Sancta B. St Cyr**: Data Curation, Writing–Review & Editing.

Yonatan H. Grad: Conceptualization, Writing–Review & Editing.

Joshua L. Warren: Conceptualization, Methodology, Software, Writing–Review & Editing, Supervision.

Reza Yaesoubi: Conceptualization, Methodology, Investigation, Writing–Original Draft, Writing–Review & Editing, Supervision, Funding acquisition.

JL and RY has accessed and verified the data.

Data sharing statement

The dataset used in this analysis is available to download under Supplementary Data.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2025.101006.

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