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Gonococcal Isolate Surveillance Project (GISP)
Annual Report - 1998

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GONOCOCCAL ISOLATE SURVEILLANCE PROJECT (GISP) ANNUAL REPORT - 1998

Introduction

Gonorrhea is the second most frequently reported communicable disease in the United States. Overall gonorrhea rates in the United States declined 72% since 1975. However, between 1997 and 1998, the rate increased by 8.9% from 122.0 cases per 100,000 persons to 132.9 (**Figure 1**). Gonorrhea rates remain high in the southeastern states, among minorities, and among adolescents of all racial and ethnic groups (**Figures 2, 3, and 4**).¹ The health impact of gonorrhea is largely related to its role as a major cause of pelvic inflammatory disease, which frequently leads to infertility or ectopic pregnancy.² In addition, recent data suggest that gonorrhea facilitates HIV transmission.^{3,4}

Control of gonorrhea has been complicated by the development of resistance to antimicrobial agents. The appearance of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) and chromosomally mediated penicillin- and tetracycline-resistant *N. gonorrhoeae* (CMRNG) in the 1970s eventually led to the abandonment of these drugs as therapies for gonorrhea. The currently recommended primary therapies for gonorrhea are two broad-spectrum cephalosporins, ceftriaxone and cefixime, and two fluoroquinolones, ciprofloxacin and ofloxacin.⁵ However, fluoroquinolone-resistant *N. gonorrhoeae* have been reported from many parts of the world, including the United States.⁶⁻⁹

GISP Overview

The Gonococcal Isolate Surveillance Project (GISP) was established in 1986 to monitor trends in antimicrobial susceptibilities of strains of *N. gonorrhoeae* in the United States in order to establish a rational basis for the selection of gonococcal therapies.¹⁰ GISP is a collaborative project between selected sexually transmitted diseases (STD) clinics, five regional laboratories, and the Centers for Disease Control and Prevention (CDC) (Division of STD Prevention, National Center for HIV, STD, and TB Prevention, and the Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases).

In GISP, *N. gonorrhoeae* isolates are collected from the first 20 men with urethral gonorrhea attending sexually transmitted diseases clinics each month in 28 cities in the United States. At regional laboratories, the susceptibilities of these isolates to antimicrobial agents, including broad-spectrum cephalosporins and fluoroquinolones currently recommended for the treatment of uncomplicated gonorrhea, are determined. Minimum inhibitory concentrations (MICs) are measured, and resistance interpreted according to criteria recommended by the National Committee for Clinical Laboratory Standards (NCCLS).^{11,12}

Important GISP findings have included the ongoing high prevalence of resistance to penicillin and tetracycline; the appearance, at low levels, of decreased susceptibility and resistance to the fluoroquinolones; the absence of resistance to the broad-spectrum cephalosporins; and the increasing proportion of gonorrhea cases coming from men who have sex with men.^{7-9,13} These findings contributed to the development of CDC's STD treatment recommendations in 1993 and

1998,^{5,14} and stimulated further investigation of the increase in gonorrhea among men who have sex with men.¹³

1998 GISP Sites

A total of 28 STD clinics contributed 4,712 gonococcal isolates to GISP in 1998 (**Figure 5**). Eighteen sites have participated continuously since 1988: Albuquerque, Anchorage, Atlanta, Baltimore, Birmingham, Cincinnati, Denver, Honolulu, Long Beach, New Orleans, Philadelphia, Phoenix, Portland, San Antonio, San Diego, San Francisco, Seattle, and West Palm Beach. Eight sites joined GISP after 1988: Fort Lewis in 1989; Cleveland, Kansas City, Nassau County, and Orange County in 1991; Minneapolis in 1992; Chicago in 1996; and Miami in 1998. Two sites have had intermittent participation: Fort Bragg 1987-90 and 1997-98, and St. Louis 1987-93 and 1995-8. The GISP Regional Laboratories are located in Atlanta, Birmingham, Cleveland, Denver, and Seattle.

DESCRIPTION OF GISP DATA

Aggregate data from all GISP sites are described and illustrated in the first part of this report. The clinic-specific data illustrate substantial geographic variation in patient characteristics and antimicrobial susceptibility of gonococcal strains; clinic-specific figures are provided in the second part of this report.

Demographic and Clinical Characteristics

Age The age distributions of GISP participants in 1988 and 1998 are shown in **Figure 6**. Ages ranged from 13 to 82 years in 1998. The age distribution has previously been shown to be similar to the age distribution of nationally reported cases of gonorrhea in men.¹⁵

Race/Ethnicity The 1998 race/ethnicity distribution of GISP participants is shown in **Figure 7**. Previous comparison has shown that GISP participants include proportionally more Hispanics than nationally reported gonorrhea in men;¹⁵ several GISP sites where Hispanics account for a high proportion of gonorrhea cases explain this difference.

Sexual Orientation In 1998, 12.0% of GISP participants were men who have sex with men (MSM), compared with 4.0% in 1988 (**Figure 8**). Nine clinics reported the majority (439/503; 87.3%) of MSM in GISP in 1998; in all nine clinics, the proportion of participants who were MSM increased in 1997, 1998, or both. The percentages of isolates that came from MSM in these nine clinics from 1988 through 1998 are shown in **Figure 9**. A study of eight of these cities performed in 1996 showed that in five of the eight (Honolulu, Portland, San Diego, San Francisco, and Seattle) the proportional increases corresponded to absolute increases in numbers of MSM with gonorrhea.¹³

Reason for Clinic Attendance Most GISP participants in 1998 presented to the clinic as volunteers; others were gonorrhea contacts or presented for test-of-cure cultures (**Figure 10**). There has been little change in this distribution over time. Dysuria and/or urethral discharge was

present in 96.7% of GISP participants in 1998; 3.3% had no symptoms.

History of Gonorrhoea The percentage of GISP participants who reported a history of gonorrhoea (ever) increased from 38.3% in 1991, the first year this information was collected, to a peak of 49.9% in 1996, but declined to 46.8% in 1998. The percentage of GISP participants with a documented previous episode of gonorrhoea in the last 12 months decreased from 21.5% in 1992, the first year this information was collected, to 17.5% in 1998 (**Figure 11**).

Gonorrhoea Treatment The treatments used for gonorrhoea are shown in **Figure 12**. The proportion of GISP cases treated with cephalosporins decreased from a high of 84.6% in 1990 to 65.4% in 1998, while the proportion treated with fluoroquinolones (ciprofloxacin or ofloxacin) increased from none in 1988 to 31.2% in 1998.

Susceptibility to Antimicrobial Agents

Antimicrobial Resistance Criteria

Antimicrobial resistance in *N. gonorrhoeae* is defined by the criteria recommended by the NCCLS:¹²

Penicillin, MIC ≤ 2.0 Fg/ml

Tetracycline, MIC ≤ 2.0 Fg/ml

Spectinomycin, MIC ≤ 128.0 Fg/ml

Ciprofloxacin, MIC 0.125 - 0.5 Fg/ml (intermediate resistance)

Ciprofloxacin, MIC ≥ 1.0 Fg/ml (resistance)

Ceftriaxone, MIC ≥ 0.5 Fg/ml (decreased susceptibility)

Cefixime, MIC ≥ 0.5 Fg/ml (decreased susceptibility)

Criteria for resistance to ceftriaxone, cefixime, erythromycin, and azithromycin have not been established.

Susceptibility to Penicillin and Tetracycline

Overall, 29.4 % (1384/4712) of isolates collected in 1998 were resistant to penicillin, tetracycline, or both (**Figure 13**); this proportion has been relatively constant since 1988. The percentage of penicillinase-producing *N. gonorrhoeae* (PPNG) declined from a peak of 11.0% in 1991 to 3.0% in 1998 (**Figure 14**). In contrast, the percentage of isolates with chromosomally mediated resistance to penicillin (PenR) has increased annually, from 0.5% in 1988 to 5.1% in 1998 (**Figure 15**). The prevalence of plasmid-mediated resistance to tetracycline (TRNG), 6.6% in 1998, has varied little since 1988 (**Figure 14**). Similarly, the prevalence of chromosomally mediated resistance to tetracycline only (TetR), 6.8% in 1998, has been relatively stable since 1989, except for a transient increase in 1995 (**Figure 15**). However, the prevalence of isolates with chromosomally mediated resistance to both penicillin and tetracycline (CMRNG) increased from 3.0% in 1989 to 7.2% in 1998. The prevalence of isolates with plasmid-mediated resistance to both penicillin and tetracycline (PPNG-TRNG), 0.7% in 1998, continues to be low.

Susceptibility to Spectinomycin

All isolates were susceptible to spectinomycin in 1998. There have been five spectinomycin-resistant isolates in GISP; their locations and years were: St. Louis-1988, Honolulu-1989, San Francisco-1989, Long Beach-1990, and West Palm Beach-1994.

Susceptibility to Ceftriaxone

The distribution of MICs to ceftriaxone in 1988 and 1998 are shown in **Figure 16**. Over this period, there has been a subtle shift towards higher ceftriaxone MICs. In 1998, all isolates were susceptible to ceftriaxone.

Susceptibility to Cefixime

The distributions of MICs to cefixime in 1992 (the first year of cefixime susceptibility testing) and 1998 are shown in **Figure 17**. In 1998, five isolates had decreased susceptibility to cefixime: two isolates from St. Louis with MICs=0.5 Fg/ml and three isolates from Philadelphia with MICs=1.0 Fg/ml. One isolate from each location was also TetR.

Susceptibility to Ciprofloxacin

The distributions of MICs to ciprofloxacin in 1990 (the first year of ciprofloxacin susceptibility testing) and 1998 are shown in **Figure 18**. A total of 1.0% (48/4712) of isolates exhibited intermediate resistance or resistance to ciprofloxacin (MICs \geq 0.125 Fg/ml) compared with 0.6% (29/4544) of isolates tested in 1997 (**Figure 19**).

In 1998, 0.9% (44/4712) of all GISP isolates exhibited intermediate resistance to ciprofloxacin (MICs 0.125-0.5 Fg/ml). Of these isolates, 29.5% (13/44) came from Cleveland patients, where they accounted for 5.8% (13/225) of Cleveland isolates and 25.0% (11/44) came from Atlanta patients, where they accounted for 4.8% (11/227) of Atlanta isolates tested in 1998. Isolates of *N. gonorrhoeae* exhibiting intermediate resistance to ciprofloxacin were also found in Anchorage, Baltimore, Cincinnati, Honolulu, New Orleans, St. Louis, San Antonio, San Francisco, Seattle, and West Palm Beach in 1998.

Four isolates (0.1%; 4/4712) were resistant to ciprofloxacin (MICs \geq 1.0 Fg/ml) in 1998; the locations, number, and MICs of these isolates were: Cincinnati (1), 1.0 Fg/ml; Honolulu (2), 1.0 Fg/ml and 2.0 Fg/ml; and San Francisco (1), 8.0 Fg/ml.

The clinical significance of strains with ciprofloxacin MICs of 0.125-0.5 Fg/ml, when a fluoroquinolone is used to treat a gonococcal infection, is not well established. However, one study of infections with resistant strains treated with ciprofloxacin 500 mg orally showed a treatment failure rate of 45% for strains with MICs of \geq 4.0 Fg/ml.¹⁶ Gonococcal isolates with intermediate resistance and resistance to ciprofloxacin also have intermediate resistance and resistance to other fluoroquinolones. Criteria recommended for interpreting ofloxacin MICs are: intermediate resistance, MICs 0.5-1.0 Fg/ml; resistance, MICs \geq 2.0 Fg/ml.¹²

ADDITIONAL RESOURCES

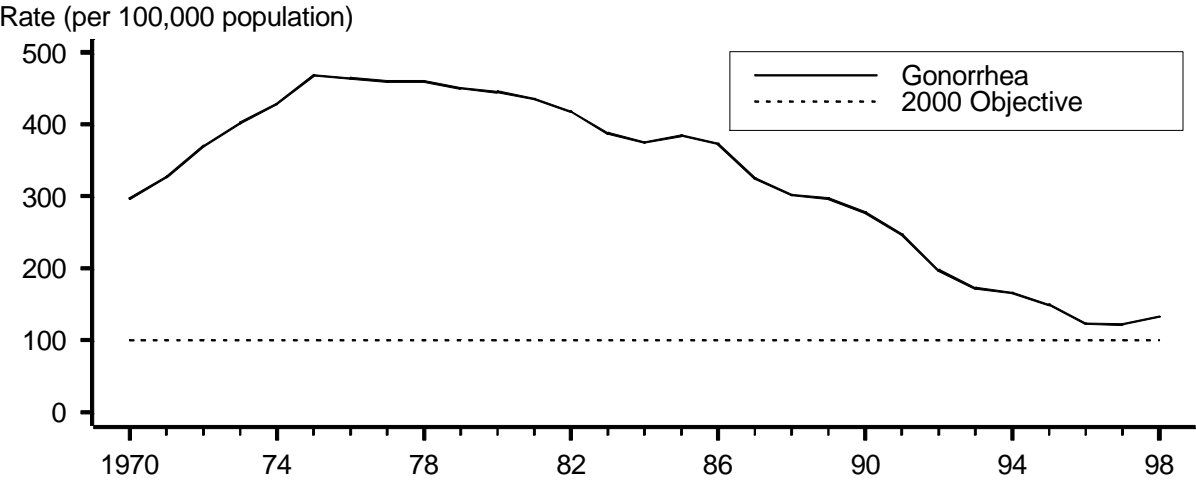
Recent publications using GISP data include a paper in the Journal of Infectious Diseases⁷ and MMWR articles in September, 1997¹³ and March, 1998.⁹ Presentations of GISP data were made at the Annual Meeting of the Infectious Diseases Society of America in September, 1997,¹⁷ the International Congress of STDs in October, 1997,¹⁸ and the International Conference on Emerging Infectious Diseases in March, 1998.¹⁹ Detailed information on susceptibilities of *N. gonorrhoeae* isolates from each clinic may be obtained through CDC's website (<http://www.cdc.gov/ncidod/dastlr/gcdir/Resist/gisp.html>). Updates on emerging resistance of *N. gonorrhoeae* strains to the fluoroquinolones may also be obtained through CDC's website (<http://www.cdc.gov/ncidod/dastlr/gcdir/gono.html>). Additional surveillance data on *N. gonorrhoeae* and other sexually transmitted diseases may be found in the 1998 STD Surveillance Report (http://www.cdc.gov/nchstp/dstd/Stats_Trends/1998_Surv_Rpt_main_pg.htm).

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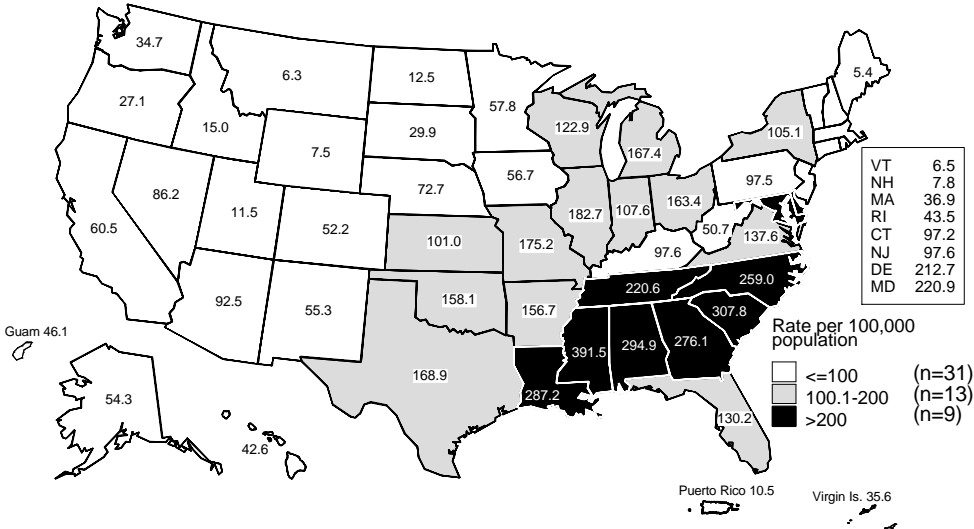
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Figure 1: Gonorrhea -- Reported rates: United States, 1970-1998 and the Healthy People year 2000 objective



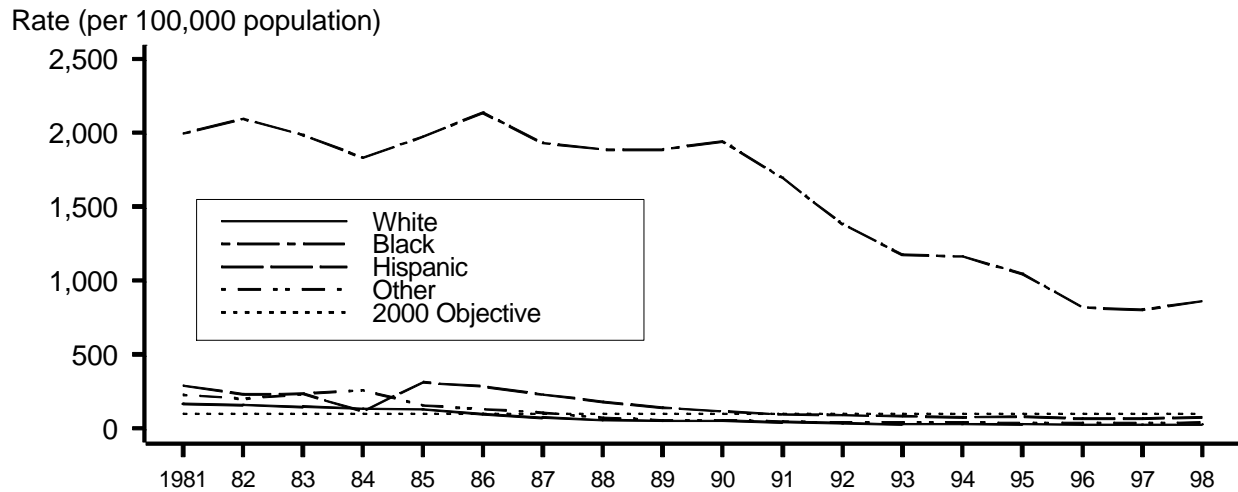
Note: Georgia did not report gonorrhea statistics in 1994.

Figure 2: Gonorrhea -- Rates by state: United States and outlying areas, 1998



Note: The total rate for gonorrhea for the United States and outlying areas (including Guam, Puerto Rico and Virgin Islands) was 131.1 per 100,000 population. The Healthy People year 2000 objective is 100 per 100,000 population.

Figure 3: Gonorrhea -- Rates by race and ethnicity: United States, 1981-1998 and the Healthy People year 2000 objective



Note: Georgia did not report gonorrhea statistics in 1994.

Figure 4: Gonorrhea -- Age- and gender-specific rates: United States, 1998



Figure 5: Gonococcal Isolate Surveillance Project (GISP) -- Location of participating clinics and regional laboratories: United States, 1998

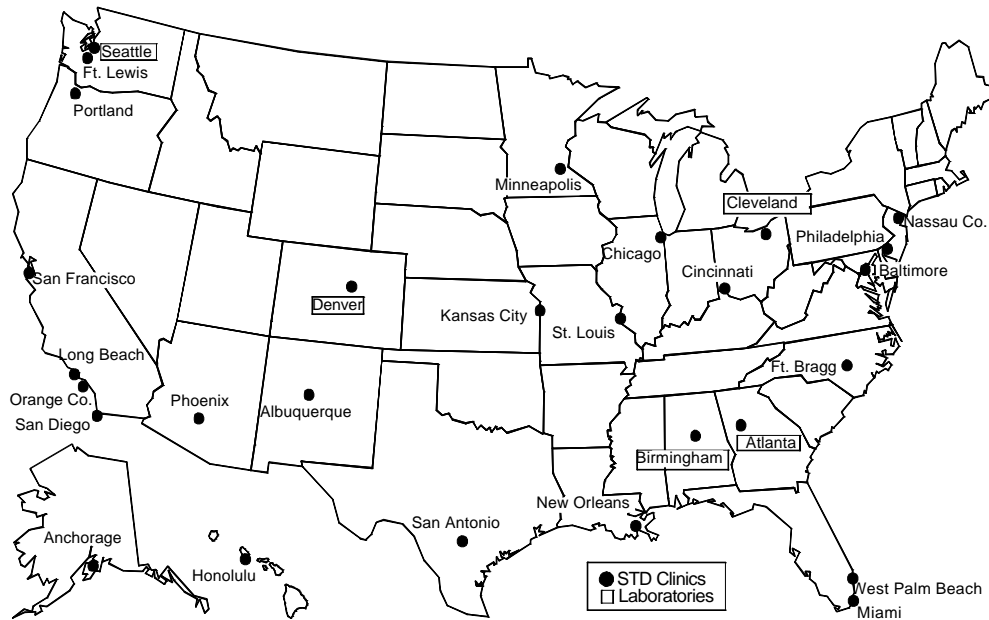
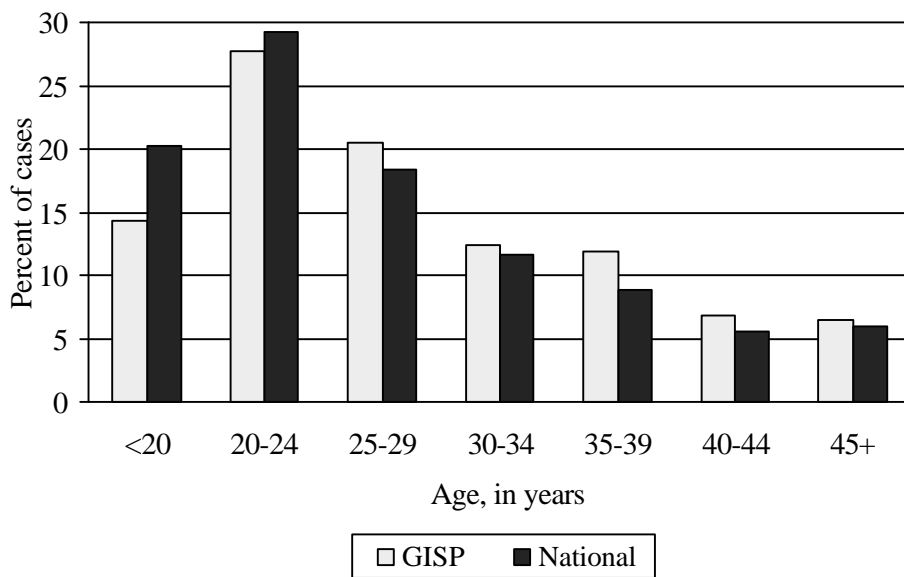
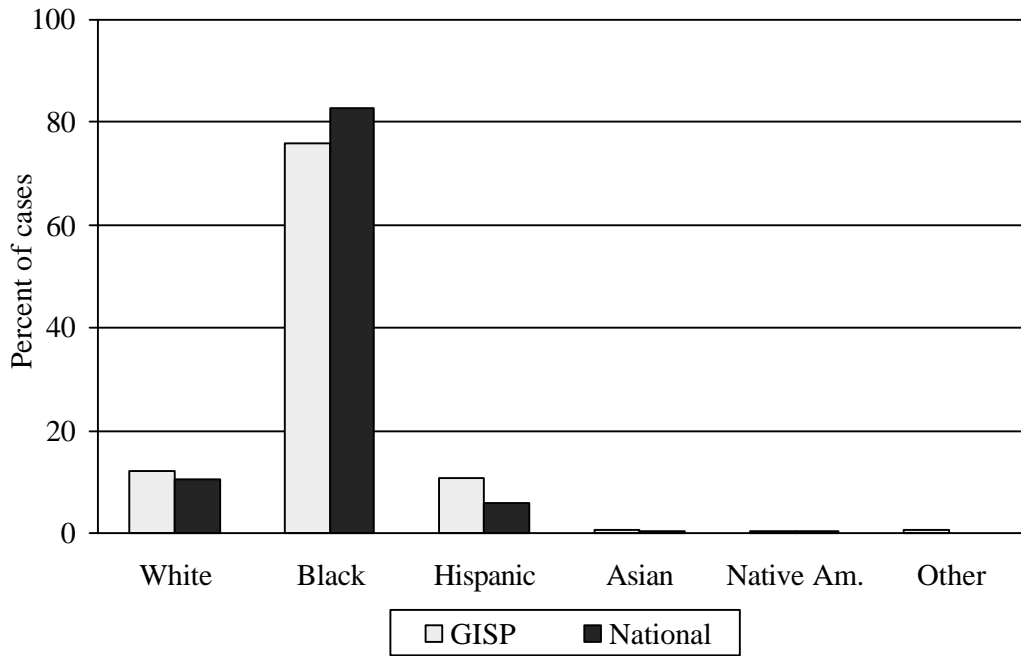


Figure 6: Age distribution of GISP participants and nationally reported gonorrhea cases in men, 1998



Note: The age<20 category includes ages 10-19 for national cases, and ages 13-19 for GISP; over 99% of the GISP cases in the <20 category are ages 15-19. National cases with unknown ages were excluded.

Figure 7: Race distribution of GISP participants and nationally reported cases of gonorrhea in men, 1998



Note: The “Other” category is not used in national gonorrhea reporting. National cases with unknown race were excluded.

Figure 8: Percentage of GISP cases that were men who have sex with men (MSM)

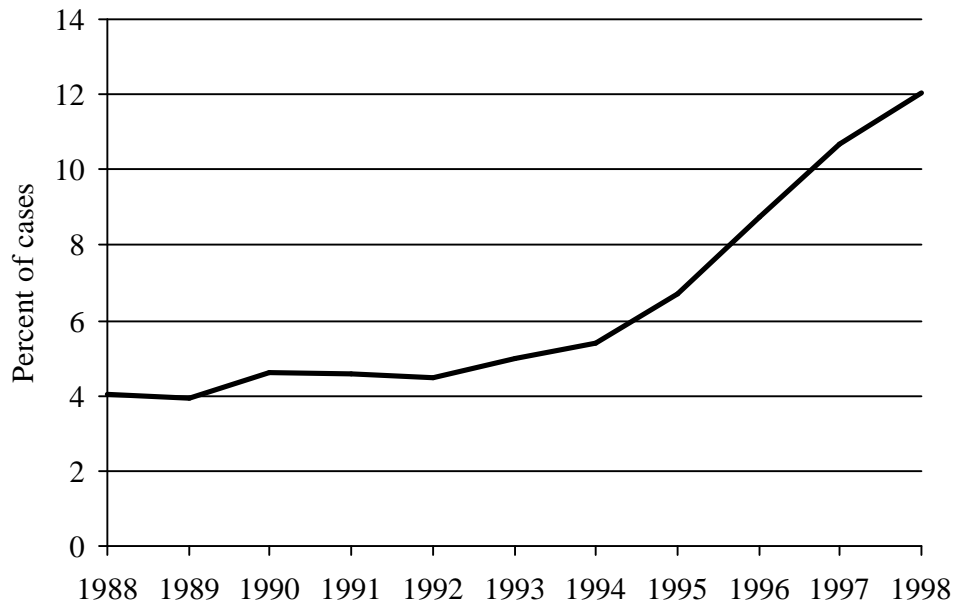


Figure 9: Percentage of GISP isolates from men who have sex with men in nine clinics, 1988-1998

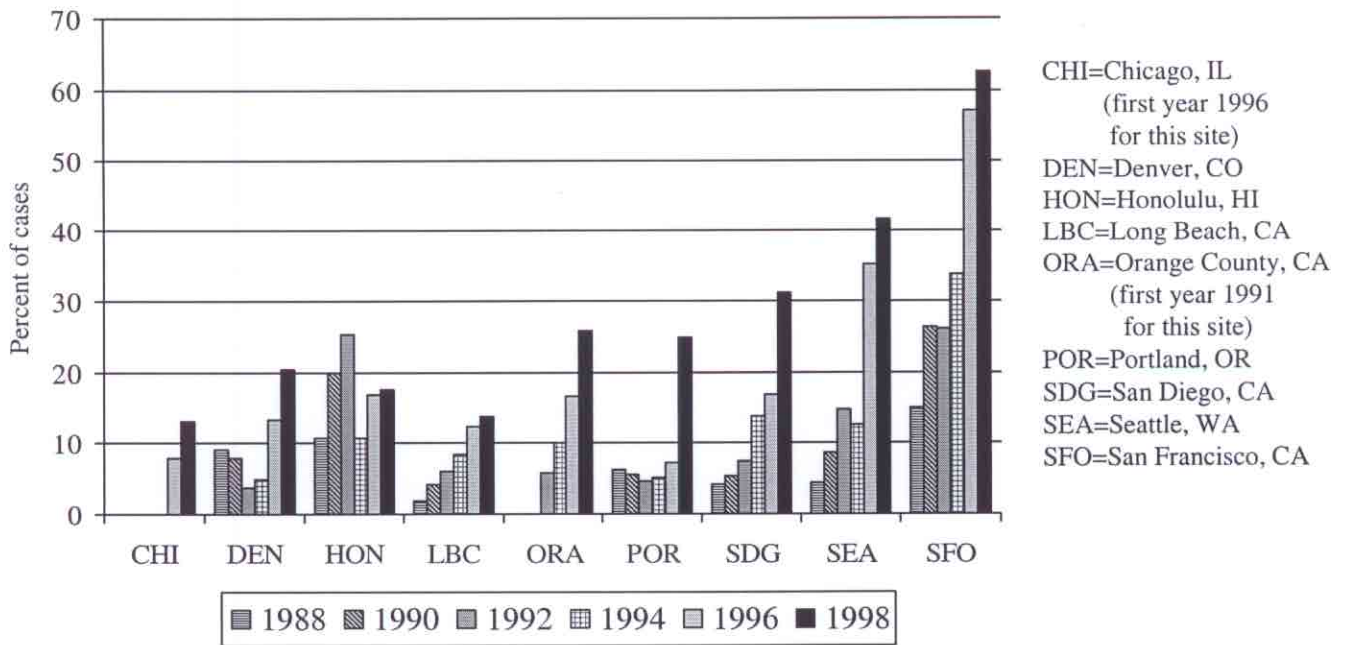
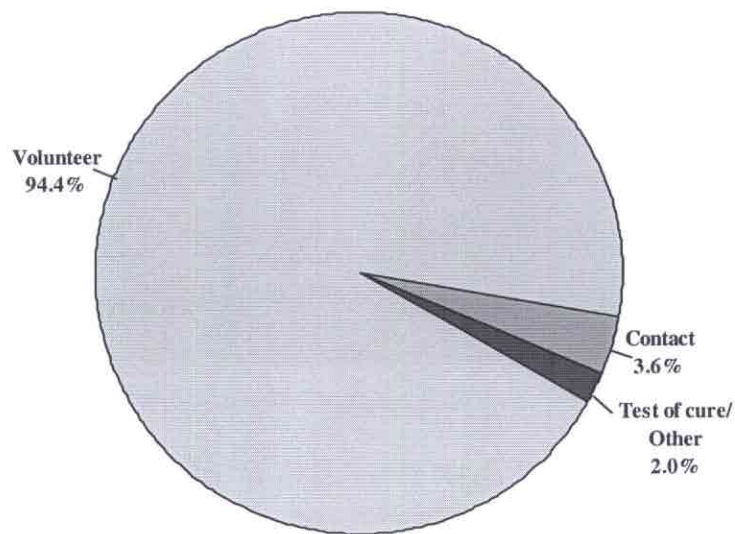
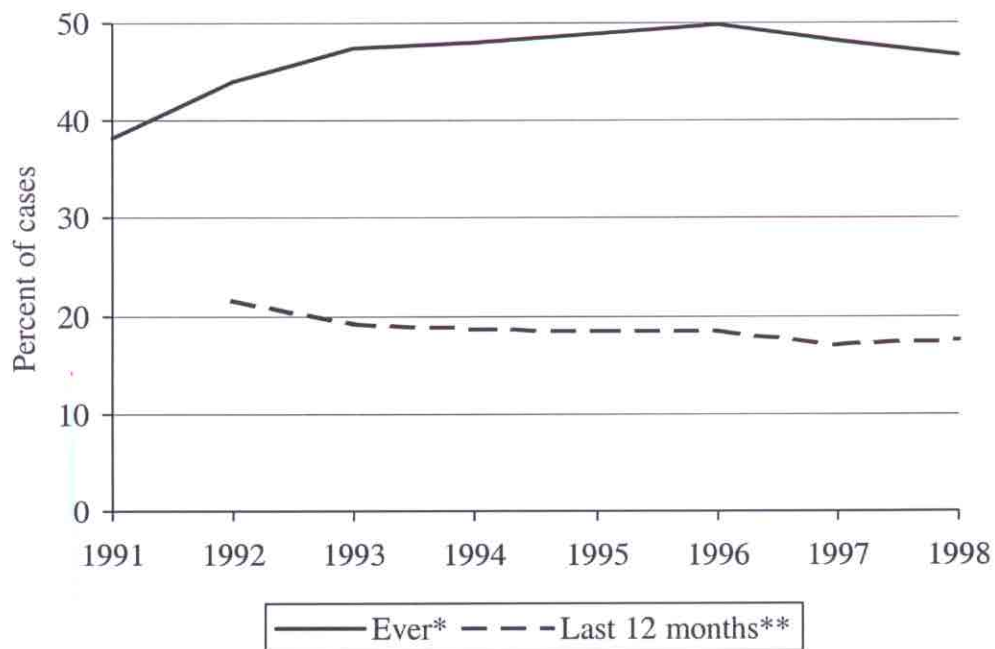


Figure 10: Reason for clinic attendance among GISP participants, 1998



Contact=has sexual partner with gonorrhea

Figure 11: History of gonorrhea in GISP participants



*Data first collected in 1991.

**Data first collected in 1992.

Figure 12: Drugs used to treat gonorrhea in GISP participants

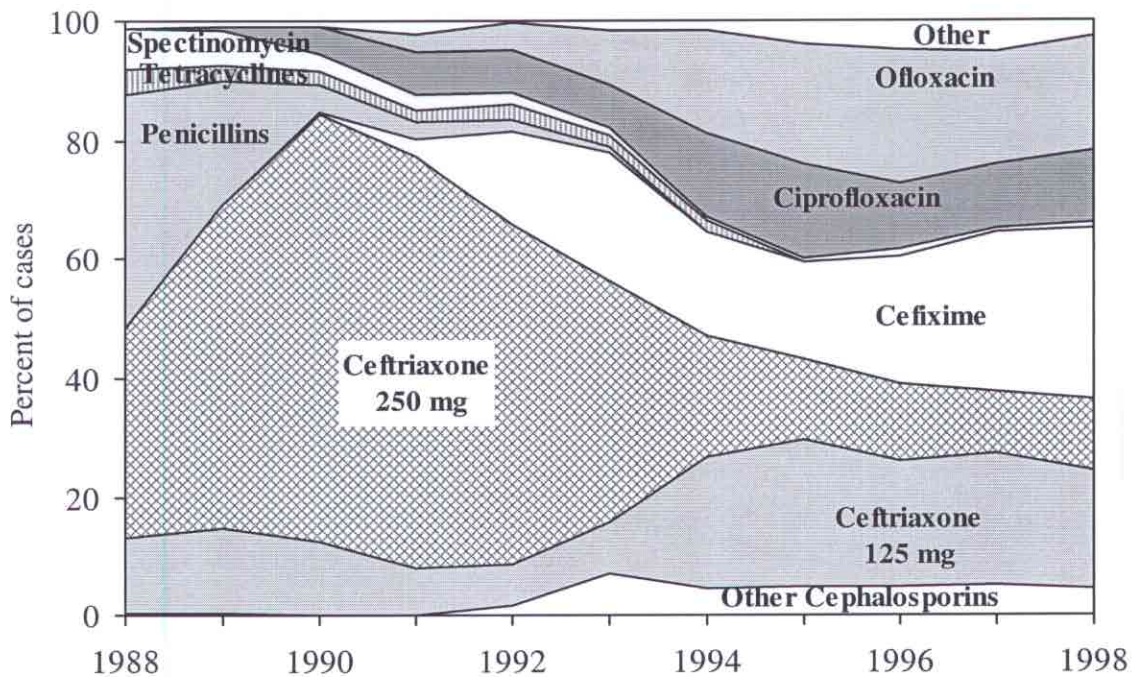


Figure 13: Penicillin and tetracycline resistance among GISP isolates, 1998

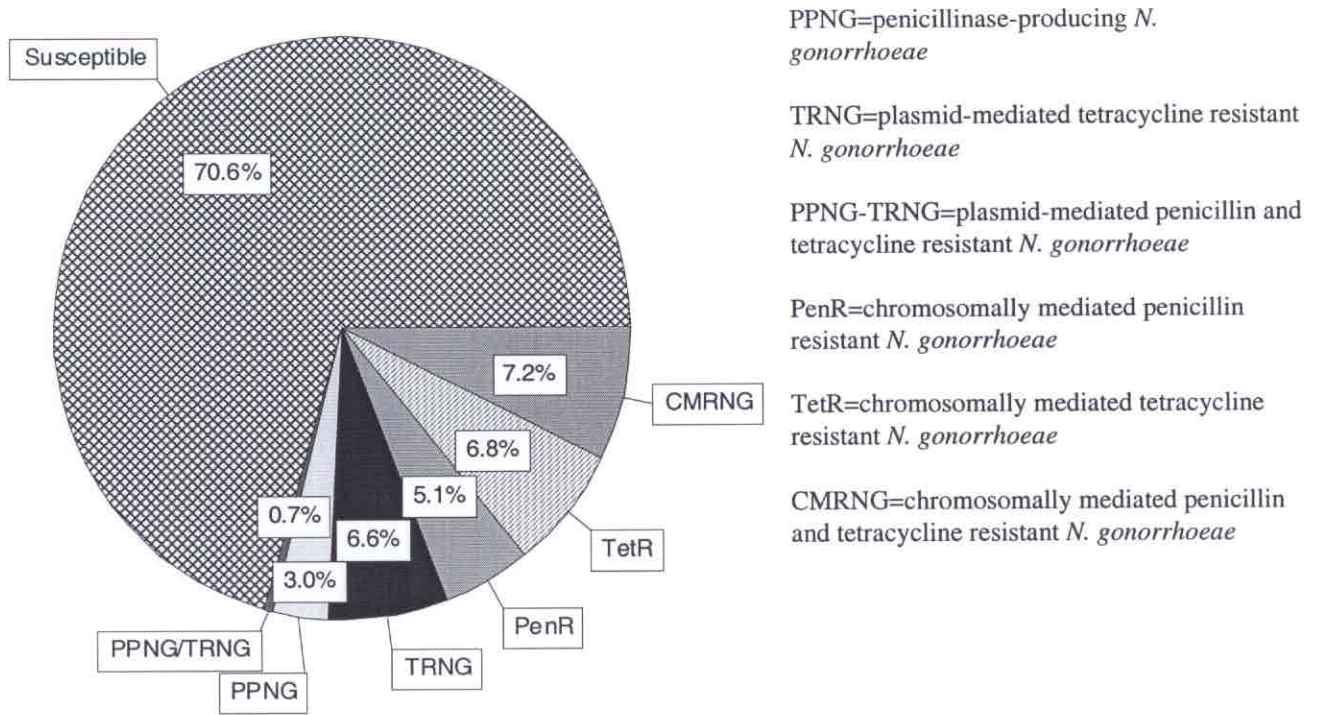


Figure 14: Plasmid-mediated resistance to penicillin and tetracycline among GISP isolates

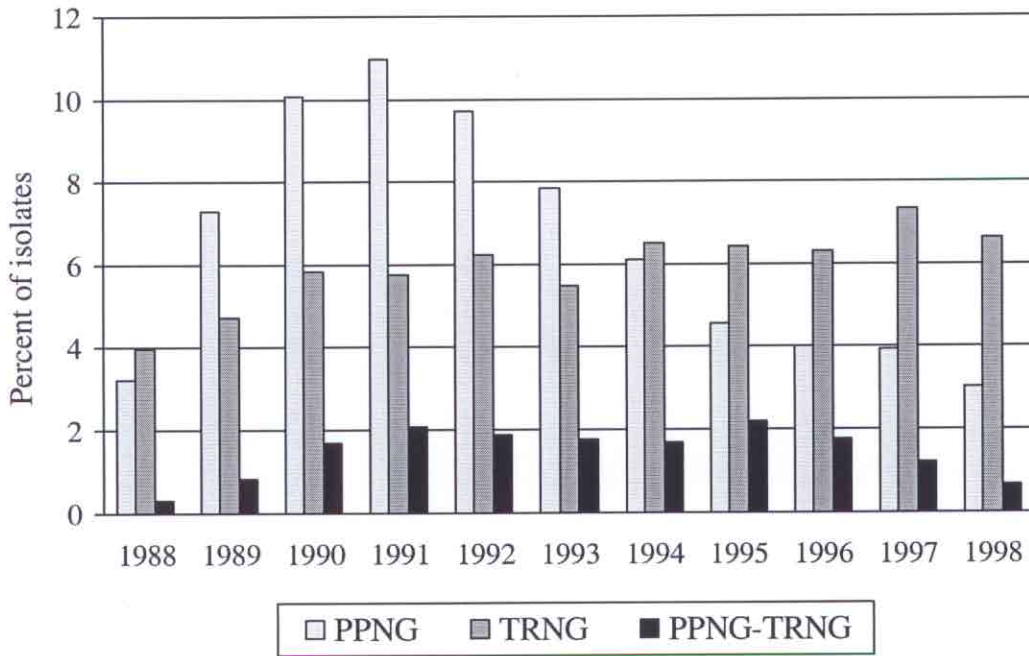


Figure 15: Chromosomally mediated resistance to penicillin and tetracycline among GISP isolates

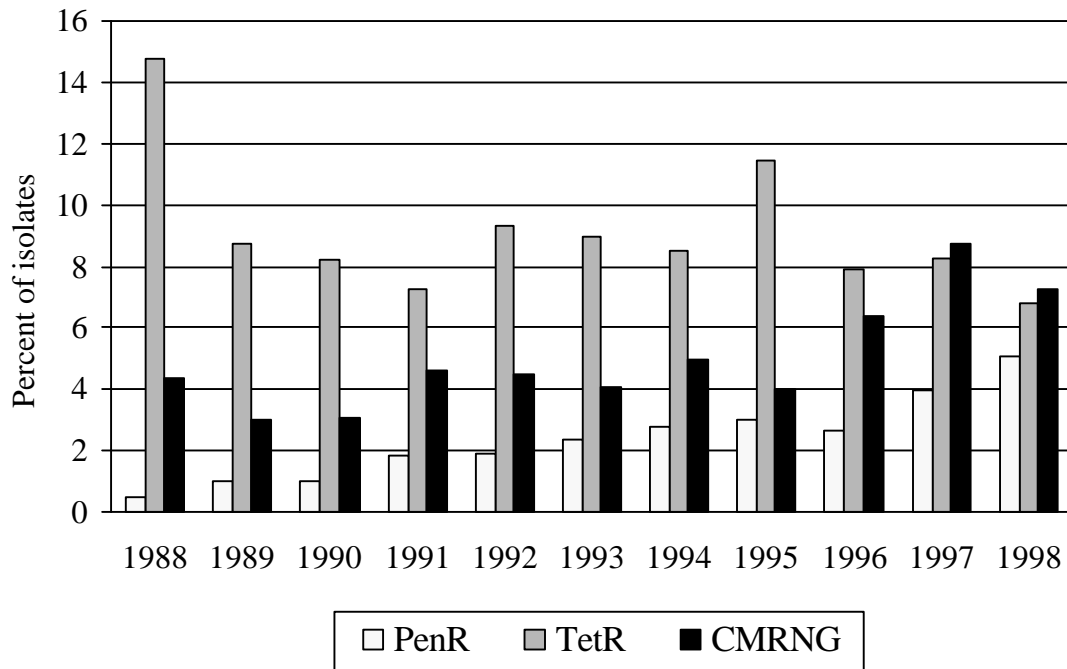


Figure 16: Distribution of MICs to ceftriaxone among GISP isolates, 1988 and 1998

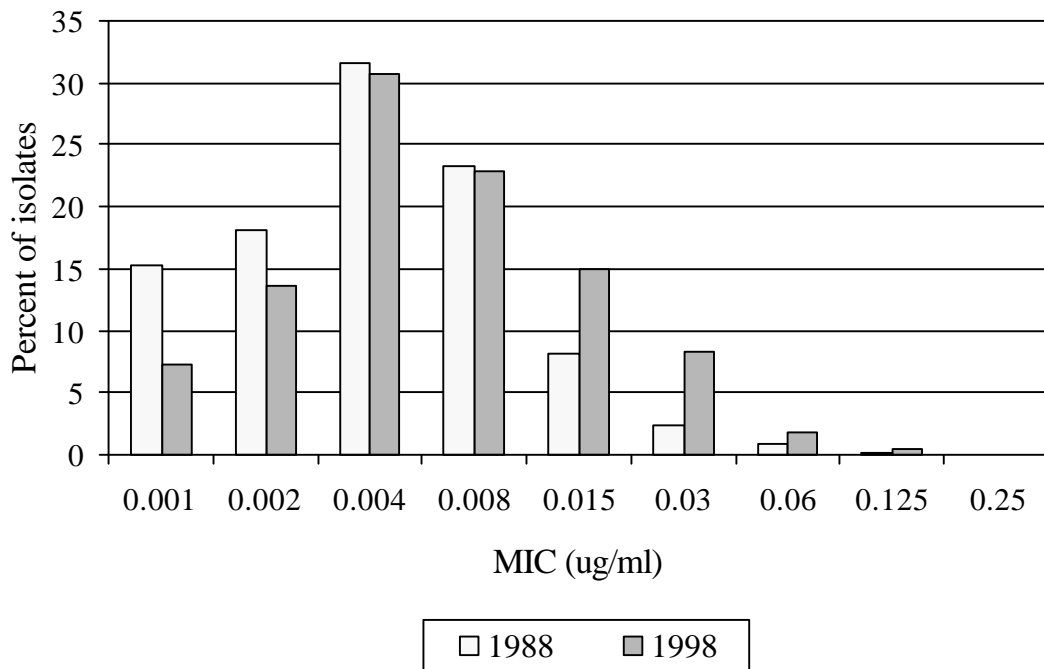


Figure 17: Distribution of MICs to cefixime among GISP isolates, 1992 and 1998

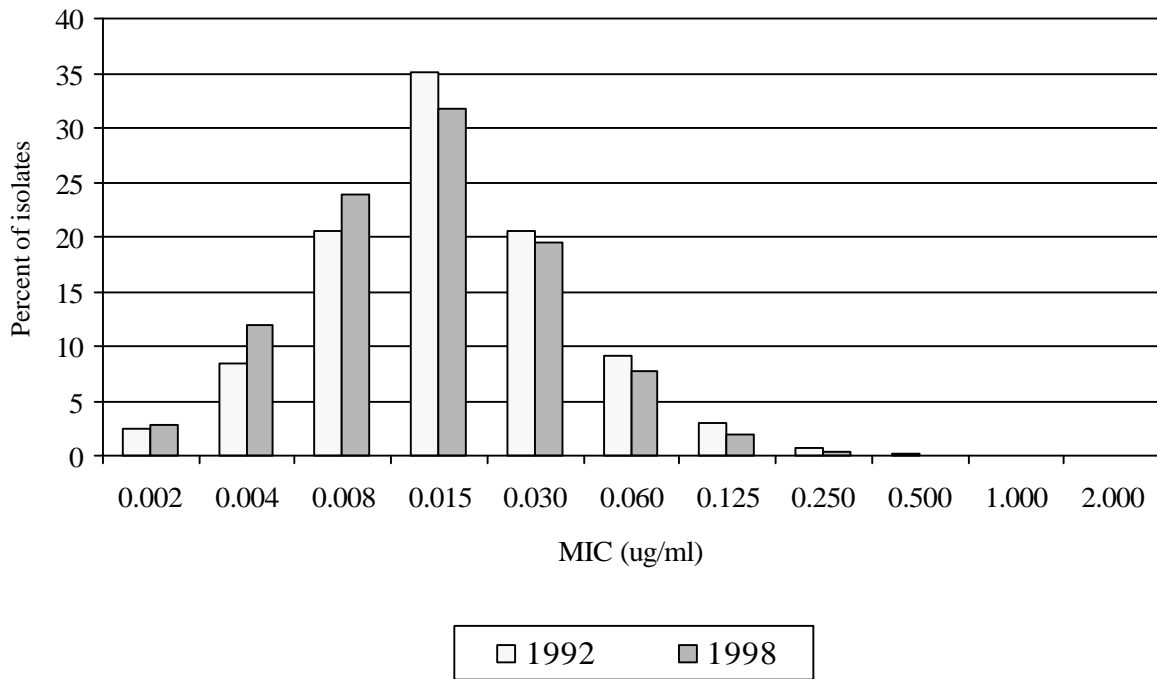


Figure 18: Distribution of MICs to ciprofloxacin among GISP isolates, 1990 and 1998

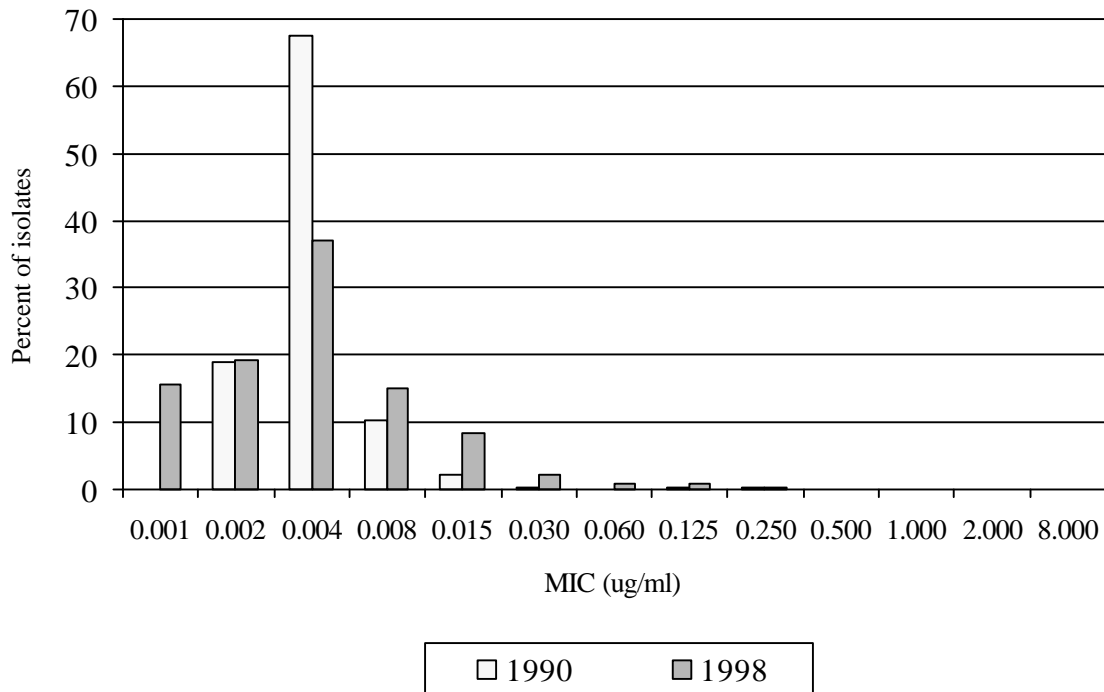
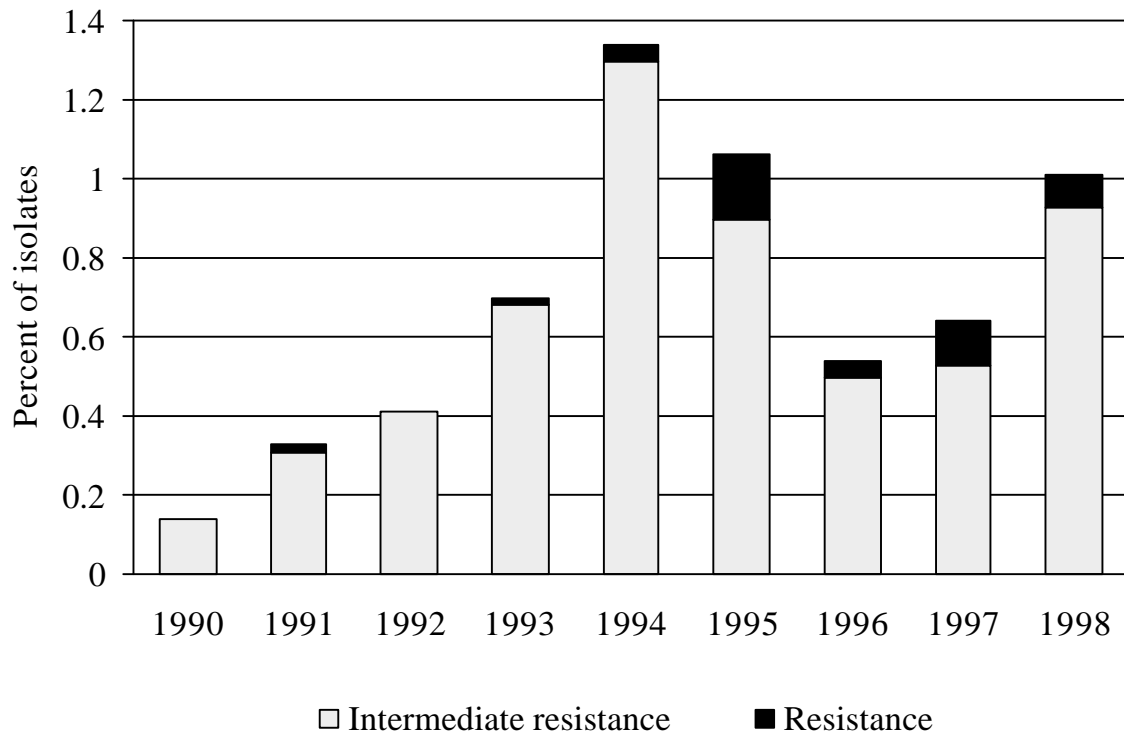


Figure 19: Percentage of GISP isolates with intermediate resistance or resistance to ciprofloxacin



CLINIC-SPECIFIC DEMOGRAPHIC, CLINICAL, AND LABORATORY DATA

The remainder of this report provides clinic-specific figures for each of the 28 currently participating clinics. Individual figures for each clinic show demographic and clinical characteristics of the men with gonorrhea enrolled in GISP, as well as antimicrobial susceptibilities for the *N. gonorrhoeae* isolates. The number of isolates submitted by each clinic is 240 when the full sample of 20 isolates per month is obtained. However, the number of isolates submitted is lower for many clinics located in areas with low gonorrhea rates. Each page of figures is labeled with the city of the participating clinic and the actual number of isolates on which the clinic's 1998 data are based.

Definitions of terms and abbreviations used in the clinic-specific figures are given below.

Figure D: contact=has sexual partner with gonorrhea

Figure F: ceftriaxone 250=ceftriaxone 250 mg
ceftriaxone 125=ceftriaxone 125 mg
other cephalo=other cephalosporins

Figure G: PPNG=penicillinase-producing *N. gonorrhoeae*
TRNG=plasmid-mediated tetracycline resistant *N. gonorrhoeae*
PPNG-TRNG=plasmid-mediated penicillin and tetracycline resistant *N. gonorrhoeae*
PenR=chromosomally mediated penicillin resistant *N. gonorrhoeae*
TetR=chromosomally mediated tetracycline resistant *N. gonorrhoeae*
CMRNG=chromosomally mediated penicillin and tetracycline resistant *N. gonorrhoeae*

Figure J: intermediate res=intermediate resistance