

BMJ Open Is there an ethnic variation in the epidemiology of gonorrhoea? A retrospective population-based study from northern Israel over 15 years between 2001 and 2015

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ABSTRACT

Objective: To investigate the trends in the incidence of gonorrhoea through an extended period of time and to compare the epidemiology of gonorrhoea infection between 2 distinct ethnic groups (Jews and Arabs).

Design: A retrospective population-based cohort study was conducted on all consecutive patients diagnosed with gonorrhoea through the years 2001–2015.

Setting: National Department of Epidemiology of the Ministry of Health, Haifa District, Israel.

Participants: A total of 837 reports on gonorrhoea were received, derived from 779 (93.1%) male and 58 (6.9%) female patients. Approximately 1 million people reside in the Haifa region.

Primary and secondary outcome measures: We examined the incidence rate of gonorrhoea among residents of Haifa District, northern Israel from 2001 to 2015, by reviewing archives of the Department of Epidemiology, Israeli Ministry of Health. Notified cases were stratified by age, gender and ethnicity.

Results: The overall gonorrhoea incidence was 6.4 cases per 100 000 population per year. The annual incidence rate dropped from 20.5 per 100 000 population in 2001 to a period of 2.2 cases per 100 000 population in 2005, showing a >9-fold decline. This was followed by a relatively steady increase of incidence of 2.5–4.5 per 100 000 population from 2006 to 2015. Men were predominantly more affected than women, with a 13.4-fold higher incidence rate. The most affected age group was residents between 25 and 34 years old. The estimated rate among Jews was 2.5-fold higher relative to Arabs. Only 1.3% recurrent episodes of gonorrhoea were reported. The prevalence of HIV positivity among patients with gonorrhoea is significantly higher than that of the general population (500.0 vs 88.1 cases per 100 000 population, respectively, $p<0.001$).

Conclusions: Gonorrhoea incidence rate decreased dramatically until 2005, with no substantial subsequent fluctuations. The infection is much more prevalent among patients of Jewish ethnicity, possibly due to riskier sex practices.

Strengths and limitations of this study

- The study sheds light on novel and remarkable differences in the epidemiology of gonorrhoea among different ethnic populations within the same geographic region.
- The study uses data collected over an extensive period of time (from 2001 to 2015).
- The validity of notifications is very high, as Israeli law mandates reporting of gonorrhoea cases, both from physicians and from microbiological laboratories.
- The retrospective design of the study itself is a limitation.
- Data are from a relatively small region populated with no more than one million inhabitants. This may weaken the external validity and generalisability of our observations.
- There was no elucidation of the precise method of gonorrhoea transmission or the sexual orientation of cases, which reduced the potential to focus on the exact causes and target populations. Furthermore, we could not examine trends of the infection among men who have sex with men, which is the group associated with the majority of outbreaks of gonorrhoea infection in industrialised countries.

INTRODUCTION

Gonorrhoea has affected humans for centuries and remains common, with an estimated 88 million cases occurring annually worldwide.¹ It is the second most commonly reported notifiable sexually transmitted disease (STD) in Israel.² Infections due to *Neisseria gonorrhoeae* are a remarkable aetiology of pelvic inflammatory disease, which can lead to several complications in women such as tubal infertility, ectopic pregnancy and chronic pelvic pain. In men, the majority of infections cause urethritis with painful

urination and, less commonly, epididymitis or disseminated gonococcal infection. Epidemiological and biological studies demonstrate that gonococcal infections raise the transmission of HIV infection by 3–5-fold.^{3–5} Although an individual's sexual practice might increase the susceptibility to gonorrhoea, social determinants of health, such as socioeconomic status, may contribute to the burden of gonorrhoea in a community.⁶

Earlier studies monitoring gonorrhoea in Israel reported a significant decline in the incidence rate starting in the early 1970s, resulting in <1 case per 100 000 population between 1993 and 1997. There was a reversal in this trend seen from 1998 to 2002, as the annual rate increased until reaching peak incidence in 2002; however, since then, incidence rate again is declining.² Recent reports from several European Union (EU) countries have revealed increases in gonorrhoea incidence, particularly in populations with higher frequency of spread of STD, such as men who have sex with men (MSM) and young heterosexual individuals of both genders.^{7–9}

Gonorrhoea disproportionately affects racial and ethnic groups, with higher rates reported among certain minorities.¹⁰ However, not much is known about differences in the epidemiology of gonorrhoea between the Jewish and Arab populations in Israel.

In this paper, we examined the epidemiology of gonorrhoea in the Haifa District over a period of 15 years in order to clarify the differences between Jews and Arabs. Moreover, we examined the proportion of HIV positivity among patients with confirmed comorbid gonorrhoea compared with those with gonorrhoea alone within the general population, estimated the rate of reinfections, and assessed the seasonal pattern of infection.

METHODS

Gonorrhoea is a notifiable disease in Israel. The first law in Israel mandating reporting of venereal diseases, contact tracing and treatment of cases and their contacts came into force in 1940 by the British mandate. Notification was performed by primary care physicians and hospitals or by microbiology laboratories throughout the country to the corresponding public health districts. The information was then collated at the Department of Epidemiology of the Ministry of Health of Israel. This passive surveillance system established in the early 1950s and still in use today provides long-term assessment of the trends in disease incidence in Israel. As in other venereal disease, contact tracing and recommendation for treatment of cases and their contacts is conducted by an epidemiological nurse from the Ministry of Health, who contacts all cases by telephone and performs an epidemiological investigation.

The definition of gonorrhoea was grounded on satisfying the laboratory criteria alongside corresponding suggestive clinical presentation. The laboratory criteria are as follows: (1) *N. gonorrhoeae* has been isolated from a

clinical specimen using bacterial culture, (2) *N. gonorrhoeae* nucleic acid has been demonstrated in a clinical specimen, and/or (3) *N. gonorrhoeae* Gram-negative *Diplococci* have been identified in a urethral smear from a man reporting on dysuria and urethral discharge. In the past few years, nucleic acid amplification tests using PCR are more widely implemented in microbiological laboratories, especially when examining clinical specimens from female patients.

In this retrospective population-based cohort study, we calculated incidence using all reported gonorrhoea cases per 100 000 population (total, female or male, age group-specific). Population data within Haifa District was extracted from Israel's Central Bureau of Statistics (<http://www.cbs.gov.il>). According to the 2008 census of the Central Bureau of Statistics, 650 000 (75.7%) Jews and 211 000 (24.3%) Arabs reside within the Haifa District.

Our way to avoid information bias that may have originated from the cross-sectional design of the study was to adopt a standardised and even method of notification; all reports included in the analysis were based on a uniform and validated forms created by the Ministry of Health.

Data analysis

We examined cases of gonorrhoea infection occurring between 2001 and 2015 that were reported to the local Haifa District Department of Health. Cases were included if either a correct physical address or postal code for Haifa District was available. We excluded cases in which the address was unknown or did not belong to Haifa District. We also excluded cases if there had been a repeat test within an interval of <90 days. We then stratified the number of cases by year, age group, gender, and Jewish or Arab ethnicity. Trends over time were tested by Poisson regression. The seasonal incidence rate for summer (April to September) and winter (October to March) were calculated on the basis of the ratio between the number of cases during the 6-month period under study and the average monthly number of inhabitants in each year.

The χ^2 analysis was used to compare rates. relative risks (RRs) and 95% CIs were calculated. All calculations were performed using Stata V.11.0, StataCorp LP, College Station, Texas, USA.

RESULTS

Overall trends

In the study period, 837 reports on gonorrhoea were received, corresponding to an overall annual incidence rate of 6.4 (95% CI 6.0 to 6.8) cases per 100 000 population. One hundred and seventy-eight (21.3%) cases were reported by clinicians from STD clinics, dermatology and gynaecology departments. The remainder of the notifications were provided by microbiological laboratories. Twenty-four anonymous notifications were excluded from

all analyses. A significant overall decrease was observed throughout the study period ($p_{\text{trend}}=0.023$). There was a steep decline in the incidence rates over the first 5 years of the study ($p_{\text{trend}}=0.014$), followed by a relatively steady increase of incidence from 2006 to 2015, interspersed with several peaks of decline ($p_{\text{trend}}=0.590$). The incidence rate of gonorrhoea dropped from 20.5 per 100 000 population in 2001 to a low of 2.2 cases per 100 000 population in 2005, representing a 931.8% decline ($p<0.001$; figure 1).

Gender

Our study cohort consists of 779 (93.1%) male and 58 (6.9%) female patients. The overall incidence rate was significantly higher among men compared with women; 12.1 cases (95% CI 11.3 to 13.0) vs 0.9 (95% CI 0.7 to 1.1) cases per 100 000 population per year, respectively (RR=13.4, $p<0.001$).

Among men, the incidence rate declined significantly from 39.4 cases per 100 000 population in 2002 to 3.8 cases per 100 000 population in 2005 ($p<0.001$). After 2005, the rates ranged between 4.3 and 7.8, excluding a one-time increase to 12.2 cases per 100 000 population in 2007. Among women, a 12-fold decline in the incidence rate was reported, from 2.4 cases in 2001 to 0.2 cases in 2007 per 100 000 population ($p<0.001$). Since 2008, the incidence began to rise, culminating in 1.4 cases per 100 000 population in 2015.

The male-to-female incidence ratio increased to a peak of 54.1 in 2007, followed by a steep decline to 9.4 in 2008. Between 2009 and 2015, male-to-female ratio ranged between 5.7 and 15.1.

Age

The mean age of patients was 30.4 ± 10.3 years, and the median age was 27.5 (range 6 months to 79.1 years). No significant difference was noted between female (30.1 ± 12.3 years) and male (30.4 ± 10.1 years) patients ($p=0.857$).

The incidence of gonorrhoea in the age group of 25–34 years was both the highest and showed the greatest decrease (from 70.6 cases in 2001 to 7.2 cases in

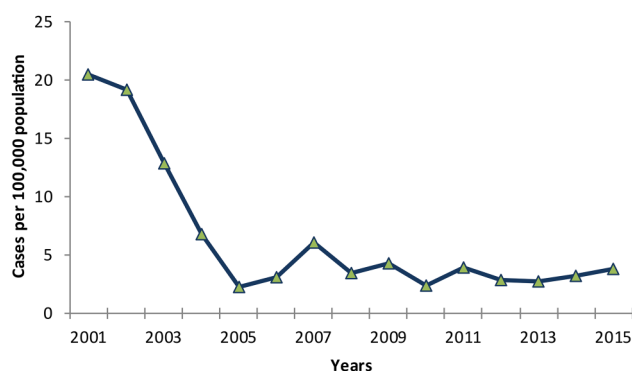


Figure 1 Incidence of gonorrhoea, notified cases in Haifa District, 2001–2015.

2005 per 100 000 population, showing a 10-fold drop, $p<0.001$). A substantial decrease was also seen in the age group of 35–44 years (from 24.1 cases in 2001 to 3 cases in 2005, representing an eightfold decrease, $p<0.001$; figure 2).

Ethnicity

The total number of cases in Jews was 742 (88.6%) and in Arabs was 95 (11.4%), corresponding to an overall incidence rate of 7.5 (95% CI 7.0 to 8.1) and 3.0 (95% CI 2.4 to 3.6) per 100 000 population per year, respectively ($p<0.001$). The incidence rate decreased consistently among Jews, falling from 22.8 cases in 2001 to 2.5 cases in 2015 per 100 000 population ($p<0.001$). Among the Arab population, the rate fell dramatically from a peak of 14.1 cases per 100 000 population in 2001 to an absence of case notifications in 2014 ($p<0.001$; figure 3).

Repeat infection with gonorrhoea

During a passive follow-up period ranging from 3 months to 15 years, contributing 7765.8 person-years, 11 (1.3%) recurrent episodes of infection with gonorrhoea were registered in our study cohort, occurring in nine different patients. The mean age of patients who suffered from repeat episodes was 23.1 ± 4.6 years, and the median was 21 (range 19–32) years. All of them were men of Jewish ancestry.

For patients who had at least one repeat infection during the study period, the average time to first repeat infection was 3.7 ± 3.2 years.

HIV co-infection

When the registries of HIV and gonorrhoea in Haifa District were cross-linked, we identified four patients (500 cases per 100 000 population) who tested positive for gonorrhoea and HIV. This proportion is significantly higher than HIV positivity in the general population of Haifa (88.1 cases per 100 000 population; $p<0.001$).

Seasonal epidemiology

The seasonal incidence of gonorrhoea is illustrated in figure 4. The average monthly incidence rates varied from a low of 0.4 cases per 100 000 population in September to a high of 0.9 cases per 100 000 population in January. The difference in the seasonal incidence rates for winter (3.8 cases per 100 000 population) and summer (2.6 cases per 100 000 population) was statistically significant ($p<0.001$).

DISCUSSION

From the beginning of the previous decade until 2005, a marked decline in the incidence of gonorrhoea was observed in Haifa District ($p_{\text{trend}}=0.014$), followed by a constant rate until the end of follow-up in 2015 ($p_{\text{trend}}=0.590$).

Figure 2 Incidence of gonorrhoea by age group, notified cases in Haifa District, 2001–2015.

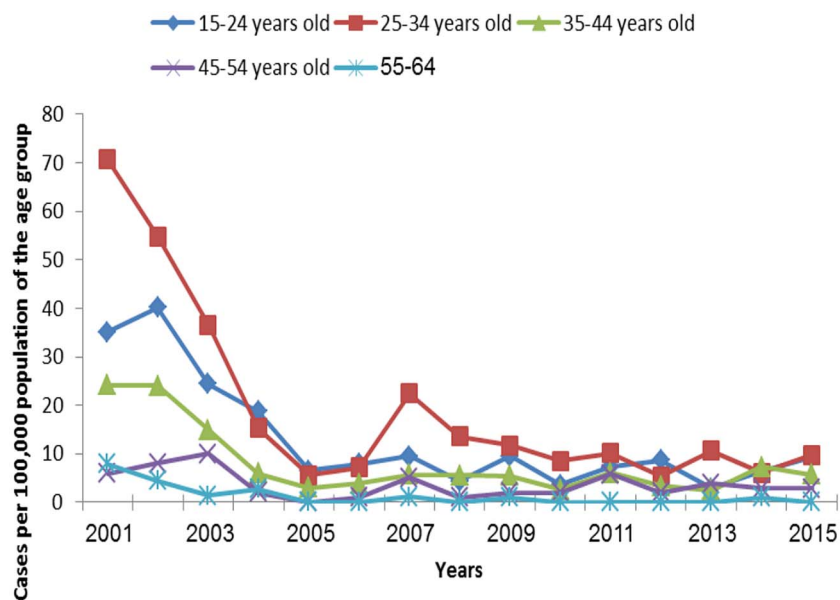


Figure 3 Incidence of gonorrhoea by ethnicity, notified cases in Haifa District, 2001–2015.

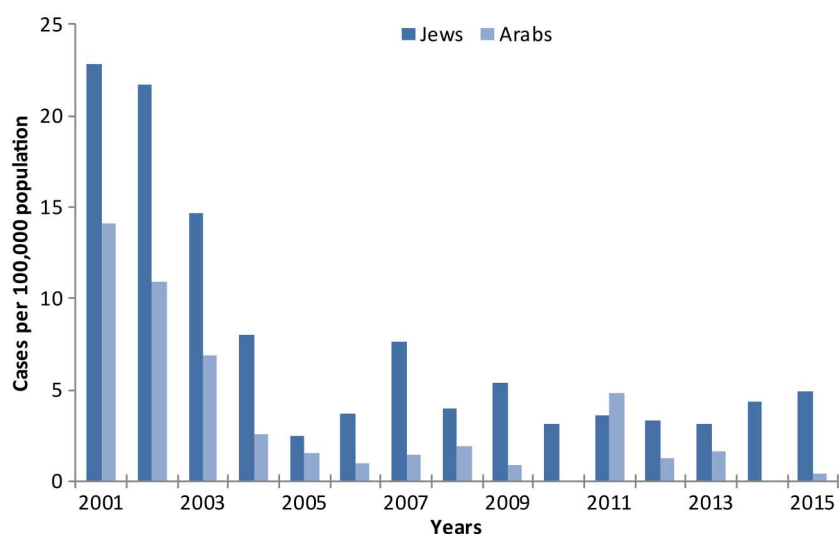
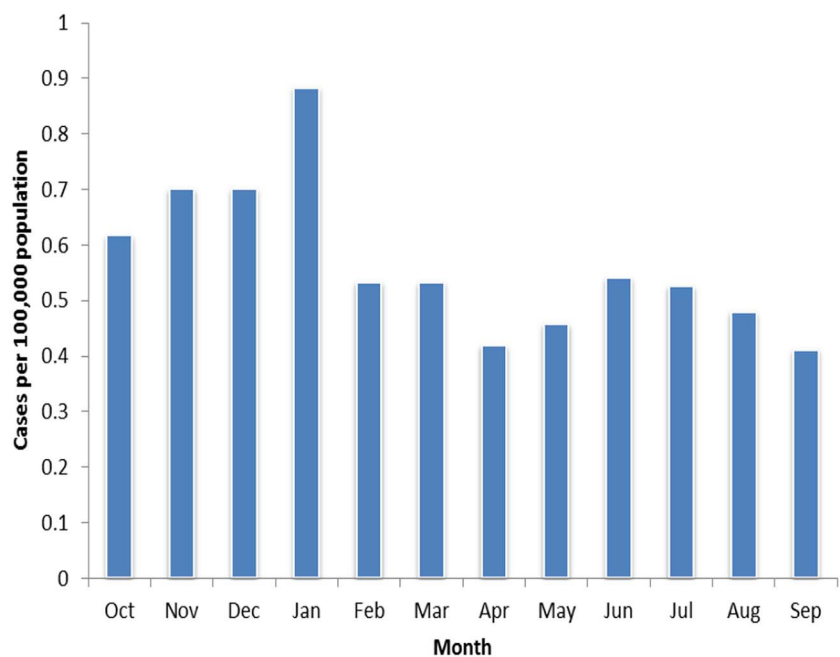


Figure 4 Monthly incidences of gonorrhoea, notified cases in Haifa District, 2001–2015.



Explanations for the trends

The consistent drop in the incidence of gonorrhoea since the late 1980s in Israel was attributed mainly to the worldwide HIV epidemic. It is assumed that widespread fear of HIV infection led to less hazardous sexual practices, especially among MSM, and to an overall decline in all STDs.¹¹ Although evidence for sexual behaviour risk reduction in response to the HIV epidemic among heterosexuals is limited, increased condom use has been documented.¹² This decline was not exclusive for Israel; it was also observed in Europe and the USA and was reinforced by researches demonstrating an association between the rise in prevalence of anti-HIV antibodies in homosexual and bisexual men and a decline in the frequency of gonorrhoea.^{2 13} Interestingly, this decrease is valid also for early syphilis in Haifa District (Grifat R, unpublished data).

A rise in gonorrhoea incidence was reported in the general Israeli population during the years 1999–2002, and paralleled the increasing rates in the UK and several other European countries.^{14–18} Subsequent to this surge, some interventions were adopted by the Israeli Ministry of Health in order to control the disease's occurrence. Health education and prevention programmes were intensified, and free medical check-up for commercial sex workers were initiated. Furthermore, free outpatient and mobile STD clinics have been made accessible to the public. These interventions may have contributed to the observed decline in gonorrhoea.¹⁹

In the USA, an ongoing decline since the 1970s can be explained by the shift in the age distribution of the US population towards increased ages, indicating that a decreasing proportion of people belong to the highest risk age groups.²⁰ This explanation is far from being relevant in Israel due to increasing birth rates and an increasing proportion of younger people within the general population.

Gender and ethnic distribution of patients

Reported incidence rates of gonorrhoea had historically been higher in men than in women, a discrepancy ascribed mainly to the higher rate of asymptomatic disease in women and higher incidence of infection among MSM. In the USA, increased active case finding among women and the decline in the occurrence among MSM since the 1980s have resulted in a nearly equal proportion of cases in men and women nationally.²¹ However, the incidence rate in our study was 134-fold higher among men compared with women. The male-to-female ratio fluctuated but generally trended downwards until it reached an all-time low in 2015 (4.5:1). The main explanation for the male predominance in relation to reports from other western countries is the lack of screening programmes for gonorrhoea among pregnant women, which might lead to underdiagnosis of the infection among women. Furthermore, according to local social norms, it is more

acceptable for men to have multiple sexual partners, while it is less acceptable for women.

Risk factors for gonococcal infections include belonging to a minority ethnic group, having a low educational level, and being from a low socioeconomic level.^{10 22 23} However, the risk of infection with gonorrhoea in Arabs, who constitute the minority disadvantaged ethnic population in Israel, was 2.5-fold lower than in Jews. The main explanation of this finding is the unsafe sexual practice among Jews who adopt a more western and liberal lifestyle as compared with conservative norms in the Arab society. Many polls, articles and surveys suggest that Israeli-Arabs as a group are generally conservative, traditional and hierarchical with regard to sex roles, the centrality of the family and sociocultural hierarchy.²⁴ Another potential interpretation of the discrepancy, although less probable, is the lower testing rate among Arab patients due to lower health awareness. This interpretation is less probable because the two populations share the same healthcare facilities and are exposed to similar primary prevention campaigns.

HIV co-infection

Gonorrhoea has a significant epidemiological association with HIV. First, the acquisition of gonococcal infection indicates risky sexual practice that is, in turn, an identified predictor for HIV infection. Second, gonococcal infections seem to facilitate both the transmission and acquisition of HIV,^{3 4} and conversely, the presence of HIV infection is associated with increased acquisition of *N. gonorrhoeae*.²⁵ The concentrations of HIV RNA in semen were eightfold higher among patients with gonococcal urethritis as compared with controls.³ Moreover, treatment of the urethritis lowered HIV RNA levels by two-thirds. The molecular mechanisms accounting for the enhanced HIV transmission may include activation of HIV-infected CD4 cells by *N. gonorrhoeae*, causing increased HIV expression and viral production.²⁶ Furthermore, gonococcal infection during the acquisition of HIV is associated with an altered HIV-specific CD8 cell response.²⁷ In our study, we found that the prevalence of HIV among patients with gonorrhoea (500.0 per 100 000) was significantly higher than in the general population (88.1 per 100 000; $p < 0.001$).

Seasonality

Israel is located between 29° and 33° north of the equator and is characterised as a subtropical region. The northern and coastal regions of Israel have a Mediterranean climate, characterised by hot and dry summers with cool, rainy winters. Israel generally has two main seasons—winter (October to March) and summer (April to September).

Our data depict that gonococcal infections are more prevalent in the winter. This observation is in contrast to previous reports on the seasonality of gonorrhoea^{19 28 29} and other STDs,^{29 30} which illustrate a higher frequency in summer. Our results are in line with the findings of

numerous studies demonstrating higher levels of testosterone in the fall months.^{31–33}

Our reporting system may suffer from a delay that can potentially interfere with the seasonal analysis. However, it is less probable that such a delay would affect data collected over an extended period of 15 years.

Limitations of the study

In addition to the retrospective design of the study, we provide data from a relatively small region populated with no more than one million inhabitants, which may limit the generalisability of the results. Second, we could not elucidate the precise way of transmission and the sexual orientation of the infected patients, thus reducing the possibility of focusing on the exact causes and target populations. Furthermore, we could not examine trends of the infection among MSM, which were associated with the majority of outbreaks of the infection in industrialised countries.^{34–37}

CONCLUSION

This population-based study demonstrates that the incidence rate of gonorrhoea infection decreased dramatically from 2001 to 2005, with no substantial subsequent fluctuations. People of Jewish ancestry were significantly more affected by the infection than were Arabs, which may be attributed to less safe sexual practices. An overwhelming male predominance of infection was observed. The infection was more frequent in winter and was significantly more prevalent among patients with coexisting HIV infection.

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Contributors KK and RG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KK and MK were involved in study concept and design, and acquisition, analysis and interpretation of data. KK and RG were involved in drafting of the manuscript and critical revision of the manuscript for important intellectual content. MK was involved in statistical analysis. RG was involved in administrative, technical and material support. MK and RG were involved in study supervision.

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