Dynamics and Control of the Transmission of Gonorrhea

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Calculations revealed that approximately a third of the reported cases of gonorrhea in women during 1973–1975 were discoveries of the screening program. Theoretical models and epidemiologic data showed that the prevalence of gonorrhea adjusts rapidly to changes in social behavior, medical treatment, and control programs, that prevalence oscillates seasonally around an equilibrium state determined by the current social and medical conditions, and that this equilibrium moves as epidemiologic conditions change. The incidence of gonorrhea is theoretically limited by saturation in a sexually active core population, and this core causes gonorrhea to remain endemic.

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GONORRHEA is a worldwide health problem. The U. S. Public Health Service estimates that there are about 2.6 million cases annually of infection with *Neisseria gonorrhoeae* in the United States.[1] This total represents an estimate of 1.3 million treated cases in men and takes into account under-reporting by private physicians; also included in the total are approximately 1.3 million treated and untreated cases in women.

Gonorrhea has distinct epidemiologic characteristics that must be considered in the development of a conceptual model. Only the sexually active individuals in a community who could be infected by their contacts need be considered. Since individuals do not recover spontaneously from gonorrhea for a long time after exposure, many infected persons remain infectious until they receive antibiotic treatment.[2] Since little immunity is derived from having been infected, most treated individuals are susceptible again as soon as the antibiotics have left the body.

Since gonorrhea differs from frequently modeled infectious diseases, such as influenza and measles, where the infective levels are limited by the accumulation of immune individuals, new models for gonorrhea had to be developed. Cooke and Yorke[3] analyzed a mathematical model for gonorrhea. Reynolds and Chan[4] developed a model for gonorrhea in the United States, estimated the model parameters, and projected the prevalences for women and men, both without and with controls. Hethcote[5] developed communicable disease models and used a host–vector model in a calculation for control of gonorrhea. Lajmanovich and Yorke[6] presented a very general model for gonorrhea. The purpose of this paper is to develop useful theoretical concepts about the dynamics of transmission of gonorrhea and its control.

The Screening Program

In fiscal year 1972 a program was begun in the United States for bacteriologic culturing of cervical specimens from women to detect asymptomatic infection with *N. gonorrhoeae*.[1] In this report we estimate the number of women who are being discovered to have gonococcal infection but who would not be discovered without the screening program. We define a new case report as "diagnostic" when the (positive) culture test was administered to the woman because she had symptoms suggesting gonococcal infection or because she had had sexual contact with an individual thought to be infected. Screening program "discoveries" are those cases reported because of positive results of culture tests performed as

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TABLE 1. Calculation of Numbers of "Discoveries" of Gonorrhea in Women Made through Screening Program in United States

Factor Measured	Fiscal Year 1973	1974	1975
(1) Culture tests processed	4,939*	8,017	8,864
(2) Estimated no. of culture tests in screening program	3,939	7,017	7,864
(3) Reports of gonorrhea in men	505	523	562
(4) Reports of gonorrhea in women	305	351	384
(5) Expected no. of diagnostic reports of gonorrhea in women as inferred from no. of reports of gonorrhea in men			
Method A	197	205	220
Method B	227	244	277
(6) No. of discoveries ([4] minus [5])			
Method A	108	146	162
Method B	83	107	104
(7) Percentage of discoveries in screening tests ([6] divided by [2])			
Method A	2.7%	2.1%	2.1%
Method B	2.1%	1.5%	1.3%
(8) Percentage of discoveries in all women with gonorrhea ([6] /1.3 million × 100)			
Method A	8.3%	11.2%	12.5%
Method B	6.4%	8.2%	8.0%

*Number of cases in thousands.

part of routine pelvic examinations or when there was no special reason to expect infection.

The data used in this section are from the Center for Disease Control *VD Fact Sheet*.[7] We estimate (Table 1) that approximately a million of the culture tests performed each year were done for purposes other than screening. No accurate estimate is available, but this figure is not crucial to our results. In fiscal year 1971, the male-to-female ratio for reported cases was 1:0.391, and essentially all reports of gonorrhea in women were diagnostic; screening did not start until fiscal year 1972. Method A assumes the ratio 1:0.391 of reported cases in men to diagnostic cases in women is maintained each year through fiscal year 1975. In fact, during 1967–1971, the percentage increase for reports of gonorrhea in women was 6% per year higher than that for reports of the infection in men (Fig. 1). Method B assumes that the number of diagnostic cases in women continued to increase 6% faster than the number of reported cases of the disease in men. Hence, the ratio of reported cases in men to diagnostic cases in women would be 1:0.414 for fiscal year 1972, 1:0.439 for fiscal year 1973, etc. These assumptions become less reasonable as we move further from the base period ending in 1971.

The estimated yearly number of discoveries in Table 1 is the number of reports of gonorrhea in women that exceeds the estimated number of diagnostic reports. From lines 4 and 6 in Table 1, we conclude that in fiscal years 1973–1975 approximately a third of the reported cases of gonorrhea in women were discoveries of the screening program. We used the estimate of 1.3 million as the actual yearly incidence in women[1] for calculation of the percentage of discoveries among all reported cases in women. We also conclude that in fiscal years 1974 and 1975, approximately 10% of all actual cases of gonococcal infections in women in the Unites States were discoveries of the screening program. Some of the improved detection of infection in women during 1972–1975 may have resulted from improvements in other aspects of control of gonorrhea, such as clinics, case investigations, educational programs, and medical treatment. These factors may explain why the number of reports of gonorrhea in women rose 6% faster than the corresponding number of reports for men prior to 1972. Method B for estimating discoveries assumes that this trend has continued.

The estimate of 10% is probably an underestimate, for two reasons. First, we have assumed that the number of reported cases in men is a fixed percentage of the actual incidence in men. The cases in women discovered by screening undoubtedly brought some of their male contacts to treatment; these men otherwise might not have received treatment. Overestimation of the actual incidence in men would cause the number of diagnostic cases in women to be overestimated and, consequently, the number of discoveries to be underestimated. Second, some discoveries of the screening program otherwise would have been later diagnostic cases, so that we are overestimating the diagnostic cases and underestimating the discoveries.

We can estimate the percentage of all gonococcal infections in women in the United States that represents discoveries of the screening program in another way. Although accurate estimates are not available, values consistent with those used by Constable[8] and Reynolds and Chan[4] are 10 days, 55 days, and 100 days for the average durations of infectious periods for men, both sexes, and women, respectively. If about 7.4 million screening culture tests were performed per year in fiscal year 1974 and fiscal year 1975, then about 2.0 million screening culture tests were performed per 100-day period. If the population being screened were the 30.6 million women in the United States who are between the ages of 15 and 34 years, then the percentage of infectious women who would be tested during their infectious period would be $(2.0 \div 30.6) \times 100\% = 6.6\%$. However, the actual percentage would be higher because the screening program concentrates on sexually active women; thus we feel the 10% estimate obtained above is reasonable.

Rapid Response

We claim that the prevalence and, consequently, the incidence of gonorrhea change rapidly when epidemio-

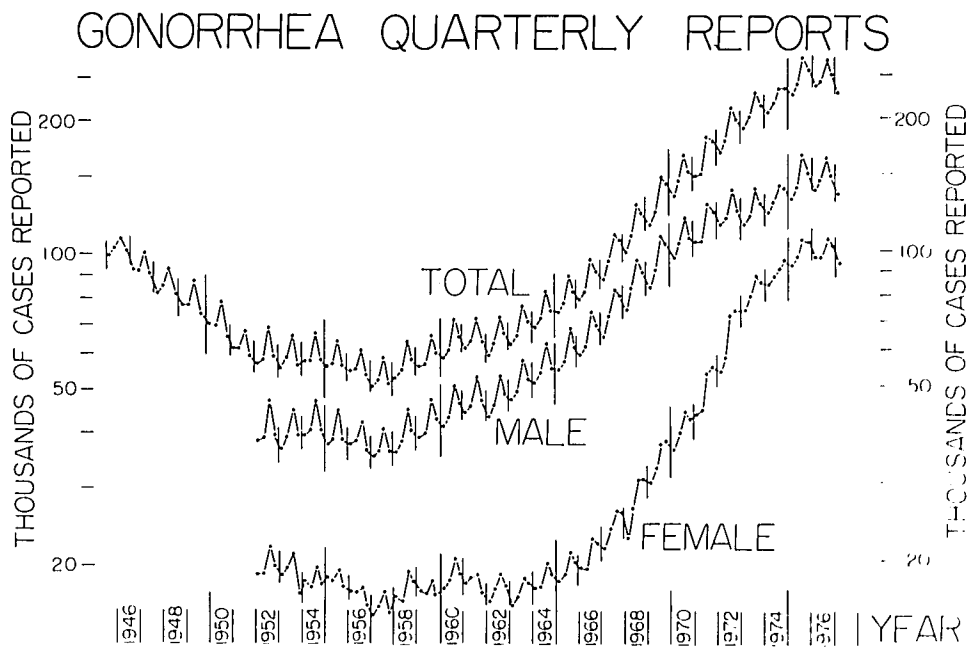

Fig. 1. Incidence of gonorrhea in the United States, 1946–1977. The quarterly incidence data are taken from U. S. Public Health Service reports.[7]

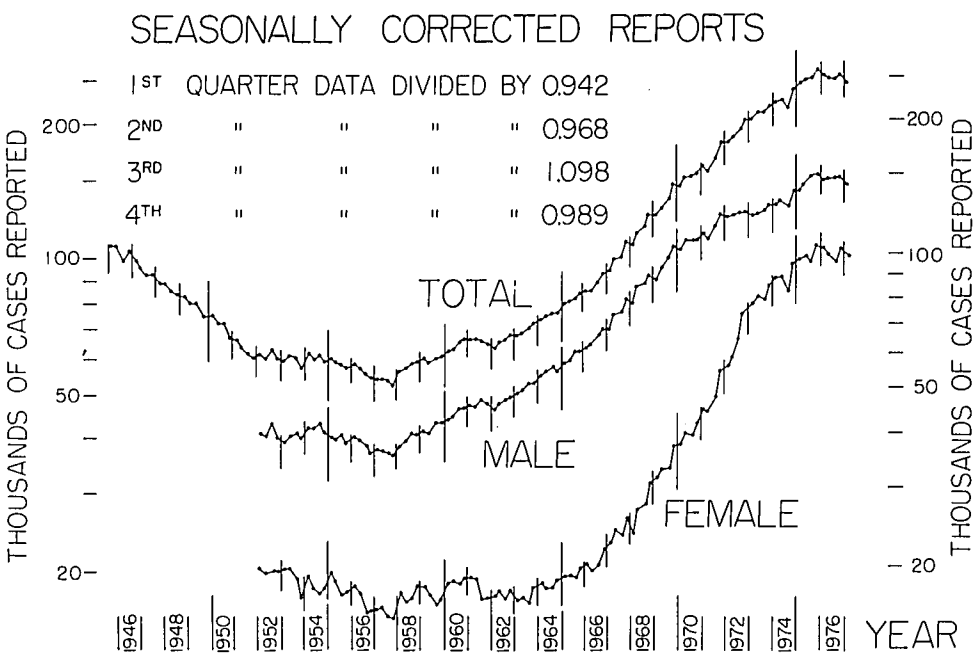

Fig. 2. Seasonally corrected incidence of gonorrhea in the United States, 1946–1977.

logic conditions change, and we present a variety of evidence to support this claim. By rapid response we mean that the responses of the incidence of infection to changes in factors such as control programs or sociosexual behavior do not take years, but occur within, at most, a few months. For example, we predict that if all venereal disease clinics in a state were suddenly closed, the actual incidence of gonorrhea in that state would increase sharply to a new level within a few months. On the other hand, if the change were spread out in time, the resulting change in incidence would be correspondingly spread out.

The incidence of gonorrhea has always oscillated seasonally.[9] Figure 1 shows that the seasonal oscillation occurred every year from 1946 to 1977. It was also evident in data from 1919–1926 (O. G. Jones, personal communication). This seasonal change in the incidence of gonorrhea must be due to seasonal changes in epidemiologic conditions; therefore, the response time must be a few weeks or months, and not years.

Another example of the rapid response of gonorrhea is reflected in the observed increases in nationally reported cases of gonorrhea about four weeks after Christmas and New Year's Day, when most treatment facilities are closed (O. G. Jones, personal communication).

It is not possible to predict a priori the effect of a

screening program that has been estimated to detect 10% of the gonococcal infections in women, but we can estimate the effect from observations. Seasonal correction factors (Fig. 2) were computed by the method described by Cornelius.[9] Incidence trends are easier to see in Figure 2 because the seasonal oscillations have been factored out. From Figure 2 it appears that for the last quarter of 1974 the reported incidence in men was approximately 20% less than what it would have been had the trend for 1968–1972 continued. If the number of reported cases in men reflects the actual incidence in men, then the response to the screening program was a 20% decrease from what the actual incidence in men would otherwise have been. There was probably a corresponding 20% decrease in the actual incidence in women (compared with what it otherwise would have been). Thus, the effect of the screening program, which discovered approximately 10% of all gonococcal infections in women, was a decrease of approximately 20% in total incidence. After the screening program was fully implemented in 1975, the actual incidence, reflected by the reported incidence in men, started to increase again. As mentioned in the previous section, the changes in incidence trend observed during 1972–1974 may have been partly due to other factors in the control of gonorrhea. For example, during this period the rate of therapeutic failure for gonococcal infection decreased because of general acceptance of large-dose therapies, and the strains of *N. gonorrhoeae* that were isolated stopped becoming increasingly resistant to the antibiotics used for treatment of gonorrhea.

The Infector Number

A disease is endemic in a population when it is always present, and it is at equilibrium when the prevalence remains constant for some time. We define the infector number to be the average number of susceptible persons infected per infective person during his or her infectious period. A basic principle for all diseases is that the infector number is precisely one when the disease is at an endemic equilibrium.

This result is intuitively reasonable: if the average infective person passed the disease on to more than one susceptible person, the prevalence would increase; if the average infective person passed the disease on to less than one individual, the prevalence would decrease. Of course, it is assumed that the population is closed (*i.e.*, no immigration or emigration) and that each case results from a contact between a susceptible person and an infective person in the population. The principle is an averaging result in the sense that some infective persons might infect no one, whereas others might infect two or more people. This principle has been proved for general mathematical models by Nold[10] and has been observed for particular models by other investigators.[5] We give a simple proof in the appendix.

Thus, in an endemic equilibrium situation, each infective person has an average of two effective contacts during the course of the infection, namely, a contact with an infector (source of the infection) and a contact with a person to whom the infection is transmitted. An infective person may also have additional sex partners to whom the infection is not transmitted.

The average of at least two sex partners per infective person is conceptually useful. In a study by Darrow,[11] a large number of patients were interviewed by professional personnel in venereal disease clinics in a large city. Among the questions asked was the number of sex partners during the preceding 30 days. The average patient with gonococcal infection reported 1.46 partners. Men, especially white men, reported a slightly higher average, while women reported a lower average. But even the white men reported an average of less than two. Only 2% of the patients reported more than three partners. There are several possible explanations for the difference between the theory and the data. (*1*) The 30-day reporting period may not have been long enough. (*2*) Some sex partners may not have been reported. (*3*) The patients may not have been a random sample of all individuals in the city with gonorrhea. (*4*) The population sampled may not have been closed (*i.e.*, migration may have been an important factor).

A Moving Equilibrium

Epidemiologic factors are the characteristics of the disease and its environment; these factors include contact rates among individuals and among subpopulations, average incubation and latent periods, average durations of infection, resistances of bacterial strains to antibiotics, the quality and quantity of medical treatment, and the control programs. At a given time, the epidemiologic factors determine a theoretical equilibrium level, and the actual prevalence will approach this equilibrium level when the epidemiologic factors do not change. Before this theoretical equilibrium level is attained, the epidemiologic factors often may change, so that there is a new theoretical equilibrium level. Even though the theoretical equilibrium levels may never be completely attained, it is useful to conceptualize the prevalence of gonorrhea as a moving equilibrium where the movement is due to changes in epidemiologic factors.

From Figures 1 and 2, it is clear that the incidence of gonorrhea increased every year from 1957 to 1976. The theory presented above would explain this increase as the result of continuous changes in one or several of the epidemiologic factors (*e.g.*, it could have been due to the continuous changes in social and sexual behavior in the United States). An alternative theory is that the observed increase is due to exponential growth that followed a basic change in the epidemiologic factors in approximately 1957. This theory is unreasonable because the growth rate would be only 1% per month and the

screening program started in 1972 should have overwhelmed this extremely slow growth rate.

The equilibrium level for a disease can move as the epidemiologic factors change with the seasons. For example, the large seasonal oscillations of measles, chickenpox, and mumps (which have their peak incidences in the winter) are probably due to conditions of closer contact among schoolchildren in the winter.[12,13] Seasonal oscillations in the incidence of gonorrhea are shown in Figure 1. The smoothness of the seasonally corrected curve in Figure 2 shows the regularity of the seasonal variation of the incidence of gonorrhea. The epidemiologic factor or factors for gonorrhea that vary seasonally might be the effective contact rate or the virulence of the gonococci.

When a mathematical model for the dynamics of transmission of gonorrhea was used to study seasonal oscillations (authors' unpublished observations), it was found that an oscillation of less than 5% in the contact rates yielded oscillations of the same magnitude as observed oscillations in incidence rates. Moreover, the incidence in women peaked approximately two weeks after the peak incidence in men, and the incidence in men peaked approximately two months after the peak contact rate. The imprecise data available suggest that the observed peak incidence in women does follow the observed peak incidence in men by about two weeks. Furthermore, the model suggests that the observed peaks of incidence of gonorrhea that occur in August or September are probably due to peak contact rates in June or July. This is consistent with the prediction (W. W. Darrow, personal communication) that the peak contact rate for gonorrhea occurs in the summer, when students and other individuals often move and change sex partners.

Saturation and the Core

When a population is initially almost completely susceptible and the infector number is initially greater than one, the prevalence of disease will initially increase; however, the prevalence cannot increase indefinitely in a finite population. The factor that limits the prevalence is called a saturation factor. The average prevalence of measles in the United States is limited by the fact that most contacts of an infective person that are sufficient for transmission are with immune individuals and, consequently, do not result in new cases of measles.[12,13] Thus, acquired immunity is the saturation factor for measles and for other infections that produce immunity.

Acquired immunity cannot be a saturation factor for gonorrhea, since gonococcal infection does not appear to confer immunity or substantial resistance.[2] After a person is cured of gonorrhea by antibiotics, the person is again susceptible. A clear saturation effect takes place when infectious individuals contact individuals who are already infected from different sources. This will be called the preemption effect, since potential infections have been preempted. Preemption appears to be the only saturation factor that can affect a disease such as gonorrhea for which infection does not confer immunity.

Assuming the actual incidence of gonorrhea in the United States is 2.6 million cases per year, the average duration of infection for women and men is 55 days as described above, and the at-risk population is approximately 20 million, then the prevalence is about 392,000. Thus, approximately 2% of the at-risk population is infected at one time (assuming the at-risk population to be 10 or 50 million would not affect the essence of the arguments to follow). Since only about 2% of the contacts of an average infective person are also infected, preemption cannot be a significant factor when the population is considered to be one large, uniform, homogeneously mixing population. However, the population is not uniform and homogeneously mixing: some individuals have many more sex partners than others. Thus, the preemption that limits gonorrhea must be occurring primarily in a subset of the at-risk population.

Conceptually we may separate the population at risk for gonorrhea into many subgroups, by dividing according to sex, age, race, sexual practices, number of sex partners, and other relevant factors. Groups having high prevalences (20% or more) have substantial preemption effects. We call the population in the groups that have significant preemption effects the core. If the prevalence in the core is assumed to be 20%, then if even half of the infected individuals (half of about 200,000 people) were in the core, it would have only 500,000 members, or 2.5% of the assumed 20 million people at risk. The core is probably smaller than this estimate indicates.

Suppose that all infective persons in the core were suddenly cured and subsequently were kept free of gonorrhea by some means that did not change the pattern of sexual contacts, *e.g.*, a hypothetical vaccine. Cases outside the core that would have been caused directly or secondarily by infected core members thus would be prevented. The number of infections in each noncore group would decrease, so that the infector number for the whole population immediately after this immunization of the core would have a value of less than one. Note that before the intervention the infector number was greater than one for the core and less than one for the noncore; after the intervention the infector number is zero for the core and decreased for the noncore. Since the infector number is less than one and there is no saturation in noncore groups, gonorrhea would die out. In other words, since any non-zero equilibrium prevalence requires some saturation in some groups, if the core infections are removed so that there is no saturation in the remaining groups, then the equilibrium prevalence must be zero. Therefore, essentially all cases are either directly or indirectly caused by the core, and it is the core that causes gonorrhea to remain endemic.

Discussion

The current screening program in the United States seems to be holding the incidence of gonorrhea at an equilibrium incidence approximately 20% below that which would exist without the screening program. There is probably a corresponding 20% reduction in complications of gonorrhea, such as pelvic inflammatory disease. The hospitalization costs saved by this reduction in complications of gonorrhea would be approximately 20% of $211 million annually,[1] which exceeds the yearly cost of the gonorrhea-screening program.

One implication of the results described above is that changes in the gonococci or in the behavior of the sexually active population may cause rapid and substantial changes in the incidence of infection. Moreover, any diminution of the effectiveness of health care delivery may increase the incidence of gonorrhea. When the incidence of gonorrhea is at equilibrium, an increase in the extent or effectiveness of the control program is necessary to reduce it.

Since essentially all cases are either directly or indirectly caused by the core, detection and treatment of core members would be particularly effective in preventing further cases. By our definition, the average group in the core has a prevalence of 20% or more, so the average person in the core must have the disease more than 20% of the time, that is, at least once a year. Thus, it might be possible to detect core members by checking clinic records for individuals who have been infected more than once. Detailed studies might reveal social, economic, demographic, or psychological characteristics of core members.

Many epidemiologists believe that some kind of core of frequently infected, highly active, efficient transmitters does exist. The core may consist primarily of women, whose infections would most often be asymptomatic for long periods. It will also contain some asymptomatic men and people who continue sexual intercourse in spite of symptoms. Control programs aimed at persons who have histories of previous infection are potentially highly effective preventive measures. The national strategy to control gonorrhea has been changed to include a test of cure a week after treatment and rescreening 4–6 weeks after treatment (R. H. Henderson, personal communication). These changes should help to identify repeaters who may be core members.

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Appendix

Here we prove the result stated in the section on the infector number. Assume that the cases of a disease in a finite population are numbered consecutively, starting with present cases, according to the starting time of their infectious period. Assume that the difference between the case numbers of the infector and of the susceptible who is infected is always less than a maximal gap size, G. The maximal gap size, G, is a finite number, because it is less than the maximal number of cases occurring in a single lifetime. The infector number ϕ_n for case number n is the number of cases caused by case number n. The average infector number for the first n cases is

$$\bar{\phi}_{1,n} = \frac{\phi_1 + \phi_2 + \cdots + \phi_n}{n}.$$

Theorem: The average infector number $\bar{\phi}_{1,n}$ for the first n cases approaches 1 as n approaches infinity.

Proof: Let n_0 be the present number of cases. The cases numbered $n_0 + 1, \ldots, n$ will all be initiated by previous cases, so that the total $\phi_1 + \cdots + \phi_n$ must be at least $n - n_0$. Also, every case initiated by cases $1, \ldots, n$ must have a case number less than $n + G$, so that $\phi_1 + \cdots + \phi_n \leqslant n + G$. Thus,

$$1 - \frac{n_0}{n} \leqslant \frac{\phi_1 + \cdots + \phi_n}{n} \leqslant 1 + \frac{G}{n},$$

which completes the proof because n_0/n and G/n can be made as small as desired by choosing n sufficiently large.

Since the long-term average infector number is 1 and the long-term pattern is the same as the present pattern in a situation of constant equilibrium, the present average infector number is also 1. Notice that when we sample the infected population at random, the average of the infector numbers of the cases studied will tend towards 1 as the sample size grows. For an endemic communicable disease whose incidence varies in a regular seasonal pattern with a one-year period, the average infector number taken over a one-year period would be 1.