evidence that suggests that NAATs may not be useful for conducting studies of susceptibility to reinfection or test of cure, because a positive NAAT result could reflect a variety of states, including (1) a current clinically active infection, (2) residual DNA from a previous infection, (3) residual DNA as a result of stochastic or systematic contamination in the laboratory, or (4) a genuine false-positive result. In a recent statistical analysis using hierarchical latent class models, we [5] estimated that, of all of the chlamydia DNA–positive samples, 25% were negative for current infection. Schillinger et al. [6] showed that, of 13 index persons who were NAAT positive but culture negative, none of their sex partners was positive. Similarly, Rogers et al. [7] showed that, among partners of index subjects with a *C. trachomatis* infection that was detected by NAAT but not detected by traditional assays, only 50% tested positive for chlamydia.

From 1983 to 1995, before the introduction of NAATs, Canadian rates of hospital discharges for pelvic inflammatory disease (PID) mirrored chlamydia and gonorrhea prevalence rates [8]. During this period, PID hospital admission rates declined from 281.8 to 110.8 per 100,000 population—and yet, since the introduction of NAATs and contrary to previous parallel trends, there has been an inverse relationship between trends in PID hospital admission rates (declining) and chlamydia and gonorrhea prevalence rates (increasing) in Canada (Public Health Agency of Canada, personal communication) and New South Wales, Australia [9]. This recent and apparent ecological fallacy may be primarily a result of switching laboratory tests to NAATs, even though other factors are plausible. For example, hospital admissions due to PID may have declined as a result of more-effective therapy or as a result of patients' preferences for ambulatory care.

Finally, Brunham et al. state that all reported cases were confirmed by culture, immunoassay, or polymerase chain reaction. If their analysis is restricted only to cases confirmed by non-NAATs, is there still a resurgence of chlamydia cases in British Columbia? Similarly, in the analysis of reinfection rates, if one also controls for the type of assay used in diagnosis in the proportional-hazards model, what happens to the main variable of interest—time to first infection, expressed in years?

Alula Hadgu

Centers for Disease Control and Prevention, Division of Sexually Transmitted Diseases Prevention, Atlanta, Georgia

References

1. Brunham RC, Poubohloul B, Mak S, et al. The unexpected impact of a *Chlamydia trachomatis* infection control program on susceptibility of reinfection. J Infect Dis **2005**; 192:1836–44.
2. Dicker LW, Mosure DJ, Levine WC, et al. Impact of switching laboratory tests on reported trends in *Chlamydia trachomatis* infection. Am J Epidemiol **2000**; 151:430–5.
3. Hadgu A, Dendukuri N, Hilden J. The evaluation of nucleic acid amplification tests for detecting sexually transmitted diseases—a review of the statistical and epidemiological issues. Epidemiology **2005**; 16:604–12.
4. Abbott Laboratories. Device correction memo, *LCx Chlamydia trachomatis.* Abbott Park: Abbott Laboratories, **2001**.
5. Hadgu A, Dendukuri N. Modeling conditional dependence between multiple diagnostic tests: a hierarchical latent class model [abstract 142]. In: Program and abstracts of the 2004 XXIInd International Biometric Conference (Cairnes, Australia). Washington, DC: International Biometric Society, **2004**.
6. Schillinger J, Batteiger B, Stothard D, et al. Transmission of *Chlamydia trachomatis* between heterosexual sex partners: preliminary results from genotype-specific concordance study [abstract A01F]. In: Program and abstracts of the 2004 National STD Prevention Conference (Philadelphia). Atlanta: Centers for Disease Control and Prevention, **2004**:A11.
7. Rogers SM, Miller WC, Ellen JE, et al. Transmissibility of *Chlamydia trachomatis* infections detected using nucleic acid amplification tests [abstract TP-070]. In: Program and abstracts of the 2005 Biennial Meeting of the International Society for Sexually Transmitted Diseases Research (Amsterdam). Amsterdam: International Society for STD Research, **2005**:217.
8. Public Health Agency of Canada. Sequelae of STD: pelvic inflammatory disease and ectopic pregnancy. Sexually Transmitted Diseases in Canada: 1996 Surveillance Report. Canada Communicable Disease Report, vol. 25S1(Suppl). Ottawa: Health Canada, **1999**.
9. Chen MY, Fairley CK, Donovan B. Discordance between trends in chlamydia notifications and hospital admission rates for chlamydia related diseases in New South Wales, Australia. Sex Transm Infect **2005**; 81:318–22.

Potential conflicts of interest: none reported.

Reprints or correspondence: Dr. Alula Hadgu, Centers for Disease Control and Prevention, Div. of Sexually Transmitted Diseases Prevention, 1600 Clifton Rd., Mail Stop E-63, Atlanta, GA 30333 (axh1@cdc.gov).

The Journal of Infectious Diseases 2006; 193:1335–6
 0022-1899/2006/19309-0023

The Decline in Clinical Sequelae of Genital *Chlamydia trachomatis* Infection Supports Current Control Strategies

To the Editor—Brunham et al. observed increasing rates of genital infection and reinfection with *Chlamydia trachomatis* in the greater Vancouver area beginning in the mid-1990s after initial declines [1]. They attribute that increase to decreases in population levels of host immunity, resulting from more-aggressive control measures for *C. trachomatis* infection instituted in the early 1990s, including expanded screening and treatment. Although *C. trachomatis* infection rates may be influenced by control measures and, in time, demonstrate paradoxical increases, it is much more important to focus on changes in the epidemiological profile of chlamydia-associated diseases. In the evaluation of a disease control program—in this case, *C. trachomatis* screening—emphasis should be placed on the health outcomes rather than on just the number of infections. *C. trachomatis* infection is a significant cause of many gynecological disorders, including pelvic inflammatory disease (PID), chronic pelvic pain, ectopic pregnancy, and infertility, as well as urological disorders like epididymitis [2]. Furthermore, the benefit of screening at-risk women for chlamydia to prevent cases of PID has been demonstrated previously [3].

In San Francisco, after the institution of *C. trachomatis* infection control measures in 1990, we observed similar declines

in *C. trachomatis* case rates, followed by steady increases (figure 1). We acknowledge that trends in case rates may be due to a number of factors, including changes in actual prevalence, disease reporting laws, diagnostic tests, and clinical practice. For example, in 2005, Burstein et al. reported that simple changes in routine clinical protocols had a profound impact on *C. trachomatis* screening rates, with only a modest impact on the prevalence of infection [4]. We agree, however, that the notable increases in *C. trachomatis* infection rates seen in San Francisco and Vancouver are not wholly explained by sexual risk behavior and health system changes alone, given the role that immunity plays in susceptibility to infections like *C. trachomatis* [5].

To evaluate the impact of our *C. trachomatis* screening program on disease outcomes, we reviewed countywide case reports of PID from the San Francisco sexually transmitted diseases registry and hospital discharge diagnoses for ectopic pregnancy (International Classification of Diseases–9 633.x) at the county public hospital from 1993 to 2004. Figure 1 presents the trends in reported *C. trachomatis* infections, PID cases, and ectopic pregnancies during that period.

In San Francisco County, the number of reported cases of *C. trachomatis* infection declined between 1993 and 1996 and then steadily increased from 1997 to 2004. During that same period, however, disease-associated sequelae of *C. trachomatis* infection—PID and ectopic pregnancies—actually declined. Poisson regression models show a 5.3% per year decline in PID cases ($P = .077$) and a 7.4% per year decline in ectopic pregnancies ($P < .0001$).

Our data suggest that, although rates of *C. trachomatis* infection may be increasing, rates of associated diseases continue to decline. Similarly, Chen et al. reported in August 2005 that trends in hospital admissions for PID, ectopic pregnancy, and epididymo-orchitis did not parallel increases in reported cases of *C. trachomatis* infection in New South Wales, Australia

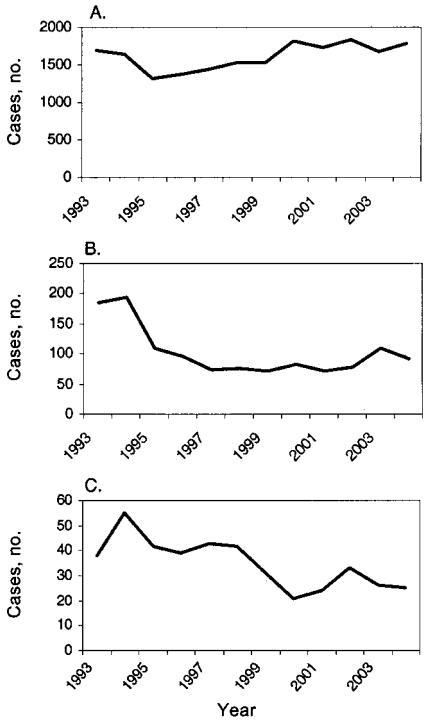

Figure 1. *A,* Reported cases of genital infection with *Chlamydia trachomatis* in San Francisco women, 1993–2004. *B,* Reported pelvic inflammatory disease cases, San Francisco County, 1993–2004. *C,* Ectopic pregnancies, San Francisco General Hospital, 1993–2004.

[6]. Also, in December 2005, Sutton et al. noted a decline from 1985 to 2001 in estimates of rates of hospitalization for PID and ambulatory diagnoses in the United States derived from several National Center for Health Statistics surveys [7].

Whether the rates of these disease outcomes will continue to decline is unknown, and the role that other pathogens, like *Neisseria gonorrhoeae* or *Mycoplasma genitalium,* play in these diseases is important to acknowledge. It may be, however, that chronic inflammation resulting from prolonged *C. trachomatis* infection is more important in causing disease outcomes than frequency of infection [8]. If this were true, identifying and treating incident infections quickly would be more important then reducing new infections, so that the public health benefits of decreased *C. trachomatis*–associated disease, like PID and infertility, could still be realized. *C. trachomatis* infection control programs should focus on expanding the identification of patients and assuring rapid treatment of those infected to decrease the duration of infection and prevent disease. Control programs should not overemphasize the prevention of the acquisition or transmission of infection at the expense of patient screening, timely treatment, and retesting.

Acknowledgment

We thank Anson Moon for his help in acquiring data on ectopic pregnancies at San Francisco General Hospital.

Nicholas J. Moss, Katherine Ahrens, Charlotte K. Kent, and Jeffrey D. Klausner

City and County of San Francisco, Department of Public Health, STD Prevention and Control Services, San Francisco, California

References

1. Brunham RC, Pourbohloul B, Mak S, White R, Rekart ML. The unexpected impact of a *Chlamydia trachomatis* infection control program on susceptibility to reinfection. J Infect Dis **2005**; 192:1836–44.
2. Stamm WE. *Chlamydia trachomatis* infections of the adult. In: Holmes KK, Sparling PF, Mardh PA, et al., eds. Sexually transmitted diseases. 3rd ed. New York: McGraw-Hill, **1999**: 407–22.
3. Scholes D, Stergachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. N Engl J Med **1996**; 334:1362–6.
4. Burstein GR, Snyder MH, Conley D, et al. Chlamydia screening in a health plan before and after a national performance measure introduction. Obstet Gynecol **2005**; 106:327–34.
5. Schachter J, Cles LD, Ray RM, Hesse FE. Is there immunity to chlamydial infections of the human genital tract? Sex Transm Dis **1983**; 10: 123–5.
6. Chen MY, Fairley CK, Donovan B. Discordance between trends in chlamydia notifications and hospital admission rates for chlamydia related diseases in New South Wales, Australia. Sex Transm Infect **2005**; 81:318–22.
7. Sutton MY, Sternberg M, Zaidi A, St Louis ME, Markowitz LE. Trends in pelvic inflammatory disease hospital discharges and ambulatory visits, United States, 1985–2001. Sex Transm Dis **2005**; 32:778–84.
8. Mardh PA. Tubal factor infertility, with special regard to chlamydial salpingitis. Curr Opin Infect Dis **2004**; 17:49–52.

Potential conflicts of interest: none reported.

Financial support: City and County of San Francisco (to J.D.K., K.A., and C.K.K.).

Reprints or correspondence: Dr. Jeffrey D. Klausner, Director, STD Prevention and Control Services, City and County of San Francisco, Dept. of Public Health, 1360 Mission St., Ste. 401, San Francisco, CA 94103 (jeff.klausner@sfdph.org).

The Journal of Infectious Diseases 2006; 193:1336–8
 0022-1899/2006/19309-0024$15.00

Reply to Hagdu and to Moss et al.

To the Editor—In his letter, Hadgu [1] states that the resurgence in chlamydia cases in British Columbia is a result of switching laboratory tests to nucleic acid amplification tests (NAATs) and argues that NAATs suffer from poor specificity and that, therefore, the results published in our article [2] may not be valid.

Hadgu, among others [3–5], has previously raised methodological concerns regarding the evaluation of NAATs, suggesting that discrepant analysis may have overestimated NAAT sensitivity and specificity. Although this debate between laboratory investigators and statisticians remains unresolved [6], we do not believe that this bias significantly impacts our interpretation of the results.

First, during the 14 years of the chlamydia control program in British Columbia, a variety of laboratory tests were used sequentially, including cell culture, direct fluorescent antigen detection, EIA, and NAAT. Yet, as shown in figure 4 in our article, the relative risk of *Chlamydia trachomatis* reinfection steadily increased between 1989 and 2003, at the rate of 4.6% per year, despite the introduction of new diagnostic modalities at different times. Second, one would have to assume that NAATs have differing false-positive rates in individuals with and without a prior positive test, to account for the observation that reinfection rates have increased since the mid-1990s. However, it is not clear that a compelling biological basis exists to support this assumption. Additionally, the 2 distinct trends observed in first infection and reinfection rates cannot be solely attributed to sensitivity/specificity differences of a specific diagnostic test, since the same laboratory testing technique was used to identify all cases during any time interval. Third, Hadgu suggests that NAATs are, for a variety of reasons, poorly suited for the evaluation of reinfection status, in part because of the possibility of residual DNA from a previous infection remaining in the host. However, we noted that, whether 1-, 3- or 6-month intervals between 2 positive laboratory tests were used to define reinfection, virtually identical relative risks of reinfection were obtained. The effect of residual DNA from prior infection, if real, should have significantly increased the relative risk when a shorter, rather than longer, interval was used. Lastly, although neither US Centers for Disease Control and Prevention (CDC) nor Canadian guidelines specifically recommend (or advise against) NAATs as part of a national chlamydia control program, "the majority of CDC consultants believe that non-NAATs are substantially less sensitive than NAATs when used on urine specimens" [7]. For these reasons, we conclude that the increasing reinfection rates observed with a population-based chlamydia control program are more likely to reflect changes in population-level immunity than nonspecificity in NAATs.

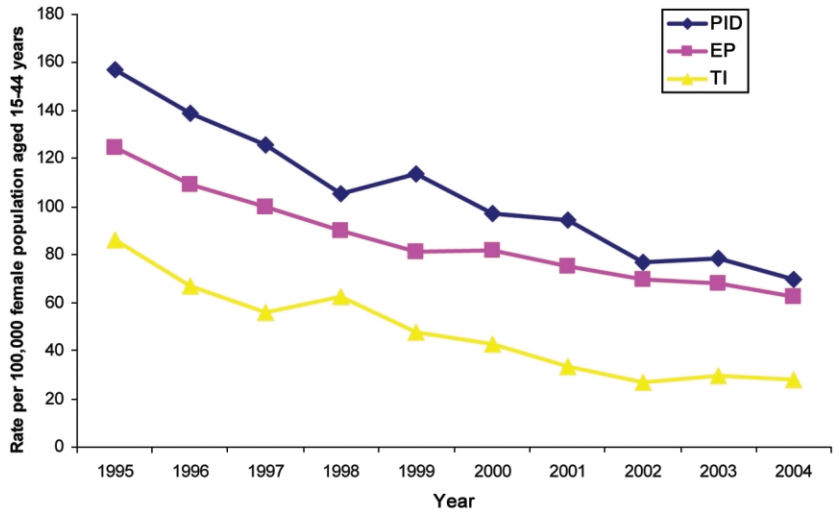

Figure 1. Improvement in reproductive health in British Columbia, 1995–2004. EP, ectopic pregnancy; PID, pelvic inflammatory disease; TI, tubal infertility.

Moss et al. [8] raise an important question—namely, have chlamydia control programs uncoupled incident infection rates from reproductive sequelae rates? This is critical, because the central goal of a chlamydia control program is to improve reproductive health. A similar question has also been asked by Cassel et al. [9] in the United Kingdom and Chen et al. [10] in Australia.

We have also observed improved reproductive health during the era of the British Columbia chlamydia control program (see figure 1). Using hospital discharge diagnoses, we have noted an ~80% decline in tubal infertility rates, a 60% decline in pelvic inflammatory disease rates, and a 40% decline in ectopic pregnancy rates. However, these data have limitations, including the fact that they are unlinked to *C. trachomatis* infection history and do not track shifts in hospital versus outpatient management of these disorders.

We are about to undertake an epidemiological analysis of the relationship between chlamydia control and improved reproductive health by creating linkage among the chlamydia surveillance database, the hospital discharge diagnoses database, and the outpatient physician billings for medical services database. If we are able to validate a causal link between