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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 differ in their 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.

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 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
the temporal trends, they may shed light on chlamydia disease pathogenesis. Currently, 2 very different concepts have been proposed to explain the reproductive sequelae of *C. trachomatis* infection [11]. The first hypothesis links chronic persistent infection with tissue damage [12, 13], and the second posits that frequent reinfection drives tissue damage [14, 15]. A possible interpretation of the observed *C. trachomatis* infection and reproductive sequelae rates is that chronic persistent infection is more important in driving reproductive pathogenesis than is reinfection. It may even be that both mechanisms are involved in pathogenesis, since improving trends in reproductive sequelae have diminished during the past 3 years in British Columbia, as chlamydia reinfection rates have increased.

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References


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