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Reply to, “Proceed With Caution in Generating Evidence in the ‘Oropharyngeal-Anorectal Chlamydia Hypothesis’ in Humans”

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We thank Leenen et al. for their letter¹ regarding our recent article.² Our results support, but do not prove, the hypothesis that oral exposure is a risk factor for anorectal *Chlamydia trachomatis* (CT) infection. Our article did not report our results as being statistically significant as the underlying study was neither designed nor powered to address the oral transmission hypothesis. We argue that our findings, if proven true, are *clinically significant* and could inform screening guidelines as anorectal CT infections were detected in men after carefully controlling for known risk factors. If oral inoculation occurs, our data suggests that it is a rare occurrence in men for reasons that remain to be elucidated.

We wish to address several criticisms that Leenen et al. posed. First, we did not state, nor do we believe, that oropharyngeal chlamydia is the risk factor for anorectal CT infection. We suspect that the mechanism by which oral sex could cause anorectal chlamydia is ingestion of CT-infected vaginal secretions and/or semen. Several observations argue that oropharyngeal chlamydia is not a significant risk factor for anorectal chlamydia: (i) oropharyngeal chlamydia is short-lived; many cases clear before treatment,³ possibly due to the anti-chlamydial properties of saliva⁴; (ii) prevalence of oropharyngeal chlamydia is significantly lower than anorectal chlamydia⁵; (iii) true oropharyngeal chlamydia prevalence rates may be overestimated as oral sex practices are very common and CT screening tests cannot differentiate established infection from exposure; and (iv) a recent retrospective study failed to find an association between preceding oropharyngeal chlamydia and incident anorectal chlamydia.⁶ Second, we think it is unlikely that the two rectal CT infections in men without anal sex exposure could be the result of “coincidence.” Although false

positivity is one explanation, we proved this not to be true by demonstrating that both rectal swabs had measurable CT loads; one of which was higher than the median CT load of anorectal CT infections that likely arose from direct inoculation. Other possibilities are described in the article.

If correct, the oral hypothesis has important epidemiological and immunological implications. We agree with Leenen et al. that a cross-sectional study design cannot prove causality, and further studies are warranted. A prospective longitudinal study of rectal chlamydia infections in sexually naive subjects might reduce confounding from poor-recall of specific sexual behaviors, interim antibiotic treatment, and differing levels of anti-chlamydial immunity. However, epidemiological studies are only as powerful as the variables they capture and are inadequate to fulfill Koch's postulates. To prove causation will require human challenge studies, which have previously demonstrated causality of other treatable sexually transmitted infection

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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