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A Web of Complexity: Untangling the Routes of Rectal Chlamydia Acquisition

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Rectal *Chlamydia trachomatis* (CT) infections are common among men who have sex with men (MSM) evaluated in STD Clinics.[1] Most behavioral studies of rectal CT among MSM have focused on receptive anal intercourse (RAI) because it is the primary route of acquisition. However, MSM also engage in a variety of non-RAI anal sexual behaviors.[2–5] Oral-anal contact and other anal sex behaviors involving saliva are not currently considered to be risk factors for rectal CT, but may contribute to ongoing CT transmission. Disentangling the independent effect of these non-RAI anal sex behaviors on transmission is difficult because they often occur in proximity to RAI.

In this issue of *Sexually Transmitted Diseases*, Cornelisse and colleagues address the hypothesis that anal sexual behaviors involving saliva may increase the risk of rectal CT.[6] Between July 2014 and June 2015, the investigators conducted a cross-sectional study at the Melbourne Sexual Health Centre (MSHC) to determine the risk of rectal CT among MSM who engaged in receptive oral-anal sex (i.e., receptive “rimming”), receptive fingering or penis “dipping,” or who used a partner’s saliva as lubricant during anal sex in the past 3 months. The questions were incorporated into the clinical computer-assisted self-interview. Testing for rectal CT was performed per Australian clinical guidelines using nucleic acid amplification testing (NAAT).

The study included 1,691 MSM who were tested for rectal CT. The majority reported engaging in receptive rimming (67%), fingering/dipping (82%), or using saliva as a lubricant (66%) in the past 3 months. The prevalence of these behaviors was similar in the subset of MSM who reported no RAI or always using condoms for RAI. Overall, 7.1% of MSM tested positive for rectal CT, including 9.4% of men who did not always use condoms for RAI and 4.9% who reported no condomless RAI. Due to collinearity of the behaviors, the investigators examined the odds of rectal CT for each behavior separately, adjusting for reported condom use for RAI and known contact to CT. They found each of the behaviors was independently associated with rectal CT: receptive rimming (aOR=1.5; 95% CI=1.0-2.4), receptive fingering/dipping (aOR=1.8; 95% CI=1.0-3.2) and use of saliva as a lubricant for anal sex practices (aOR=1.8; 95% CI=1.1-2.8).

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The results from the Cornelisse study add to the growing body of evidence that rectal exposures other than RAI may transmit CT to the rectum. The most comprehensive data on this topic are from the Australian Health in Men (HIM) study[7], which was a longitudinal cohort study of over 1,400 MSM with a median 2.3 years of follow-up. HIM investigators found that receptive rimming was an independent risk factor for rectal CT but receptive fingering was not (though this measure did not include saliva use during fingering). Both studies' multivariate models adjusted for condomless RAI, providing evidence that these associations are truly independent of RAI.

Together, these two studies offer several intriguing observations. First, both the Cornelisse study and HIM support the possibility that CT can be transmitted through saliva to the rectum. Second, these studies support previous findings that non-RAI anal sexual behaviors are common practices among MSM, including those who do not have RAI or always use condoms for RAI. In at least some cases, men with rectal CT who deny recent receptive penile-anal intercourse may have truly acquired the infection through other means. Third, these studies provide an alternative explanation for the previously published observation that lubricant use for anal sex is associated with an increased risk of STIs among MSM.[8,9] If MSM who use commercially-available lubricants for anal sex are also more likely to use saliva as a lubricant, it is possible that the higher risk of STIs among men who use lubricants is attributable to saliva as a vehicle of STI transmission.

Additionally and importantly, the Cornelisse study and HIM underscore the inherent difficulties in identifying which specific sexual behaviors are associated with rectal infections. The behaviors that could lead to rectal CT often occur concurrently, and separating out each behavior's independent risk is challenging. In the Cornelisse study, there was significant collinearity between sexual behavior variables, which limited the investigators' ability to identify the independent association of each non-RAI rectal exposure.

The results from the Cornelisse study and HIM highlight several gaps in our understanding of CT transmission and the extent to which behaviors other than RAI contribute to rectal CT acquisition. First, the biologic plausibility of CT transmission from the mouth to the rectum remains uncertain. The epidemiologic data from Cornelisse and HIM suggest that this transmission route is possible; however, the prevalence of pharyngeal CT among MSM is low[10], and, as the authors point out, there have been no studies to examine the presence of viable CT in the saliva. Interestingly, *Neisseria gonorrhoeae* (GC) has been cultured from saliva[11] and the prevalence of pharyngeal GC is nearly four times that of pharyngeal CT.[10] But the association between rectal GC and use of saliva as a lubricant in a previous study (aOR=2.2)[12] is similar to that for rectal CT identified in the Cornelisse study (aOR=1.8). Further, in HIM there was no association between receptive rimming and rectal GC, but receptive rimming was independently associated with rectal CT. It is possible that CT does not have an affinity for the pharynx, but is still present at transmissible levels in saliva. Second, we do not know what proportion of rectal CT positive tests resulting from saliva exposure are representative of true rectal CT infections. NAATs, which were employed in the Cornelisse study, detect nucleic acid – not the presence of viable bacteria – and the transient passage of non-viable organisms from a sexual partner's saliva may result in a false

positive test. Third, we do not know if oral acquisition of CT (via receptive oral-penile sex) can lead to rectal CT via transit through the gastrointestinal tract. This is a relatively nascent hypothesis that has been posed primarily for women,[13–15] a population for whom rectal CT is not associated with RAI,[16] which has important health implications due to the possibility of autoinoculation of CT from the rectum to the vagina and cervix.

These questions are intellectually intriguing and answering them would expand our understanding of CT transmission. But from a clinical and public health perspective, do we need to invest additional resources in finding the answers? Among MSM, rectal CT (non-lymphogranuloma venereum) is typically asymptomatic and does not directly lead to substantial morbidity, though it is associated with HIV acquisition.[17–19] The United States Centers for Disease Control and Prevention (CDC) recommends screening for rectal infections among MSM who report RAI, and to the extent that men who engage in non-RAI anal sex behaviors also engage in RAI, any infections acquired through saliva will be identified by routine screening. But any rectal CT infections that occur among MSM who do not have RAI will be missed by current screening guidelines. Studying the extent to which this occurs and better understanding the role of pharyngeal chlamydia in ongoing transmission could potentially influence screening and treatment recommendations for MSM.

If researchers in the field continue to pursue the question of CT transmission via saliva or other non-RAI routes, what other evidence do we need to confirm or refute the hypothesis that transmission via saliva occurs? Longitudinal data collected from MSM who do not engage in RAI can measure incident rectal CT acquisition that occurs in the absence of RAI. However, the incidence of rectal infections in such a population would presumably be relatively low and thus require a large sample size to achieve adequate statistical power. Additionally, disentangling the independent effects of different non-RAI rectal exposures would remain difficult. A human challenge study that inoculated individuals with CT could provide a more definitive answer about whether oral acquisition of CT leads to rectal infection through the gastrointestinal tract. This approach, which has been utilized to study GC in men,[20] would be unethical in women due to the reproductive sequellae and morbidity risk of CT. Such a study in men would require a clear justification for why the knowledge resulting from it would be important enough to justify the risks to human subjects. In our view, that would require a clear link to a clinical or public health implication, such as a change in practice for CT screening, treatment, or partner management.

In summary, the work by Cornelisse and colleagues supports the possibility of CT transmission via saliva. This report exposes our gaps in understanding about CT transmission routes and brings up many scientifically interesting questions, but where to go from here remains unclear. It will be difficult to prove (or disprove) that CT is transmitted through saliva and to obtain the level of evidence on this topic that would be needed to change clinical guidelines for the management of CT infection. Nevertheless, in the context of historically high CT rates, we need to consider new approaches to CT control, and further studying the possibility of transmission via saliva is one part of that endeavour.

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