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Comprehensive Molecular Screening in a Cohort of Young Men Who Have Sex with Men and Transgender Women: Effect of Additive Rectal Specimen Source Collection and Analyte Testing

Erik Munson, PhD, D(ABMM)[1], **Alyssa Reynoso**[1], **Morena Pass**[1], **Kathleen Buehler, MS**[2], **Daniel Ryan, MS**[2], **Antonia Clifford, MSW**[2], **Ethan Morgan, PhD**[2], **Brian Mustanski, PhD**[2,*]

[1]College of Health Sciences, Marquette University, Milwaukee, Wisconsin 53201-1881;

[2]Northwestern University Institute for Sexual and Gender Minority Health and Wellbeing, Chicago, IL 60611

Abstract

Background: This study's purposes were to characterize detection rates of several sexually-transmitted infection (STI) agents and describe the effect additional specimen source and analyte screening has on STI detection within a cohort of young MSM and transgender women.

Methods: Within a sixteen-month interval, 1966 encounters involved dual urine and rectal swab submissions assessed by commercial transcription-mediated amplification (TMA)-based assays for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* and by off-label TMA-based *Trichomonas vaginalis* and *Mycoplasma genitalium* testing. Identification of STI carriers utilized algorithms involving FDA-cleared screening methods, laboratory-modified testing for extra-urogenital *C. trachomatis* and *N. gonorrhoeae*, and laboratory-developed tests for *T. vaginalis* and *M. genitalium*.

Results: FDA-indicated urine *C. trachomatis* and *N. gonorrhoeae* screening revealed 39 encounters (2.0%) yielding one or both agents. Via *C. trachomatis* and *N. gonorrhoeae* screening that included rectal swab analysis, 264 encounters (13.4%) yielded evidence of either (140 *C. trachomatis*; 88 *N. gonorrhoeae*) or both (36 participants) infections. Detection rates for *C. trachomatis* and *N. gonorrhoeae* were 1.4% and 0.6% for urine screening and 8.2% and 6.2% for rectal screening respectively. Off-label screening identified 413 additional encounters with STI (5 *T. vaginalis*; 396 *M. genitalium*; 12 with both). 81.9% of these identifications were generated from analysis of rectal swabs (4 participants with *T. vaginalis*; 323 participants with *M. genitalium*; 12 with both). Overall detection rates of *T. vaginalis* (0.2% urine; 1.3% rectal) and *M. genitalium* (9.1% urine; 21.5% rectal) were variable.

Conclusion: Additive analyte testing, including extra-urogenital collections, contributes to comprehensive STI screening within a high-risk demographic.

SHORT SUMMARY

[*]-- Corresponding author: Brian Mustanski, Ph.D. Northwestern University, Feinberg School of Medicine, 625 North Michigan Avenue, Suite 14-061, Chicago, IL 60611, Telephone: (312) 503-6509, brian@northwestern.edu.

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Additive, non-FDA-cleared specimen (rectal swab) and analyte (*Trichomonas vaginalis* and *Mycoplasma genitalium*) screening identified seventeen-fold more STI carriers in a cohort of young MSM and transgender women.

Keywords

RADAR; MSM; Rectal swab; *Mycoplasma genitalium* ; *Trichomonas vaginalis*

INTRODUCTION

Men who have sex with men (MSM) and transgender women are at increased risk for acquisition of sexually-transmitted infection (STI), with the rectal mucosa being particularly susceptible to infection by a number of bacterial pathogens.[1] Several factors may be responsible for the increased risk of STI among this population including a greater number of sexual partners, increased use of illicit substances, and declining rates of condom use.[2] Among transgender women specifically, past research has observed that those who have sex with men often engage in receptive anal intercourse, increasing risk of STI acquisition when compared with insertive sexual partners.[3] In turn, the higher prevalence of STI among these high-risk populations increases risk for HIV acquisition.[4] More specifically, both rectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections have been associated with increased risk of HIV seroconversion among MSM.[5] Further, MSM who were newly diagnosed with HIV infection were more likely to be asymptomatically infected with either *C. trachomatis* or *N. gonorrhoeae* than those who were HIV-seronegative.[6]

In its most recent STI guidelines, the United States Centers for Disease Control and Prevention (CDC) recommended annual screening of urethral STI (urine testing cited as a preferred approach) for sexually-active MSM who participate in insertive anal intercourse.[1] Screening for rectal STI is also recommended for MSM who have engaged in receptive anal intercourse within the past year. While preferred assays within the guidelines for both *C. trachomatis* and *N. gonorrhoeae* detection are those based on nucleic acid amplification testing (NAAT),[1] such commercialized testing assays have not traditionally possessed United States Food and Drug Administration (FDA) indications for extra-urogenital testing. Laboratories with sufficient resources and technical expertise have the capability to bring laboratory-developed tests or laboratory-modified assays onto their respective testing platforms[7] to assist their clinician and community partners in following CDC STI screening guidelines. One investigation of two commercial NAAT assays for off-label detection of STI agents from rectal sources[8] revealed sensitivity values of ≥ 93.1% and ≥ 94.7% for detection of *N. gonorrhoeae* and *C. trachomatis*, respectively. Corresponding culture sensitivity indices were 41.4% and 21.1%.

Recent studies have documented significant detection of *C. trachomatis*- and *N. gonorrhoeae*-specific nucleic acid from extra-urogenital specimens collected from STI clinic populations and from other at-risk demographics.[9,10] The urogenital parasite *Trichomonas vaginalis* and the cell wall-devoid bacterium *Mycoplasma genitalium* have been found to be more commonly-identified agents of STI than previously considered. NAAT technologies

have advanced to the point where men can now be screened for these agents, with the assistance of laboratory-modified testing.[11,12] However, few reports have documented the prevalence of these agents in the young MSM and transgender women demographics. We hereby provide preliminary insight into the utility of *T. vaginalis* and *M. genitalium* screening of both urogenital and rectal swab specimens within this high-risk cohort.

MATERIALS AND METHODS

Cohort eligibility.

RADAR is a cohort study (current n=1,132) examining HIV risk factors, substance use, and relationship patterns among young MSM and transgender women in the Chicago, Illinois region. The study's multilevel design focuses on individual, dyadic, network and biologic factors that may be associated with HIV. Participants are followed through the developmental period of late adolescence to early adulthood, which is a critical period of initiation and acceleration of sexual behavior and substance use. This cohort and methods of recruitment have been described previously and were selected in order to achieve the multiple cohort, accelerated longitudinal study design. Eligibility requirements at time of participant enrollment include: ages 16–29 years; male assignment at birth; English speaking; and, report of a sexual encounter with a man in the previous year or identification as gay, bisexual, or transgender. The overall sample is also augmented by recruitment of serious partners of RADAR cohort members who meet eligibility criteria, "serious" being self-defined by the participant. Participant interviews included both self-reported and interviewer-administered sections. Data collection began in February 2015 with participants being followed for 4.5 years and study visits occurring every six months. This investigation received Institutional Review Board approval through Northwestern University. Informed consent was obtained from all study participants.

Collection of participant data and provision of specimens.

Data utilized in these analyses were collected from March 2018 through June 2019, as screening for *T. vaginalis* and *M. genitalium* was added to the protocol during this time. Participants were asked to provide 10–15 mL of first-void urine (subsequently aliquoted to an Aptima Urine Specimen Collection Kit [Hologic, Incorporated; San Diego, CA] at the study site) and to self-collect a rectal swab specimen using the Aptima Multitest Swab Specimen Collection Kit (Hologic). All specimens were maintained at 2–30°C prior to test performance. All specimens were tested within 2–14 days of collection.

Molecular assays.

Simultaneous detection of *C. trachomatis*-specific 23S ribosomal (r)RNA and *N. gonorrhoeae*-specific 16S rRNA from separate first-void urine and rectal swab specimens occurred by FDA-indicated and off-label utilizations, respectively, of Aptima Combo 2 (Hologic). Detection of *T. vaginalis* 18S rRNA from both specimen sources occurred by off-label utilization of Aptima Trichomonas vaginalis (Hologic). Detection of *M. genitalium* 16S rRNA was facilitated by a laboratory-developed test utilizing an analyte-specific reagent provided by Hologic. Accuracy of the aforementioned transcription-mediated amplification (TMA)-based assays for off-label detection of *T. vaginalis* rRNA and for detection of *M.*

genitalium rRNA has previously been demonstrated.[10,13] All testing was performed via direct tube sampling on the Panther automated system (Hologic). The analyzer provided qualitative interpretive data from *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis* testing. Relative light unit values ≥ 50,000 generated from *M. genitalium* TMA were interpreted positive for *M. genitalium* rRNA detection.[14]

Data analysis.

Frequency and proportion of detectable STI results were examined for each STI agent and specimen source. In order to account for within-subject correlation produced through repeated STI testing, generalized estimating equations (GEE) using a binary distribution were used to compute 95% confidence intervals and to test for statistical significance in proportions between STI agents and specimen sources. An *a priori* decision was made to examine statistical significance using a two-tailed test with an alpha level of 0.05. In instances where missing data was present (<1.0%), observations were excluded from analyses.

RESULTS

Demographic characteristics associated with patient encounters.

From March 2018 to June 2019, 1983 patient encounters among 888 unique participants within the RADAR cohort study involved collection of rectal swab and/or first-void urine specimens for molecular detection of *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, and *M. genitalium*. The mean age of participants at their first visit within this time period was 23.6 ± 3.1 years. 89.0% of the participants were young MSM participants with the remainder being young transgender women (Table 1). Race/ethnicity distribution included 34.5% black, 23.5% white, and 31.5% Latinx. An overall HIV-seropositive rate of 21.3% was documented, which included participants who were known positive at baseline and those who seroconverted during the course of the study. HIV point-of-care (POC) testing was conducted for all HIV-negative participants with confirmatory testing performed on all reactive results following CDC guidelines. [15] STI transmission-risk sexual practices described among participants included 46.2% being engaged in insertive condomless anal/vaginal sex and 46.3% involved in receptive condomless anal sex (Table 1).

Detection rates of STI pathogens from first-void urine and rectal swab specimens.

From 1977 encounters in which urine specimens were collected, 28 (1.4%; 95% CI: 0.9%, 2.0%) yielded detectable *C. trachomatis* rRNA and 12 (0.6%; 95% CI: 0.2%, 1.0%) were positive for *N. gonorrhoeae* rRNA (Fig. 1). The urine detection rate for *T. vaginalis* rRNA (0.2%; 95% CI: 0.0%, 0.5%) was similar to that for *N. gonorrhoeae*; however, *M. genitalium* rRNA was detected from 179 (9.1%; 95% CI: 7.3%, 10.9%) urine specimens. From 1972 encounters in which rectal swab specimens were collected, rRNA detection rates of 8.2% (95% CI: 6.9%, 9.5%) and 6.2% (95% CI: 5.0%, 7.4%) were observed for *C. trachomatis* and *N. gonorrhoeae*, respectively (Fig. 1). *T. vaginalis* rRNA was detected from 26 (1.3%; 95% CI: 0.7%, 1.9%) rectal swab specimens. In contrast, 423 (21.5%; 95% CI: 19.1%, 23.8%) rectal swab specimens yielded detectable *M. genitalium* rRNA (Fig. 1). This percentage exceeded those of other STI agent rectal swab detections ($P < 0.0001$).

All increases in rectal swab detection rates per analyte when compared to first-void urine specimens were significant ($P < 0.01$). Multi-site detection rates for *C. trachomatis, N. gonorrhoeae, T. vaginalis and M. genitalium* were 0.6% (95% CI: 0.3%, 1.0%), 0.5% (95% CI: 0.2%, 0.8%), 0.2% (95% CI: 0.0%, 0.4%) and 4.2% (95% CI: 3.1%, 5.3%).

Effects of additive specimen source on detection of *C. trachomatis* and *N. gonorrhoeae* rRNA.

1966 (99.1%) of participant encounters involved the collection of both first-void urine and rectal swab specimens. Utilization of FDA-indicated NAAT for *C. trachomatis* and *N. gonorrhoeae* detection (urine testing only) would have resulted in 39 encounters with documented STI detection (Fig. 2). One urine specimen yielded co-detection of *C. trachomatis* and *N. gonorrhoeae* rRNA. Additive off-label rectal swab testing increased the frequency of *C. trachomatis* and/or *N. gonorrhoeae* rRNA detections to 13.4% (95% CI: 11.7%, 15.2%; n = 264 encounters) of the testing sample. 32 co-detections of *C. trachomatis* and *N. gonorrhoeae* rRNA were observed from rectal swab testing. The number of negative patient encounters decreased from 1927 to 1702 with the addition of off-label rectal swab NAAT (Fig. 2).

Detection of *T. vaginalis* and *M. genitalium* rRNA from encounters yielding negative screening results for both *C. trachomatis* and *N. gonorrhoeae*.

Addition of off-label and laboratory-developed NAAT resulted in nominal and substantial increases in *T. vaginalis* and *M. genitalium* detection, respectively (Fig. 2). From encounters that screened negative for urogenital and extra-urogenital *C. trachomatis* and *N. gonorrhoeae*, *T. vaginalis* rRNA was detected from a urine specimen at one encounter, from a rectal swab specimen during 14 encounters, and from both specimen sources during two encounters. These positive results were duplicated upon repeat analysis.

In contrast, from encounters that screened negative for urogenital and extra-urogenital *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis*, *M. genitalium* rRNA was detected from urine specimens in 74 instances, from rectal swab specimens during 256 encounters, and from both specimen sources during 66 encounters. In total, addition of *M. genitalium* rRNA detection resulted in 409 (24.0%; 95% CI: 21.4%, 26.7%) positive patient encounters out of 1702 encounters without detectable *C. trachomatis* or *N. gonorrhoeae* rRNA.

Addition of *T. vaginalis* and *M. genitalium* analytes to the comprehensive STI screen resulted in a 34.4% (95% CI: 31.7%, 37.3%) positive participant encounter rate. This value represented a 156% increase over the level of *C. trachomatis* and/or *N. gonorrhoeae* rRNA detection, even when factoring extra-urogenital testing. The number of participant encounters negative for the four STI agents decreased from the original value of 1927 to 1289 (Fig 2).

M. genitalium rRNA co-detection data.

M. genitalium rRNA was co-detected in 15 of the 26 rectal swab specimens with detectable *T. vaginalis* rRNA. In addition, *M. genitalium* rRNA was co-detected in 53 rectal swab specimens with detectable *C. trachomatis* rRNA; in 43 rectal swab specimens with

detectable *N. gonorrhoeae* rRNA; in six urine specimens with detectable *C. trachomatis* rRNA; and, in five urine specimens with detectable *N. gonorrhoeae* rRNA (data not illustrated).

DISCUSSION

NAAT has become a reference method for laboratory detection of non-ulcerative STI agents. However, at the inception of this study, commercial assays did not possess FDA indications for performance on extra-urogenital specimens, such as rectal swab specimens. Laboratory-developed assays or laboratory-modified tests are, therefore, alternative means for detection of *C. trachomatis* and *N. gonorrhoeae* nucleic acid from at-risk demographics. When developing these assays, the potential effect of endogenous specimen inhibitors of nucleic acid amplification on assay performance must be considered. With respect to analysis of rectal swab specimens, inhibitory agents endogenous to feces[16] and commensal enteric Gram-negative bacteria[17] may be encountered. Despite the potential of encountering these endogenous specimen inhibitors during the analysis of rectal swab specimens in our investigation, we report significant detection rates of *N. gonorrhoeae*- (6.2)%, *C. trachomatis*- (8.2%), and *M. genitalium*-specific (21.5%) nucleic acid from this specimen source. Analogous detection rates of the aforementioned STI agents from first-void urine were 0.6%, 1.4% and 9.1% respectively.

One component of the commercial amplification assay utilized in this study is a mechanism in which magnetic-linked oligonucleotide sequences specific for the pathogen being assayed are allowed to hybridize to target nucleic acid prior to the amplification process. This system of target capture essentially sequesters hybridized target nucleic acid to the side of a reaction tube (in the presence of a magnetic field) while a vacuum aspiration system washes the contents of the reaction tube, effectively removing endogenous agents of inhibition prior to the initiation of amplification. The target capture paradigm contributes to enhanced analytic sensitivity of the system. Using first-void urine specimens as an example, substances noted to inhibit *C. trachomatis* nucleic acid amplification have included hemoglobin, urine crystals, iron, urine nitrites, and phosphate.[18,19] One first-generation commercial amplification assay revealed an 11.9% rate of amplification inhibition from 388 urine specimens.[20] One subsequent study[21] revealed an inhibition rate of 0.3% from urine specimens when using a second-generation commercial amplification assay employing target capture.

In addition to the mitigation of endogenous inhibitory factors via target capture, laboratory detection of STI agents from extra-urogenital specimens (particularly rectal swab specimens) is facilitated by RNA amplification assays. Schachter *et al.*[22] reported 44.4% sensitivity of one commercial DNA amplification assay for detection of *N. gonorrhoeae* nucleic acid from rectal swab specimens when compared to commercial RNA amplification. Commercial RNA amplification was also 14.8% more sensitive than a second format of DNA amplification in detection of *N. gonorrhoeae* nucleic acid from rectal swab specimens. Ota *et al.*[8] reported 64.7% sensitivity of DNA amplification for detection of *C. trachomatis* nucleic acid from rectal swab specimens when compared to second-generation RNA amplification. Furthermore, RNA amplification was 30% more sensitive than a second

format of DNA amplification testing in detection of *C. trachomatis* nucleic acid from rectal swab specimens. These data parallel studies that have demonstrated increased analytic sensitivity of commercial RNA amplification over that of DNA amplification for detection of STI agents from female and male urogenital specimens.[19,21,23] Such differences may be explained by the inherent multiplicity of rRNA target in living organisms, including pathogens, when compared to single-copy DNA or plasmid DNA target sequences.

While *T. vaginalis* has been associated with non-gonococcal urethritis in males and has been potentially linked to prostate carcinoma,[11] few reports discuss its detection in male rectal swab specimens. A 2005–2006 study of MSM in San Francisco[24] reported three positive commercial *T. vaginalis* TMA results from 500 rectal swabs. Only one of these positive results was duplicated by repeat TMA analysis; the three swabs failed to generate a positive result by research PCR. In another United States study, Cosentino *et al.*[25] documented a nearly 9% TMA detection rate of *T. vaginalis* rRNA from rectal swabs obtained from women and only a 0.9% detection rate on those collected from males. These two positive male rectal swab specimen results were duplicated through the use of an alternative TMA primer set. In a region of Africa severely affected by the HIV/AIDS epidemic, the detection rate of *T. vaginalis* by rectal swab PCR was 2.1%.[26] Data recently published from South Africa[27] describe seven MSM with positive *T. vaginalis* PCR results from rectal swab specimens. Two of these patients presented with symptoms of proctitis, although one of these individuals had concomitant detection of *N. gonorrhoeae* and *M. genitalium* DNA from a urethral swab specimen. All 26 rectal swab specimen detections of *T. vaginalis* rRNA in the presented study were confirmed by repeat testing; however, symptomatic status of participants in this investigation was not ascertained. Additional studies of this cohort can assist in investigations of both the clinical significance of rectal *T. vaginalis* rRNA detection and the potential cost-benefit of site-specific screening for this STI agent. Of particular importance would be the characterization of confirmed *T. vaginalis* proctitis and its delineation from potential deposit contamination in the context of recent receptive anal sex.

Recent literature has documented several reports of rectal *M. genitalium* incidence being variable on the basis of geography and patient demographics. In Europe, a 4.8% rectal swab *M. genitalium* detection rate by PCR was reported from 165 MSM.[28] An Australian study reported an 8.9% *M. genitalium* commercial PCR detection rate from rectal swab analysis of a cohort of symptomatic and asymptomatic MSM.[29] In the United States, Dionne-Odom *et al.*[30] reported *M. genitalium* urine and rectal swab detection rates of 10.8% and 6.4%, respectively, by PCR in a cohort of 157 HIV-seropositive MSM. Cosentino *et al.*[25] documented an 11.1% detection rate of *M. genitalium* rRNA from male rectal swab specimens by commercial TMA. From a United States high-prevalence STI community, *M. genitalium* rRNA rectal swab and first-void urine detection rates of 5.8% and 6.6%, respectively, were derived from commercial TMA.[10] Age and race distribution, symptomatic/asymptomatic status, and HIV seropositivity status of that cohort were not determined. In the context of these cited studies, the substantial rates of both *M. genitalium* urine (9.1%) and rectal swab (21.5%) rRNA detection in the current study merit further investigation. Possible factors include the limited and young age-based enrollment criteria of the cohort and the preponderance of condomless transmission risk behaviors (Table 1).

Moreover, potential *M. genitalium* associations with HIV acquisition and transmission, as have been demonstrated with other STI agents,[4–6] cannot be ignored in the context of clinical and public health.

Even in light of our meaningful findings, our study should be considered in the context of its limitations. First, we were lacking both symptom and treatment data, thus we cannot be sure whether detected infectious were persistent and untreated or if these were recurrent infections. Second, participants were able to contribute multiple encounters to the data. Finally, this sample was a community sample rather than a probability sample and, as such, findings may not generalize to the larger population of young men who have sex with men, particularly those outside an urban environment.

In conclusion, procurement of (and the capability of technically-competent molecular diagnostics laboratories to test) off-label specimen sources, particularly rectal swab specimens, enhances the overall identification of male STI carrier status in high-risk demographics. [FDA clearance of rectal swab screening was granted to the commercial *C. trachomatis*/*N. gonorrhoeae* TMA assay of interest in mid-2019.] We also demonstrate that additional *T. vaginalis* and, particularly, *M. genitalium* analysis of multiple specimen sources assists in the comprehensive screening of a high-risk demographic. Additional studies are warranted to not only elucidate the elevated first-void urine and rectal swab *M. genitalium* rRNA detection rates in this cohort but to also to understand morbidity and optimal therapies for rectal *M. genitalium* infections and to determine financial and disease transmission impacts of these findings on the potential paradigm of inclusive STI screening algorithms.

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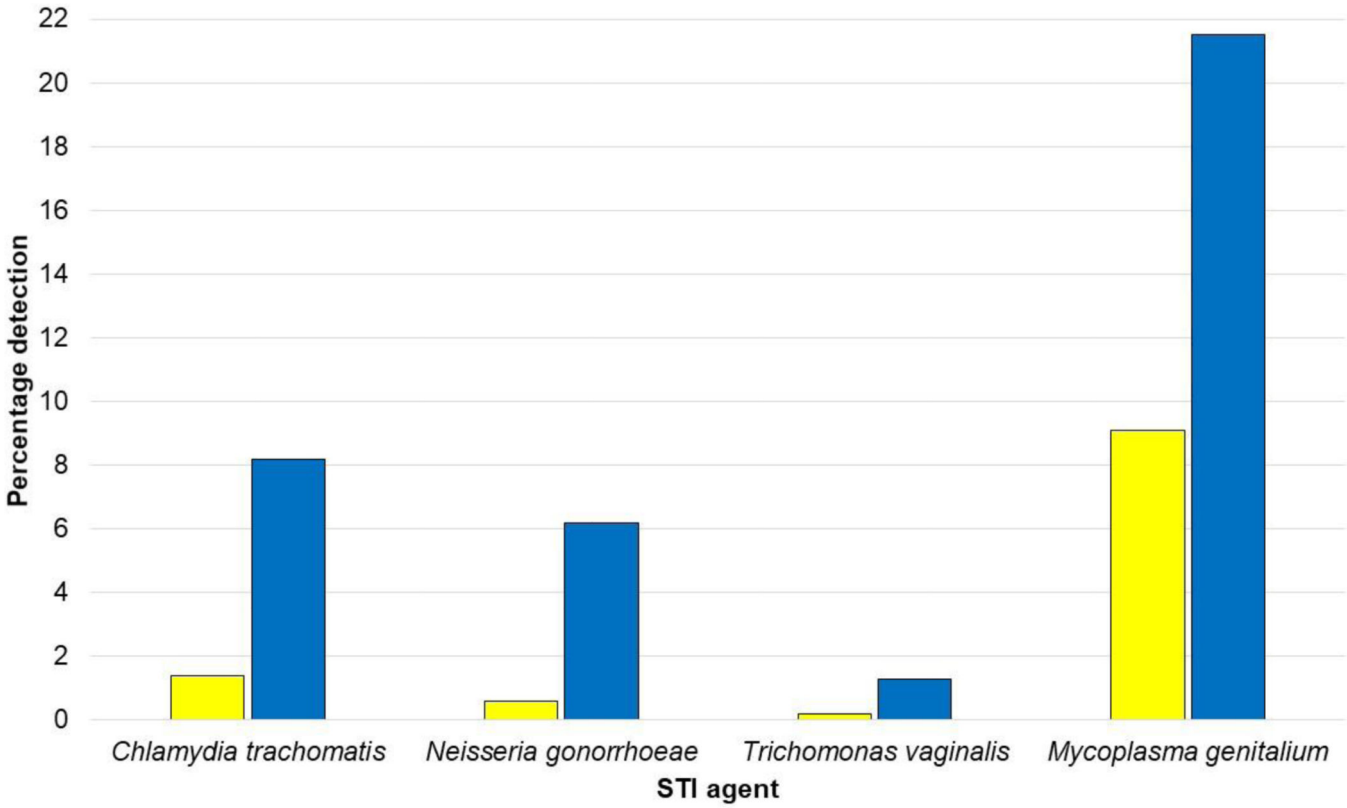

Figure 1.

Detection rates of sexually-transmitted agent-specific rRNA from primary urine (yellow bars) and rectal swab (blue bars) specimens from 1983 participant encounters in the RADAR cohort study.

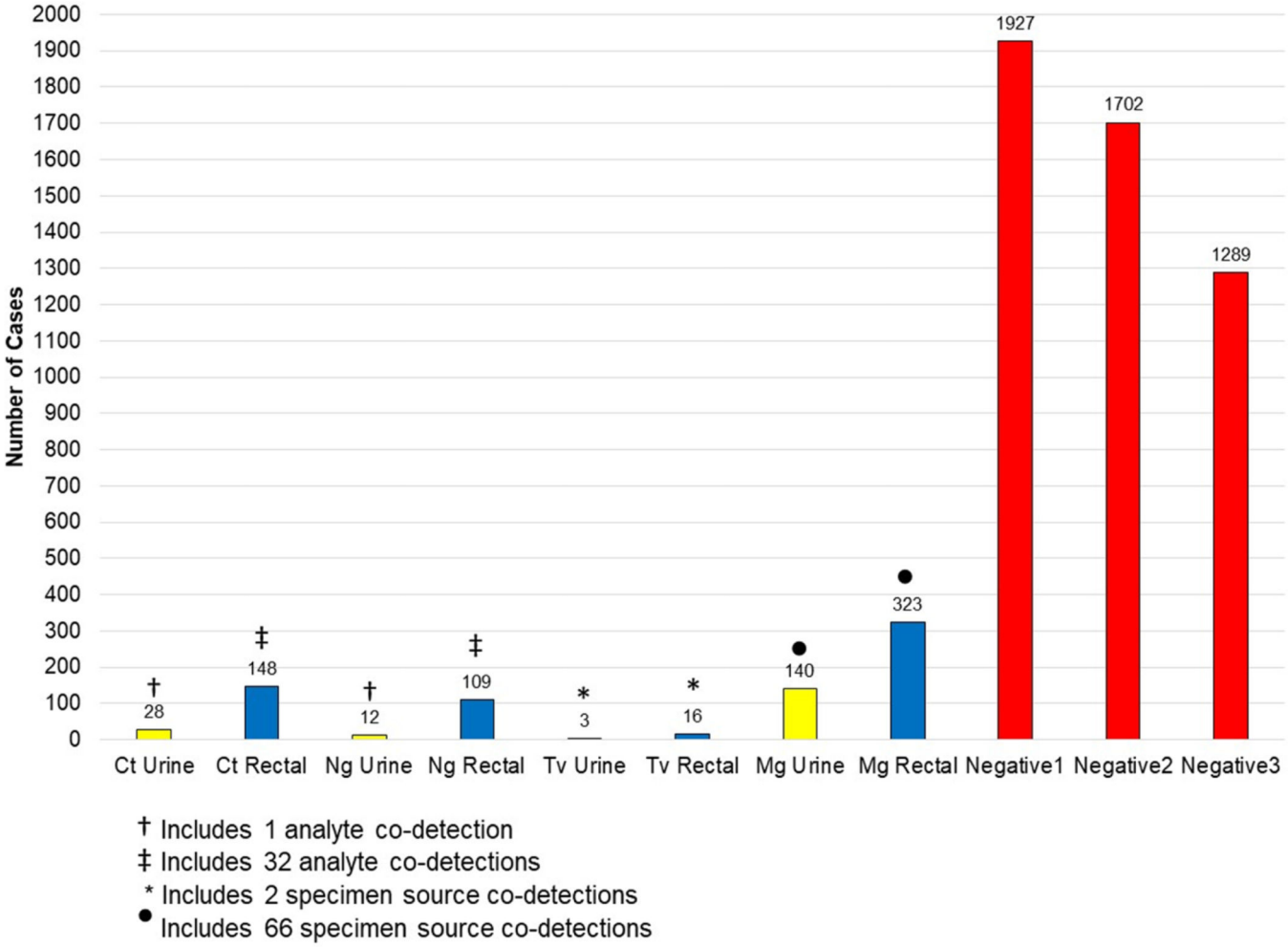

Figure 2.

Detection of Chlamydia trachomatis (Ct)-, Neisseria gonorrhoeae (Ng)-, Trichomonas vaginalis (Tv)-, and Mycoplasma genitalium (Mg)-specific rRNA from a 1966-encounter cohort. Data are presented in terms of FDA-indicated testing of first-void urine specimens (urine specimens testing negative for C. trachomatis and N. gonorrhoeae are indicated by the bar labeled “Negative1”); followed by additive testing of rectal specimens for C. trachomatis- and N. gonorrhoeae-specific rRNA (urine and rectal specimens testing negative for C. trachomatis and N. gonorrhoeae are indicated by the bar labeled “Negative2”); and followed by additive analysis of all specimens for T. vaginalis- and M. genitalium-specific rRNA (specimens testing negative for all eight analyte permutations are indicated by the bar labeled “Negative3”).

TABLE 1:

Selected demographics associated with participants in the RADAR cohort study at their first screening for *Trichomonas vaginalis* and *Mycoplasma genitalium*.

	n (%)
Gender	
Cisgender man	790 (89.0)
Transgender woman	57 (6.4)
Other gender	41 (4.6)
Race/ethnicity	
Black	306 (34.5)
Hispanic/Latinx	280 (31.5)
White	209 (23.5)
Other	93 (10.5)
HIV serostatus	
Positive	189 (21.3)
Negative	699 (78.7)
Condomless insertive anal/vaginal sex in the past 6 months	
No	478 (53.8)
Yes	410 (46.2)
Condomless receptive anal sex in the past 6 months	
No	477 (53.7)
Yes	411 (46.3)