

Developments in STD Screening: Chlamydia Testing

BACKGROUND

Chlamydia is the most commonly reported communicable disease in the U.S., occurring most often among adolescent and young adult females. Acute chlamydia infections often have no symptoms, leaving many cases undetected and untreated. However, the infection may progress to serious health outcomes, including pelvic inflammatory disease (PID), which is a cause of infertility and pregnancy complications—preventable because chlamydia infections are easily treated with antibiotics.

The U.S. Preventive Services Task Force and major medical organizations recommend an annual chlamydia screening test for all sexually active adolescents and young adult females 24 years of age and younger, for pregnant females, and for females and males at high risk. Yet chlamydia screening remains an underutilized clinical preventive service with 49.9 percent of eligible females in commercial or Medicaid health plans screened during the prior two years¹. Improvements in screening test technology hold promise for increasing screening rates and preventing consequences of untreated infections.

This research brief discusses current diagnostic and testing methods; preferred specimens; new specimen types, such as urine and vaginal swabs; rectal and pharyngeal specimens; and alternative venues for screening.

TESTS FOR CHLAMYDIA SCREENING

Diagnostic Methods

Cell culture and non-culture assays, such as Direct Fluorescent Antibody (DFA) staining of direct patient material and enzyme immunoassays, have been replaced by molecular tests called Nucleic

Acid Amplified Tests (NAATs)², which are currently recommended by the Centers for Disease Control and Prevention (CDC) as the chlamydia and gonorrhea diagnostic assays of choice³. These highly sensitive and specific tests are the primary tests used to screen for chlamydia infections.

NAATs permit the detection of non-living bacteria, thus extending the time permitted for specimen transit and expanding handling and storage conditions from the moment of collection to testing in the laboratory. The four commercially available NAATs in the U.S. can be used to test cervical, urine, and vaginal specimens as indicators of chlamydia infection⁴⁻⁷. Table 1 shows the sensitivity and specificity of diagnostic tests for chlamydia.

Point-of-care tests—rapid tests which produce results in a short time—are not yet of sufficient sensitivity to be recommended, but new assays are under development⁸.

Preferred Specimen Types for Screening

Urine testing: Traditionally, chlamydia tests were conducted on cervical swabs for females and urethral swabs for males. Due to the greater sensitivity and specificity of NAAT assays, less invasive samples, such as urine for females and males, can be used. Urine specimens are a convenient option for settings, such as primary care offices, that do not perform gynecologic services and in outreach screening programs. Non-invasive specimens can eliminate the necessity for a clinician-performed pelvic examination for asymptomatic females and may be cost-saving when a Pap test is not required⁹. For males, a urine specimen is the sample of choice for chlamydia detection¹⁰⁻¹¹.

Cervical swabs: When pelvic examinations are being performed due to the presence of symptoms or because a Pap test is required, the cervical swab is usually preferred as the sample type. Cervical swabs have been shown to have a slightly higher organism load than urine for chlamydia¹².

Additionally, cervical specimens are acceptable for NAAT testing that conducts Pap and chlamydia tests from the same sample, as with the use of liquid cytology media. Liquid cytology transport media are cleared by the Food and Drug Administration (FDA) for some commercial assays. However, using liquid cytology samples for chlamydia screening may lead to unnecessary chlamydia testing of older women for whom screening is not recommended because of low risk of infection.

Vaginal swabs. Three of four commercially available NAATs are FDA cleared for use with vaginal swabs collected during a health care visit either by clinicians or patients. Clinician and self-obtained vaginal specimens (SOVS) perform equally with regard to sensitivity and specificity. Vaginal swab specimens are less invasive than cervical swabs and, when patients are given the choice, are often preferred over urine collection¹³⁻²⁴. In one study women reported they would be more likely to be screened for STDs if they could collect their own samples. As of now self-obtained vaginal specimens are FDA-cleared only for collection in a clinical setting. Home collections using SOVS have been used successfully in many research studies²⁰.

These SOVS have been shown to be equal or better to cervical swabs, and slightly better than urine specimens, for chlamydia detection when NAAT assays are performed. Furthermore, patients can perform self-collection without a loss in sensitivity as measured against clinician-collected vaginal swabs. Since they are slightly more sensitive than urine, CDC recommends the self-obtained vaginal specimens be used, if possible, for screening asymptomatic females³.

Home-based or alternate site testing using vaginal swabs

Current Research Focus for Self-obtained Vaginal Swabs

There has been much interest recently in the possibility of using samples collected at home for direct mailing to a laboratory for testing, thereby by-passing the clinic all together for routine screening when the individual does not have symptoms. Although home collection is not yet FDA-cleared, the focus of current research has shown that vaginal swabs can be collected at home and sent through the U.S. mail to a laboratory for testing^{13, 16, 21}. Several studies have indicated that home collection is preferred by many to most women^{16, 21}.

Innovative Internet Recruitment for Home Collected Vaginal Swabs

Recently, two on-going studies have recruited women through specially designed websites that offer information and test kits to collect samples at home and mail to a testing laboratory^{25, 26}. [I Want the Kit](#) is available in several cities and [I Know](#) operates in Los Angeles, CA. Both of these research projects mail a test kit to users, report results back to the participant and link her directly with treatment services. *I Know* has developed extensive public awareness materials in English and Spanish, including [public service announcements](#), as a way to promote the test kits.

Women have reported satisfaction with this method of screening and report they would use the Internet again to obtain a screening kit. For women tested in these studies, the reports have indicated a high prevalence of 9-10% for chlamydia and reports of high sexual risk behavior²⁵. These web-based sites have been designed with input from focus groups of young women^{26, 27}.

These research projects are not to be confused with the many commercial STD online test sites that refer users to a laboratory and report results, but do not link persons with positive test results directly to treatment options. Persons who have a positive test then have to obtain needed medical care, and often be re-tested, in a clinical setting. Many of these online sites do not use NAATs and

have not been sanctioned by professional organizations.

Alternative specimen types

Rectal and pharyngeal specimens are important sample types for detection of chlamydia in men who have sex with men (MSM). These sample types have been demonstrated to perform well with NAAT assays and yield better results than culture, but are not cleared by the FDA^{28,29}. Thus, practitioners can only request testing for these types of samples if the laboratory they use has performed a “test performance verification.” This verification is required to be performed by each individual laboratory before these types of samples can be assayed. Eye specimens or ocular samples can be tested by NAATs, but again, laboratories must perform their own verification studies before they can offer to perform the tests on these specimens for clinicians.

Diagnostic Limitations

CDC does not recommend a test-of-cure following chlamydia treatment. However, because incidence studies have demonstrated that previous chlamydia infection increases one’s probability of becoming reinfected³⁰, CDC recommends that previously infected individuals be rescreened three months after treatment, a test of *reinfection*, for chlamydia or gonorrhea³¹.

If conducting a test-of-cure, for example for a pregnant woman, clinicians should not use NAATs until at least three weeks after treatment is completed. Because NAATs measure nucleic acids instead of live organisms, residual nucleic acid from cells rendered non-infective by antibiotics may still give a positive amplified test up to three weeks after treatment, even though the patient is cured of viable organisms^{32,33}.

Barriers to testing

Multiple barriers to chlamydia screening exist for both clinicians and patients. Clinicians who are reluctant or too busy to perform pelvic examinations to collect cervical swabs now have the opportunity to screen females with either urine, which can be collected in multiple settings, or vaginal swabs collected by the clinician or the patient in clinical settings. Patients fearful of an

invasive procedure now can submit urine or a self-collected vaginal swab for screening. Use of self-collected samples for chlamydia testing may eliminate some screening barriers. Making testing available free of charge from novel Internet and school-based health centers may remove financial barriers^{25,32-34}, as will implementation of coverage expansions for preventive services offered at no-cost to commercially-insured patients by the Patient Protection and Accountable Care Act.

IMPLICATIONS FOR SCREENING

Urine testing has facilitated expansion of chlamydia screening programs and has shown to be widely acceptable to patients, healthcare providers and laboratory staff. Screening programs are beginning to be offered in school-based settings, at walk-in events at campus health centers and family planning clinics, and at outreach events in communities. However, urine testing is not without disadvantages. Collection and processing of urine may sometimes result in spillage, requiring additional time for clean-up. Patients may also be reluctant to provide a urine specimen due to fear of undisclosed drug testing. In addition, urine specimens are unlikely to be feasible for home-based testing, due to restrictive requirements for bulky packaging of moderate volumes of fluid (i.e. 30mL or 1 ounce).

Continued expansion of chlamydia screening likely will rely on more consistent screening in primary care as well as screening in community-based venues, especially in areas with high prevalence. Potentially, urine specimen collection will be feasible using low-cost medical staffing models or trained, non-medical personnel. The next promising alternative is home collection. Ideally, specimen collection in the home would involve the use of discreet or small collection devices that are packaged easily for delivery to the testing facility by standard mail services^{21,25,27}. Self-obtained vaginal swabs appear to be the most appropriate specimen type for home collection based on discreet packaging, less restrictive postal requirements, and no link to drug testing. Until FDA clearance has been granted for home specimen collection for chlamydia testing, program and medical directors must consult with their

constituent laboratory directors on study design to satisfy CLIA regulations for off-label procedures.

Next Steps

In order to obtain clearance from FDA for use of innovative sample types so as to facilitate more widely accessible tools for chlamydia screening, more research is needed on alternative sample types, such as SOVS collected at home, rectal swabs, and pharyngeal specimens. Additionally “buy-in” from commercial companies to perform trials will be required in order to achieve FDA clearance of these sample types. Additional health services research is needed for improving and implementing the use of urine screening in alternative, community-based settings by non-medical personnel.

The development and improvement of point-of-care tests for chlamydia screening will be required to facilitate immediate treatment of infected individuals before they leave the health care setting. Cost effectiveness models and cost comparisons of different approaches to chlamydia screening will be needed in order to guide the most judicious use of scarce health care resources. Education of both clinicians and individuals at risk for chlamydia infections will be necessary in order to remove barriers that exist now for routine screening of young women. Resources and recommendation are needed for screening men.

Conclusions

We have the tools to increase chlamydia screening and provide more diagnostic services in innovative venues using many new and traditional specimen types. Although some new screening program types are still in the research arena, as they move into clinical and public health practice we have the opportunity to make a difference in reducing the epidemic of chlamydia in the U.S., thereby reducing morbidity in women. This will require carefully targeting resources and education—both of health care providers as well as adolescents and young adults. Both resources and education will be key components in this endeavor.

Table 1. Estimates of Sensitivity and Specificity for Diagnostic Test for *Chlamydia trachomatis* in urogenital specimens.

Diagnostic Method	Sensitivity	Specificity
Tissue Culture	70-85%	100%
Direct Fluorescent Antibody	80-85%	>99%
Enzyme Immunoassay	53-76%	95%
Direct Hybridization	65-83%	99%
Polymerase Chain Reaction ^a		
Cervical Swabs	89.7%	99.4%
Female Urine	89.2%	99.0%
Male Urine	90.3%	98.4%
Strand Displacement Amplification ^b		
Cervical Swabs	92.8%	98.1%
Female Urine	80.5%	98.4%
Male Urine	94.5%	91.4%
Male Urethral Swabs	94.6%	94.2%
Transcriptional Mediated Amplification ^c		
Cervical Swabs	94.2%	97.6%
Vaginal Swabs	96.6-96.7%	97.6-97.1%
Female Urine	94.7%	98.9%
Male Urine	97.0%	99.1%
Male Urethral	95.2%	98.2%
Real Time PCR ^d		
Cervical Swabs	80.9-87.7%	99.4-99.7%
Vaginal Swabs	84.8-94.7%	98.8-99.1%
Female urine	92.6-95.7%	99.2-99.5%
Male Urine	97.3-97.8%	99.6-99.7%
Male Urethral	88.6-93.3%	98.3-99.1%

Sensitivities and specificities adapted from clinical trial data, package inserts, and selected published papers.

- a. Roche Molecular, Indianapolis, IN
- b. Becton Dickinson, Sparks, MD
- c. GenProbe, Inc., San Diego, CA
- d. Abbott Molecular, Inc., Des Plaines, IL

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