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Abilities of APTIMA, AMPLICOR, and ProbeTec Assays To Detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in PreservCyt ThinPrep Liquid-Based Pap Samples[▽]

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Infections with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are often asymptomatic. Liquid-based Pap (L-Pap) screening may provide samples for testing by commercial assays. Women attending a health clinic or a street youth clinic had a PreservCyt ThinPrep sample and a cervical swab (CS) collected. The L-Pap sample was tested for cytopathology; then 1 ml was transferred to an L-Pap specimen transfer tube for testing by the Gen-Probe APTIMA assays (APTIMA Combo 2 [AC2], APTIMA *C. trachomatis* [ACT], and APTIMA *N. gonorrhoeae* [AGC]). The residual L-Pap sample was tested for *C. trachomatis* and *N. gonorrhoeae* using Roche AMPLICOR (AMP) and Becton Dickinson ProbeTec (PT). The CS was tested by AC2. A patient was considered infected if two specimens were positive or if a single specimen was positive in two tests. The prevalence of infection was 10% (29/290) for *C. trachomatis* and 2.4% (7/290) for *N. gonorrhoeae*. Most of the positive patients had specimens that were reactive in all assays (20/29 for *C. trachomatis*; 6/7 for *N. gonorrhoeae*). Four patients had double infections. The sensitivities and specificities of the various tests for the specimens tested were as follows. For *C. trachomatis* on L-Pap, sensitivity and specificity were 100 and 98.1%, respectively, for ACT, 93.1 and 98.8% for AC2, 86.2 and 91.2% for AMP, and 72.4 and 92.7% for PT. For *N. gonorrhoeae* on L-Pap, sensitivity and specificity were 100% for both AGC and AC2, 85.7 and 100% for AMP, and 85.7 and 100% for PT. For AC2 with CSs, sensitivity and specificity were 93.1 and 98.5%, respectively, for *C. trachomatis*, and both were 100% for *N. gonorrhoeae*. There were significant differences in sensitivity and specificity ($P < 0.001$). The APTIMA assays were more sensitive and specific than AMP or PT for detecting women's *C. trachomatis* and/or *N. gonorrhoeae* infections by testing ThinPrep samples.

Women with lower genital tract *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* infections often have no symptoms, putting them at risk of spreading the infections to sexual contacts. Without diagnosis and treatment, they are at risk of ascending infections of the upper genital tract, with serious complications of pelvic inflammatory disease, ectopic pregnancy, or infertility (5, 11). Screening programs are necessary to prevent morbidity and to reduce costs. The nucleic acid amplification (NAA) assays are effective for screening cervical swabs (CS), vaginal swabs, and first-catch urine (FCU) (2). Liquid-based Pap (L-Pap) samples have been used to screen women for human papillomavirus (9), and a few studies have examined the possibility of detecting *C. trachomatis* or *N. gonorrhoeae* from the Pap sample (1, 4, 6–8; D. Fuller et al., presented at the 105th General Meeting of the American Society for Microbiology, 2004). The objective of this study was to compare three commercial NAA systems for the detection of *C. trachomatis* and *N. gonorrhoeae* in PreservCyt ThinPrep L-Pap samples (Cytyc Incorporated) that had previously been processed for Pap cytopathology.

MATERIALS AND METHODS

Study design. A cross-sectional study was performed by enrolling 290 women from April to October 2005. Attendees were either from a Toronto street youth clinic or from the Hamilton Community Health Centre. Patients signed consent forms for the collection of a PreservCyt ThinPrep L-Pap sample with a cervical brush and for the collection of a CS (Gen-Probe APTIMA unisex swab transport collection).

Testing. The L-Pap sample was processed according to the PreservCyt package insert, and cytopathology readings were scored as normal, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, or carcinoma. The age of each patient was also recorded.

From approximately 4 ml of the L-Pap sample, 1 ml was transferred to a Gen-Probe APTIMA specimen transfer tube containing 2.9 ml of APTIMA transport medium, and 100 μl was tested in the APTIMA assays (Gen-Probe Incorporated), including APTIMA Combo 2 (AC2), which tests simultaneously for *C. trachomatis* and *N. gonorrhoeae*, and the individual tests that detect alternate *C. trachomatis* and *N. gonorrhoeae* targets individually, APTIMA *C. trachomatis* (ACT) and APTIMA *Neisseria gonorrhoeae* (AGC), according to the kit package inserts for these tests.

For AMPLICOR (AMP) *C. trachomatis*/*N. gonorrhoeae* testing (Roche Molecular Diagnostic Systems), a protocol published by Cytyc Corporation in 2003 (as a package insert for the PreservCyt solution kit [part no. 86013-001 Rev. C]) was followed. A 500-μl aliquot of each L-Pap sample was vortexed for 3 to 10 s before transfer to a 1.5-ml screw-cap polypropylene tube. The sample was then centrifuged at 12,500 × *g* for 10 min before the supernatant fluid was discarded. *C. trachomatis*/*N. gonorrhoeae* lysis buffer (100 μl) was added to the pellet before vortexing. After incubation of the vials at room temperature for 15 min, 100 μl of *C. trachomatis*/*N. gonorrhoeae* specimen diluent was added to each tube, mixed, and incubated for 10 min at room temperature. Within 2 h, a 125-μl aliquot of the processed specimen was transferred to A-tubes containing working Master Mix. Urine specimen working controls were used, according to the instructions on the AMP package insert.

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TABLE 1. Numbers of CS and ThinPrep L-Pap samples identifying women infected with *C. trachomatis* and/or *N. gonorrhoeae* using the AMP, APTIMA,[a] and PT assays

Organism	Profile of results with each sample type and test						No. of positive samples with the indicated profile
	CS (AC2)	ThinPrep L-Pap sample					
		AC2	ACT	AGC	AMP	PT	
C. trachomatis	+	+	+		+	+	20
	+	+	+		−	−	3
	+	+	+		−	+	1
	+	+	+		+	−	3
	−	+	+		+	−	2
	−	+	+		−	+	0
N. gonorrhoeae	+	+		+	+	+	5
	+	+		+	−	+	1
	+	+		+	+	−	1

[a] APTIMA assays include AC2, ACT, and AGC.

For ProbeTec (PT) ET CT/GC (Becton Dickinson) testing, we constructed an experimental protocol based on the work of C. Martinaitis et al. (presented at the 21st Clinical Virology Symposium, Clearwater, FL, 2005). Two milliliters of the residual L-Pap sample was transferred to a 4-ml centrifuge tube (BD Falcon). Samples were centrifuged at 3,000 rpm (2,000 × g) for 30 min and carefully decanted. Pellets were resuspended in 1 ml of BD *C. trachomatis*/*N. gonorrhoeae* sample diluent buffer, vortexed, and heated, and 200 μl was tested according to the manufacturer's instructions in the package insert. The CS was tested by AC2 according to the package insert.

Data analysis. A patient was considered infected with *C. trachomatis* or *N. gonorrhoeae* if two specimens were positive or if a single specimen was positive by at least two tests. Statistical analyses were performed using SPSS software for Windows, version 11.5. The Cochrane Q test was used as a global test for differences between the five tests, and the McNemar test was used for pairwise comparisons of tests. Sensitivities, specificities, positive and negative predictive values, and their associated 95% confidence intervals (CI) were calculated using Confidence Interval Analysis software (version 2.2, 2004; T. Bryant, University of Southampton, Southampton, United Kingdom). A P value of <0.05 was deemed statistically significant.

RESULTS

The prevalence of infection was 10% (29/290) for *C. trachomatis* and 2.4% (7/290) for *N. gonorrhoeae*. Of the 267 women whose ages were recorded, 85.4% (228) were younger than 30 years. There was no correlation between having a *C. trachomatis* or *N. gonorrhoeae* infection and an abnormal Pap result; 27 of the 29 *C. trachomatis*-infected women and 3 of the 7 *N. gonorrhoeae*-infected women had negative Pap reports. Of the four women infected with both *C. trachomatis* and *N. gonorrhoeae*, three (75%) had an ASCUS Pap report and the fourth had a negative report. Table 1 summarizes the numbers of different samples positive by one or more of the five assays. The specimens of the majority of the positive patients were reactive in all of the assays (20/29 for *C. trachomatis* and 5/7 for *N. gonorrhoeae*). Three *Chlamydia*-infected patients were positive only by the APTIMA assays, and another four were missed by either AMP or PT testing of the L-Pap specimen. Four patients were infected with both organisms (not shown in Table 1).

Table 2 shows the sensitivities, specificities, and predictive values of the assays performed on L-Pap samples compared to each other and to the AC2 test performed on CS for the diagnosis of *C. trachomatis* infections. Both AC2 and ACT performed on L-Pap samples detected all of the 29 *C. trachomatis* infections, compared to 25 (86.2%) detected by AMP and 21 (72.4%) by PT. The AC2 test performed on the CS detected 27 (93.1%) of the *C. trachomatis* infections. A total of 23 *C. trachomatis*-negative women had false-positive results by AMP (specificity, 91.2%) compared to 19 with false-positive results by PT (specificity, 92.7%). There were three false-positive results by AC2 (specificity, 98.8%) and five by ACT (specificity, 98.1%) on L-Pap samples and four false-positive results by AC2 testing of CS (specificity, 98.3%). The global test for differences between tests (Cochrane Q test) was highly significant ($P < 0.001$) for both sensitivity and specificity. In pairwise comparisons, AC2 and ACT were superior to PT in sensitivity and to both AMP and PT in specificity (Table 2).

The results for *N. gonorrhoeae* testing are shown in Table 3, where both the AC2 and AGC tests were 100% sensitive and specific on CS and L-Pap samples. On the L-Pap samples, both AMP and PT were 85.7% sensitive, and only one false-positive result was recorded for the AMP assay (99.6% specificity).

Samples from the seven positive women with discordant testing results were also tested with kit amplification or internal controls. Table 4 shows their testing profiles. Patient 21, whose L-Pap sample was positive for *N. gonorrhoeae* by the AC2, AGC, and PT assays but negative by AMP, was positive with the AMP internal control (AMPIC), indicating that the negative AMP result was not due to inhibitors in the sample. Similarly all four of the *C. trachomatis*-positive patients testing

TABLE 2. Sensitivity, specificity, and predictive values[a] of AMP, PT, and APTIMA[b] assays for detecting *C. trachomatis* in 29 infected and 261 uninfected women by testing CS and ThinPrep L-Pap samples

Sample	Test	No. testing positive (sensitivity [95% CI] [%])[c]	No. testing negative (specificity [95% CI] [%])[d]	PPV (%)	NPV (%)
CS	AC2	27 (93.1 [81.1–97.7])	257 (98.5 [9.6–99.3])	87.1 (74.1–94.1)	99.2 (97.7–99.7)
L-Pap	AC2	29 (100 [91.4–100])	258 (98.9 [97.2–99.5])	90.6 (78.7–96.2)	100 (99.0–100)
	ACT	29 (100 [91.4–100])	256 (98.1 [96.1–99.1])	85.3 (72.7–92.7)	100 (98.9–100)
	AMP	25 (86.2 [72.5–93.7])	238 (91.2 [87.9–93.7])	52.1 (40.4–63.5)	98.3 (96.4–99.3)
	PT	21 (72.4 [57.3–83.7])	242 (92.7 [89.6–95.0])	52.5 (39.7–64.4)	96.8 (94.4–98.2)

[a] PPV, positive predictive value; NPV, negative predictive value.
[b] Including AC2 and ACT.
[c] Comparison of the sensitivities of the five tests found highly significant differences ($P < 0.001$ by the Cochrane Q test). In pairwise comparisons, PT was inferior to AC2 or ACT ($P = 0.01$ by the McNemar test).
[d] Comparison of the specificities of the five tests found highly significant differences ($P < 0.001$ by the Cochrane Q test). In pairwise comparisons, AMP was inferior to AC2 or ACT ($P < 0.001$ and $P = 0.001$, respectively, by the McNemar test) and PT was inferior to AC2 or ACT ($P = 0.001$ and $P = 0.007$, respectively).

TABLE 3. Sensitivity, specificity, and predictive values[a] of AMP, PT, and APTIMA[b] assays for detecting *N. gonorrhoeae* in 7 infected and 283 uninfected women by testing CS and ThinPrep L-Pap samples

Sample	Test	No. testing positive (sensitivity [95% CI] [%])[c]	No. testing negative (specificity [95% CI] [%])[c]	PPV (%)	NPV (%)
CS	AC2	7 (100 [72.0–100])	283 (100 [99.0–100])	100 (72.0–100)	100 (99.0–100)
L-Pap	AC2	7 (100 [72.0–100])	283 (100 [99.0–100])	100 (72.0–100)	100 (99.0–100)
	AGC	7 (100 [72.0–100])	283 (100 [99.0–100])	100 (72.0–100)	100 (99.0–100)
	AMP	6 (85.7 [54.7–96.8])	282 (99.6 [98.4–99.9])	85.7 (54.7–96.8)	99.6 (98.4–99.9)
	PT	6 (85.7 [54.7–96.8])	283 (100 [99.0–100])	100 (72.0–100)	100 (99.0–100)

[a] PPV, positive predictive value; NPV, negative predictive value.
[b] Including AC2 and AGC.
[c] No statistically significant difference was found between tests ($P = 0.86$ by the Cochrane Q test).

negative by AMP (patients 36, 52, 165, and 179) also had positive results with the AMPIC. L-Pap samples from the five *C. trachomatis*-positive women (patients 36, 52, 151, 157, and 165) who tested negative by PT were tested with the PT internal control (PTIC); three of them (patients 36, 157, and 165) may have been negative by PT due to inhibitors, since the internal control did not break through as positive.

DISCUSSION

On ThinPrep L-Pap samples, the clinical sensitivities of the amplification assays used in this study differed for the detection of *C. trachomatis* and *N. gonorrhoeae*. Both AC2 and ACT were significantly more sensitive than the AMP or PT assay for the detection of *C. trachomatis*. These observations are similar to differences seen on other specimen types such as CS, vaginal swabs, and FCU (2, 10). These clinical observations are probably due to differences in the analytical sensitivities of the assays. We have previously shown the APTIMA assays to be 10- to 100-fold more sensitive than AMP and PT (2, 3). This is probably a reflection of the increased amount of rRNA target for the AC2 test relative to the plasmid DNA targets for the AMP and PT tests; up to 1,000-fold more was found in *C. trachomatis*-infected cells. Testing for inhibitors in the L-Pap samples from *C. trachomatis*- or *N. gonorrhoeae*-positive patients that were negative by other assays (Table 4) showed that five that were negative by AMP were positive in the AMPIC well, suggesting that inhibitors were not responsible for the AMP false-negative results. In contrast, of the five samples negative by PT, three showed inhibition in the PTIC wells, suggesting that those false-negative results (patients 36, 157, and 165) may have been due to inhibitors. We have previously shown inhibitor rates of 2% in vaginal swabs and CS and 27.2% in urine being tested by PT (2). The other two PT and five AMP false-negative results may have been due to lower levels of nucleic acid. An additional factor that deserves consideration in an attempt to explain the differences in the performances of the assays on L-Pap samples was our use of only the AC2 assay to test the CS to establish the reference standard. Since previous studies (2, 3) have shown AC2 to be more sensitive and specific than AMP or PT on CS, we chose to use the most sensitive assay. No apparent bias was introduced by this maneuver, since the number of *C. trachomatis*- and *N. gonorrhoeae*-positive patients would remain the same if the CS results were eliminated from the analysis. The L-Pap residuum volume for testing in the three assays may have influenced the testing results. We did not record volumes routinely, but Hawthorne et al. (4), using Cobas AMP PCR, showed that of 840 ThinPrep L-Pap samples with a volume of >5 ml, 33 (3.9%) were positive for *C. trachomatis* and 8 (0.9%) were positive for *N. gonorrhoeae*, whereas 80 samples with a volume of <5 ml were negative for both organisms. This hypothesis should be examined in more detail in future studies.

TABLE 4. Testing profiles of CS and ThinPrep L-Pap samples from seven infected women with discordant results from testing by APTIMA,[a] AMP, and PT assays, including AMP and PT internal-control results

Patient ID	Result for the following sample type and test:							
	CS (AC2)	L-Pap						
		AC2	ACT	AGC	AMP	AMPIC	PT	PTIC
21	+	+		+	−	+	+	ND[b]
36	+	+	+		−	+	−	−
52	+	+	+		−	+	−	+
151	−	+	+		+	+	−	+
157	−	+	+		+	+	−	−
165	+	+	+		−	+	−	−
179	+	+	+		−	+	+	ND

[a] Including AC2, ACT, and AGC.
[b] ND, not determined.

There are relatively few publications on the performance of NAA tests on L-Pap samples for the detection of *C. trachomatis* and/or *N. gonorrhoeae*. An early study by Bianchi et al. (1) detected 22/1,000 *C. trachomatis*-positive ThinPrep samples using the AMP test. On repeat sampling for nine of the patients, all retested positive. These investigators also demonstrated that *C. trachomatis* nucleic acids were amplified in the AMP test 6 weeks after storage at room temperature. We have performed similar stability experiments using dilutions of *C. trachomatis* and *N. gonorrhoeae* in ThinPrep L-Pap fluid, showing detection by AC2, ACT, and AGC 20 weeks after storage at room temperature, with only a gradual decline in the assay signal (data not shown).

Other studies have used a direct fluorescent-antibody staining assay, ligase chain reaction (LCR), PACE 2, hybrid capture (HC2; Digene Corporation, Gaithersburg, MD), and AMP to detect *C. trachomatis* and/or *N. gonorrhoeae* in ThinPrep L-Pap samples. Inhorn et al. (7) compared a direct fluorescent-antibody staining assay of ThinPrep L-Pap samples for *C. trachomatis* to CS smears from 636 women, reporting positive agree-

ment for 43 (6.8%) and discrepant results for 11 (1.7%). The performance of LCR and PACE 2 favored the CS smear 55% and the L-Pap sample 45%, but the differences were not statistically significant. Hopwood et al. (6) showed 100% concordance of 19 LCR-positive and 562 negative results in comparing CS and ThinPrep samples. In our study, the AC2 and ACT assays performed on L-Pap samples detected 100% of the *C. trachomatis* infections compared to 93.1% by CS testing. Koumans et al. (8) tested 255 ThinPrep samples from sexually active adolescent women by using LCR for *C. trachomatis* and *N. gonorrhoeae*. They also broadened the reference standard for positivity by testing CS and FCU using LCR, PCR, transcription-mediated amplification, and culture. They were able to report strong agreement (0.97) between LCR on ThinPrep samples and LCR on CS for *C. trachomatis* (kappa, 0.92) and *N. gonorrhoeae* (agreement, 0.99; kappa, 0.96). The sensitivity of LCR on the L-Pap sample was higher for the detection of *C. trachomatis* (93%) than for that of *N. gonorrhoeae* (81%). Our study also used a broadened reference standard for comparison. For *C. trachomatis* diagnosis, AC2 or ACT performed on L-Pap samples was 100% sensitive; for *N. gonorrhoeae*, the sensitivity was also 100% by AC2 and AGC. AMP and PT were equally less sensitive for detecting both organisms in L-Pap samples. Very few false-positive results were obtained by using the APTIMA assays on L-Pap samples. AC2 gave three (98.8%) and ACT gave five (98.1%) false-positive results for *C. trachomatis*, with no false positives for *N. gonorrhoeae* (100% specificity for AC2 and AGC). In contrast, for *C. trachomatis*, AMP testing of L-Pap samples recorded 23 false positives (specificity, 91.2%) and PT gave 19 false positives (specificity, 92.7%). For *N. gonorrhoeae* testing, AMP gave only one false-positive result (specificity, 99.6%) and PT was 100% specific. In the Koumans et al. study cited above (8), the specificity of LCR was 95.5% for *C. trachomatis* and 99.6% for *N. gonorrhoeae*. The false-positive results in assays detecting *C. trachomatis* DNA targets may be explained by incompatible conditions in L-Pap samples, which might be reduced by optimization of the specimen type for the AMP and PT tests. Contamination can sometimes account for false positives, but strict procedures to reduce contamination were used. Alternatively, some of these apparent false positives may have contained small amounts of target DNA not detected by the other DNA test.

Some of these studies led Cytyc Corporation to seek FDA approval for AMP testing of ThinPrep samples, which was granted in February 2003, and we followed that published protocol in our study. Although there were no published studies on the use of PT on ThinPrep L-Pap samples, Martinaitis et al. presented a poster at the Clinical Virology Symposium in 2005 demonstrating the feasibility of using the PT test to diagnose *C. trachomatis* and *N. gonorrhoeae* in SurePath preservative fluid. We established a similar testing protocol for ThinPrep L-Pap samples. Gen-Probe Incorporated recently received clearance from the FDA for AC2, ACT, and AGC testing of ThinPrep samples transferred to a specimen transfer tube. From a multicenter trial using the APTIMA assays to test ThinPrep L-Pap samples, Fuller et al. (105th General Meeting of the American Society for Microbiology, 2004) reported sensitivities and specificities of 96.7 and 99.3%, respectively, for detection of *C. trachomatis* and 92.3 and 99.8%, respectively, for *N. gonorrhoeae*. These values did not correlate with the presence or absence of symptoms for 1,626 women. Our results confirm these findings and also show that for both organisms, the AMP and PT assays were not as accurate in identifying infected or uninfected women by testing of their ThinPrep L-Pap samples.

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