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Accuracy of *Chlamydia trachomatis* Antigen Detection Methods in a Low-Prevalence Population in a Primary Care Setting

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We compared a direct fluorescent-antibody stain (DFA) and an enzyme immunoassay (EIA) with a standard cell culture technique for the detection of *Chlamydia trachomatis* infection in women in an urban family practice setting. We also evaluated a DFA sample in a commercial laboratory to determine the interlaboratory reliability of this test. There were 268 women in the study; the EIA provided a higher sensitivity (83 versus 50%) and a higher positive predictive value (83 versus 69%) than the DFA test and comparably high specificity (99 versus 96%). Concordance between the two laboratories on the DFA test was not high when data were adjusted for chance agreement (kappa coefficient = 0.64). DFA validity was optimal with an elementary body cutoff of greater than 5, while EIA validity was optimal at the recommended cutoff of 0.1 optical density unit. None of 11 women with negative cultures after treatment had false-positive antigen tests. False-negative results with both tests were associated with low culture inclusion counts but were not strongly associated with the presence or absence of symptoms, menses, pregnancy, or recent antibiotic use. False-positive results with EIA were seen only for three women who had a chief complaint of vaginal discharge. Although the positive predictive value of DFA could be increased in high-prevalence subpopulations, EIA was still more valid in two such groups: teenagers and prenatal patients. These results indicate that EIA might be preferable for low- or moderate-prevalence populations in primary care settings and that a falloff in DFA sensitivity could be explained by lower infection burdens in low-prevalence groups.

*Chlamydia trachomatis* is responsible for approximately four million infections each year in the United States, far more than any other sexually transmitted disease (3). The sequelae of initial infection with *C. trachomatis* include the majority of cases of pelvic inflammatory disease, tubal infertility, epididymitis, and neonatal infection of the eye and lung (3). These facts, combined with the introduction of culture-free antigen detection tests in recent years, have stimulated a great deal of interest in widespread screening for chlamydial infection in primary care settings. Current recommendations state that screening of women in populations of low to moderate risk should be considered (3). However, the proper method, target populations, and procedures for screening in primary care settings have yet to be established (7).

Several studies have determined the validity of the direct fluorescent-antibody stain (DFA) and the enzyme immunoassay (EIA) by comparing the results from each test alone with culture results (for a review, see reference 15). These studies have found wide variation in the sensitivity and specificity of each method. Only four studies to date have simultaneously compared direct immunofluorescent stain and EIA with culture (1, 4, 14, 16). Furthermore, nearly all previous studies of test validity for women have been conducted in high-risk populations, such as those with a high prevalence of infection in sexually transmitted disease and adolescent referral clinics. In this article, we report the results of a direct comparison of the DFA test and EIA to culture in an urban primary care setting with a relatively low prevalence of infection.

Recent analyses of the cost-effectiveness of the antigen detection methods have concluded that widespread screening of low-risk populations might be economically feasible (9, 10, 19). The test validity assumptions used in these analyses have not always been verified in actual low-risk populations. Moreover, false-negative or false-positive results with antigen methods could arise from factors such as prior antibiotic treatment and cross-reactions between antichlamydial antibodies and bacterial antigens. We therefore explored associations between the occurrence of false results and characteristics of the patient or the test conditions—such as pregnancy, menses, smoking, or recent antibiotic use—that could interfere with the antigen tests by altering the cervical milieu. In addition, because the DFA test relies on visual pattern recognition by a technologist, we compared the results when two samples from the same patient were evaluated at two different laboratories. The efficacy and efficiency of a test are influenced by the criteria for the designation of a positive result and by disease prevalence in selected subpopulations. We therefore analyzed our data to determine optimal cutoff values for each antigen test and investigated whether the antigen tests performed better among women who were younger, were pregnant, or had presumptive signs of infection.

**MATERIALS AND METHODS**

**Patient population.** Seven family practice physicians and three nurse practitioners at a neighborhood health center affiliated with the University of Massachusetts Medical Center, Worcester, agreed to participate in the study. To be eligible for the study, each patient was determined to need a pelvic exam for any reason during the visit. All eligible patients seen during a session were enrolled or, during some sessions, a random sample was selected. A total of 286 women enrolled in the study. The population sample included 19% under age 20 and 24% over age 30. The main reasons for the visit were as follows: checkup (28%), con-
traception (28%), genitourinary symptoms (18%), and pre-
natal care (18%).

Data collection. After obtaining informed consent, the
clinicians filled out a data sheet for each patient, recording
demographic information, reason for visit, prior medical
history, sexual history, signs, and symptoms. We used
standardized definitions of physical findings such as cervical
ectopy, friability, and endocervical exudate to increase
interobserver reliability. During the pelvic exam, clinicians
took three swabs from the endocervical canal for chlamydia
testing. They used the following order of sampling of the
cervix in each case: (i) culture for Neisseria gonorrhoeae (if
indicated), (ii) cytology test (if indicated), (iii) DFA (at
laboratory 1; swab 1), (iv) cell culture (swab 1), (v) EIA
(swab 2), and (vi) DFA (at laboratory 2; swab 3). Previous
investigators have concluded that sampling order is probably
not a factor in test outcome (4, 16). We elected not to use
cytobrushes for DFA testing because it has not been de-
monstrated that they improve test validity and because of
concerns of clinicians regarding bleeding, patient discom-
fort, and possible disruption of known or undiagnosed preg-
nancy. Weiland et al. have subsequently reported that in
patients with positive DFA specimens collected by cyto-
brush, 100% were also positive with swab samples (20). DFA
specimens were fixed and dried according to the specifica-
tions of the manufacturer. For analysis by laboratory 2, the
DFA slide specimen was shipped by mail at ambient tem-
perture to the commercial laboratory that had previously
performed DFA tests at the health center. Patients with
positive DFA results from the commercial laboratory
returned within 2 weeks for treatment and were scheduled to
return to the health center 2 weeks after the start of
treatment for collection of posttreatment samples in the
manner described above.

Laboratory methods. (i) Cell culture. For isolation of C.
trachomatis from clinical specimens, a microdilution plate
procedure was used as previously described (21). We prop-
agated McCoy cells (Flow Laboratories, Inc., McLean, Va.)
in minimum essential medium (MEM) supplemented with
10% fetal calf serum, l-glutamine, nonessential amino acids,
and gentamicin (10 ìg/ml). Cells were seeded in 96-well
microdilution plates at 6 X 10^4 cells per well in the same
medium and incubated 24 to 48 h later. Sterile cotton-tipped
plastic swabs (Scientific Products, Inc., Detroit, Mich.)
were used for collection of cervical specimens, and each swab
was placed in a tube containing 1.5 ml of 2-SP transport medium
(0.2 M sucrose, 0.02 M potassium phosphate, 0.005% phenol
red, nystatin [25 ìU/ml], vancomycin [25 ìg/ml], gentamicin
[10 ìg/ml]). The swab in 2-SP was mixed on a vortex
manner described above.

(ii) Direct immunofluorescent stain. The MicroTrak C.
trachomatis Direct Specimen Test (Syva Co.) was used for
DFA. Clinicians followed directions provided by the manu-
facturer to obtain patient samples and prepare slides. An
experienced technician examined the slides with a fluores-
cence microscope for chlamydial elementary bodies. We
considered a specimen inadequate if fewer than five epithel-
ial cells were visible. For analyses reported here, more than
five elementary bodies were required to declare a test
positive.

(iii) EIA. The Chlamydizyme system (Abbott Laborato-
ries, North Chicago, Ill.) was used to detect chlamydial
antigen in the specimens. The sample collection and trans-
port kits for patient specimens were used according to the
test protocol given by the manufacturer. We stored speci-
mens at 4°C until tested (within 5 days). We performed the
assay as directed by the manufacturer and analyzed samples
with a Quantum II spectrophotometer at a wavelength of 492
nm. The spectrophotometer automatically processed the
EIA results of the control and test specimens, yielding a
printout of a net A_{492} and a designation of positive or
negative for each sample.

Analysis. We calculated sensitivity, specificity, and pre-
dictive values according to standard formulas (6). Chi-square
tests, and Fisher's exact test when appropriate, were used to
compare proportions. The Mann-Whitney rank sum test was
used to compare the distribution of ordinal variables such as
inclusion counts. For comparisons of binary outcome data
when neither data source could be considered inherently
more accurate (e.g., DFA and EIA), we calculated kappa
coefficients, which adjust for agreement expected because of
chance (17). To examine associations between "exposure" to
patient or test factors and false test results, we compared the
proportion of exposed cultures among false-positives with
that among true-negatives and the proportion among
false-negatives with that among true-positives. Under the
null hypothesis, the proportions compared would be equal.
Specimens rated as inadequate were excluded from these
analyses.

RESULTS

We obtained specimens for all three tests from 276
women. Results from a DFA test performed at the commer-
cial laboratory (laboratory 2) were available for 255 of these
women. DFA results are reported for laboratory 1 unless
otherwise specified. Eight culture specimens were discarded
before laboratory analysis because of handling problems,
yielding a total of 268 complete triplicates of specimens for
culture, DFA, and EIA.

In total, 6.7% of the cultures (18 of 268) were positive for
C. trachomatis. Comparison of sensitivity, specificity, and
predictive value for EIA versus DFA (laboratory 1) revealed
lower sensitivity and a lower positive predictive value for the
DFA test (Table 1). A total of 25 DFA samples (9.1% of all
DFA samples collected) were judged to be inadequate for
reading because of an insufficient number of epithelial cells.
Exclusion of these subjects from the analysis, however, did
not significantly improve sensitivity. In addition to the
samples included in Table 1, there were 11 sets of culture,
DFA, and EIA samples collected 2 weeks after initial

treatment as "tests of cure." All 33 of these test results were
negative, indicating no false-positive antigen tests under
these circumstances. The overall concordance between EIA
and DFA tests was high (Table 2) because of the relatively
low prevalence of infection; however, we found agreement
for only 9 of 22 positive results, and the kappa coefficient
was only 0.56.
Lowering the cutoff value of a positive direct immunofluorescent stain test (more than five elementary bodies in our study) produced essentially no gain in sensitivity and a decline in positive predictive value (Fig. 1). If the cutoff was changed to two or fewer elementary bodies for a positive test, then less than half of the positive tests would constitute true infections. Varying the cutoff value for EIA (from the recommended 0.1 optical density unit above controls) would not have resulted in improved sensitivity, since false-negative EIA results were all less than 0.03 unit and lowering the cutoff to that level would create a large number of false-positive results.

DFA results from the two laboratories were concordant in 96% of the paired samples (Table 3). However, the kappa coefficient was only 0.64, and of 16 samples positive for either test, only 8 were positive for both tests. Only 3 of 246 (1.2%) DFA specimens were judged to be inadequate by laboratory 2. None of the specimens were judged positive by laboratory 2 and inadequate by laboratory 1. The occurrence of inadequate specimens in either laboratory was not associated with date of sampling, specific clinicians, or sampling for Neisseria gonorrhoeae or cytology prior to sampling for C. trachomatis. For DFA, false-positive and false-negative tests were not strongly associated with the date of testing, smoking status, clinician, parity, pregnancy, ectopy, oral contraceptives, menses, or recent (within 1 month) antibiotic use. All 4 false-positive DFA subjects had no symptoms, compared with 108 of 221 of the true-negatives ($P = 0.059$, two-tailed Fisher’s exact test). For EIA, all 3 false-positives occurred in women who complained of a vaginal discharge, compared with discharge in 89 of 245 true-negatives ($P = 0.050$, two-tailed Fisher’s exact test).

The results in Table 4 show that false-negative results for DFA and EIA had lower inclusion counts on culture, although only three false-positive EIA were available for analysis. The results also show that inclusion counts were not lower in infected women without genitourinary symptoms. The sensitivities of the DFA test for symptomatic and asymptomatic women were 50 and 55%, respectively.

A total of 50% (9 of 18) of the women with chlamydial infection reported no genitourinary symptoms. Eight of the infected women had vaginal discharge, alone or combined with urinary tract symptoms, and one woman had urinary symptoms only. Table 5 shows the validity of observing endocervical exudate (indicated by a yellowish sampling swab) as a test for chlamydia in this population. This clinical test had a very low sensitivity (22%) and positive predictive value (12%), even when used strictly among symptomatic subjects. Use of endocervical exudate in parallel with DFA produced only a trivial increase in sensitivity over DFA alone, with a large deterioration in positive predictive value—from 69 to 23%.

The prevalence of infection in women under 20 was 17% (9 of 53). DFA detected six of these infections, and EIA detected all nine. In another high-prevalence subpopulation, prenatal patients, the prevalence was 14% (7 of 49). DFA detected only three of seven infections in this group, while EIA detected all seven. For EIA among teens and prenatal patients, there were no false-positives or -negatives, resulting in a sensitivity and specificity of 100%.

**DISCUSSION**

These data indicate that in a low-prevalence population in a primary care setting (prevalence = 6.7%), EIA had a higher sensitivity and predictive value than DFA. These differences held whether we included inadequate DFA spec-

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**TABLE 1. DFA and EIA methods versus cell culture**

<table>
<thead>
<tr>
<th>Method</th>
<th>Rate (no. of samples/total)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PV+</th>
<th>PV−</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFA</td>
<td></td>
<td>0.50b (9/18)</td>
<td>0.98 (246/250)</td>
<td>0.69b (9/13)</td>
<td>0.96 (246/255)</td>
</tr>
<tr>
<td>DFA without inadequate samples</td>
<td></td>
<td>0.53 (9/17)</td>
<td>0.98 (223/227)</td>
<td>0.69 (9/13)</td>
<td>0.96 (223/231)</td>
</tr>
<tr>
<td>EIA</td>
<td></td>
<td>0.83c (15/18)</td>
<td>0.99 (247/250)</td>
<td>0.83c (15/18)</td>
<td>0.99 (247/250)</td>
</tr>
</tbody>
</table>

$^a$ PV, Predictive value.

$^b$ $P = 0.03$.

$^c$ $P = 0.31$, Fisher’s exact test.

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**TABLE 2. Agreement between DFA and EIA**

| DFA result | No. of EIA results | | | | | |
|-------------|-------------------|---|---|---|---|
| Positive    | Positive | Negative | Total |
| Positive    | 9        | 4        | 13   |
| Negative    | 9        | 254      | 263  |
| Total       | 18       | 258      | 276  |

$^a$ Observed level of agreement = 0.953; kappa coefficient (correction for chance agreement) = 0.557.
imens as negative tests or excluded them from the analysis. In clinical practice, it is difficult to notify and quickly retest patients whose tests were inadequate. Therefore, the infections of patients who have inadequate DFA specimens are frequently undetected. The sensitivity of DFA was lower in our study than in previous studies conducted in high-prevalence populations. However, Tijam et al. did report a DFA sensitivity of 46% for cervical specimens taken from sexually transmitted disease clinic patients in the Netherlands. Some decrease in sensitivity from earlier studies might be expected, because of the differences between the more controlled settings of earlier studies and the more routine sampling and transport conditions reflected in this field study. Specificity values were high for both tests, as has generally been observed elsewhere. In a summary of 15 studies on the DFA test, sensitivity ranged from 61 to 96% in intermediate-prevalence populations (9 to 11%), and specificity ranged from 94 to 99% (15). It is noteworthy that in this summary of 15 studies, the median sensitivities for EIA and DFA were virtually equal in high-prevalence populations (89 and 90%), but in intermediate-prevalence populations, the median sensitivity for EIA was higher—85 versus 77%. In a gynecology clinic population with a prevalence of only 4.4%, Phillips et al. reported a DFA sensitivity of 70% and a positive predictive value of 62%—both values similar to those reported here (11).

A comparison of our results with those of four previous studies that have simultaneously evaluated the validity of both antigen tests reveals several important points. The higher positive predictive values reported in three of these studies, ranging from 85 to 93% for DFA and from 79 to 100% for EIA, result mainly from a higher prevalence of infection, which ranged from 15.8 to 26.0% (1, 4, 16). It is also probable, as discussed further below, that the use of high-risk populations in these studies increased the sensitivity and negative predictive value by including a larger proportion of severe infections and younger women. Chernsky et al. (4) found that EIA had a slightly higher sensitivity than DFA (98 versus 88%), while Taylor-Robinson et al. (16) found the opposite: DFA sensitivity was 95%, compared with 67% for EIA. Comparison with the results of Taylor-Robinson et al. is constrained by the inclusion of both men and women in their data. The sensitivity of both antigen tests is presumed to be higher for women than for men when asymptomatic subjects are included (15). In any event, our data do not support the conclusion by Taylor-Robinson et al. that EIA is neither sufficiently sensitive nor sufficiently specific for routine use.

In the only other study among women in a low- to moderate-prevalence population (prevalence = 9.7%), Smith et al. (14) reported sensitivities for DFA and EIA of 71 and 67%, respectively. However, when they excluded as true-positives those cases identified during a second reading of equivocal slides by the manufacturer of the DFA test, the sensitivity dropped to 50%. In addition, if we reanalyze their data to count inadequate specimens as negative results, the sensitivity drops further to 40%. Nearly 40% of the DFA samples collected in this study, which were obtained during routine care in obstetrics and gynecology clinics, were judged to be inadequate. This points out the importance of considering the criteria for specimen adequacy and the handling of inadequate specimen results in comparing estimates of DFA validity.

Since there is no a priori basis on which to assume superior validity for either EIA or DFA, we did not calculate sensitivity or specificity for these tests compared with each other. In this context, in which neither test is acceptable as a "gold standard," the kappa coefficient can provide an appropriate measure of agreement. It can be interpreted as the proportion of possible excess agreement that is obtained beyond what is expected by chance alone. The kappa coefficient of 0.56 from our data is much lower than a kappa coefficient of 0.90 we derived from similar data reported by Chernsky et al. (4).

We used cell culture as the standard for comparison, but it is possible that some infected patients might have negative cultures (13). False-negative cultures would usually distort the estimated validity of the antigen tests by creating more apparent false-positive antigen tests, thus lowering specificity and positive predictive values. In a study comparing more than one antigen test, we can make some estimates about the occurrence of false-negative cultures. Since false-positive antigen tests are relatively uncommon, we can assume that most subjects with two positive antigen tests are truly infected. Of the nine subjects with positive results in both antigen tests, none had negative cell cultures. Using a binomial probability model, we calculated that the upper
boundary of a 90% confidence interval for the percentage of false-negative cultures among those truly infected is 28%. Therefore, we do not believe that false-negative cultures were a substantial problem in our study, especially since specificity, which would be the most vulnerable validity characteristic, was already very high for both tests.

The manufacturer of the DFA test recommends a cutoff number of 10 or more elementary bodies for a positive test. Previous investigators have used less stringent cutoff points—most often greater than or equal to five, but ranging down to one elementary body (12). We found that a cutoff of more than five elementary bodies gave the optimal validity characteristics (maximum sensitivity and positive predictive value) for the DFA test in our population, whereas Chernesky et al. (4) reported that lowering the DFA cutoff to one increased sensitivity without lowering specificity.

The interlaboratory agreement for DFA observed in this study raises concern about the reliability of this antigen test. Laboratory 1 used a single experienced technician, while during the study period, laboratory 2 (a commercial lab) used a small group of technicians who were similar to each other in training and experience. Previous investigators have studied the agreement between readers evaluating the same DFA slide and have concluded that disagreements are fairly common (5). In this study, some of the discordance between laboratories could have been due to variation in sampling from swab to swab. This additional source of variation is important to evaluate because it could be a major contributor to reproducibility problems when the test is actually used in the field. The relatively small number of DFA specimens from laboratory 1 reflects a difference in the laboratory criteria for specimen adequacy and possibly the more efficient collection of epithelial cells on a subsequent swab. The criterion of at least five epithelial cells was used by laboratory 1, but this number might be too high, although it did not influence DFA validity in this study. We had expected that certain clinicians would be responsible for an increased share of inadequate specimens but instead found the number of inadequate specimens to be fairly equally distributed among the 10 clinicians who participated.

The power of this study for the detection of small or moderate associations between false results and patient characteristics was limited because of the low prevalence of infection and consequently the small number of false results. Larger numbers of false-positive and false-negative results from antigen tests should be analyzed to provide more precise estimates of the possible association between these errors and specific clinical features. However, the finding that all three false-positive EIAs were for patients with a chief complaint of vaginal discharge could be explained by cross-reaction with antibodies used in the tests; this phenomenon has been reported in the laboratory for both monoclonal and polyclonal antibodies (16; T. Krech, D. Gerhard-Fsadni, N. Hoffmann, and S. M. Miller, Letter, Lancet ii:1161–1162, 1985). Taylor-Robinson et al. reported a cross-reaction between EIA antibody and three of seven strains of Gardnerella vaginalis, a frequent cause of vaginitis seen in primary care (16). Although we might expect antigen tests to remain positive after treatment because of persisting free antigen or nonviable organisms in the cervix, we found no evidence for false-positive antigen tests when the tests were used as tests for cure 2 weeks after antibiotic treatment.

Our results provide evidence that false-negative results of DFA, and perhaps of EIA, are more likely in women with low culture inclusion counts. Thus, the proportion of subjects with low infection burdens could be an important factor in the sensitivity reported for an antigen detection method. It is possible that low-prevalence populations such as ours contain a higher proportion of women with low infection burdens. This could explain, in part, the lower sensitivities observed here in comparison with studies of higher-prevalence populations. We failed to find that asymptomatic infections had lower inclusion counts, so it might not be correct to presume that populations that include large numbers of asymptomatic chlamydia infections would yield lower test sensitivities for that reason alone (8). Further studies are needed to clarify the determinants of infection burden in individual patients.

As others have noted, clinical predictors such as signs and symptoms could have a role in the diagnosis of chlamydial infections, either when used alone or in conjunction with a rapid test. We found that the detection of yellowish exudate on a sampling swab was by itself a very insensitive test, even when considered among symptomatic patients only. Bunsam et al. have reported a sensitivity of 59% for visible yellow exudate in a population attending a sexually transmitted disease clinic (2). Consideration of endocervical exudate in addition to DFA failed to increase sensitivity to a significant degree. Selection of high-prevalence subpopulations on the basis of clinical risk indicators can be used to improve the positive predictive value of the antigen tests. However, in contrast to the data reported by Smith and co-workers (14), our results provide no evidence that the DFA test is more sensitive for pregnant women.

On the basis of our results, EIA appears to be better than DFA for screening low-risk primary care populations of women for C. trachomatis infection. Despite the expense of performing validity studies of low-prevalence populations, more data of this nature are needed before firm conclusions regarding the best approach to screening can be made. Recent cost-effectiveness analyses regarding chlamydia screening with the antigen tests have used generally higher figures for DFA sensitivity than we have obtained. However, at least one such analysis concluded that the economic benefits of screening with DFA were relatively impervious to variations in test validity: with a drop in sensitivity to 70%, costs equaled savings at an infection prevalence as low as 2.4% (19). Our data suggest that infection burden plays a major role in DFA test sensitivity and could be an important explanation for the differing sensitivities reported in populations with various risk profiles. Routine use of any chlamydial antigen detection method is likely to remain controversial in primary care settings until these test accuracy issues are clarified. Meanwhile, since genital infection with chlamydia is so pervasive, large reductions in morbidity might depend on aggressive programs for low- or moderate-risk populations.

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LITERATURE CITED


