The Pacific Northwest Laboratory Medicine Sentinel Monitoring Network Practices with rapid Group A Streptococcus antigen test kits

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BACKGROUND

In 1995, the Pacific Northwest Laboratory Medicine Sentinel Monitoring Network was created through a cooperative agreement between the Washington State Department of Health and the Centers for Disease Control and Prevention (CDC). This network currently comprises 590 hospital, independent and physician office laboratories in Washington, Alaska, Idaho and Oregon. Twenty-four studies have been conducted which provide information about laboratory testing quality, accuracy, reliability and accessibility. The information gathered from this network allows regulators and interest groups to make informed decisions, based on actual laboratory testing practices.

Full text reports of the findings of these studies and references to published journal articles can be found at: www.phppo.cdc.gov/dls/mlp/pnlmsmn.asp

QUESTIONNAIRE ON PRACTICES WITH RAPID STREP ANTIGEN TEST KITS

The intent of this questionnaire was to evaluate testing practices in sites using a CLIA-waived, rapid Group A Streptococcus antigen test kit. What proportion of these sites confirm negative patient test results by obtaining a throat culture? How do their practices for culture confirmation compare with their specific antigen test kit product insert instructions? What factors influence whether a culture is obtained or not?

METHODS

In April 2002, an inventory of CLIA-waived tests performed in Washington State was created from Washington Medical Test Site (MTS) relicensure application forms processed between August and October 2000 and from new applications for licensure received between November 2000 and March 2002. In November 2002, a questionnaire was mailed to 667 testing sites in Washington that were identified by this inventory as performing a CLIA-waived rapid Group A Strep antigen test. (One hundred eleven of these sites are members of the Pacific Northwest Network).

RESPONDENTS

Three hundred eighty-one testing sites returned a completed questionnaire in time for analysis, a 57% response rate. As of the date of this questionnaire, 366 sites performed a rapid Strep antigen test. Demographic characteristics of the questionnaire respondents that performed a rapid Strep antigen test kit are summarized in the following table.

Table 1 - Questionnaire respondents

Demographic characteristic	**Questionnaire respondents that perform a rapid Strep antigen test** (N=366)	**All testing sites in Washington that perform a CLIA-waived Strep antigen test** (N=667)	**All testing sites in Washington** (N=2696)
	Percent		
Laboratory type			
Hospital	7	5	4
Independent	2	1	3
Physician office laboratory *	91	94	93
Laboratory category			
Waived	19	23	41
PPMP	49	53	33
Moderate/high (WA-MTS)	28	21	20
Moderate/high (Accredited)	4	3	6
U.S. Census Bureau designation			
Urban	73	77	81
Rural	27	23	19

* Includes all other types of testing sites, such as: Physician offices; Clinics; Community health clinics; Rural health clinics; Student health clinics; Health departments.

FINDINGS

Rapid Strep antigen test kits used

Table 2 shows the test kits used by the questionnaire respondents. Note that some sites reported the use of more than one brand of test kit.

Table 2 - Rapid Strep antigen test kits

Manufacturer and brand name	Number of responses	Percent
Quidel QuickVue In-Line One Step	154	41
Thermo Biostar Acceava	64	17
Abbott Signify	62	16
Wyntek OSOM or OSOM Ultra	16	4
Polymedco Inc Poly stat A	13	3
Beckman Coulter Primary Care ICON FX	10	3
Becton Dickinson LINK 2	9	2
Fisher HealthCare Sure-Vue	7	2
Quidel QuickVue Dipstick	6	2
Genzyme Contrast	6	2
Genzyme OSOM or OSOM Ultra	6	2
SmithKline Diagnostics ICON FX	3	<1
Acon Rapid Strip Test	2	<1
Applied Biotech SureStep	1	<1
Mainline Confirms Strep A Dots	1	<1
Binax NOW	1	<1
ICON FX	1	<1
Other test kits listed (non-waived): Becton Dickinson Directigen; Becton Dickinson Q Test; Thermo BioStar OIA Max; Henry Schein One Step; Quidel QuickVue +; Quidel QuickVue Flex; Clearview Strep	12	3
Other test kits listed (test complexity unknown): Redwood Biotech; AccuVue In-Line	2	<1

Test volumes

Participants were asked "How many patient tests for rapid Group A Strep antigen were performed in your site in January 2002?"

A total of 24,791 patient tests were performed by the respondents in January 2002. This represents an average of 70 per month (or approximately 3 per day), with a range of 0 to 2500 per month.

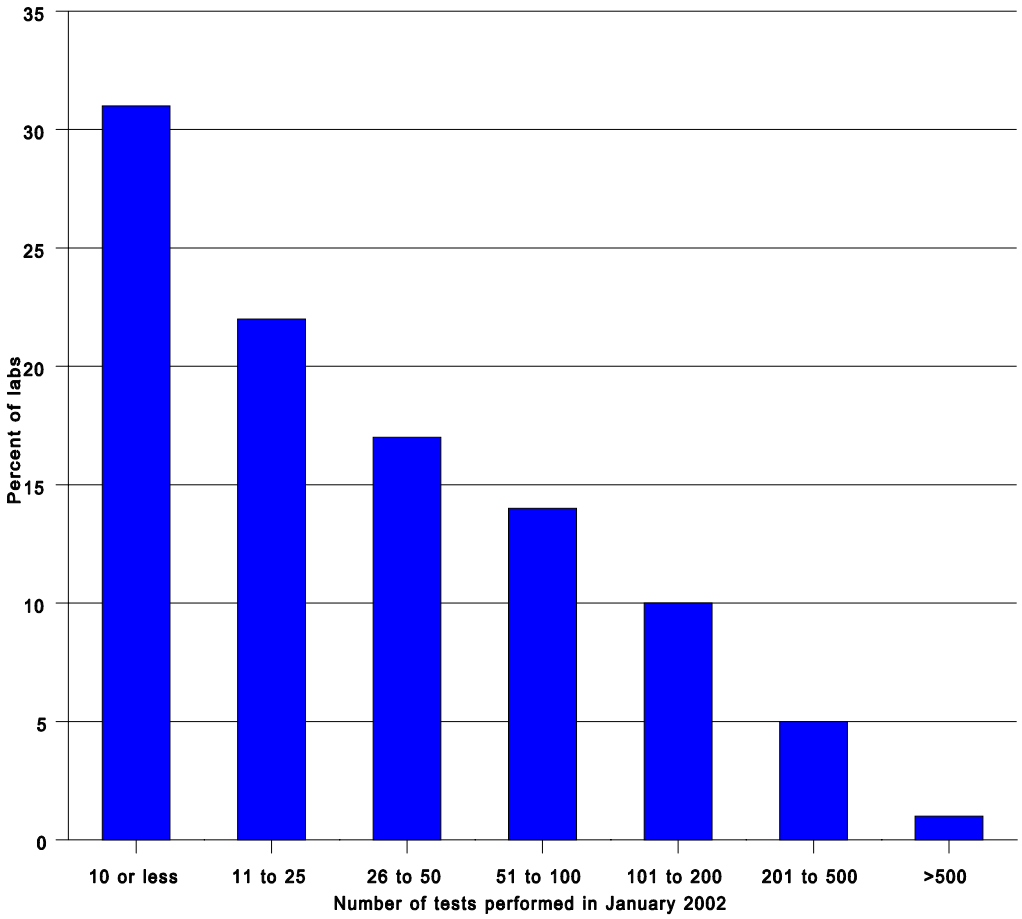


Figure 1 - Distribution of patient test volumes in January 2002

Culture confirmation of negative antigen test results

Participants were asked "When a patient test result is negative by your rapid Group A Strep antigen test kit, do you confirm those results by obtaining a throat culture test? (By either sending the specimen to another laboratory or performing the test on-site)." They were asked to choose one of the following responses:

- Yes, all negatives are routinely confirmed by the culture method
- Yes, but only on an occasional patient sample
- No, negatives are not confirmed by the culture method

Thirty percent of the respondents obtained a culture with all negative antigen test results, 48% obtained cultures on an occasional patient sample, and 22% did not confirm any negatives by the culture method.

A number of the respondents stated that the physician used their professional judgement, based on clinical examination and other considerations, in deciding to culture or not.

Cultures performed on-site

Participants were asked "Do you perform throat cultures on-site?" My intent was to find out if the site inoculated culture media, incubated the media, reviewed and interpreted culture growth characteristics, and generated test results on-site. When reviewing a number of affirmative responses to this question by waived and PPMP sites (who would not be performing moderate- or high-complexity throat cultures), I realized that some of the participants may not have understood my intent for this question. When responding affirmatively, some sites may have meant that they collected samples for cultures or swabbed culture media on-site, but did not incubate, interpret growth characteristics or generate test results on-site. For every site giving an affirmative response for this question, I checked the Washington MTS database to see if "throat culture" was listed as a moderate- or high-complexity test for which the site was fully regulated (i.e., compliance with all standards, proficiency testing participation, and an on-site inspection). The results for "on-site cultures" are based on this verification process.

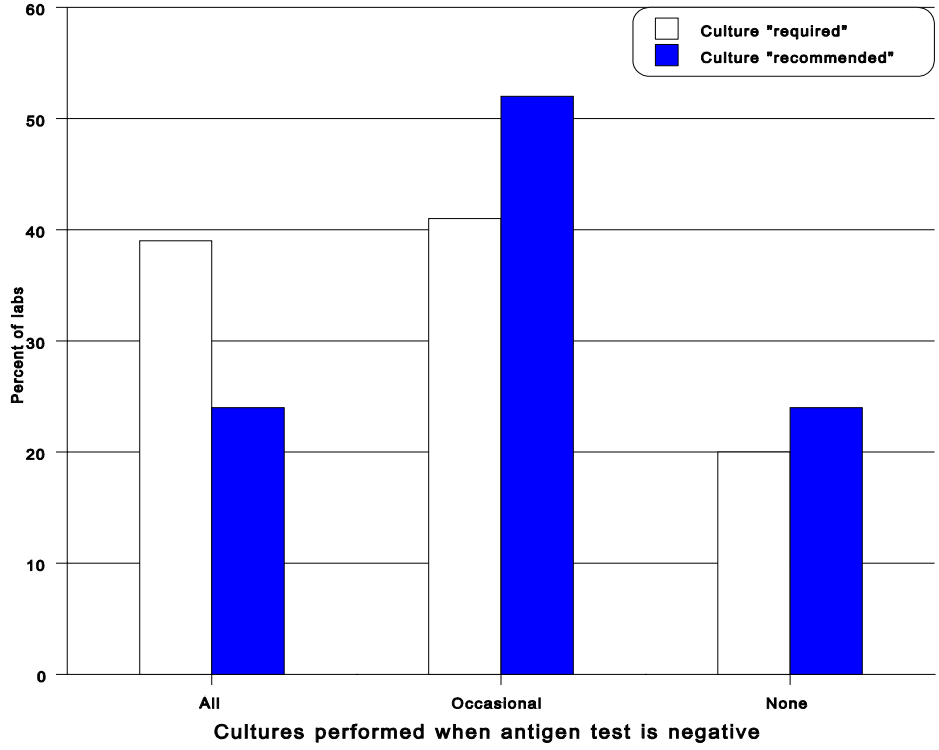
Forty-three respondents (12%) performed cultures on-site.

Differences in practices based on product insert instructions

Each brand of rapid Strep antigen test kit has a unique set of instructions for the performance of the test. Under the product insert sections called “Interpretation” and/or “Limitations” some of these test kits will “require” the user to perform a culture if the antigen test results are negative, using language such as “shall,” “must” or “required.” For other test kits, the product insert will “recommend” that the user perform a follow up culture, using terms such as “should” or “recommended,” Addendum B.

Among the 152 sites using test kits where the culturing of negatives was “required” in the product insert, 39% did so with all negative antigen tests. This rate was lower (24%) in the 187 sites that used test kits where the culturing of negatives was “recommended,” Figure 2.

Figure 2 - Differences based on product insert instructions



Culture **“required”** includes: Abbott Signify, Acon Rapid Strip Test, Applied Biotech SureStep, Becton Dickinson LINK2, Thermo BioStar Acceava, Fisher HealthCare Sure-Vue, Mainline Confirms Strep A Dots, Polymedco Inc Poly stat A.

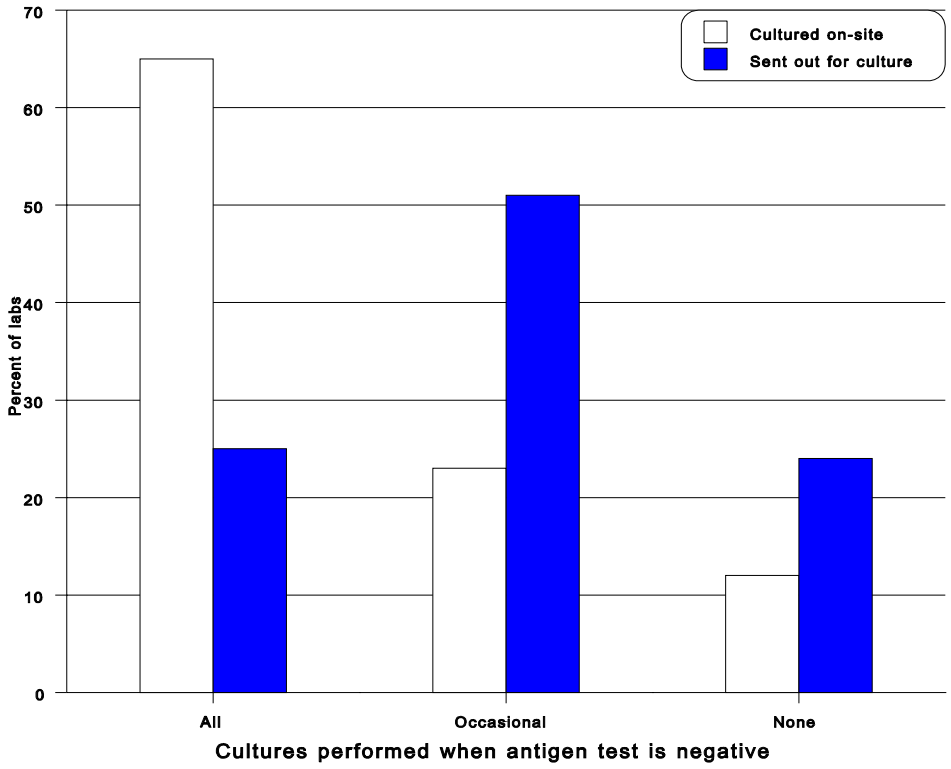
Culture **“recommended”** includes: Beckman Coulter Primary Care ICON FX, Binax NOW, Genzyme Contrast, Genzyme OSOM and OSOM Ultra, Quidel QuickVue In-Line One Step, Quidel QuickVue Dipstick, SmithKline Diagnostics ICON FX, Wyntek Diagnostics OSOM and OSOM Ultra.

(Note: Insert instructions for a particular product can differ between versions and/or dates published)

Differences in practices based on where the culture is performed

Among the 43 sites that performed cultures on-site, 65% did so with all negative Strep antigen test results. This rate was significantly lower (25%) in the 323 sites that sent out their orders for cultures, Figure 3.

Figure 3 - Differences based on where the culture is performed



Differences in practices based on the category of the testing site

For sites that did not perform cultures on-site, the difference in the rates of obtaining follow up cultures between waived/PPMP sites and higher complexity sites was not significant, Table 3.

Table 3 - Differences based on the category of the testing site

	Number of sites	Percent that obtain a follow up culture on all negative antigen results
Waived/PPMP sites	248	24
Moderate/high sites that do not culture on-site	75	28
Moderate/high sites that perform culture on-site	43	65

DISCUSSION

Due to the variable sensitivity of rapid Group A Strep antigen detection tests, the American Academy of Pediatrics (AAP) and the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the American Heart Association recommend culture confirmation for a negative antigen detection test result.[1, 2] Some studies show that pediatricians follow the diagnostic approach recommended by the AAP more than do internists or family or general practitioners.[3]

Other studies show that physicians who cultured on-site were significantly more likely to follow the recommended approach than those who did not incubate or read cultures on-site.[4] We found this to be true in our current study as well.

When reviewing rapid Strep antigen test kit product inserts, we noted a wide variation in the language used to recommend or require the confirmation of negative antigen test results by the culture method. Some product inserts state that a negative test response is to be considered a "presumptive" result, Addendum A. Some recommend that cultures be performed for negative test results. Others are more definitive, stating that follow up cultures must be performed on all negative antigen test results, Addendum B. Two test kits have instructions that go even further, stating that, in addition to culture, a grouping procedure be performed. Two test kits offer conflicting instructions, recommending that follow up cultures be performed under the section called "Interpretation" and requiring cultures under the section called "Limitations".

Under CLIA and the Washington MTS rules for waived testing, a testing site is required to follow the manufacturer's instructions for performance of the test. The practice of culturing all negative patient antigen tests was not 100% among sites using a test kit that "required" this practice, but the rate was higher in sites using test kits "requiring" rather than "recommending" it. We found similar patterns with respect to quality control practices with waived test systems in

previous studies with the Pacific Northwest Network. In these studies, adherence to the instructions for quality control was not 100% among sites when required in the product insert, but was significantly higher when required than recommended.[5, 6, 7]

It is unclear whether reflex testing (obtaining additional confirmatory testing) is considered "performance of the test" and would therefore be required if so stated in the product insert.

On November 7, 2002, the Food and Drug Administration (FDA) approved a new rapid HIV diagnostic test kit, the OraQuick Rapid HIV-1 Antibody Test. While this test is currently categorized as moderate-complexity, the Health and Human Services (HHS) Secretary Tommy G. Thompson "strongly urged the OraSure company to apply for a CLIA waiver." A press release about the approval of this HIV test kit stated that a reactive test result "must be confirmed with an additional specific test."

The results of this and other network studies show how well laboratories comply with waived test product insert instructions for both confirmatory testing and quality control. If this test is granted waived status and the confirmation of the rapid HIV test is truly required, the manufacturer and the FDA may need to take additional precautions (beyond standard product insert instructions) to assure this will be done on all patients in all testing sites.

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ADDENDUM A

Strep antigen test kit instructions
A negative test response is considered a **presumptive** result

Examples	Section of product insert where discussed	
	Interpretation	**Limitations**
"A red Control Line but no blue Test Line is a **presumptive** negative result" "A negative sample will give a single pink to purple control line in the top half of the window, indicating a **presumptive** negative result" "Reporting of negative results as "no Group A Strep antigen detected, **presumptively** negative for Group A Streptococcus" is recommended" "Negative: This result indicates that the specimen is a **presumptive** negative for the presence of group A streptococcal antigen"	Abbott Signify Beckman Coulter ICON FX Biostar Acceava Lifesign Status AccuStrep Princeton Biomeditech BioStrep Quidel QuickVue In-Line Quidel QuickVue Dipstick Quidel QuickVue Flex	Genzyme Contrast

(Note: Insert instructions for a particular product can differ between versions and/or dates published)

ADDENDUM B

Strep antigen test kit instructions
Perform culture if results of antigen test are negative

Examples	Section of product insert where discussed	
	Interpretation	**Limitations**
Culture is **recommended** "The patient's sample **should** be cultured to confirm the absence of Strep A infection . . ." "Culture confirmation is **recommended** for all negative test results" "The American Academy of Pediatrics **recommends** that presumptive negative results be confirmed by culture" "It is **recommended** by the American Academy of Pediatrics that presumptive negative results be confirmed by culture"	Acon Rapid Test Strip Beckman Coulter ICON DS Genzyme Contrast Lifesign Status AccuStrep Princeton Biomeditech BioStrep	Beckman Coulter ICON FX Binax NOW Genzyme Contrast Genzyme OSOM Ultra Lifesign Status AccuStrep Princeton Biomeditech BioStrep Quidel QuickVue In-Line Quidel QuickVue Dipstick SmithKline ICON FX Wyntek OSOM Ultra
Culture is **required** "A negative test result **shall** be followed up using the culture method" "A negative result obtained from this kit **must** be confirmed by culture" "When a patient has a negative result, additional testing using the culture method is **required**"		Abbott Signify Acon Rapid Test Strip Applied Biotech SureStep Beckman Coulter ICON DS Becton Dickinson LINK 2 Biostar Acceava Fisher HealthCare Sure-Vue Jant Pharmacal AccuStrip Mainline Confirms Strep A Dots Meridian ImmunoCard STAT Polymedco Poly stat Remel RIM A.R.C.

(Note: Insert instructions for a particular product can differ between versions and/or dates published)