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Evaluation of Automated Processing of Electronically Reported Serological Tests for Syphilis Using Current and Historical Syphilis Results Compared with Traditional Reactor Grid Processing in Florida

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Abstract

Background: Syphilis in Florida increased 49% from 2016-2020. Moreover, many serological tests for syphilis (STS) do not indicate current infection. Traditionally, syphilis surveillance systems used reactor grids, a method for prioritizing STS for investigation based on age, non-treponemal titer, and/or sex. In 2022, Florida's STD surveillance system implemented an automated method for processing electronically reported STS (eSTS), expanding upon the reactor grid, using an individual's current STS (treponemal and non-treponemal), treatment history, and historical STS results aiming for more efficiently processing eSTS. We compared the new method of processing eSTS results against the reactor grid and determined potential value in time/cost savings of this change.

Methods: All eSTS (n=4,144) from 1/2/2023–1/8/2023 were compared by how the logic-based method processed test results vs. how the reactor grid processed test results. Each method was compared using measurements of accuracy (e.g., sensitivity/specificity). Time and cost savings in eSTS processing were estimated.

Results: Using the surveillance case definition as reference, the accuracy of the logic-based method for processing eSTS was nearly double (82.3% vs. 43.6%), had greater specificity (79.0% vs. 33.0%), and increased positive predictive value (47.5% vs. 22.0%) when compared to the reactor grid method. Sensitivity (99.5% vs. 98.6%) and negative predictive value (99.9% vs. 99.2%) remained similar. The logic-based method is estimated to save 7,783 hours annually (~$185,000).

Conclusions: Processing eSTS based on current and historical STS results is significantly more accurate than using a reactor grid. Moreover, these improvements save time and resources that can be better allocated to other program prevention activities.

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Short Summary:

Processing electronically reported syphilis test results based on current and historical patient syphilis results has greater specificity (2.4 times greater) and accuracy (1.9 times greater) than traditional reactor grids.

Keywords

ELR; Automation; Syphilis; Reactor Grid

Introduction

Reported syphilis has increased both in Florida (49% increase from 2016–2020) and nationally (52% increase from 2016–2020).[1] Reported infections and reported reactive serological tests for syphilis (STS) results increase in tandem.[2] This results in an increased workload for disease investigation specialists (DIS) and a need for finding solutions to improve efficiency and prioritization for increasing reported STS and syphilis.

Syphilis is a sexually transmitted infection (STI), caused by the bacterial spirochete *Treponema pallidum*; though syphilis is curable with antibiotic treatment reinfections are possible.[3,4] Consistent with other spirochetes, direct detection of *T. pallidum* using available laboratory testing is challenging. Currently, case definitions for syphilis and other notifiable spirochetes use a combination of indirect detection methods to assess clinical and surveillance significance.[5,6] Two (or more) tests support syphilis diagnosis: 1) treponemal-antigen based antibody detection tests, which are specific, but typically remain reactive for life, which limits detection of reinfections and 2) non-treponemal antibody tests (quantitative and qualitative), which are non-specific but can be used to determine titers useful for monitoring successful treatment and potential reinfections.[7]

This indirect method of pathogen detection, particularly leads to false positive results in over 10% of non-treponemal and treponemal tests; these are caused by antibody cross-reactions from a variety of other conditions.[8,9] Moreover, reactive non-treponemal tests often persist in persons who have received appropriate treatment for syphilis per recommended guidelines (including those who are serofasting, serological non-responders, and in the process of seroreversion).[10,11] Thus, sexually transmitted disease (STD) surveillance programs use a combination of current results for STS against historical STS results, along with treatment history, to determine which individuals warrant additional response..

Not all reported STS results are determined to be new infections. Prior studies found false positive STS and previously treated individuals with reactive STS account for 50-65% of reactive STS not resulting in new infections.[2,12] For decades, including prior to the wide adoption of electronic notifiable disease surveillance systems, Florida and many other STD programs have used non-treponemal titer reactor grids, an administrative tool to prioritize syphilis case investigations. These reactor grids have been based on current reported non-treponemal titer, patient’s age, and gender or sex to process and prioritize reported STS results for field investigation.[13,14] (Florida Reactor Grid; Table 1) Because of the indirect

method of syphilis laboratory determination, using reactor grids to process STS indirectly prioritizes current STS results and may lead to missed primary syphilis cases or investigation of non-infections.[14,15] For example, a 62 year-old with a 1:4 non-treponemal titer would not be assigned for investigation from STS results while a 22 year old with serofasting STS results following adequate treatment for syphilis would continue to have follow-up STS results assigned for follow-up/investigation.

Modernization of surveillance systems to electronic databases and an expansion of electronic laboratory reporting has allowed greater automation in processing infectious disease test results.[16-18] Previous studies have retrospectively examined the value in more directly assessing current electronically reported STS (eSTS) informed by prior reported STS results.[2,12] These studies found using an algorithm to include historical result when processing current eSTS would increase specificity, positive predictive value (PPV), and overall accuracy over processing eSTS via the reactor grid. However, these studies were theoretical.[2,12] In practice, implementation of automatic eSTS processing remained challenging due to the need to assess all incoming laboratory results for an individual, match person/laboratory data, and abide by existing practical design application within current processes including user trust in the rules for automating eSTS.

In 2023, the Florida Department of Health (FDOH) developed and implemented an automated process for bundling eSTS results received on the same day. This automated processing compared bundled current eSTS results against historical eSTS results (when available). Additionally, logic-based stepwise processing was performed to determine which eSTS constituted a potential new infection requiring investigation by field staff. We compared how this logic-based method processed eSTS results against how the reactor grid processed the same results and explored the impact of the logic-based method on program resources.

Materials and Methods

Automated processing of eSTS

FDOH uses a person-based system for STD surveillance (STDSS). This allows for storing and comparing historical test results for reportable diseases by person. Prior to the automation of eSTS, all eSTS were placed on an unassigned test list to determine which eSTS needed further investigation and which can be closed using the reactor grid. The unassigned test list was no longer possible once this process was automated as eSTS are bundled to process together rather than by individual STS results.

The automated processing of eSTS starts with an exact comparison of name, date of birth, and social security number, when available, as each of these components are required in Florida disease reporting requirements.[19] Those under one year of age are excluded and processed separately as congenital syphilis (supplemental figure 1). The STDSS creates a holding table for all incoming electronic laboratory results to be processed overnight. The holding table allows the system to bundle and process all eSTS reported to FDOH for the same person, on the same day (e.g., quantitative non-treponemal, qualitative non-treponemal, treponemal, duplicate tests). Results received over several days are examined

on the day each result arrives and processed based on past and current STS history. If a sole treponemal test is received, it is held for 24-hours for women of childbearing age and 72-hours for all other persons to await non-treponemal tests before processing as a treponemal only event.

For persons with at least one reactive eSTS and no prior record of syphilis in the system, the automated process focuses on current eSTS. Those with discordant test results (e.g., reactive non-treponemal test and non-reactive treponemal test) do not meet the case definition (without provider-reported symptoms) and are closed.[6] Those with concordant positive results are assigned to the field for investigation for all test combinations except when only reactive treponemal test results are reported. Results for those with only reactive treponemal test results are maintained in the holding table for designated time periods (up to 72 hours) while awaiting additional non-treponemal test results before assignment solely based on the treponemal result.

For those with at least one reactive eSTS and a prior history of syphilis in the surveillance system, processing of current eSTS results is based on current results, treatment history, and previously reported historical STS results. Persons with discordant results are processed like those with no history. These two groups (reactive eSTS among persons with a syphilis history and those with discordant results) are processed through a series of logic steps comparing current titer against previous titers, prior syphilis treatment, and time between current and previous titers to determine if the current results meet laboratory criteria for a potential new infection (e.g., seroconversion of STS, 4-fold increase in non-treponemal titer). Results suggestive of meeting the laboratory criteria, based on the national syphilis surveillance case definition, for a potential new infection are assigned to the field for investigation.[6] Again, those with only treponemal eSTS results will be held for the specified time periods. To handle duplicate or follow-up tests reported within 30 days of prior test results, the current result is compared to the prior historical result. If there is no change in titer status for investigation (i.e., no four-fold non-treponemal titer increase, no seroconversion), then results are appended to the most recent infection record. If there is a change in titer status, a new disease record is assigned to the field for investigation. Florida's 30-day cutoff is not a requirement of STDSS but generated to differentiate syphilis testing events. Other programs may not create new disease records until the change in titer status is observed.

Data collection, variables, and analyses

All reported eSTS in Florida from 1/2/2023-1/8/2023 were reviewed to determine how the automation procedure performed. eSTS were examined to determine the number of persons (unique by date of report) with reported results and if the eSTS matched a person who had been previously identified in FDOH STDSS for any STI. Bundled eSTS results were assessed if they were processed into a new event record assigned to the field, a new event record not assigned to the field, appended to a previous event record, or held awaiting non-treponemal test results. For eSTS results generating new events not assigned to the field, they were reviewed for the reason they were not assigned to the field. In addition,

eSTS results were retrospectively assessed using the traditional reactor grid method and determined whether they would have been assigned to the field.

For both the logic-based processing method and traditional reactor grid, bundled laboratory results for an individual are assigned to a single event record. Event records were reviewed to determine if they resulted in a reported case of syphilis using the surveillance definition.[4] Following infection determination, measures of accuracy and corresponding confidence intervals were calculated based on outcomes of the automated processing method and the traditional reactor grid. Each method was assessed for sensitivity, specificity, PPV, negative predictive value (NPV), and overall accuracy in processing STS against the syphilis surveillance case definition.[6] All statistical tests were performed using MedCalc V.20.218.[20]

Time savings for program staff were estimated by comparing the difference in automated tasks performed between the logic-based method of processing eSTS and the reactor grid. Tasks that were previously done by field staff and now automated were given conservative estimates of two minutes of time savings to match person and laboratory data and three minutes to enter all requisite demographic information for a person's profile. For each new case found by either the logic-based method or reactor grid, 90 minutes of investigation, treatment verification, and partner services would be assigned. Finally, 10 minutes were allocated for every non-case assigned to the field resulting in investigation and other related follow up by field staff.

Each of these estimates were multiplied by the difference in the number of events processed by the logic-based method or reactor grid. Estimates were then turned into annualized time savings (multiplying the 1-week of results by 52), full-time employee (FTE) equivalents (annualized time savings divided by 2,080 hours), and cost savings (multiplying FTE equivalents by $50,000 estimated salary and benefits for staff conducting eSTS processing).

This study was reviewed by the Florida Department of Health Institutional Review Board Office (protocol number: 2023-012). It was determined to be exempt from review and to be non-research: public health practice in accordance with United States federal code 45 CFR 46.102(d).

Results

A total of 4,144 eSTS were processed and bundled daily from 1/2/2023 through 1/8/2023 (Table 2), these were from 1,831 individuals with an average of 2.26 reported results per person. Most individuals matched a preexisting profile in the STDSS (85%; n=1,561). Of the eSTS results, new event records were created for 81% (n=3,346), 10% (n=420) were treponemal tests awaiting assignment until the end of their holding period or receipt of corresponding non-treponemal test results, and 9% (n=378) were assigned to the most recent prior event records. Of the 3,346 eSTS resulting in new event records creation, only 31% (n=1,033 eSTS) were assigned to the field for investigation, whereas 69% (n=2,313 eSTS) were not assigned to the field for investigation based on current and historical STS results.

The 3,346 reported eSTS results led to 1,331 event records (often more than 1 eSTS per event record) being generated in the STDSS (Table 3). When comparing the automated

logic-based method to the traditional reactor grid, the logic algorithm assigned less than half as many records to the field for investigation (448 records vs. 959 records). In addition, the logic algorithm assigned 213 of 214 (99.5%) reported syphilis cases for investigation; more than the reactor grid (211 of 214; 98.6%). The logic algorithm missed only one case that should have been assigned to the field for investigation; this was from a person with prior non-treponemal testing only, who did not meet surveillance case definition at initial testing. Therefore, the event record had previously assigned a disposition as administrative closure (as compared to unable to locate or infected not treated, which would have been assigned for investigation) when new results were received including the treponemal test results. In comparison, the three syphilis cases not assigned by the reactor grid had no prior reported history of syphilis; were between 60–65 years of age; had 1:2 non-treponemal titers; and following investigation, were determined to be primary syphilis (n=1) or unknown/late latent duration syphilis (n=2). Overall, event records assigned for investigation by the logic algorithm were more than two times more likely to result in newly diagnosed syphilis: 48% (2.1 event records per newly identified infection) assigned by the logic algorithm resulted in new syphilis compared to 22% (4.5 event records per newly identified infection) for the reactor grid.

Non-cases that were closed by the logic-based method and not assigned to the field were predominantly from individuals with a prior documented history of treated syphilis and no evidence of reinfection (82%, n=725) (Supplemental Table 1). Discordant reactive STS event records comprised an additional 16% (n=143) of records not assigned and the remaining 2% (n=15) were among individuals older than age 65 with a non-treponemal titer 1:2 or less and no documented history of syphilis.

The overall accuracy improved significantly was nearly two times greater using the logic-based method (82.3% 95%CI 80.1-84.3) versus the reactor grid (43.6% 95%CI 40.9-46.3) (Table 4). Similarly significant, the logic algorithm had 2.4 times greater specificity (79.0% [76.4-81.3] vs. 33.0% [30.3-35.9]) and 2.2 times higher PPV (47.5% [44.7-50.4] vs. 22.0% [21.2-22.8]) than the reactor grid. Sensitivity (99.5% [97.4-99.9] vs. 98.6% [96.0-99.7]) and NPV (99.9% [99.2-99.9] vs. 99.2% [97.6-99.7) were equivalent or slightly improved, although not significantly, with the logic algorithm than with the reactor grid. The logic-based method was estimated to save nearly 150 hours per week through improvements in laboratory-to-person data matching (67 hours per week) and 513 fewer event records assigned to the field per week (26,000 records per year) saving 85 hours of FTE person time per week (Table 5). Due to a small number of additional cases found using the logic-based method, field work for completing patient case information and partner services would increase by 3 hours per week; 156 hours per year. Overall, however, the new logic-based method could reduce laboratory processing efforts at the field level by 7,783 hours per year, equivalent to 3.7 full-time employees or over $185,000 per year (using an estimated $50,000 salary and benefits per employee).

Discussion

The logic-based method using current and historical STS to process eSTS results is a significant improvement over the traditional reactor grid. The automated processing using

the logic-based method reduced the number of STS assigned to the field for investigation while nearly doubling the overall accuracy of STS assignment for investigation. Much of the improvement in accuracy was due to an increase in specificity when non-syphilitic infection-related STS were removed from potential investigation. The improvements in our implemented logic-based eSTS processing were consistent with results from studies examining theoretical application of processing eSTS in a similar manner.[2,12] The improved accuracy of the logic-based method would be expected to save thousands of hours in eSTS processing through eSTS-to-surveillance system matching and fewer eSTS assigned to field for investigation reducing worker burden and improving surveillance efficiency.

Typically, when an increase in specificity is observed, it comes at the expense of sensitivity; as with fewer false positive results more true positives may be missed.[21] However, this trade-off was not observed in the results from the logic-based model, as it uses an approach to assessing eSTS that is more direct and more aligned with the syphilis case definition.[6] Though auto-processing eSTS using the logic-based method did not have perfect sensitivity, it was as sensitive as the eSTS processed via the reactor grid. Both methods missed a few cases, but the logic-based method also allowed for additional cases among persons with primary syphilis or older individuals to be diagnosed and receive timely treatment, as the reactor grid method does not assign such cases to the field to investigate.[15] As logic-based processing of eSTS relies heavily on information available on laboratory reports, adding patient and disease-specific information through electronic case or health information exchanges and improved person and laboratory data matching could further improve accuracy and data completeness of processing eSTS.[22]

This study used the syphilis surveillance case definition as the reference for determining persons infected with syphilis.[6] Using the case definition as the standard is consistent across STD programs in the United States. However, nearly all STS indirectly assess whether an individual is currently infected. Until syphilis is more frequently directly detected through laboratory tests, the case definition remains the gold standard to compare measurements of accuracy in processing STS.

The results of this evaluation were based on only one week of data, but disparities in performance using the logic-based model were so great, an effect was observed. Moreover, our study sample size, including 4,000 plus observations, over 1,300 events, and 214 infections is not considered small for accuracy determination.[23] Continued evaluation of the effects of the logic-based model on more indirect impacts beyond measurements of accuracy, such as any potential effects on the STD prevention program metrics, will take more time and data to observe.

One aspect of overall time/resource/cost savings not explored in this evaluation is the requisite subject matter expertise, software development expertise, and overall cost of development, implementation, maintenance, and evaluation of making these significant data modernization improvements. Without each of these requisites, resources, and organizational support, implementation of a data modernization and informatics project of this scope may be difficult to achieve.[22]

This exact logic-based method may not be able to be directly applied to all surveillance systems or all reportable diseases. However, many parts of the process can be incorporated into a program's systems regardless of platform or approach to surveillance. Automation of processing ELR has been found to save time and allow organizations to focus resources on other program or prevention activities.[18] Differences in system processing of eSTS may vary the time and resource savings. Despite this, programs should consider similar concepts in their systems and public health activities to ease worker burden, improve data, and inform public health.

This evaluation highlights data modernization in action and the need for continued funding and reinforcement of the requisite technical expertise.[23,24] STD programs should consider implementation of a logic-based method for syphilis. Similarly, other public health programs might consider adapting logic-based approaches of processing electronic laboratory results consistent with the needs of their program. Programs should not consider automation of ELR processing as the final point of their data modernization but should continue to find opportunities to use technology and available health data to improve data quality and inform public health action.[25]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Non-Treponemal Titer and Age-Based Reactor Grid Used in Florida for Prioritizing STS Results for Investigation

	Non-Treponemal Titer								
Patient Age (Years)	**WR**	**R**	**1:1**	**1:2**	**1:4**	**1:8**	**1:16**	**1:32**	**1:64+**
0-30	ER	ER	ER	ER	ER	ER	ER	ER	ER
31-40	AC	ER	ER	ER	ER	ER	ER	ER	ER
41-50	AC	ER	AC	ER	ER	ER	ER	ER	ER
51-60	AC	ER	AC	AC	ER	ER	ER	ER	ER
61-69	AC	AC	AC	AC	AC	ER	ER	ER	ER
>70	AC	AC	AC	AC	AC	AC	ER	ER	ER

WR = Weakly Reactive. R= Reactive. ER = Event Record created for field staff investigation. AC = event record Administratively Closed without Investigation.

Table 2.

Results of Processing Electronically Reported Serological Tests (STS) for Syphilis Using Logic Algorithms and Processes in Florida

STS Result Process	Frequency	% of Total[b]
Laboratory Results[a]	4,144	--
Persons[a]	1,831	--
Matching Persons in STDSS	1,561	85%
New Persons	301	15%
Labs for New Events Created[a]	3,346	81%
Labs Assigned to the Field	1,033	25%
Labs Not Assigned to the Field	2,313	56%
Labs Appended to Previous Events	378	9%
Labs Awaiting Assignment	420	10%

[a] Note: there is more than one (n=2.26) eSTS result per person (bundled for processing) and more than one eSTS was assigned to a new event (1,331 new events created).

[b] For persons categories(n=1,831), the percentage of total are calculated using the total persons. For laboratory categories (n=4,144), the percentage of total was calculated using the total laboratory results.

Table 3.

Comparison of Outcomes of Syphilis Events Between Processing Serological Tests for Syphilis Using the Logic-Based Method or Reactor Grid

Logic-Based Method	Frequency	%	Reactor Grid	Frequency	%
Total New Events	**1,331**	--	**Total New Events**	**1,331**	--
New Events Assigned to the Field [a]	**448**	**34%**	**New Events Assigned to the Field** [a]	**959**	**72%**
New Events Leading to New Cases[b]	213	48%	*New Events Leading to New Cases*[b]	211	22%
New Events Determined to Not Be a New Case[b]	235	52%	*New Events Determined to Not Be a New Case*[b]	748	78%
New Events Not Assigned to the Field [a]	**883**	**66%**	**New Events Not Assigned to the Field** [a]	**372**	**28%**
New Events Leading to New Cases[b]	1	< 1%	*New Events Leading to New Cases*[b]	3	1%
New Events Determined to Not Be a New Case[b]	882	100%	*New Events Determined to Not Be a New Case*[b]	369	99%

[a] Percentage is calculated as part of total.

[b] Percentage is calculated as part of category (i.e., of the events assigned or not assigned).

Table 4.

Measurements of Accuracy of STS Processing via Logic-Based Method versus Reactor Grid in Florida

Metric	Logic-Based Method	95% CI (%)	Reactor Grid	95% CI (%)
Sensitivity	99.5%	97.4-99.9	98.6%	96.0-99.7
Specificity	79.0%	76.4-81.3	33.0%	30.3-35.9
PPV[a]	47.5%	44.7-50.4	22.0%	21.2-22.8
NPV[b]	99.9%	99.2-99.9	99.2%	97.6-99.7
Accuracy	82.3%	80.1-84.3	43.6%	40.9-46.3

[a]PPV = Positive Predictive Value.

[B]NPV = Negative Predictive Value.

Table 5.

Estimated Change in Time Spent Processing Electronic Serologic Tests for Syphilis via the Logic-Based Method versus the Reactor Grid

Automated Process	Logic-Based Method	Reactor Grid	Difference	Time Saved (Min) [a]	Time Savings (Hr) [b]	Annualized Time Savings (Hr) [b]
Laboratory to Person Matching	1,561	0	1,561	2	52.0	2,705.7
Automatic Profile Creation	301	0	301	3	15.1	782.6
Events Assigned to the Field - Case	213	211	2	−90	−3.0	−156.0
Events Assigned to the Field - non-Case	235	748	−513	−10	85.5	4,446.0
Total	N/A	N/A	N/A	N/A	149.6	7,778.3

[a] Time saved is estimated for each automated process.

[b] Time savings are calculated using the difference in automated events between the logic-based method and the reactor grid and multiplied by estimated time saved.