An Automated Syphilis Serology Record Search and Review Algorithm to Prioritize Investigations by Health Departments

Saugat Karki, MD, MS[*], **Thomas A. Peterman, MD, MSc**[*], **Kimberly Johnson, MS**[†], **Robin R. Hennessy, MPH**[*,†], **James Matthias, MPH**[*,‡], **Craig Wilson**[‡], **Ninad Mishra, MD, MS**[*], **Hillard Weinstock, MD, MPH**[*]

[*]Division of Sexually Transmitted Diseases Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA

[†]New York City Department of Health and Mental Hygiene, New York City, NY

[‡]Florida Department of Health, Tallahassee, FL

Abstract

Background: Reactive syphilis serologies are investigated by health departments to determine if they represent new infection, reinfection, or treatment failure. Serologies prioritized for investigation based on nontreponemal test titer and age (using a "reactor grid") undergo manual record search and review. We developed a computerized algorithm that automates the record search and review.

Methods: We developed and tested the algorithm using a Florida Department of Health data set containing serologies reported January 2016 to December 2018 and previous records linked to each individual. The algorithm was based on the syphilis case definition, which requires (except primary cases with signs and symptoms) (1) a positive treponemal test result and a newly positive nontreponemal test result or (2) a 4-fold increase in nontreponemal test titer. Two additional steps were added to avoid missing cases. New York City Department of Health and Mental Hygiene validated this algorithm.

Results: The algorithm closed more investigations (49.9%) than the reactor grid (27.0%). The algorithm opened 99.4% of the individuals investigated and labeled as cases by the health department; it missed 75 cases. Many investigations opened by the algorithm were closed by the reactor grid; we could not assess how many would have been cases. In New York City, the algorithm closed 70.9% of investigations, likely because more individuals had previous test in the database (88.2%) compared with Florida (56.5%).

Conclusions: The automated algorithm successfully searched and reviewed records to help identify cases of syphilis. We estimate the algorithm would have saved Florida 590 workdays for 3 years.

Screening and Diagnosis of Syphilis

A serologic diagnosis of syphilis usually requires 2 reactive antibody tests, treponemal, and nontreponemal.[1] The treponemal test is specific to syphilis and usually remains positive for life.[1–3] The reactivity of the nontreponemal test is correlated with duration of infection; titers peak in secondary syphilis and then decrease over time. Nontreponemal test titers are useful for following the response to treatment and for diagnosing a new infection in people with a syphilis history because a 4-fold increase in titer suggests reinfection or treatment failure. In the United States, reactive syphilis tests are reportable to health departments.[4] Historical test results are routinely maintained on file to aid with interpretation of any subsequent tests.[5]

The Syphilis Reactor Grid

Some health departments began conducting syphilis surveillance in the 1930s. Consistently compiled national data are available dating back to 1941.[6] Since 1962, laboratories have been required to report reactive syphilis serologic tests to health departments in an effort to identify syphilis cases that might not otherwise be reported by clinicians.[7] Ideally, every new reactive serologic test should be investigated. Because of the overwhelming volume of incoming tests and limited resources, health departments could not search historical records to determine if the newly reported tests might represent new cases of syphilis.[8] By 1970s, 1.4 million positive syphilis serologies were reported each year in the United States, and only half of these had a record search to see if they met the case definition for syphilis.[9] These administrative procedures typically involved the use of "reactor grids," which prioritize record search and investigation of syphilis serologies based on patient's age, sex, test type, and test titer[10,11] (Supplemental Fig. 1, http://links.lww.com/OLQ/A704). Tests with low titers from older patients are closed to further investigation because they are deemed unlikely to lead to a new case or are a lower public health priority.[10] Serologies considered to be of high priority undergo a search and review of historical records, which takes 4 to 19 minutes for each new serology.[9] A study evaluated the performance of 5 different reactor grid designs on 4 different populations and found that the percentage of "cases" missed is determined by the reactor grid design and prevalence of syphilis in the population. That study reported missing up to 66% of cases in populations where the prevalence of syphilis was more than 2%, prompting the investigators to recommend against using a reactor grid in populations with a high prevalence.[12]

Objective

Recently, researchers suggested an algorithm that used in conjunction with electronic laboratory reporting might be used to automatically search historical records and apply the case definition.[13] Electronic laboratory reporting has been widely adopted in the past few years.[14] Our goal was to build a computerized algorithm that could be used by any

health department to compare incoming electronic laboratory reports with previous serology records. We developed the program and tested it using health department serology records to see if the program successfully prioritized serologies that required investigation.

METHODS AND MATERIALS

Automated Processes With Streamlined Workflow

Syphilis serology reports usually include multiple test results, both nontreponemal and treponemal, that can be reported simultaneously or over a period of weeks related to a single diagnosis. Reported serologies are typically prioritized for further investigation based on patient age and test titer using a reactor grid (Supplemental Fig. 1, http://links.lww.com/OLQ/A704), and tests that are considered low priority are administratively closed (Fig. 1). If tests are not closed by the reactor grid (step 2, Fig. 1), public health officials perform a manual record search (step 3) and compare previous tests to determine whether a test merits further investigation based on the patient's serologic history or the investigation should be closed because the new test result is consistent with an old infection (step 4). The algorithm that we propose eliminates step 2, automates the initial record search (steps 3 and 4), and closes investigations when newly reported serology results do not meet the syphilis case definition. Because this algorithm is based on the case definition, we expect it to be more accurate than the reactor grid in identifying new cases. Many newly reported serology results do not meet the case definition, so closing them automatically could save time for the health department, eliminate the need for the reactor grid, and avoid missing cases.

Data Used for the Study

Florida Department of Health extracted syphilis serologies reported between January 2016 and December 2018 along with all previous serology records linked to a person. Surveillance data for each record were added, including age, sex, associated reported syphilis morbidity, test type and their associated qualitative and quantitative results (titers), disposition assigned by the health department, and the dates of the tests and when the dispositions were assigned. All personal identifiers were removed after unique identifiers for each profile and field record were created through an intermediary key linking to the data. An agreement was signed that prohibited the release of the key to the Centers for Disease Control and Prevention investigators under any circumstances. This work was determined not to be human subjects research.

Testing and Validation: A Reproducible and Scalable Approach

This new algorithm was designed, tested, and built on the data set provided by Florida Department of Health using Python Jupyter Notebooks that can be run on any individual personal computer.[15,16] Python Jupyter Notebook was used to allow for the algorithm to be reproducible and implemented at any health department. The algorithm was designed to work with the minimum data available on an electronic laboratory reporting feed such as test type, qualitative and quantitative test results, sex, age, and previous dispositions (if applicable) from the health department's surveillance data by loading data in a simple but specific format. The algorithm code was shared with New York City Department of Health

and Mental Hygiene (NYC DOHMH), where the results of the algorithm were validated on their data. Surveillance data from 2010 to 2019 were extracted, formatted, and fed into the algorithm. The aggregate results were then shared with the study team.

The Algorithm: Case Definition, Considerations, and Outcome Step

The algorithm is based on the syphilis case definition (Fig. 2). Step 1 starts when reactive nontreponemal tests are reported to the health department and are identified by the algorithm so that they can be compared with previous test results to determine whether they should be further investigated or not. Cerebrospinal fluid or cord blood serologic tests cannot be compared with regular serologic tests using this algorithm, so all positive results for these specimens were opened for further investigation by creating a new syphilis field record (step 2, box B). The remaining tests, after excluding cerebrospinal fluid and cord blood samples, were then compared with previous test results for the same individual. If the individual had a nonreactive treponemal test in the previous 14 days, with no reactive treponemal test, in the previous 14 days; the investigation was administratively closed by the algorithm (step 3 and box A). Next, individuals with a reactive treponemal test within the past 14 days and a penultimate negative treponemal test were opened for further investigation (step 4 and box B). Weakly or minimally reactive titers, along with their reported titer value (if present), were considered as reactive (we did not want to include them as nonreactive titers). Positive nontreponemal test results for patients with no previous titers in the database were opened for investigation because they could not be compared with previous test records, and further investigation would be needed to determine if they were new infections (step 5, box B). New nontreponemal titers were compared with historical titers and opened if there was a 4-fold or greater increase compared with the most recently reported titer (step 9, box B), or if the previously recorded serology was negative (seroconversion; step 10, box B). Two additional steps were added to avoid missing cases that did not meet the case definition based on available test results but could still merit investigation. We opened an investigation if a patient's previous disposition was "patient not located or not previously treated" (step 6, box B). We also opened an investigation for all women of reproductive age (younger than 50 years) who had a titer greater than 1:8 and no other reported serologic titers in the previous 6 months (we did not compare those titers with a previous titer that was more than 6 months old; step 8, box B). Furthermore, we opened an investigation for all persons who had a titer greater than 1:32 if there were no other reported serologic titers in the previous 1 year (step 8, box B). If none of the criteria for opening investigation were met, the tests were administratively closed without further manual review and investigation (box A).

RESULTS

Algorithm Result: Outcome Associated With Each Step in the Algorithm

Result From the Florida Data Set—There were reports for 73,332 unique persons in the Florida data set with any reported reactive nontreponemal tests. Typically, for each testing event, there were 2 nontreponemal (qualitative and quantitative) tests and a treponemal (qualitative test) test reported. Many individuals had multiple tests on different days related to the same episode of infection.

The algorithm opened 36,705 (50.1%; box B in Fig. 2) for further investigation and closed 36,627 (49.9%; box A in Fig. 2; Table 1). Most were opened for investigation because they had no prior nontreponemal tests in the database (31,938 individuals, 43.6%; step 5 in Fig. 2). These 31,938 individuals accounted for 87% of all opened investigations (box B in Fig. 2). Beyond this criterion, investigations were mostly opened for those whose current titer demonstrated a 4-fold or greater increase compared with the previous titer (2.2%; step 9) and those who had a seroconversion; that is, previous serologic test result was nonreactive and the current result was reactive (1.4%, step 10). All other remaining steps collectively opened investigations for 2142 (2.9%) individuals, which represents 5.9% of all investigations. The additional steps (steps 6 and 8) added to avoid missing cases led to opening 862 more investigations. Investigations were closed for 12,236 individuals (16.7%) who had a nonreactive treponemal test and no reactive treponemal test within the previous 14 days (step 3). The remaining 24,391 (33.3%; step 10) individuals who did not meet any criteria for opening an investigation were administratively closed, which represents 66.6% (box A) of all closed investigations.

Validation by the NYC DOHMH—The algorithm was applied and validated on a NYC DOHMH data set. There were 59,292 unique individuals in this data set, and the algorithm closed 42,086 (70.9) of them without further review (Fig. 2, box A). There were fewer individuals with no previous testing history in NYC DOHMH data set (17.8%; 10,534 tests) compared with the 43.5% (31,938 tests) in Florida's data set (step 5). The performance was otherwise similar for all steps of the algorithm, except NYC had more specimens that did not meet any criteria for opening an investigation (53.4%; 31,649 tests) compared with in Florida (33.2%; 24,391 tests) (step 10).

Algorithm Performance and Comparison With Syphilis Reactor Grid

We compared the investigations opened by the algorithm with those opened by the syphilis reactor grid that was being used in Florida when the data were collected (Table 1). Investigations were closed by the reactor grid for low titers in older patients (<1:8 for >60 years old, <1:4 for 51–60 years old, and <1:2 for 41–50 years old)[13] (Table 1). The algorithm closed many more investigations (36,627; 49.9%) than the reactor grid (19,804; 27.0%). Of all tests closed by the algorithm, the reactor grid closed 8299 (22.7%). There were 11,505 investigations opened for investigation by the algorithm that were closed by the reactor grid without further investigation. Most of these (11,035; 95.9%) had low titers but were opened by the algorithm because they had no previously reported titers in the database. Because they were closed by the reactor grid in Florida, there is no way to know how many would have been cases, had they been investigated.

Of the 12,789 tests identified as cases by the health department, the algorithm opened 12,569 (98.3%). Of the 36,637 tests closed by the algorithm, Florida Department of Health coded 36,407 (99.4%) as "not cases" and 220 as "cases." The 220 reports closed by the algorithm but called cases by the program were reviewed to see if they truly were missed cases. Further analysis suggested that 145 were not really missed cases, and 75 were missed by the algorithm. Most cases (145; 66.4%) were not missed cases because: (*a*) on further review, the findings did not meet the case definition for syphilis (52); (*b*) the reactor

grid closed an investigation of a serology that the algorithm would have opened, then a subsequent serology for that person was high enough to be opened by the reactor grid and the program assigned the diagnosis to the date of the subsequent test (20); and (*c*) the case had multiple related serology results including one opened by the algorithm, but the program attributed the case to a specimen from a different date (73). In both scenarios b and c, the algorithm would have opened an investigation based on an earlier specimen, resulting in earlier investigations and possibly decreasing exposure. The algorithm missed 39 cases (17.7%) that were characterized by (*a*) previous reactive nontreponemal tests with no confirmatory treponemal tests, and there were not diagnosed during the previous investigation (25); (*b*) a 4-fold increase in nontreponemal test titer that occurred but was not manifest between 2 consecutive tests (13); or (*c*) a positive darkfield examination (1). In addition, there were 26 missed cases (11.8%) that had signs or symptoms reported, and some of them could be detected by the algorithm if they were reported by clinicians independent of any investigation by the health department. This left 10 (4.5%) closed by the algorithm that would have missed cases because they were detected by a health department investigation that uncovered past serology test results that were not in the Florida database.

After adjusting these findings, we determined that the algorithm likely missed 75 of the 12,789 cases and the revised sensitivity of the algorithm was 99.4%. This sensitivity could be further improved with minor changes to the algorithm and if cases with symptoms were reported by clinicians.

DISCUSSION

With electronic laboratory reporting, it is possible to compare every reported syphilis serology result added into the surveillance systems with previously reported serologies. The algorithm we designed correctly identified 99.4% of the cases eventually classified as new cases of syphilis through the traditional review and investigation by Florida Department of Health. We believe the algorithm misses fewer cases of syphilis than the reactor grid, but exact measurement would require investigating all reported tests. Our manual review of instances where the algorithm closed the investigation, but the health department had labeled the individual as a case, found 20 cases (9.1%) where the reactor grid closed an earlier test with a low titer that the algorithm would have opened and were ultimately labeled as cases. Furthermore, the algorithm could be more sensitive if it were modified to detect (*a*) a 4-fold increase relative to any nontreponemal test from the previous 12 months or (*b*) a positive darkfield examination.

This algorithm would streamline the public health workflow for syphilis investigations and replace manual processes with an automated record search, and a case definition–based review process. The algorithm closed 28,328 individuals (52.9%) that the reactor grid had opened. Earlier studies have shown that these manual record searches take 4 to 19 minutes each.[9] If they took an average of 10 minutes, then eliminating 28,328 investigations would have saved an additional 283,280 minutes (590 workdays) for 3 years for the surveillance staff.

In NYC, 70.9% of the tests were closed without investigation as compared with 49.9% in Florida. This algorithm compared previous testing history to determine if a test warrants further investigation. More tests were closed in the NYC data set because there were more individuals with a testing history (88.2%) compared with the Florida data set (56.5%). Even in Florida's data set, for individuals with a history of tests, the algorithm closed 88.5% of the tests.

There is no additional information available on individuals with reported serologies when the reactor grid closed an investigation. This prevented ascertaining how many cases were missed when such investigations were closed. There is no criterion standard to differentiate a new or separate episode of syphilis in people with a syphilis history. Each test has a disposition assigned to it and the date when the disposition was assigned. The same disposition and disposition date are assigned to all tests in an episode. For the purpose of the algorithm, we used the disposition date to determine whether tests were from the same or different episode. Because this is not an established method, it might be prone to some errors.

Primary and secondary syphilis cannot be diagnosed solely based on serology because diagnosis is also based on signs and symptoms.[1,17] This algorithm is based on serologies reported to the health department, and some cases do not meet the criteria for a new case based on serology alone. However, these cases may not be completely missed by the health department, as some would likely be detected via clinician reporting. In this study, we identified 15 instances of primary and 1 instance of secondary syphilis reported with clinical signs and symptoms but whose serology alone did not meet the case definition.

The current method of prioritizing reactive syphilis serologies for investigation by health department is based on manual, time-intensive processes. The algorithm developed and described in this article automates this entire process and adds scientific rigor to this method by basing the algorithm on the case definition of syphilis. We applied this algorithm and tested it on a data set provided by Florida Department of Health and was validated by the NYC DOHMH. After analyzing the results of the algorithm and performing manual review of potentially missed cases, the algorithm was found to be highly accurate and would have saved more than 1 full-time employee equivalent of working hours per year, allowing health departments to devote resources to investigating cases.

Florida Department of Health is currently working on implementing the algorithm into the regular syphilis case investigation workflow. We anticipate more such implementations by other health departments in the future.
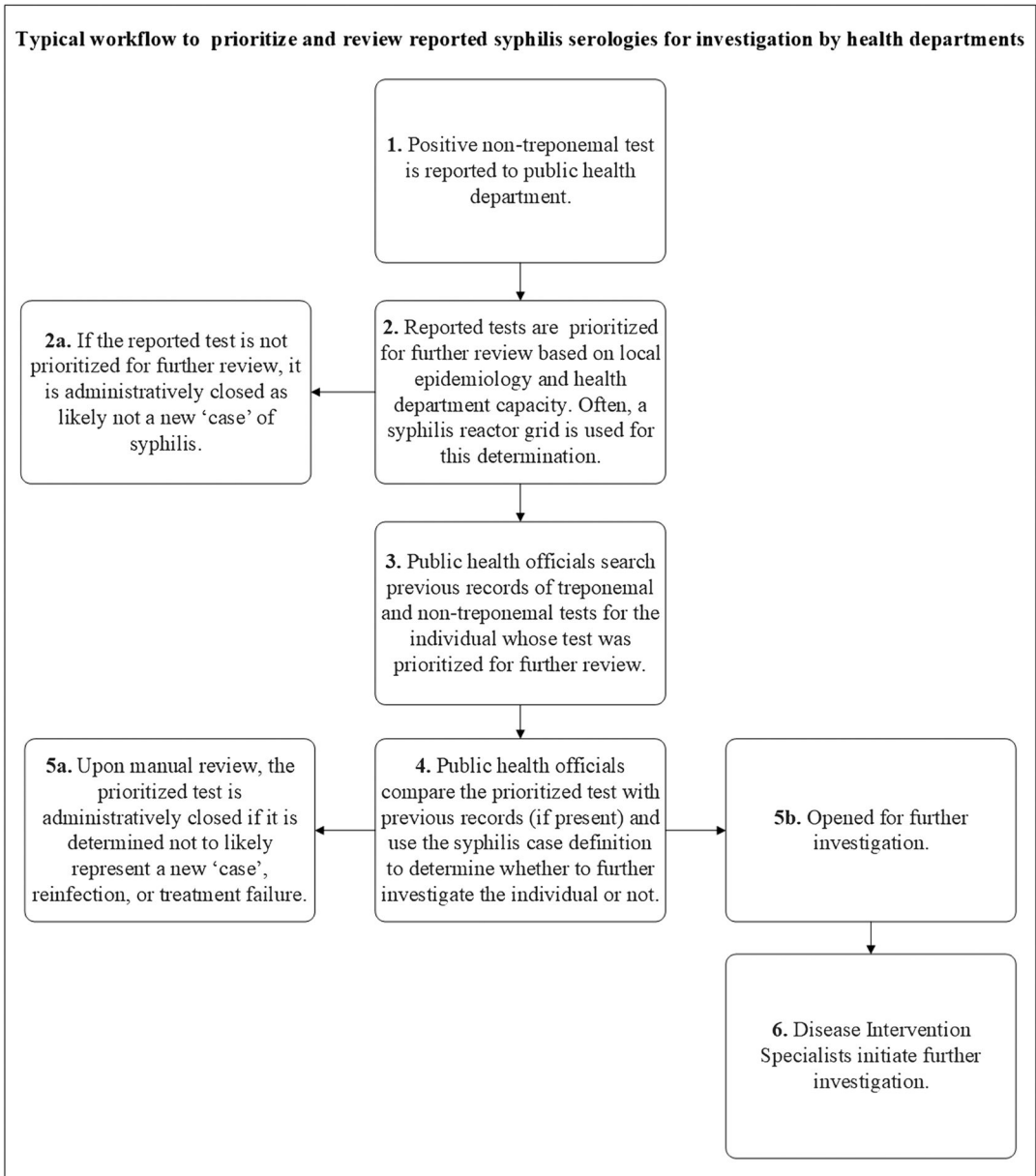
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015 [published correction appears in MMWR Recomm Rep. 2015 Aug 28;64 (33):924]. MMWR Recomm Rep 2015; 64(RR-03):1–137.

2. Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. Clin Microbiol Rev 1995; 8:1–21. [PubMed: 7704889]

3. Centers for Disease Control and Prevention (CDC). Syphilis testing algorithms using treponemal tests for initial screening—Four laboratories, New York City, 2005–2006. MMWR Morb Mortal Wkly Rep 2008; 57:872–875. [PubMed: 18701877]

4. Adams DA, Thomas KR, Jajosky RA, et al. Summary of notifiable infectious diseases and conditions—United States, 2015. MMWR Morb Mortal Wkly Rep 2017; 64:1–143. Published August 11, 2017. doi:10.15585/mmwr.mm6453a1.

5. Centers for Disease Control and Prevention. Recommendations for Public Health Surveillance of Syphilis in the United States (CDC Web Site). Available at: https://www.cdc.gov/std/syphsurvreco.pdf. Accessed November 12, 2020.

6. Nakashima AK, Rolfs RT, Flock ML, et al. Epidemiology of syphilis in the United States, 1941–1993. Sex Transm Dis 1996; 23:16–23. [PubMed: 8801638]

7. Lossick JG, Kraus SJ. Syphilis. In: Evans AS, Brachman PS, eds. Bacterial infections of Humans: Epidemiology and Control 2nd ed. New York, NY: Plenum Medical Book Company, 1991:675–695.

8. Dandoy S, McKenna EM. Laboratory reporting of syphilis reactors in the Los Angeles program. Public Health Rep 1964; 79:1015–1020. [PubMed: 14212585]

9. Cha S, Matthias JM, Rahman M, et al. Reactor grids for prioritizing syphilis investigations: Are primary syphilis cases being missed? Sex Transm Dis 2018; 45:648–654. [PubMed: 29528995]

10. Centers for Disease Control and Prevention. Program Operations Guidelines for STD Prevention: Surveillance and Data Management (CDC Web Site). Available at: https://www.cdc.gov/std/program/surveillance.pdf. Accessed July 9, 2020.

11. McLean CA, Kohl K, Baker MA, et al. The syphilis reactor grid: Help or hindrance for syphilis surveillance? Sex Transm Dis 2003; 30:650–653. [PubMed: 12897688]

12. Schaffzin JK, Koumans EH, Kahn RH, et al. Evaluation of syphilis reactor grids: Optimizing impact. Sex Transm Dis 2003; 30:700–706. [PubMed: 12972793]

13. Matthias J, Keller G, Cha S, et al. Going off grid: Modeling an automated record search to process electronically reported reactive nontreponemal syphilis tests. Sex Transm Dis 2018; 45:655–659. [PubMed: 29538278]

14. Lamb E, Satre J, Hurd-Kundeti G, et al. Update on progress in electronic reporting of laboratory results to public health agencies—United States, 2014. MMWR Morb Mortal Wkly Rep 2015; 64:328–330. [PubMed: 25837244]

15. Perez F, Granger BE. IPython: A system for interactive scientific computing. Comput Sci Eng 2007; 9:21–29.

16. Kluyver T, Ragan-Kelley B, Perez F, et al. Jupyter Notebooks—A publishing format for reproducible computational workflows. Presented at: International Conference on Electronic Publishing 2016; Göttingen, Germany.

17. Park IU, Fakile YF, Chow JM, et al. Performance of treponemal tests for the diagnosis of syphilis. Clin Infect Dis 2019; 68:913–918. [PubMed: 29986091]

Typical workflow to prioritize and review reported syphilis serologies for investigation by health departments

1. Positive non-treponemal test is reported to public health department.

2a. If the reported test is not prioritized for further review, it is administratively closed as likely not a new 'case' of syphilis.

2. Reported tests are prioritized for further review based on local epidemiology and health department capacity. Often, a syphilis reactor grid is used for this determination.

3. Public health officials search previous records of treponemal and non-treponemal tests for the individual whose test was prioritized for further review.

5a. Upon manual review, the prioritized test is administratively closed if it is determined not to likely represent a new 'case', reinfection, or treatment failure.

4. Public health officials compare the prioritized test with previous records (if present) and use the syphilis case definition to determine whether to further investigate the individual or not.

5b. Opened for further investigation.

6. Disease Intervention Specialists initiate further investigation.

Figure 1.
Typical workflow of a public health department to conduct record search and prioritize syphilis serologic tests for further investigation.
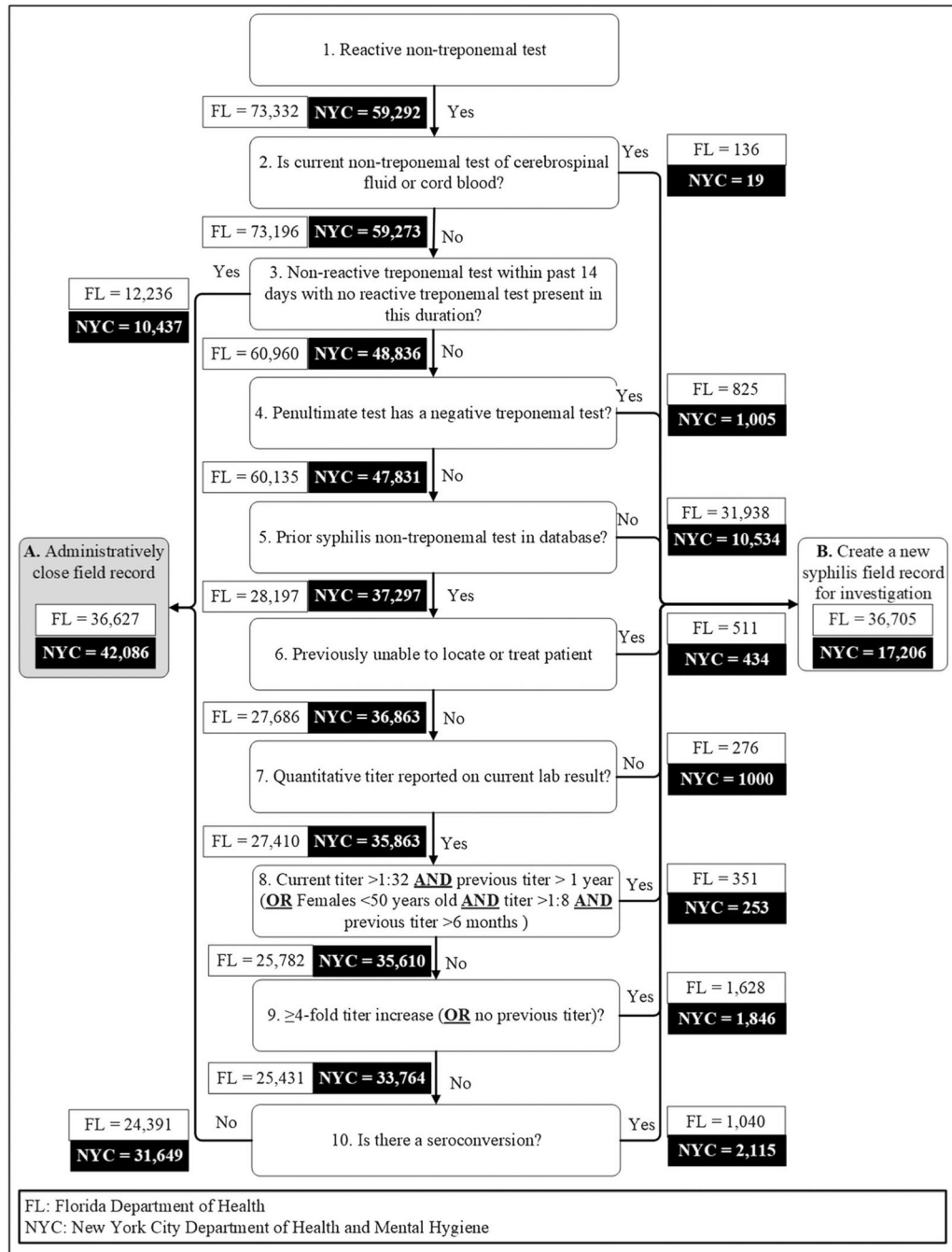
Figure 2.
New case definition–based algorithm that automates record search and prioritizes serologic tests for further investigation.

TABLE 1.

Comparison of the Investigations Opened by the Algorithm With Those Opened by the Syphilis Reactor Grid in Florida and New York City

Tests		Florida				New York City	
		Algorithm				Algorithm	
		Opened	Closed			Opened	Closed
Grid	Opened	25,200	28,328	53,528	Opened	9258	21,065	30,323
	Closed	11,505	8299	19,804	Closed	7948	21,021	28,969
		36,705	36,627	73,332		17,206	42,086	59,292

Cases		Florida				New York City	
		Algorithm				Algorithm	
	>	Opened	Closed		>	Opened	Closed
Grid	Opened	12,569	220	12,789	Opened	4651	234	4885
	Closed	?	?	?	Closed	?	?	?
		?	?			?	?	?