

**The Reverse
Sequence Syphilis Screening Webinar will begin shortly**

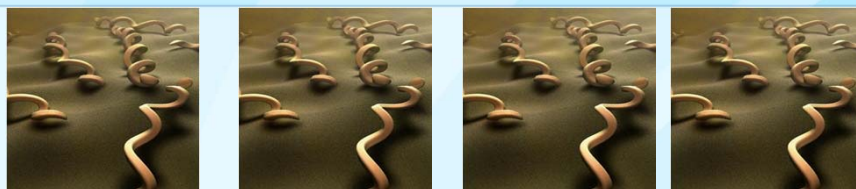
The dial-in number for the call is [800-908-9207](tel:800-908-9207)

Questions can be submitted during the Webinar via the chat function.

Due to the volume of Webinar participants and the time we have allotted, we may not be able to provide live answers to all of the submitted questions.

We will compile and answer these questions and will post them online at www.cdc.gov/std/syphilis/treatment as soon as we can.

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of STD Prevention



Instructions on how to receive CME credits are available at:
<http://www.surveymonkey.com/s/SyphilisScreeningWebinar>

An archived version of the Webinar will be available at
www.cdc.gov/std/syphilis/treatment within a few days.

If you have questions about reverse sequence syphilis screening following the Webinar you may submit them to stdtraining@cdc.gov

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of STD Prevention



CME

The Denver PTC has collected information from our planners and speakers to ensure that you are aware of any potential conflicts of interest that may lead to commercial bias. These include:

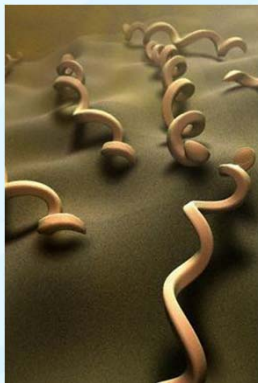
- Gail Bolan, MD – No disclosures
- Ina Park, MD, MS - No disclosures
- Karen Hoover, MD, MPH - No disclosures
- Rheta Barnes, MSN, MPH – No disclosures
- Helen Burnside, MS – No disclosures
- John Fitch, LPN – No disclosures

The Denver STD/HIV Prevention Training Center is accredited by the Colorado Medical Society to provide continuing medical education for physicians.

The Denver STD/HIV Prevention Training Center designates this educational activity for a maximum of *1 AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Reverse Sequence Syphilis Screening

An Overview by CDC



National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of STD Prevention



Gail Bolan, MD

Director
Division of STD Prevention
Centers for Disease Control and Prevention



Learning objectives

- ❑ Describe the evaluation and management of persons with a reactive treponemal enzyme immunoassay (EIA+) result
- ❑ Identify three possible explanations for discordant test results (i.e., EIA+ and RPR-) with reverse sequence screening
- ❑ Discuss the management of a person who has a discordant test result (i.e., EIA+ and RPR-) that is nonreactive by confirmatory treponemal testing with a *Treponema pallidum* particle agglutination (TP-PA) test
- ❑ Compare the performance of the reverse sequence algorithm in populations with high and low prevalence of infection

Target Audience

- ❑ **Clinicians who provide screening, diagnosis, and clinical care for persons at risk for or infected with syphilis**
- ❑ **Other health care professionals, such as laboratorians, epidemiologists and public health program staff, whose work involves syphilis screening or management of persons at risk for or infected with syphilis**

Insert Audience polling questions here

- ❑ **If you are watching in a group, how many people are in your group?**

**What is your primary profession/discipline
(select ONE)?**

- Advanced practice nurse
- Registered nurse
- Licensed practical nurse
- Physician
- Physician assistant
- Public health professional
- Laboratorian
- Other

**What is your principal employment
setting (select one)?**

- | | |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <input type="checkbox"/> Academic health center | <input type="checkbox"/> Military health system/ Veterans Health Admin facility |
| <input type="checkbox"/> College/university | <input type="checkbox"/> Private practice (solo/group) |
| <input type="checkbox"/> Community health center (federally qualified) | <input type="checkbox"/> State/local health department |
| <input type="checkbox"/> Other non-profit health center | <input type="checkbox"/> Tribal/Indian Health Service facility |
| <input type="checkbox"/> Correctional facility | <input type="checkbox"/> Other |
| <input type="checkbox"/> HMO/managed care organization | <input type="checkbox"/> Not working |
| <input type="checkbox"/> Hospital/Hospital-affiliated clinic | |

Presenters



Karen Hoover, MD, MPH
Medical Epidemiologist
Division of STD Prevention
Centers for Disease Control and Prevention



Ina Park, MD, MS
Chief
Medical and Scientific Affairs Unit
STD Control Branch
California Department of Public Health

Webinar Overview

- ❑ **Syphilis screening with serologic tests**
- ❑ **Enzyme immunoassays (EIA) and chemiluminescence immunoassays (CIA) increasingly used as syphilis screening tests**
 - Large proportion of EIA+/RPR- results
 - Confusion about patient management
- ❑ **Performance and clinical data for the use of reverse sequence screening**
 - MMWR 2011
 - JID 2011 (under review)
- ❑ **CDC recommendations for the use of EIA/CIA to screen for syphilis**
- ❑ **Research needs to provide an evidence basis for future guidelines**

Diagnosis of syphilis

- ❑ *Treponema pallidum* cannot be cultured
- ❑ Ideally, early syphilis would be diagnosed using direct detection methods
 - Darkfield microscopy
 - Polymerase chain reaction (PCR)
 - Direct fluorescent antibody test for *T. pallidum* (DFA-TP)
- ❑ Direct detection methods are not widely available
- ❑ Direct detection methods can miss cases
 - Fail to detect up to 30% of primary cases
- ❑ Most persons present without symptoms or signs of syphilis
 - Healed early lesions
 - Inapparent lesions
- ❑ Syphilis is usually diagnosed with serologic tests

Serologic diagnosis of syphilis

- ❑ Serologic diagnosis always requires detection of two types of antibodies
 - Nontreponemal antibodies
 - Antibodies directed against lipoidal antigens
 - Damaged host cells
 - Possibly from treponemes
 - Treponemal antibodies
 - Antibodies directed against *T. pallidum* proteins

Serologic diagnosis of syphilis

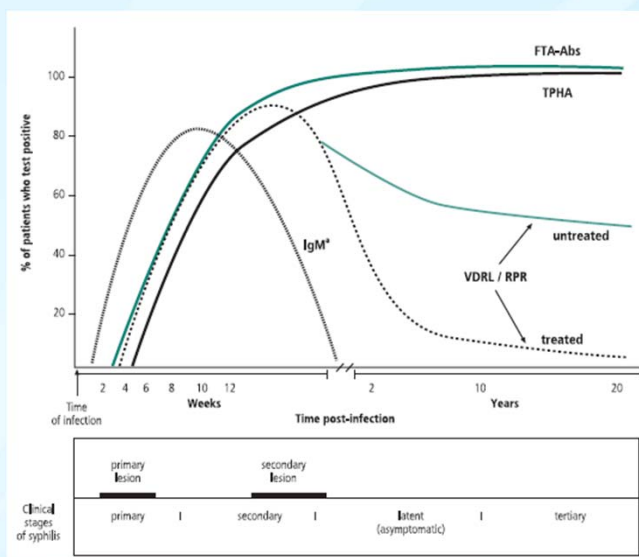
□ Nontreponemal tests

- Rapid plasma reagin (RPR) test
- Venereal Disease Research Laboratory (VDRL) test
- Tolidine red unheated serum test (TRUST)

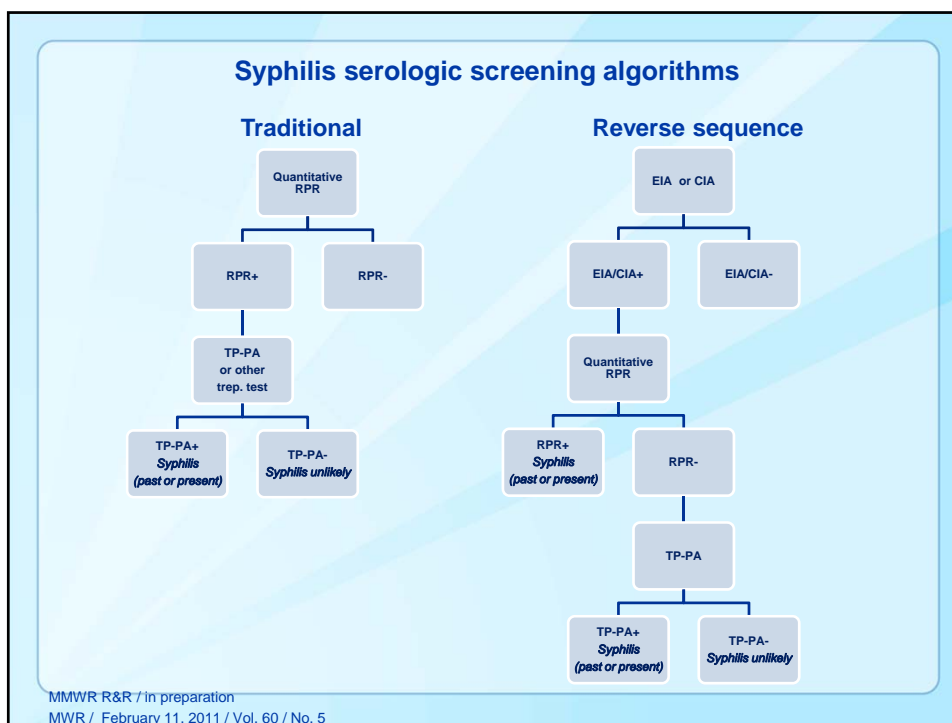
□ Treponemal tests

- Fluorescent treponemal antibody absorbed (FTA-ABS) test
- Treponema pallidum article agglutination (TP-PA) test
- Enzyme immunoassays (EIAs)
 - Trep-Check
 - Trep-Sure
- Chemiluminescence immunoassays (CIAs)
 - LIAISON
 - Architect
- Microbead immunoassays (MBIA)
 - BioPlex 2200 Syphilis IgM and IgG

Common patterns of serologic reactivity in syphilis patients



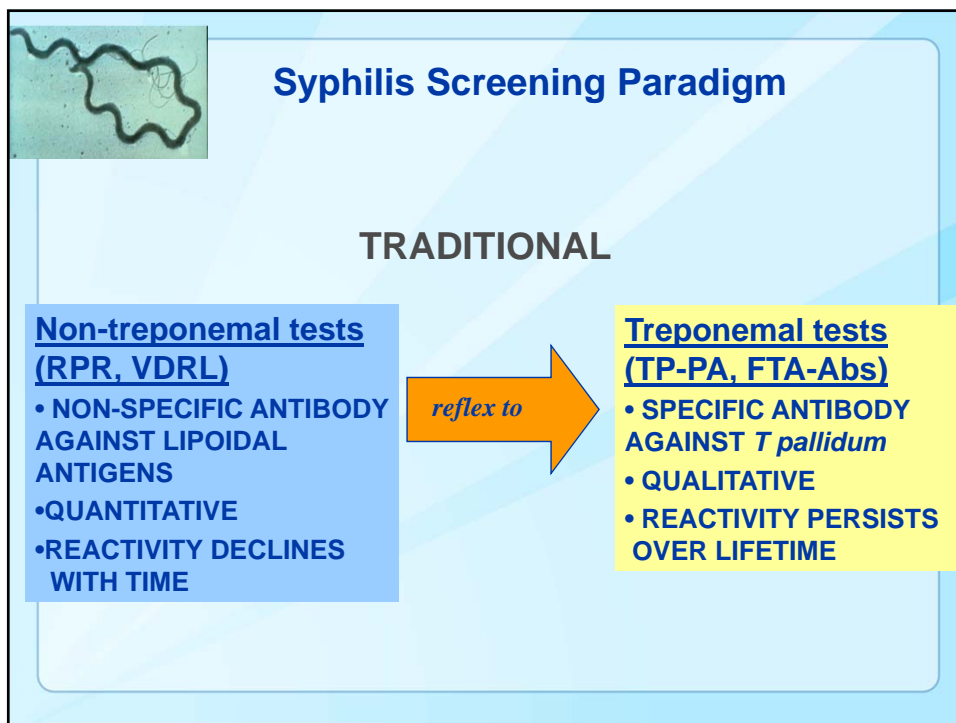
Peeling et al. / Bulletin of the World Health Organization / 2004 / Vol. 82 / No. 6



Which algorithm?

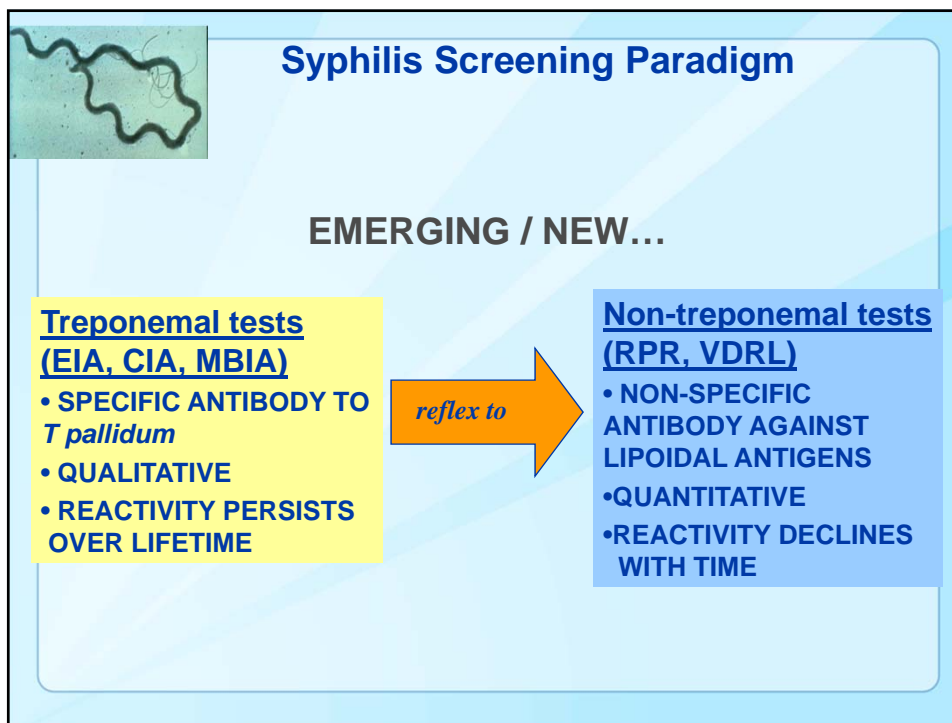
- ❑ **Traditional algorithm**
 - Detects active infection
 - High rate of biologic false positives
 - Confirmation with treponemal test
 - Use of both tests results in a high positive predictive value
 - Can miss early primary and treated infection
- ❑ **Reverse sequence algorithm**
 - Detects early primary and treated infection that might be missed with traditional screening
 - Nontreponemal test needed to detect active infection
 - Ideally, EIAs and CIAs should have perfect specificity
 - EIAs and CIAs are nonspecific
 - High rate of false positive results
 - Varies by risk of population

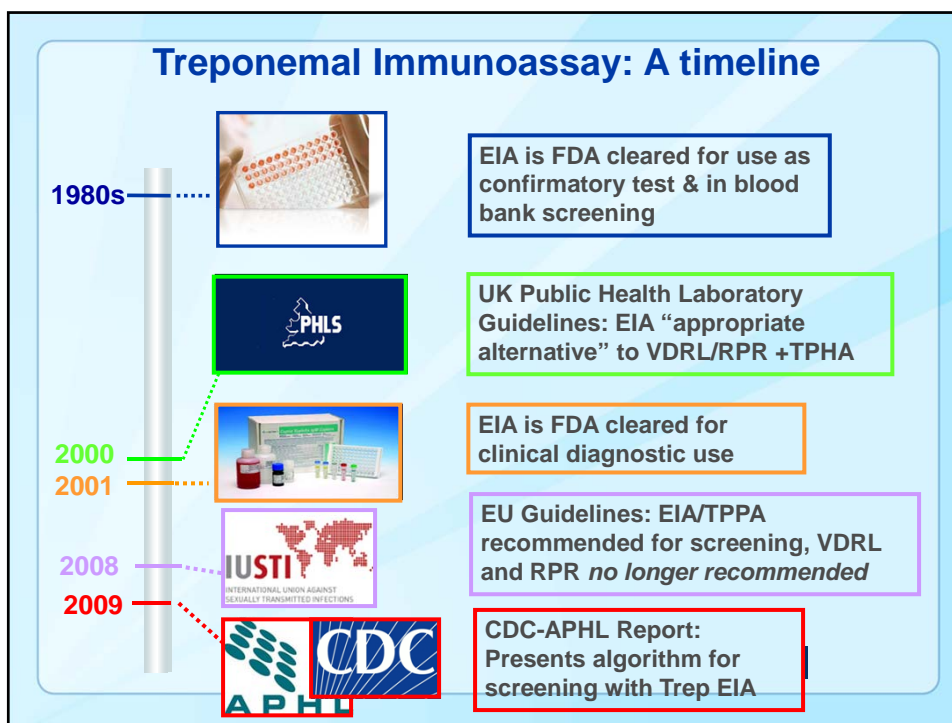
EIA/CIA AS SYPHILIS SCREENING TESTS



Traditional Use of Treponemal Tests

- Confirming reactive non-treponemal tests
- Screening the blood supply





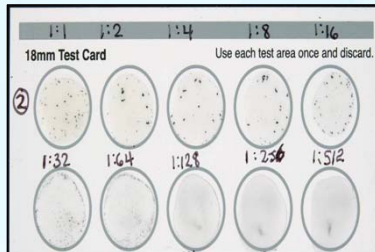
Why switch to EIA/CIA?

- ❑ Automated (high throughput)
- ❑ Low cost in high volume settings
- ❑ Less lab occupational hazard (pipetting)
- ❑ No false negatives due to prozone reaction
- ❑ Objective results
- ❑ Some EIA/CIAs detect IgM antibodies; potentially useful for diagnosis of early syphilis

Why switch to EIA/CIA?

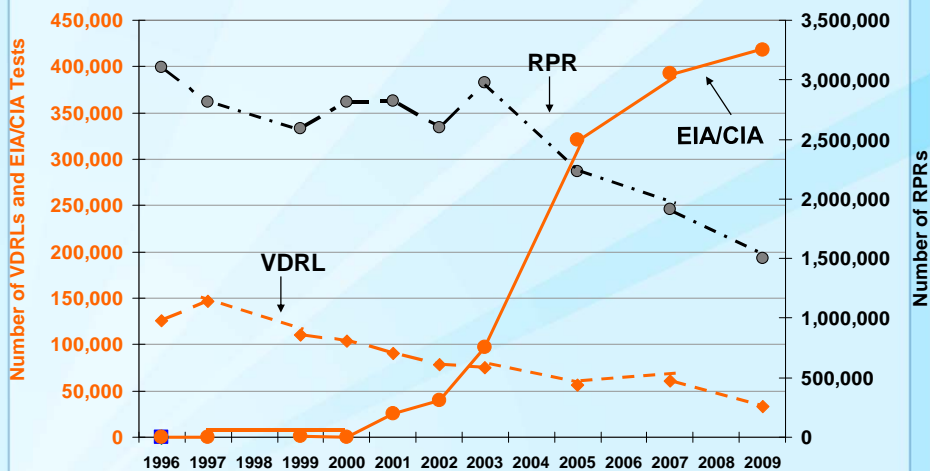


VS



180 tests per hour,
no manual pipetting

Syphilis Tests by Test Type, 1996-2009



California Department of Public Health, STD Control Branch, 2009

Challenges and limitations of the EIA/CIA

- ❑ **Cannot distinguish between active disease and old disease (treated/untreated)**
- ❑ **Studies to compare test performance with other serologic tests are lacking**
- ❑ **Studies evaluating performance of EIA/CIA to detect IgM antibodies in early syphilis are lacking**
- ❑ **Confusion re: management of patients with discrepant serology (e.g., positive EIA/CIA and a negative RPR)**

PERFORMANCE AND CLINICAL DATA FOR THE USE OF THESE TESTS

Discordant Results from Reverse Sequence Syphilis Screening Five Laboratories, United States, 2006–2010

MMWR / February 11, 2011 / Vol. 60 / No. 5

Methods

- **Analyzed data from five laboratories that used reverse sequence screening during 2006–2010**
 - 140,176 sera screened with a treponemal EIA/CIA
 - Data from sera with equivocal EIA/CIA test results were not included as reactive tests
- **EIA tests**
 - Trep-Chek
 - Trep-Sure
- **CIA test**
 - LIAISON
- **Reflex nontreponemal test**
 - RPR
- **Confirmatory treponemal tests**
 - TP-PA
 - FTA-ABS

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Methods

- **Three sites served patient populations with low prevalence for syphilis**
 - Large managed-care organizations
- **Two sites served patient populations with high prevalence**
 - MSM
 - HIV-infected patients
- **Calculated**
 - Reactive EIA/CIAs among all sera (i.e., EIA+)
 - Discordant sera among reactive EIA/CIAs (i.e., EIA+/RPR-)
 - Nonreactive confirmatory TP-PA or FTA-ABS tests among discordant sera (i.e., EIA+/RPR-/TP-PA-)

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Results of reverse sequence syphilis screening — five laboratories, United States, 2006 – 2010

Population	Test	Total N	Reactive EIA/CIA		Nonreactive reflex RPR		Nonreactive confirmatory treponemal test*	
			n	% total	n	% EIA/CIA+	n	% RPR-
Overall		140,176	4,834	3.4	2,743	56.7	866	31.6
Low prevalence		127,402	2,984	2.3	1,807	60.6	737	40.8
Southern California	Trep-Chek	47,952	1,278	2.7	765	59.9	459	60.0
Northern California	Liaison	21,623	438	2.0	287	65.5	88	30.7
Southern California	Trep-Sure	57,827	1,268	2.2	755	59.5	190	25.2
High prevalence		12,774	1,850	14.5	936	50.6	129	14.1
New York City	Trep-Chek	7,607	1,165	15.3	639	54.8	78	12.2
Chicago	Trep-Sure	5,167	685	13.3	297	43.4	51	18.6

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**Reasons for discordant test results
(i.e., EIA/CIA+ / RPR-)**

- ❑ **False-positive EIA/CIA**
 - EIAs and CIAs are very sensitive
 - But have lower specificity
- ❑ **Treated syphilis**
 - Treponemal antibodies are detected by sensitive EIAs and CIAs
 - Seroreversion of nontreponemal antibodies
- ❑ **Early primary syphilis**
 - Treponemal antibody titer rises before nontreponemal antibody titer

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Conclusions

- ❑ EIA/CIA have high sensitivity but lower specificity
- ❑ All reactive EIA/CIA must be reflexly tested with a quantitative RPR
 - Confirm reactive EIA/CIA
 - Detect active infection
- ❑ Although test performance varies by prevalence of syphilis in the population, all discordant specimens (EIA+/RPR-) must be confirmed with a confirmatory treponemal test
- ❑ Confirmatory treponemal test must have at least equivalent sensitivity and higher specificity compared to the screening treponemal test
 - TP-PA recommended
 - FTA-ABS not recommended

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Screening for syphilis with the treponemal immunoassay:

Analysis of discordant serology results and implications for clinical management

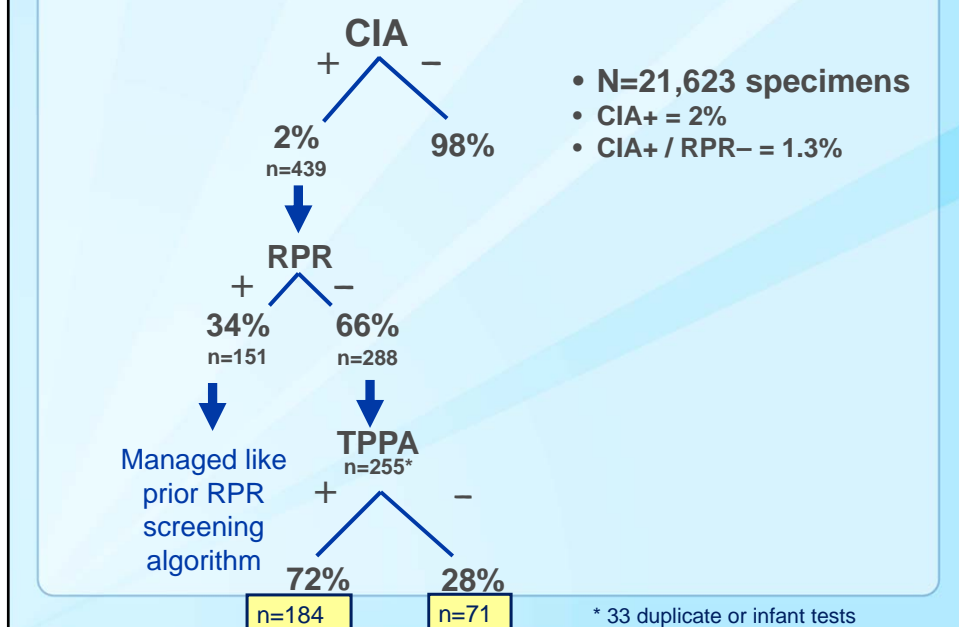


JID 2011, under review

Methods

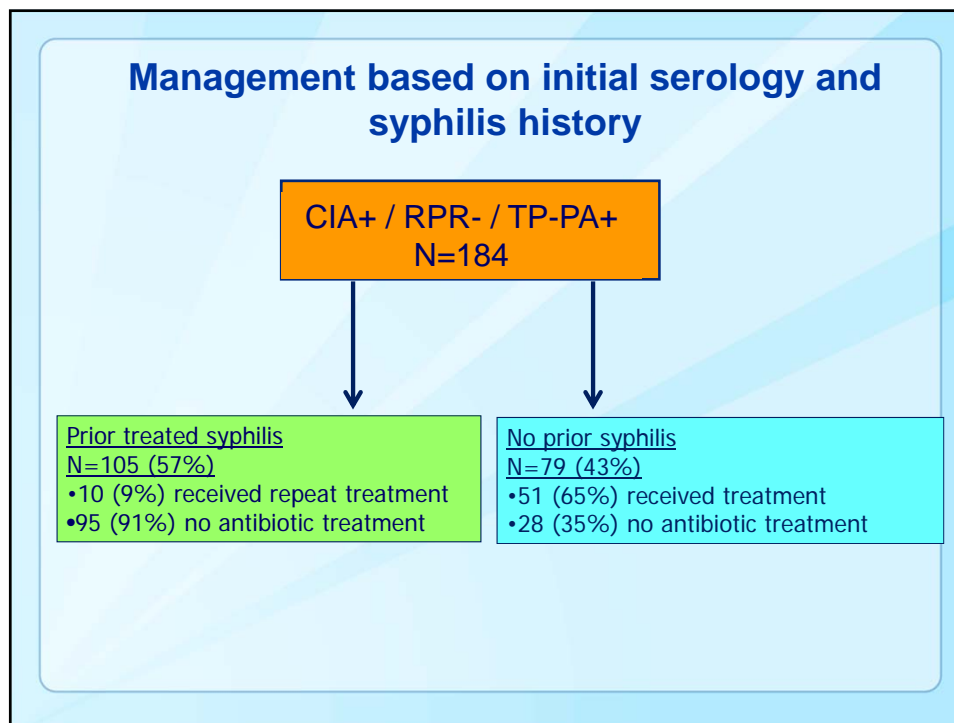
- ❑ Cross sectional analysis of individuals tested with Diasorin LIAISON chemiluminescence immunoassay (CIA) at Kaiser Permanente Northern California Regional Laboratory from Aug-Oct 2007
- ❑ Data abstracted from electronic medical records (laboratory and clinical) using standardized protocol
- ❑ HIV-status, sexual orientation, pregnancy status, prior syphilis history and CIA index values were compared for all CIA-positive, RPR-negative patients according to TP-PA status.

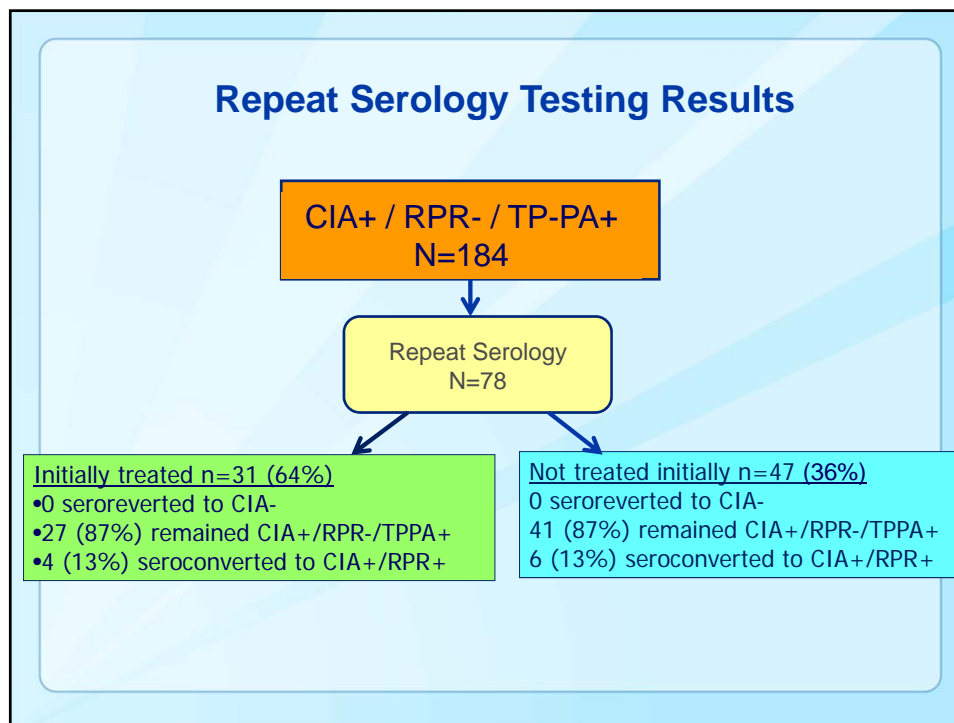
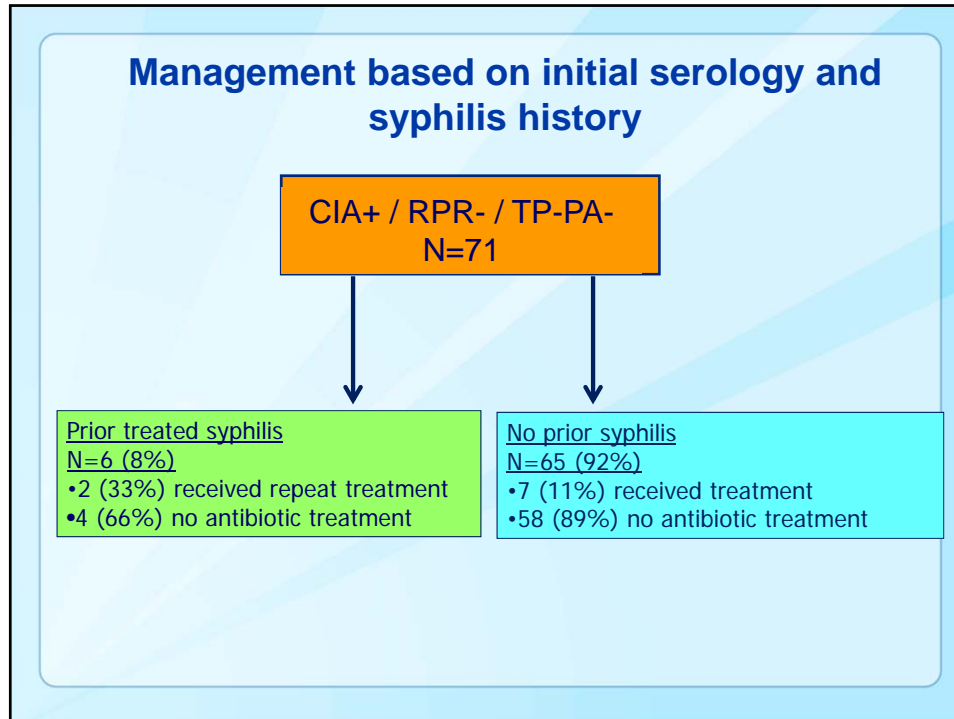
CIA Testing Results

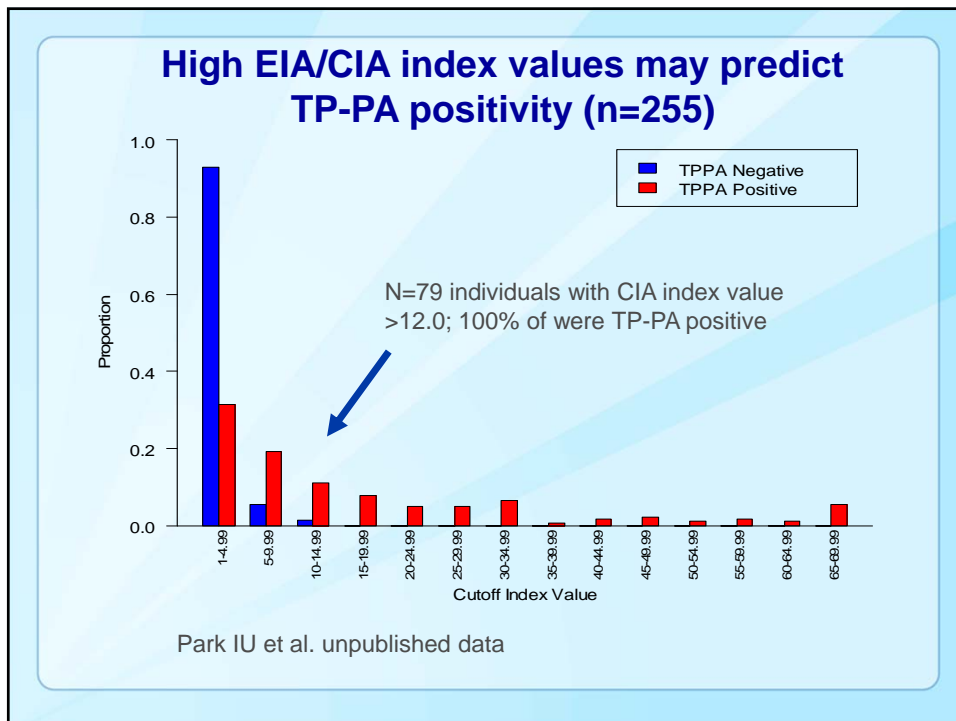
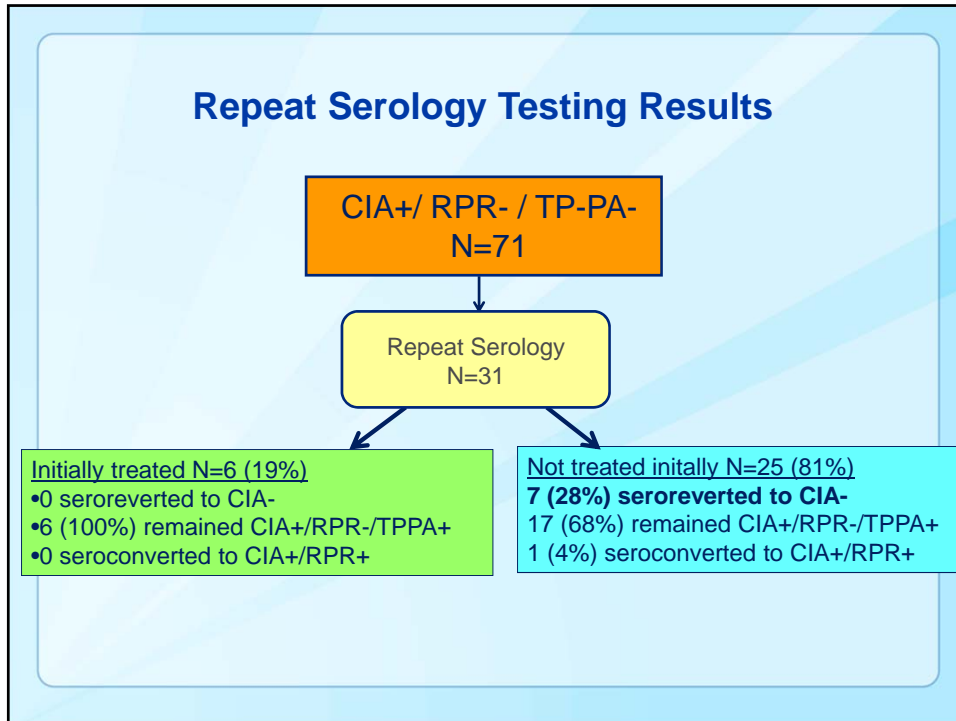


Demographics		
	CIA+/RPR- TPPA+ (N=184)	CIA+/RPR- TPPA- (N=71)
Mean age (SD)*	50 (14)	42 (16)
Males*	149 (81%)	33 (47%)
MSM*	60 (33%)	7 (10%)
Heterosexual	15 (8%)	8 (11%)
Females	35 (19%)	38 (53%)
Pregnant	12 (34%)	16 (42%)
HIV-positive*	86 (47%)	14 (20%)
Prior syphilis*	105 (57%)	6 (9%)

*P= <0.0001







Kaiser Study Conclusions

- ❑ Among CIA+/RPR- patients, performance of a second treponemal test is useful in low prevalence settings to guide treatment decisions
- ❑ Conflicting treponemal results (CIA+/TP-PA-) may represent false positives, especially if low CIA index value. Repeat testing should be considered
- ❑ Among CIA+/RPR- patients at high risk, repeat testing should be performed to rule out early syphilis

Acknowledgments

California Department
of Public Health

Joan Chow, MPH, DrPH
Gail Bolan, MD

Denise Gilson
Michael Samuel DrPH

Kaiser Permanente
Northern California
Regional Laboratory

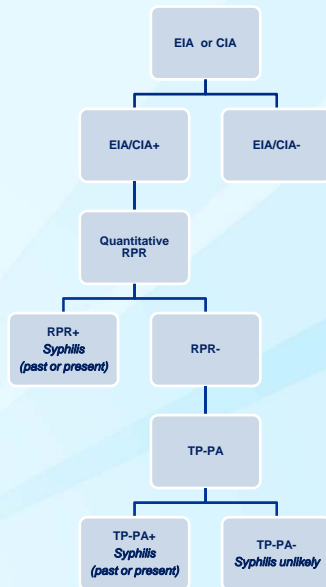
Jeffrey Schapiro, MD
Jen Shieh, PhD
Mark Stanley, MPH

San Francisco DPH: Kyle Bernstein PhD

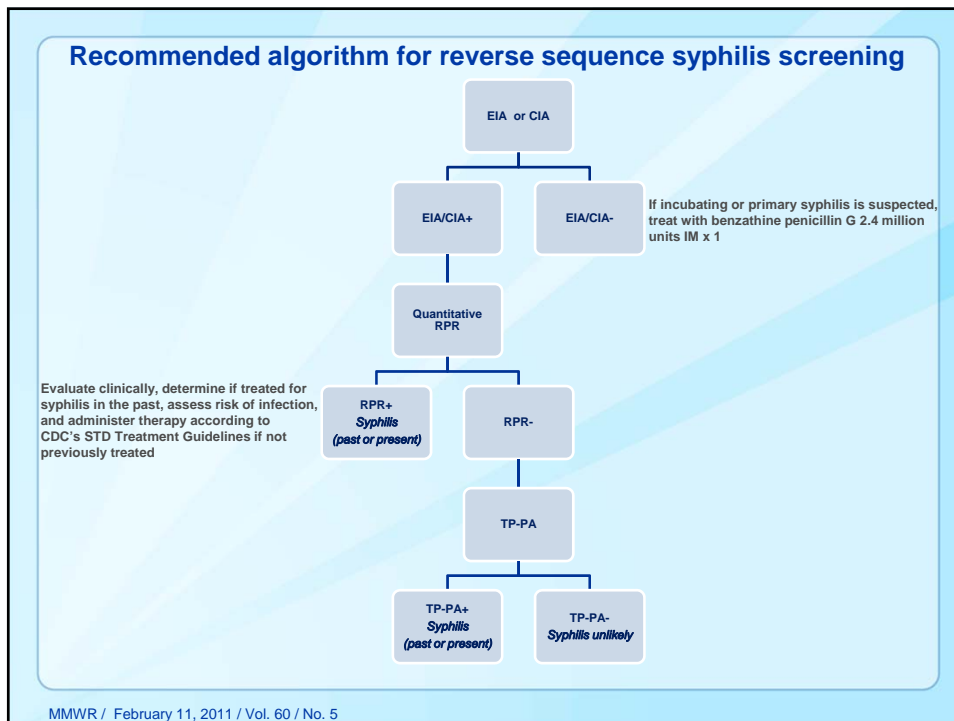
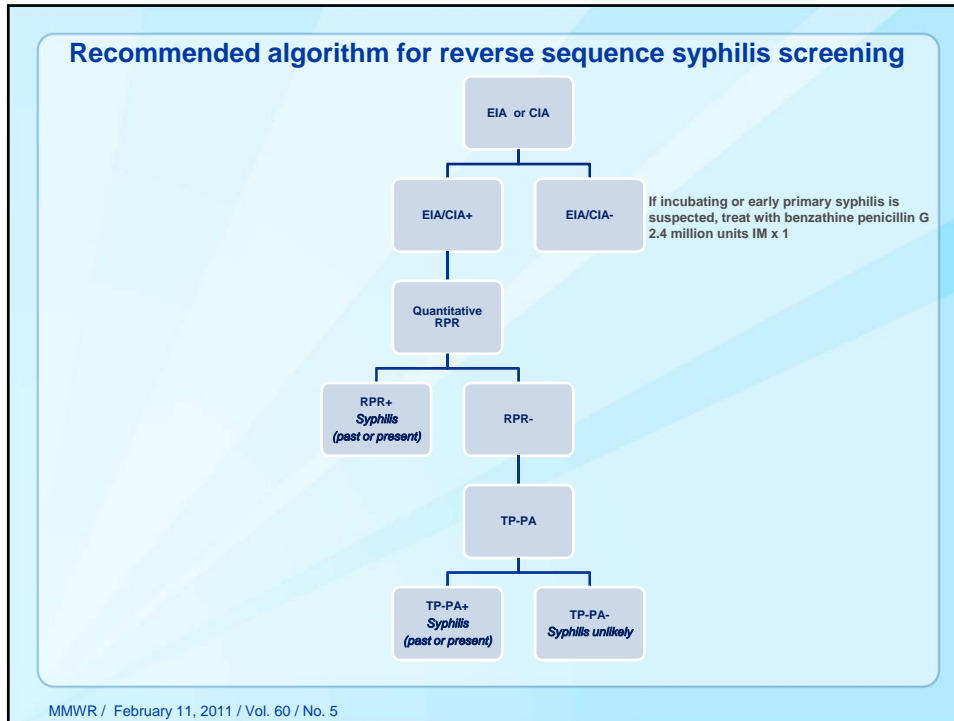
Los Angeles DPH: Monica Muñoz, Sarah Guerry MD

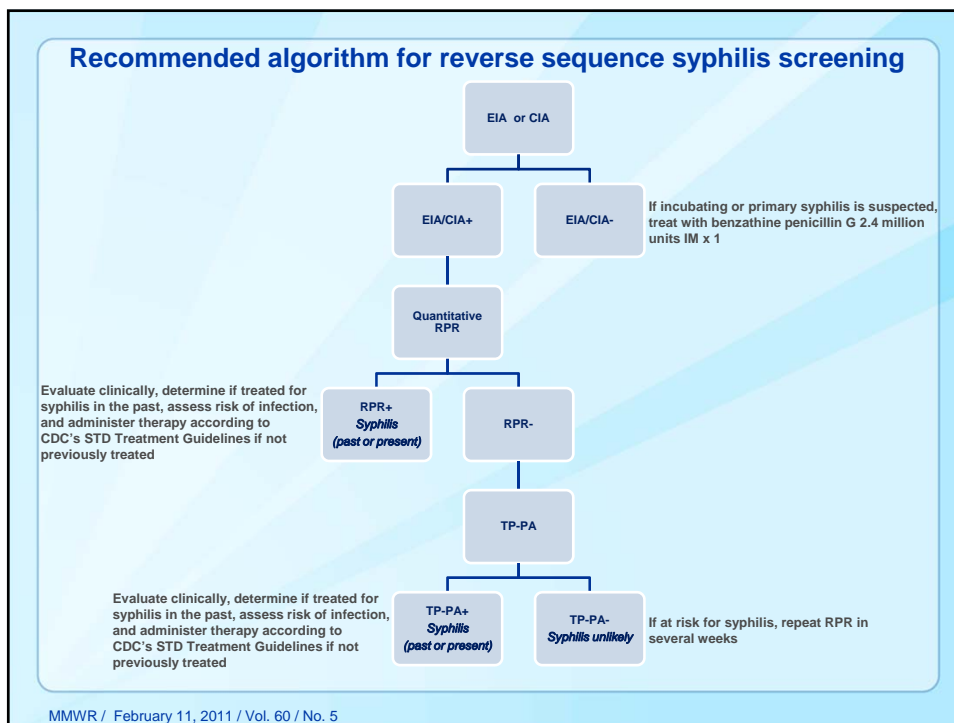
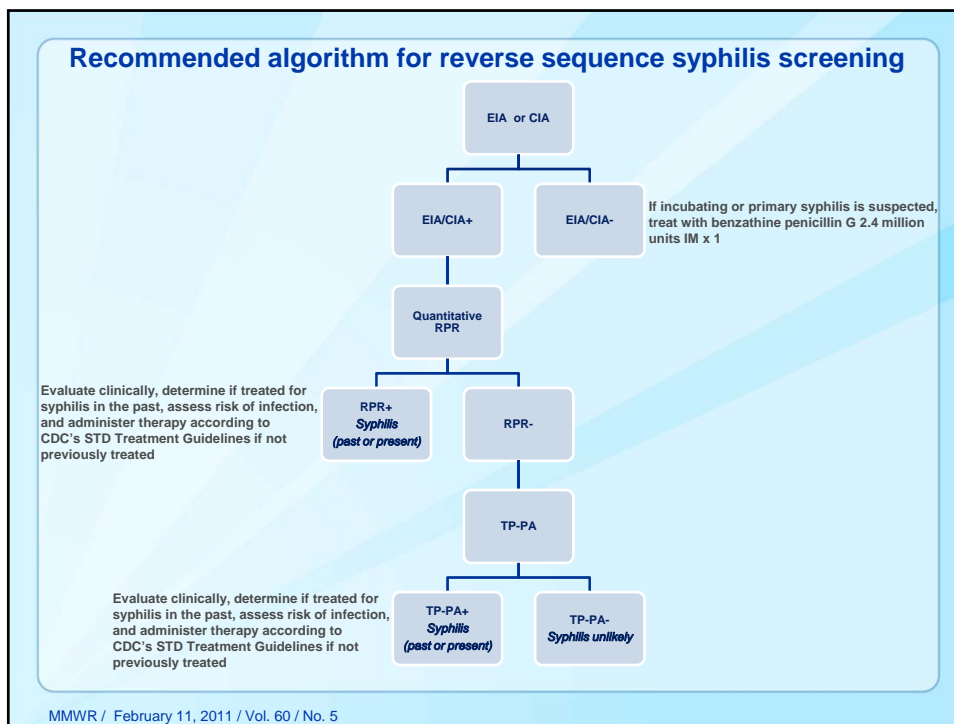
CDC RECOMMENDATIONS FOR THE USE OF EIA/CIA

Recommended algorithm for reverse sequence syphilis screening



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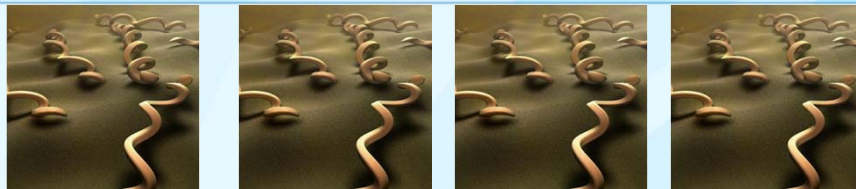




RESEARCH NEEDS TO PROVIDE AN EVIDENCE BASIS FOR FUTURE GUIDELINES

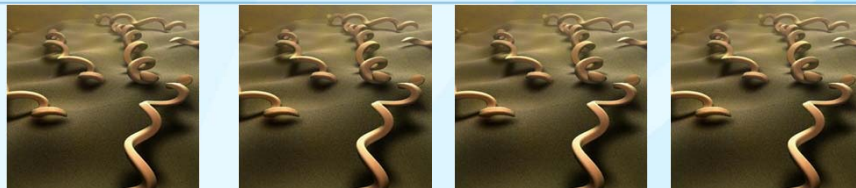
Research needs

- ❑ **Compare head-to-head the performance of EIAs, CIAs, TP-PA, FTA-ABS test, and microbead immunoassay**
 - Well-defined patient populations whose clinical history and syphilis risk are known
 - HIV-infected persons
 - Pregnant women
- ❑ **Characterize discordant sera with nonreactive confirmatory treponemal tests by immunoblotting**
 - Define reactivities with *T. pallidum* antigens
- ❑ **Study utility of immunoglobulin M treponemal testing**
 - Diagnosis of early primary syphilis
 - Evaluation of infection in asymptomatic, seropositive, untreated persons



Question and Answer Session

- Questions may be submitted during the Webinar via the chat function.
- If you have questions about the reverse sequence syphilis screening following the Webinar you may submit them to stdtraining@cdc.gov



Continuing Medical Education (CME) Information

To receive CME, an evaluation and request for certificate must be completed at:
<http://www.surveymonkey.com/s/SyphilisScreeningWebinar>

You must complete the evaluation by April 30, 2011 to receive CME credit

Certificates will be sent out via email starting April 15, 2011.

Continuing Nursing Education (CNE) and other types of Continuing Education (CE) are not available for this program.

If you have CME questions, please contact John Fitch at John.Fitch@dhha.org

April is National STD Awareness Month

"YOU WALK IN AND THEY GREET YOU LIKE IT'S OKAY TO BE THERE. YOU DON'T FEEL LIKE ASHAMED OR ANYTHING"

LEARN WHAT YOUNG PEOPLE SAY ABOUT GETTING TESTED

GET YOURSELF TALKING WITH YOUR PATIENTS

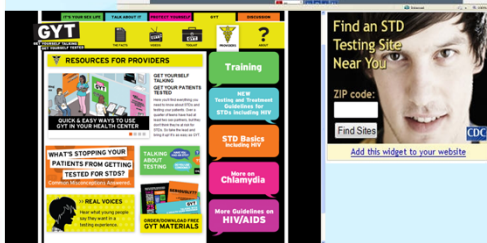
GYT

Visit our web sites for updated tools, materials, and resources to help support your local STD prevention efforts.

- www.cdc.gov/std/sam
- www.cdcnpin.org/stdawareness
- provider.gytnow.org
- www.findstdtest.org



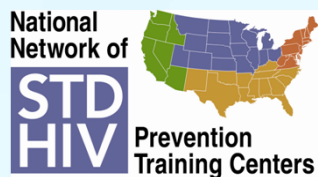
ORDER/DOWNLOAD FREE GYT MATERIALS



Educational and Training Resources

National Network of STD/HIV Prevention Training Centers

- www.nnptc.org



CDC Division of STD Prevention

- www.cdc.gov/std/training
- stdtraining@cdc.gov or 404.639.8360

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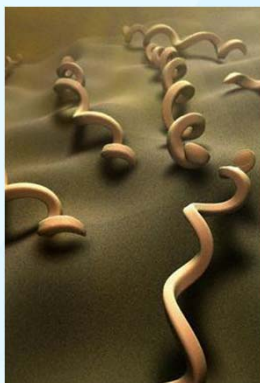
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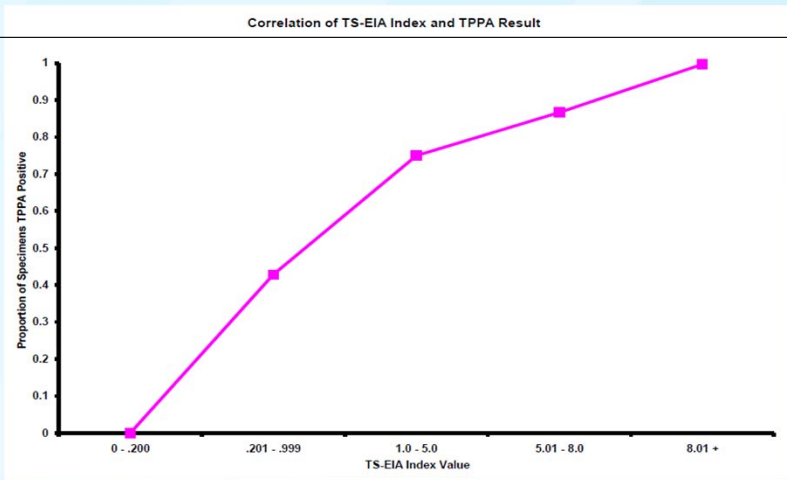
For more information please contact Centers for Disease Control and Prevention
Prevention
1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of STD Prevention



High EIA/CIA index values may predict TP-PA positivity (n=674)



Wong E and Pandori M, 2011. *STD epub ahead of print*