

Syphilis Testing, new and old, rapid and not so rapid

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The National Plan *to* Eliminate Syphilis *from the* United States

Prepared by
Division of STD Prevention
National Center for HIV, STD and TB Prevention
Centers for Disease Control and Prevention
Department of Health and Human Services
MAY 2006



Department of Health and Human Services
Centers for Disease Control and Prevention

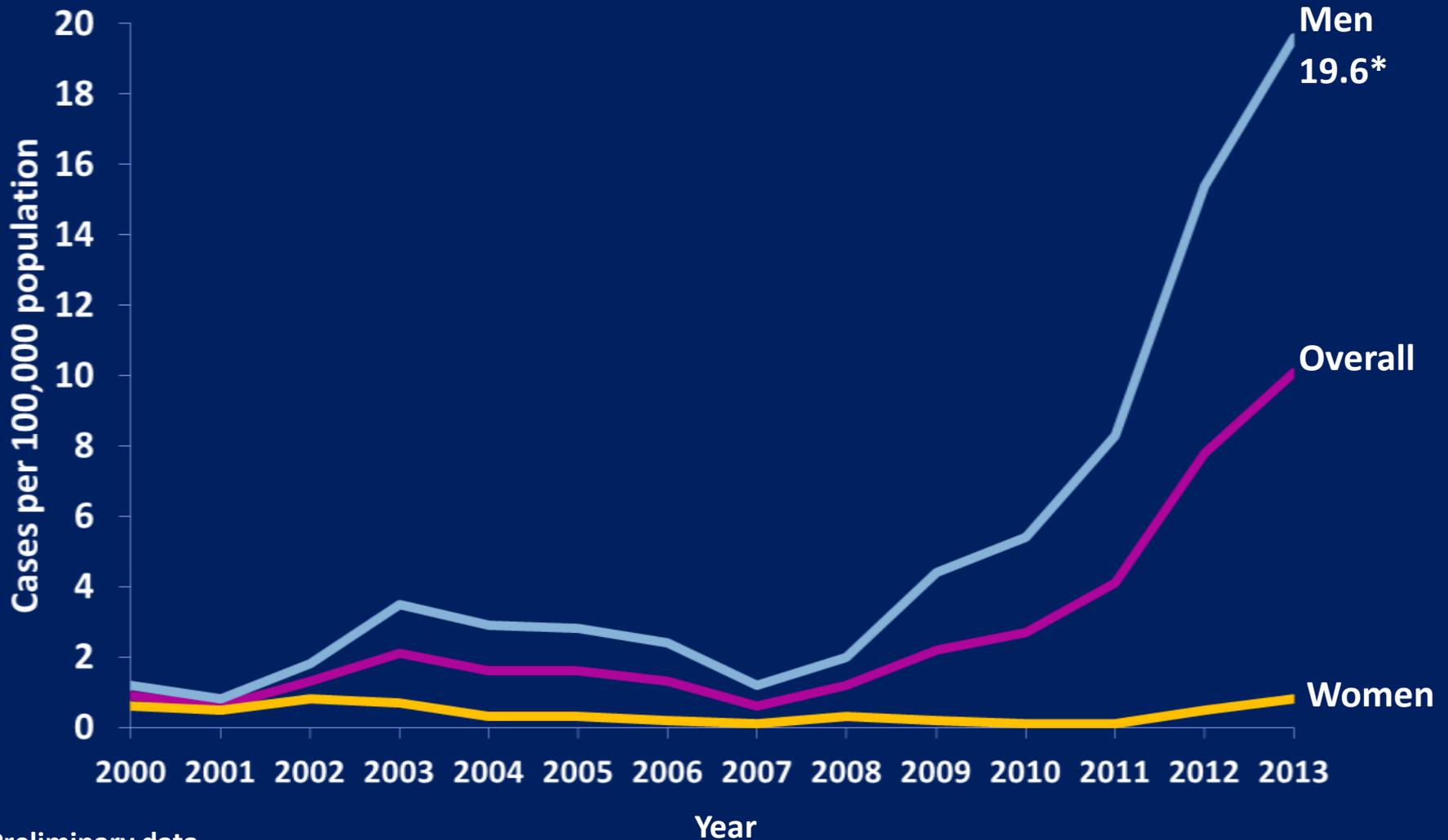


SYPHILIS ELIMINATION

History in the Making

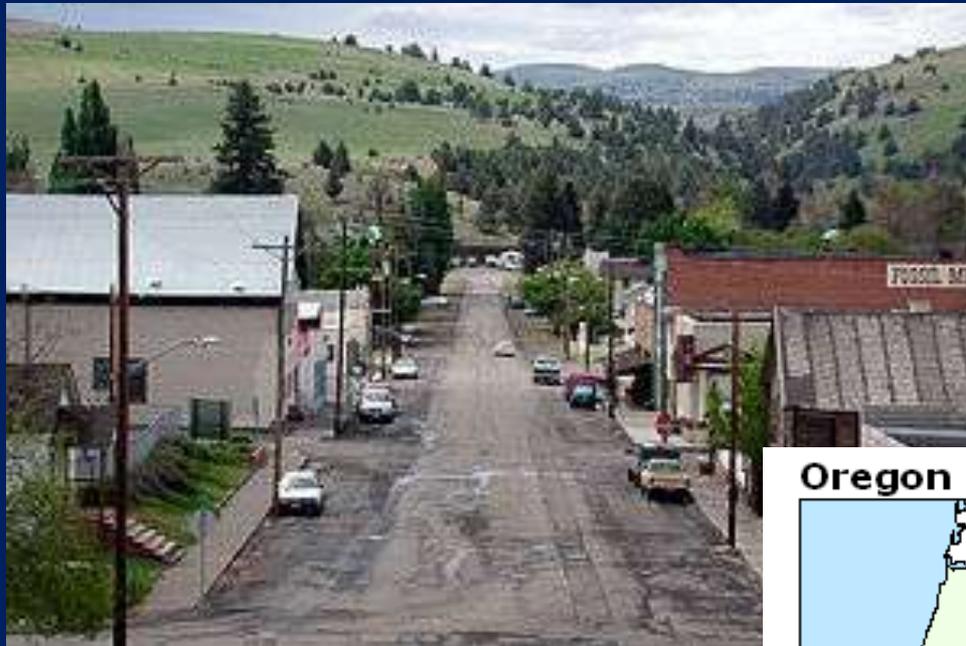


Rates of early syphilis by sex and year— Oregon, 2000–2013



*Preliminary data





Oregon



Attribution:

Many slides adapted from...

ES Theel. Serologic Testing for Syphilis: comparison of the Traditional and Reverse Screening Algorithms. Mayo Clinic, Rochester, Minnesota. October 24, 2012
Available at
<http://www.arlingtonscientific.com/assets/mayo-serologic-testing-for-syphilis--comparion-of-algorithms.ppt>. Accessed May 16, 2015

You'll leave knowing something about...

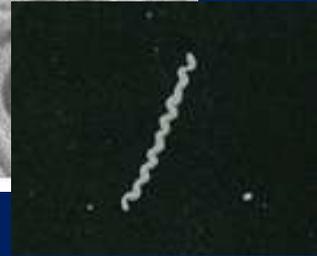
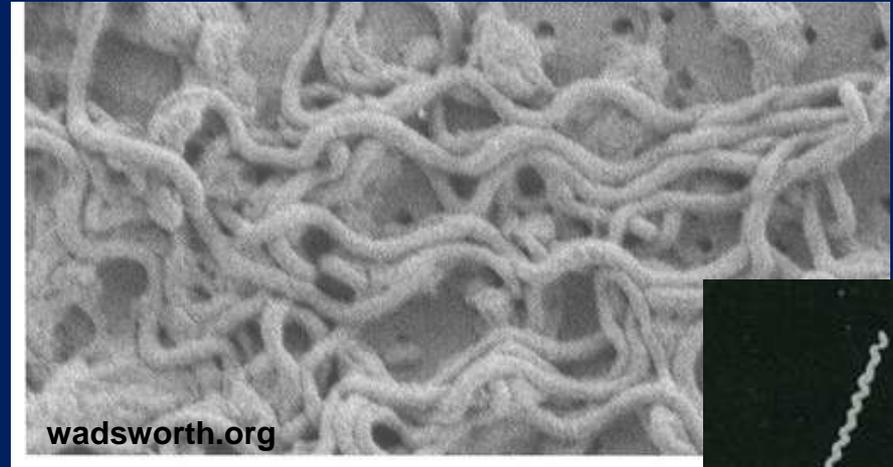
- “Treponemal” and “non-treponemal” tests for syphilis
- “Traditional” and “reverse syphilis” screening
- Rapid diagnostic tests for syphilis

Outline

- **Syphilis**
 - **Causative agent**
 - **Key facts about syphilis**
- **Laboratory tests for diagnosis of syphilis**
 - **Non-treponemal tests**
 - **Treponemal tests**
- **Traditional algorithm for syphilis screening**
- **Reverse algorithm for syphilis screening**
- **Interpretation and follow-up**
- **New rapid diagnostic test for syphilis**

Treponema pallidum

- Bacterium
 - “Spirochete”
 - Motile (“corkscrew”)
 - Can’t culture in lab
- Transmission
 - Sexual
 - Trans-placental
 - Percutaneous following contact with infectious lesions
 - Bloodborn
 - Extremely rare



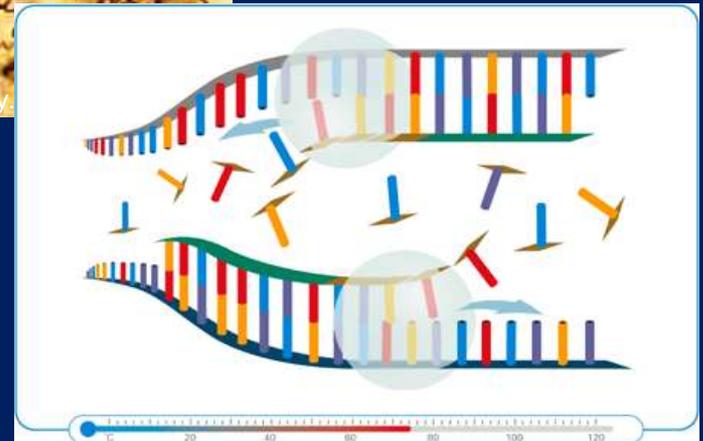
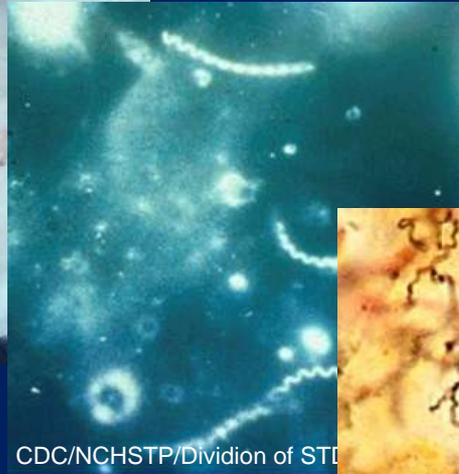
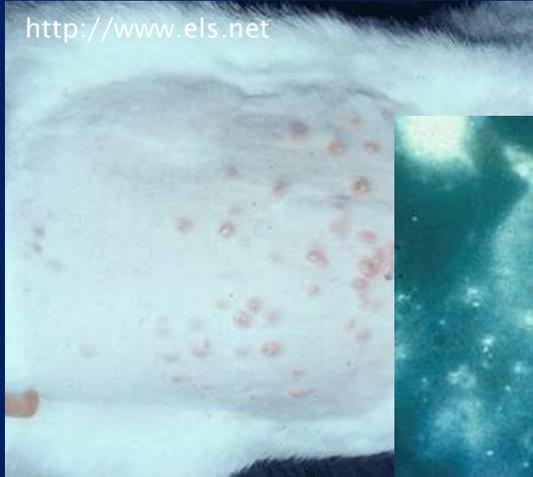
- **Spirochaete**
 - **Spirochaetaceae**
 - **Treponema**
 - *pallidum* (syphilis, yaws), *carateum* (pinta), *denticola*
 - **Borrelia**
 - *burgdorferii/afzelii* (lyme), *hermsii/duttoni/parkeri* (tick-borne relapsing fever)
 - **Leptospiraceae**
 - **Leptospira**
 - *interrogans* (leptospirosis)
 - **Spirillaceae**
 - **Spirillum**
 - *minus* (rat-bite fever)

Syphilis—a few key concepts

- **Highly infectious**
 - Infectious Dose ~57 organisms
 - Attack rate 1/3
- **Incubation – 21 days (median)**
- **3 clinical stages**
 - **Primary:**
 - Painless sore (chancre) at inoculation site
 - **Secondary:**
 - Rash, fever, lymphadenopathy, malaise
 - **Symptomatic Late/Tertiary:**
 - Dementia, tabes dorsalis, cardiovascular disease



Lab Diagnosis—uncommon methods



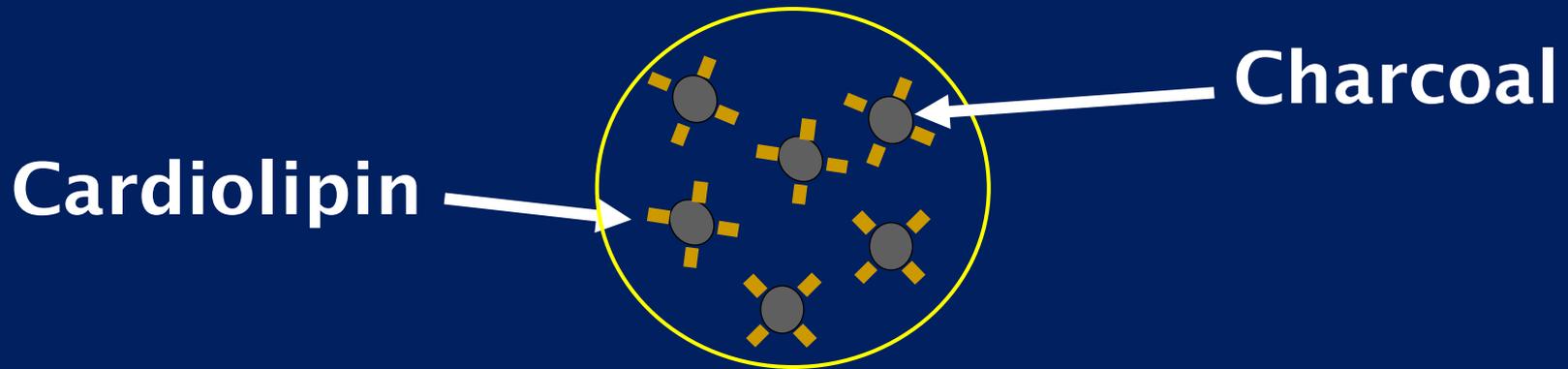
Lab Diagnosis—common methods

- **Serology (tests for antibodies produced upon syphilis infection)**
 - **Mainstay for syphilis testing**
 - **Two kinds**
 - **Non-treponemal**
 - **Treponemal**

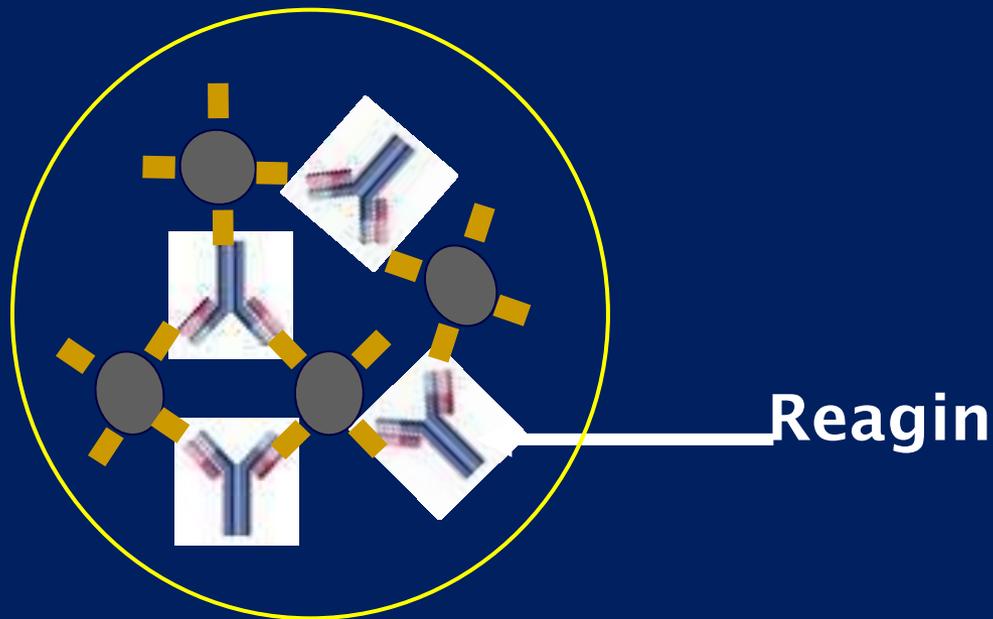
Non-treponemal serologic tests

- *T. pallidum* causes cells to release cardiolipin
- Reagin = antibody to cardiolipin
- Non-treponemal tests measure levels of reagin:
 - Rapid Plasma Reagin (RPR)
 - Venereal Disease Research Laboratory (VDRL)
 - Tolidine red unheated serum test (TRUST)

- **RPR and VDRL are agglutination assays**
- **Reagent is carbon particles+cardiolipin**
- **No reagin present, no agglutination**



Reagin present...agglutination of the charcoal

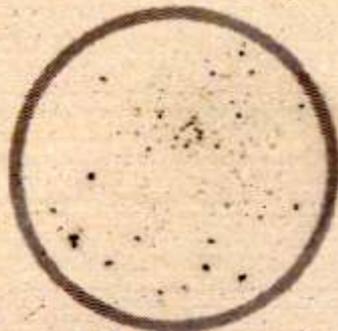


**MACRO-VUE®
RPR Card Test
18 mm CONTROL**

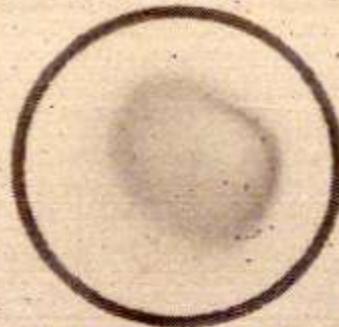
A Brewer Diagnostic Card

U. S. PAT. NO. 3,074,853

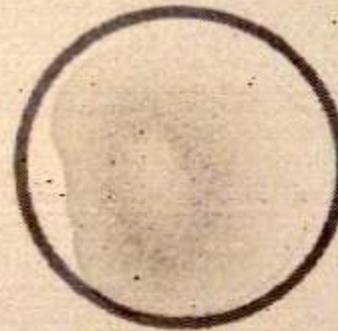
FOR IN VITRO DIAGNOSTIC USE



Reactive



Nonreactive



**Reactive
(Minimal to
Moderate)**

5011

Becton Dickinson Microbiology Systems
Div. of Becton Dickinson and Co., Cockeysville, MD USA

Non-Treponemal Test Advantages

- **Rapid turnaround time – minutes**
- **Inexpensive**
- **No specialized instrumentation required**
- **Usually revert to negative following therapy**
 - **Can be used to monitor response to therapy**

Non-Treponemal Test Limitations

- Results are subjective
 - Intra- and Inter-laboratory variability
- False positives (lower specificity)
 - lupus, pregnancy, viral hepatitis
- Might be negative (lower sensitivity) in very early syphilis and late syphilis even if never treated
- Low “throughput” = can’t be “batched”

Treponemal serologic tests

- Syphilis ⇒ Antibodies against *T. pallidum*
- Tests detect 'treponeme specific' antibodies
 - Fluorescent treponemal antibody absorption test (FTA-ABS)
 - Microhemagglutination assay (MHA)
 - *T. pallidum* particle agglutination (TP-PA)
 - Enzyme Immunoassay (EIA)
 - Immunochromatographic strips (ICS...point of care tests)



FTA-ABS



ICS

Treponemal Test Advantages

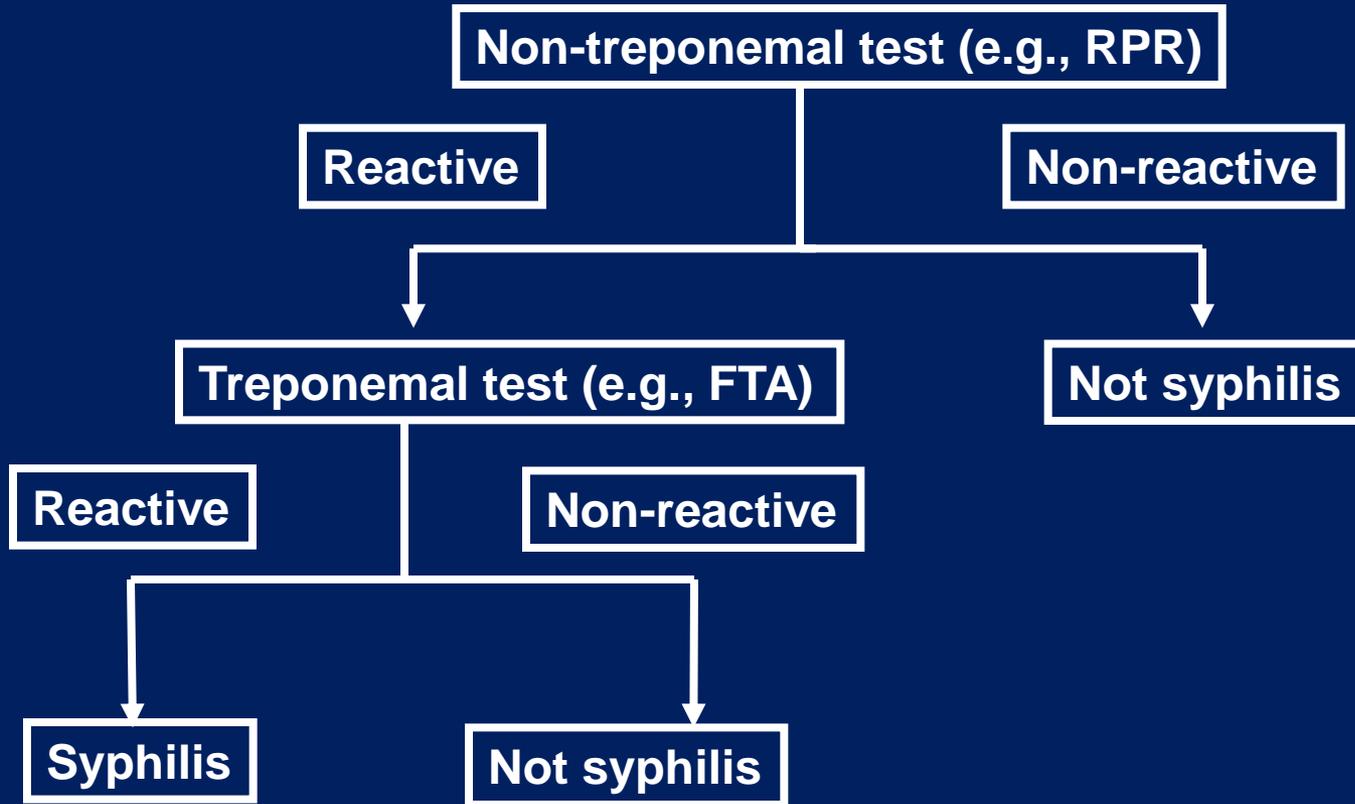
- Few false positives (high specificity)
- Fewer false negatives (more sensitive) especially during early and late syphilis
- Objective result interpretation
- Automation option
- High throughput = “batchable”
- High reproducibility/precision

Treponemal Test Limitations

- **Remain positive for life**
 - **Cannot be used to monitor response to therapy**
- **Conventional (older) versions (e.g. FTA-ABS, TP-PA)**
 - **Subjective interpretation like non-treponemal tests**
- **Newer versions**
 - **Expensive instrumentation**
 - **Higher cost/test**

Syphilis Screening Algorithms: Traditional versus 'Reverse'

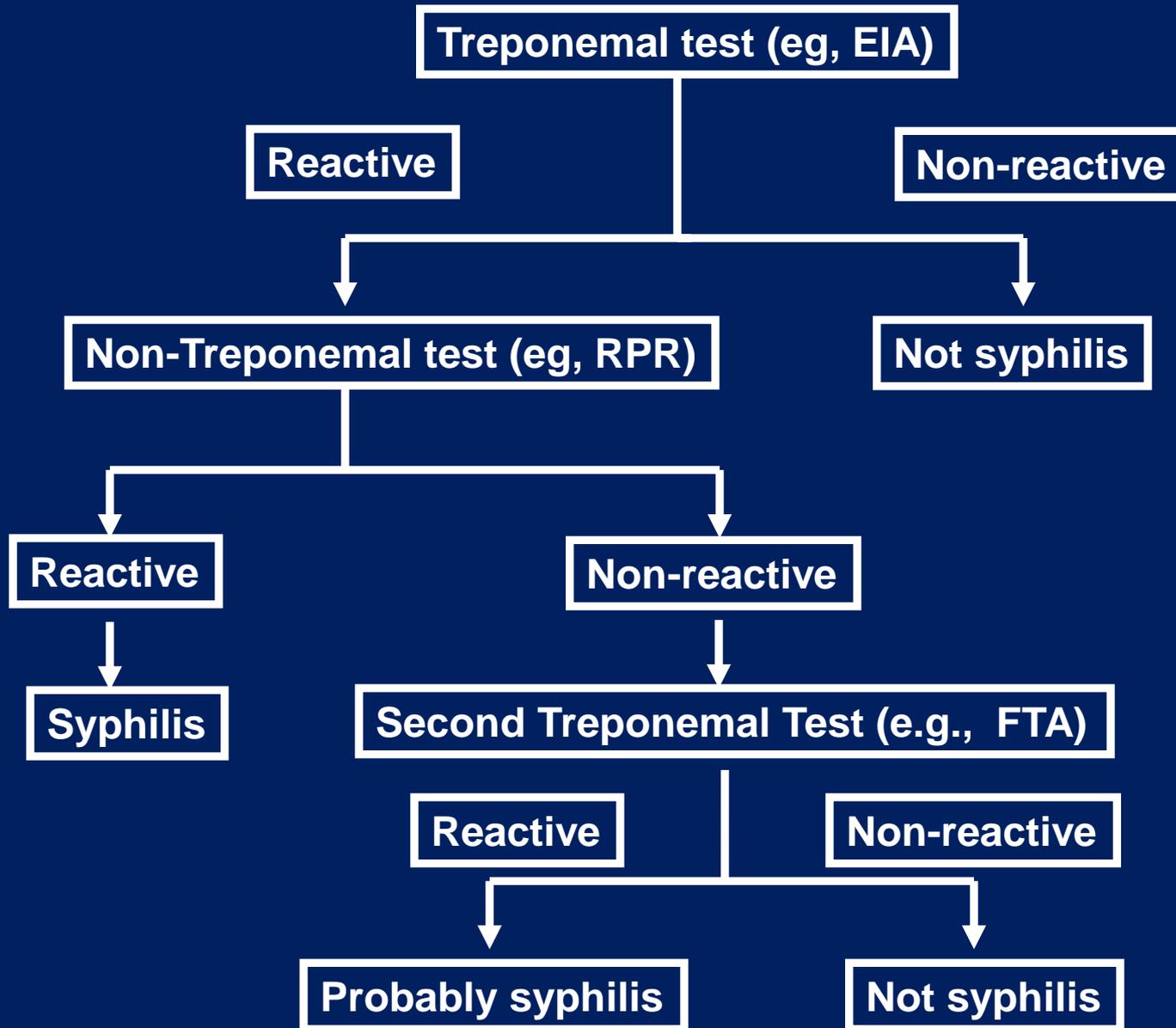
Traditional Algorithm



Traditional algorithm pros and cons

- **Pros**
 - **Familiar**
 - **One confirmation test, typically done reflexively, leads to clear result**
 - **Rapid, inexpensive**
 - **Recommended by CDC**
- **Cons**
 - **Manual**
 - **Subjective interpretation**
 - **False-positives**
 - **False negatives, especially late syphilis**

Reverse Algorithm



Reverse algorithm pros and cons

- **Pros**
 - **Objective**
 - **Can be batched for high volume labs**
 - **Recommended by public health agencies in Europe and Canada**
 - **More sensitive and more specific...more cases of syphilis diagnosed and treated**
- **Cons**
 - **Unfamiliar**
 - **Cost**
 - **Complexity – often second confirmatory test needed, not yet typically done reflexively**
 - **Disfavored by CDC**

Interpreting reverse algorithm

Case #1

- 37-year-old man with HIV
- 2-weeks of fatigue, fever and rash on palms and soles
- Previously resolved genital lesion
- Syphilis IgG by EIA: positive
- RPR: positive, titer of 1:64

Interpreting reverse algorithm

Case #1 Conclusion

- **Untreated or recently treated syphilis**
- **Follow treatment guidelines**
- **No further testing needed on this sample**
- **For follow-up after treatment**
 - **RPR titers only, should fall 4-fold (2 dilutions, e.g. 1:64 to 1:16)**

Interpreting reverse algorithm

Case #2

- 23-year-old female
- First-trimester pregnancy screening
- Previously healthy
- Syphilis IgG by EIA: positive
- RPR: negative
- Second treponemal test, FTA: negative

Interpreting reverse algorithm

Case #2 conclusion

- False positive EIA
- Not syphilis
- No further screening at this time
- Consider screening again at 28 weeks and delivery if syphilis prevalent in community

Interpreting reverse algorithm

Case #3

- 50-year-old Somali immigrant
- Kidney transplant evaluation
- No known history of syphilis or treatment
- Syphilis IgG by EIA: positive
- RPR: negative
- FTA: positive

Interpreting reverse algorithm

Case #3 Conclusion

- Possible latent syphilis
- Evaluate and treat according to current guidelines
- Consider lumbar puncture if neurologic symptoms consistent with late neurosyphilis

Interpreting reverse algorithm

Case #4

- 30-year-old inmate
- Past history of treated syphilis (10 years prior)
- Syphilis IgG by EIA: positive
- RPR: negative

Interpreting reverse algorithm

Case #4 Conclusion

- Consistent with successfully treated syphilis
- No additional testing needed

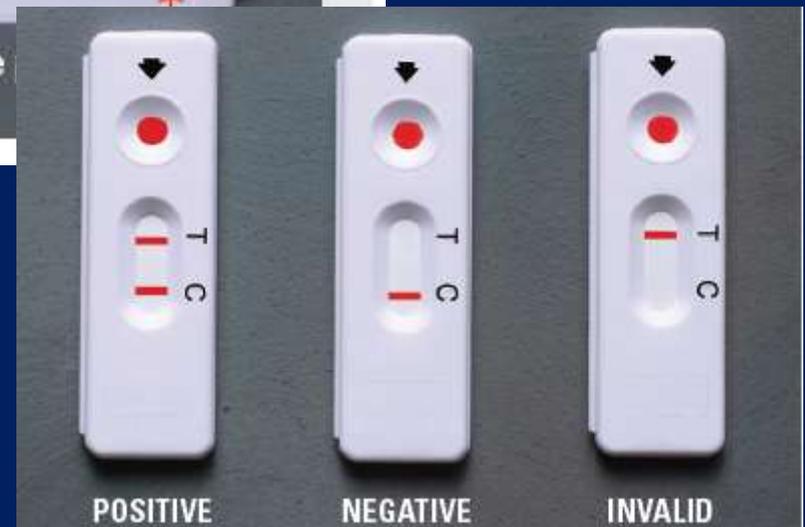
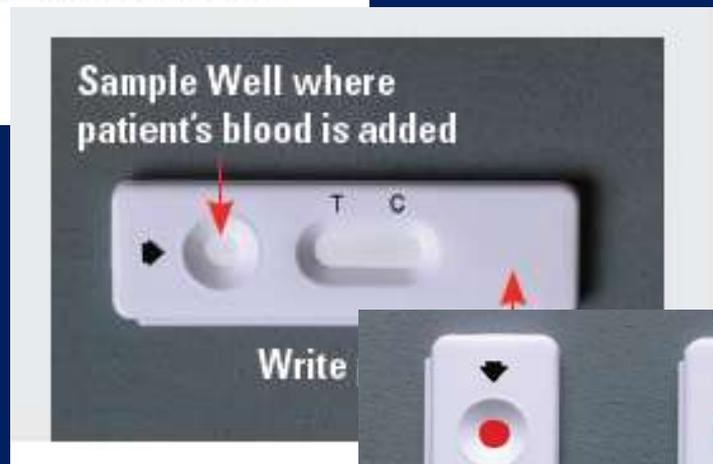
Summary

- Syphilis usually diagnosed by serology
 - Non-treponemal (e.g., RPR, VDRL)
 - Treponemal (e.g., FTA, TP-PA, EIA, MFI)
- Traditional Algorithm
 - Non-treponemal test (RPR) first
 - Treponemal test to confirm
 - Advantages
 - Recommended by CDC
 - Cost-effective
 - Suitable for most lower throughput labs
 - Limitations
 - May miss very early or late/latent infection

Summary

- **Reverse Algorithm**
 - **Treponemal test first**
 - **Confirm with RPR**
 - **If RPR negative, use different treponemal ‘tiebreaker’ test**
 - **Advantages**
 - **High volume throughput**
 - **More sensitive, same specificity**
 - **Limitations**
 - **Result interpretation can be challenging**
 - **‘Tiebreaker’ test not yet reflexive in most labs**

Rapid diagnostic tests for syphilis



DPP® Syphilis Screen and Confirm Assay (Chembio)



- Not FDA approved for US use
- Non-treponemal + treponemal test on same point-of-care device
- Immunochromatographic strip
- Accommodates serum, plasma, whole blood
- In confirmed cases, non-treponemal component is positive in 95% of low RPR titer and 98% of high RPR titer cases
- Specificity of treponemal component was poor(68%)—doesn't do a great job of weeding out previously treated syphilis or late infections

Rapid diagnostic tests for syphilis

- Many in use worldwide, only one licensed in US
- Treponemal tests
- Immunochromatographic strip test (e.g. home pregnancy test)
- Point of care tests
- Not much US experience yet

Rapid diagnostic test sensitivity and specificity

- Performance likely comparable to existing treponemal tests
- **Tucker, et al (2010)**
 - Median Sensitivity 86%
 - Median Specificity 99%
- **Humphries, et al (2014)**
 - Evaluated 3 dual HIV, *T. pallidum* rapid test
 - *T. pallidum* sensitivity 93%–99%
 - *T. pallidum* specificity 97%–100%

Rapid diagnostic tests for syphilis

Advantages

- Cheap
- Can be combined with HIV and other ICS tests for STIs
- No instrumentation required
- Point of care...could be used in bars or clubs
- Can be used as single screening test if risk or cost of overtreatment judged to be $<$ risk or cost of untreated syphilis (e.g. in pregnancy)

Disadvantages

- Might be misinterpreted by unsophisticated user
- Overdiagnosis or overtreatment if not confirmed

DEPARTMENT OF CORRECTION-CITY OF NEW YORK



70% ARE DOOMED

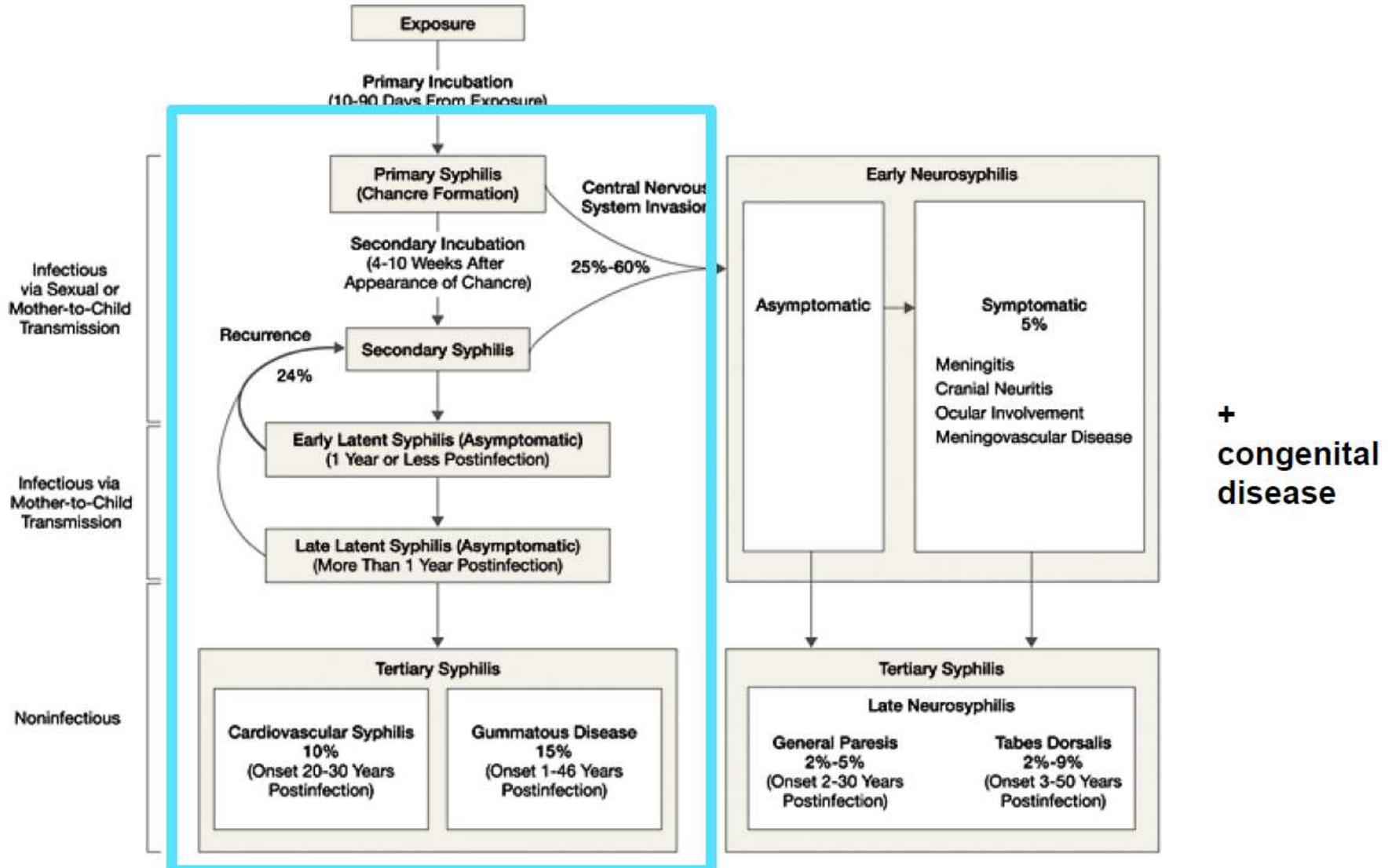
IF TREATMENT OF SYPHILIS
IS DELAYED FOR 3 YEARS
AFTER THE DISEASE IS
CONTRACTED

CONSULT A REPUTABLE PHYSICIAN

W.C.P.
W.C.P.
W.C.P.

ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED

Clinical stages of syphilis infection



Population/ laboratory	Screen test	# Screened	Reactive EIA/CIA (%)	Non reactive RPR (%)
Overall		140, 176	4834 (3.4%)	2,743 (56.7%)
Southern California	Trep-Chek	47,952	1,278 (2.7%)	765 (59.9%)
Northern California	Liason	21,623	438 (2.0%)	287 (65.5%)
Southern California	Trep-Sure	57,827	1,268 (2.2%)	755 (59.5%)
New York City	Trep-Chek	7,607	1,165 (15.3%)	639 (54.8%)
Chicago	Trep-Sure	5,167	685 (13/3%)	297 (43.4%)

5 Laboratories (N=140, 176)	High Prevalence	Low Prevalence	RR
Prevalence	14.5%	2.3%	
Discordant Results (EIA/CIA +, RPR non-reactive)	50.6%	60.6%	1.2
False positive (EIA/CIA +, TPPA/ FTA-)	14.1%	40.8%	2.9