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The Evolution of Syphilis Testing: Clinical Benefits of a Reverse Screening Algorithm

Katherine Soreng PhD

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Background

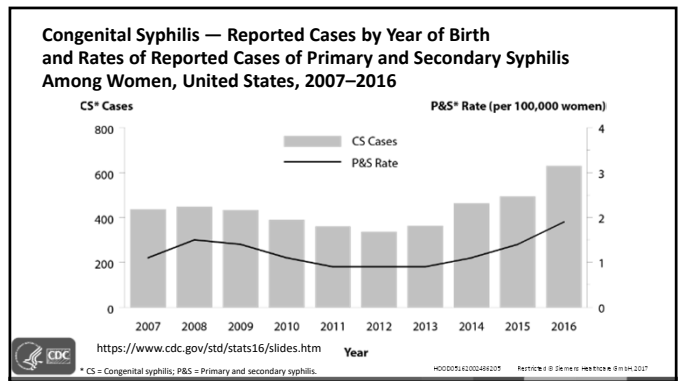
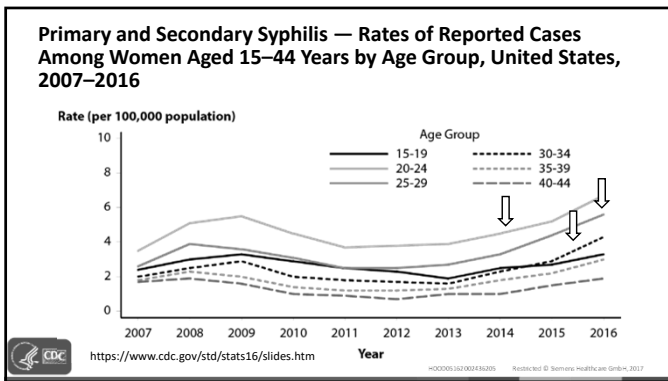
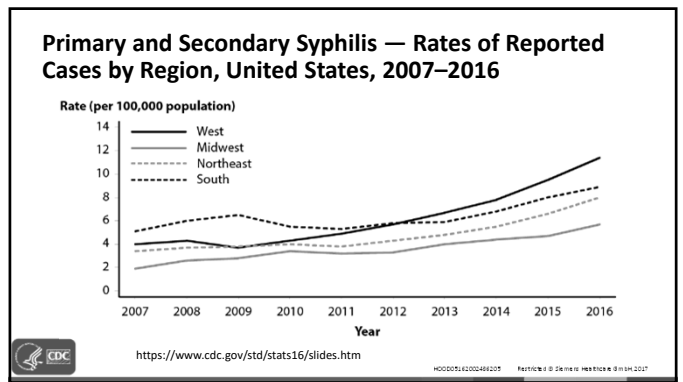
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Lafond RE, et al. Clin Microbiol Rev. 2006;19(1):29-49. H0000162002486205 Restricted © Siemens Healthcare GmbH, 2017

Disease course: Untreated

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Lafond RE, et al. Clin Microbiol Rev. 2006;19(1):29-49. H0000162002486205 Restricted © Siemens Healthcare GmbH, 2017



Consequences of Untreated Fetal Infection

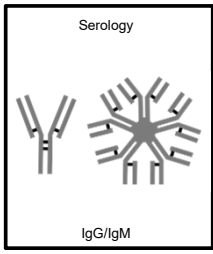
Interstitial Keratitis
Sensorineural Deafness
Optic atrophy
Mental retardation
Stillbirth
Seizures

Death
~40% mortality in the developing embryo/baby without intervention

Lafont et al. Clin Microbiol Rev. 2006;19(1):20-49. www.mayoclinic.com/health/syphilis. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017


Laboratory Evaluation

Serology



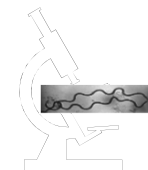
IgG/IgM

Molecular



DNA

Microscopy



Bacteria

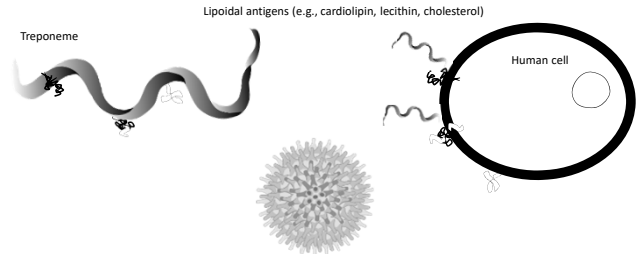
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Serological laboratory testing for syphilis

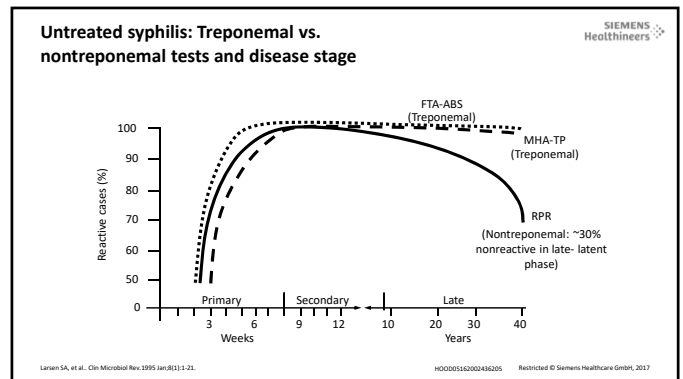
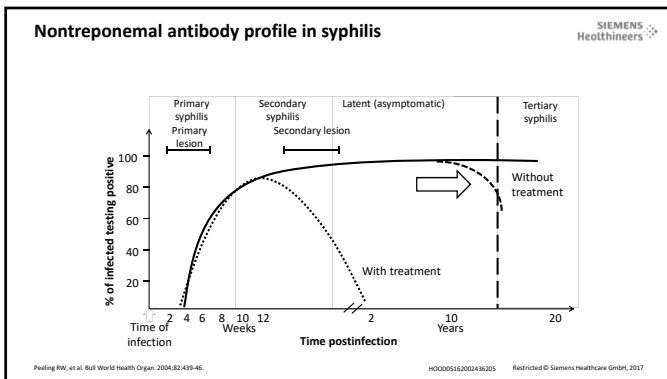
Nontreponemal Detects antibodies against cardiolipin, lecithin, cholesterol antigens	
RPR	(rapid plasma reagin test)
VDRL	(Venereal Disease Research Laboratory test)
<ul style="list-style-type: none"> Typically manual Lower sensitivity 	

Ratnam S. Can J Infect Dis Med Microbiol. 2005;16:45-55. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017

Laboratory Testing: Nontreponemal Antibodies



Singh AF, et al. Clin Microbiol Rev. 1995;11:187-209. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017



Laboratory testing: Treponemal antibodies

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Singh AJ, et al. Clin Microbiol Rev. 1999;12:187-205. H0000162002436205 Restricted © Siemens Healthcare GmbH, 2017

Treponemal antibody profile in syphilis

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Peeling RW, et al. Bull World Health Organ. 2004;82:439-46. H0000162002436205 Restricted © Siemens Healthcare GmbH, 2017

CDC-provided information on syphilis testing includes:

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- Includes disease background, testing, diagnosis, and treatment information
- Neutrally supports both traditional and reverse screening approaches
- Notes that in primary syphilis, nontreponemal tests are only ~75% sensitive

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Serology screening options: Traditional vs. reverse testing

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Traditional: TP-PA or other treponemal test

Reverse: RPR or other nontreponemal test

Rahman S. Clin J Infect Dis Med Microbiol. 2005. Jan/Feb;19(1):45-51. H0000162002436205 Restricted © Siemens Healthcare GmbH, 2017

CDC/APHL-provided information on Traditional Testing

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Suggested Reporting Language for Syphilis Serology Testing

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CDC/APHL-provided information on Reverse Testing

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Suggested Reporting Language for Syphilis Serology Testing

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Interpretation of treponemal values example: ADVIA Centaur syphilis assay results

- Qualitative
- Index Unit (ADVIA Centaur assay) cutoff based on clinical data

<0.90 → Nonreactive → Report negative

≥0.90 to <1.10 → Equivocal → Retest in duplicate

- 2 of 3 results <0.90 → Nonreactive → Report negative
- 2 of 3 results ≥0.90 to <1.10 → Equivocal → Supplemental testing recommended
- 2 of 3 results ≥1.10 → Reactive → Report positive; proceed with testing algorithm

≥1.10 → Reactive → Report positive

ADVIA Centaur Syphi RFU 10682391_IN Rev. 4, 2016-04. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017

Traditional Testing Algorithm

False positive

- Autoimmune disease
- Acute viral infections
- Drug addiction
- Age
- Pregnancy
- Temperature
- Interpretation

False negative

- Prozone reaction
- Interpretation
- Temperature

Jankir M, et al. J Eur Acad Dermatol Venereol. 2014;28:1381-93. Workowski KA, et al. MMWR Recomm Rep. 2015;64:1-137. Algorithm from https://www.apn.org/about/APHS/publication/Document/ID_Suggested_Syphilis_Reporting_Lang_122015.pdf. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017

Reverse Sequence Syphilis Screening Algorithm Advantages

- Automated assay significantly reduced workload
- Data suggested increased detection of infection

Jankir M, et al. J Eur Acad Dermatol Venereol. 2014;28:1381-93. Workowski KA, et al. MMWR Recomm Rep. 2015;64:1-137. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017

Nontreponemal/Treponemal Discordants in a Reverse Sequence Testing Algorithm

- False-positives?
- Early infection?
- Latent? (~30% untreated infections)

CDC and IUSTI recommendations:
Use a second treponemal to resolve discordance.

Jankir M, et al. J Eur Acad Dermatol Venereol. 2014;28:1381-93. Workowski KA, et al. MMWR Recomm Rep. 2015;64:1-137. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017

CDC/APHL Suggests Confirming Discordants using a Second Treponemal Assay

"If the nontreponemal test is negative, the laboratory should perform a different treponemal test (preferably based on different antigens than the original test) to confirm the results of the initial test."

Workowski KA, et al. MMWR Recomm Rep. 2015;64:1-137. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017

Automated treponemal assay advantages

Clinical

Can identify cases missed by nontreponemal tests, e.g., early primary syphilis, latent syphilis, tertiary syphilis

Workflow

Can reduce labor time and costs
Automation allows increased test volume with faster TAT
Decreased opportunity for human error/subjective interpretation

Ratman S, Can J Infect Dis Microbiol. 2005; Jan/Feb;16(1):45-51. Lerman SA. Clin Microbiol Rev. 1999; Jan;12(1):1-21. H00005162002436205 Restricted © Siemens Healthcare GmbH, 2017

TPHA, RPR, and ADVIA Centaur in the detection of early syphilis

Overall agreement: 99.8%

AD VIA Centaur Syphilis	TPHA and RPR consensus	
	Positive	Negative
Positive	157	2
Negative	0	913

Sample 1: MSM patient with genital ulceration
 • Positive according to the VDRL treponemal-specific IgM assay
 • Confirmed very recent infection (true positive)

Sample 2: Woman without a genital ulceration
 • TPHA and RPR negative
 • Considered ADVIA Centaur false positive

The resolved clinical specificity was 99.89% (913/914)

Sehrouf L, et al. Poster #337 2013 RICAL, Paris, France
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Automated assays in the detection of primary syphilis

Poster: Evaluation of four fully-automated immunoassays for diagnosis of syphilis
 Laboratoire Biomnis, Ivry sur Seine, France

VDRL	TPHA	ARCHITECT Tp 15,17, 47	IMMULITE Tp17	LIAISON Tp17	BioPlex IgM		BioPlex IgG			Immunoblot IgM				
					Tp17	Tp47	Tp15	Tp17	Tp47	TmpA	Tp17	Tp15		
1	N	N	P	P	P	N	P	N	N	N	P	P	P	P
2	N	N	P	P	P	N	P	N	N	N	P	N	N	P
3	N	N	P	P	P	N	P	N	P	P	P	P	N	P
4	P	N	P	P	P	P	P	N	P	N	P	P	P	P
5	N	N	P	P	P	P	P	N	P	P	P	P	N	P
6	N	N	P	P	P	N	P	N	P	N	P	P	N	P
7	P	N	P	P	P	P	P	P	P	P	P	P	P	P

Ly TD, et al. Poster P518, 20th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna, April 10-13, 2010.
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Zika: Clinical Background and Testing

Katherine Soreng, PhD

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Timeline of reported Zika cases

Adapted from Wilder-Smith, A. J. Travel Med. 2016; July 1, 25(1)
 Plonkiewicz, G. New Microbes and New Infect. 2016; 11:52-53
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Global areas with Zika

*Mosquitoes that can spread Zika usually live in places below 6,500 feet. The chances of getting Zika from mosquitoes being blown that high are very low.
<https://www.cdc.gov/travel/page/world-map-areas-with-zika>
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Zika transmission

PROTECT YOUR FAMILY AND COMMUNITY HOW ZIKA SPREADS

Most people get Zika from a mosquito bite

- A mosquito bites a person who has Zika.
- The mosquito becomes infected.
- The infected mosquito bites a person who does not have Zika.


Other ways people get Zika

- During pregnancy:** Zika can be passed from a pregnant woman to her fetus.
- Through sex:** Zika can be passed from a person with Zika to another person through sex.
- Through blood transfusion:** Zika can be passed from a person with Zika to another person through blood transfusion.

- Mother-to-child (Zika has been transmitted from breast milk but no consequent pathology documented)
- Sex (semen appears to harbor virus for an extended period of time)
- Blood transfusion (no documented US cases but multiple reports from Brazil)
- Lab transmission (rare but at least one report confirmed in the US)
- CDC has resources and guidance to reduce risk of occupational exposure

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ZIKA Symptoms



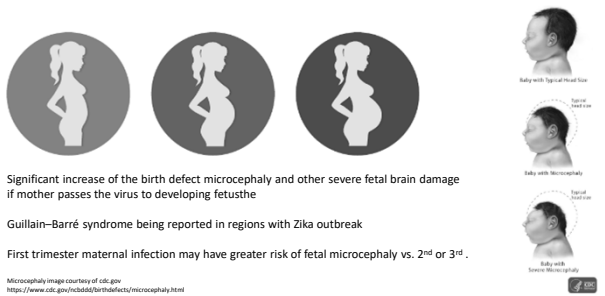
Only about 20% of infections are symptomatic

Symptoms may include:
cutaneous maculopapular rash; conjunctivitis; retro-orbital pain; arthralgia, notably of small joints of hands and feet; myalgia; headache; and mild fever (37.8C-38.5C).

Source: WHO and <https://www.cdc.gov/zika/about/faq.html>

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ZIKV can result in severe complications



Significant increase of the birth defect microcephaly and other severe fetal brain damage if mother passes the virus to developing fetus

Guillain-Barré syndrome being reported in regions with Zika outbreak


First trimester maternal infection may have greater risk of fetal microcephaly vs. 2nd or 3rd.

Microcephaly image courtesy of cdc.gov
<https://www.cdc.gov/hctdd/birthdefects/microcephaly.html>

Pregnancy image purchased from Shutterstock

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Zika is a reportable disease (2017 case counts in the US)



Laboratory-confirmed symptomatic Zika virus disease cases* reported to ArboNET by state and territory - United States, 2017 (Provisional data as of January 10, 2018)

US States
407 symptomatic Zika virus disease cases reported:
+398 cases in travelers returning from affected areas
+4 cases acquired through presumed local mosquito-borne transmission in Florida (N=2) and Texas (N=2)
+5 cases acquired through sexual transmission

US Territories
631 Zika virus disease cases reported
+1 case in a traveler returning from affected areas
+630 cases acquired through presumed local mosquito-borne transmission

Source: <https://www.cdc.gov/zika/faq/2017-case-counts.html> Accessed Jan. 23, 2018

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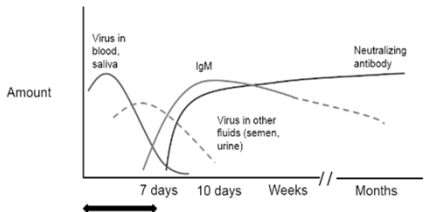
Current CDC guidance for Zika testing

Updated Guidance for US Laboratories Testing for Zika Virus Infection July 24, 2017

Accessible Version: <https://www.cdc.gov/zika/transmission/index.html>

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Serology profile for acute Zika infection



Virus in blood, saliva
IgM
Neutralizing antibody
Virus in other fluids (semen, urine)

7 days 10 days Weeks Months


Acute illness

*New data now shows some individuals may remain NAT-detectable for months

Source: <http://www.aaph.org>

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CDC: Zika testing recommendations for symptomatic non-pregnant individuals with exposure to Zika virus



Start w/ NAT (if symptoms <14 days)
(for NAT use patient-matched serum and urine)

If NAT negative: Test for Zika IgM

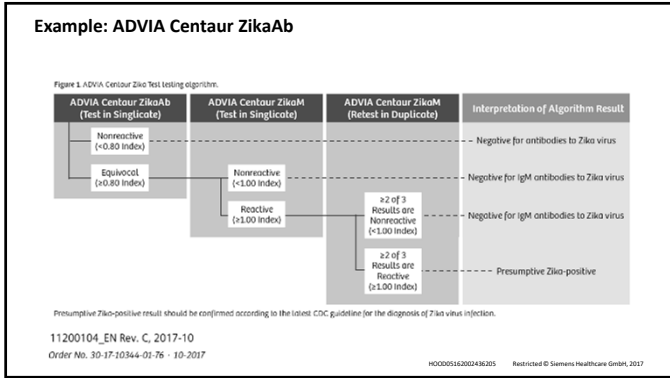
If IgM non-negative: perform PRINT analysis

Note: Non-negative can include

- Positive
- Presumptive positive
- Equivocal
- Possible positive

MMWR, July 28, 2017 / 66(29):781-793
July 2017 Update: <https://www.cdc.gov/zika/laboratory/lab-guidance.html>

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US data: Most initial Zika test results will be non-reactive

Zika Virus Testing and Outcomes during Pregnancy, Florida, USA, 2016

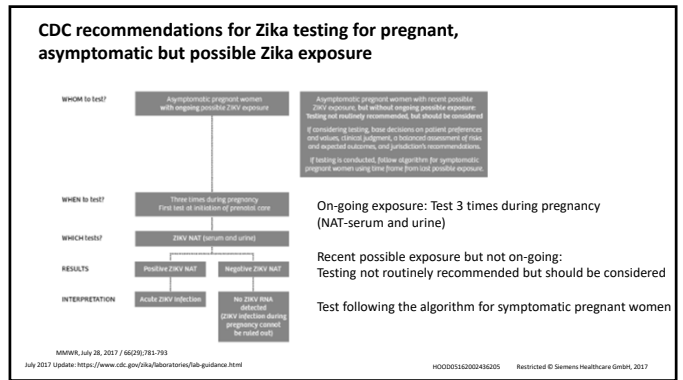
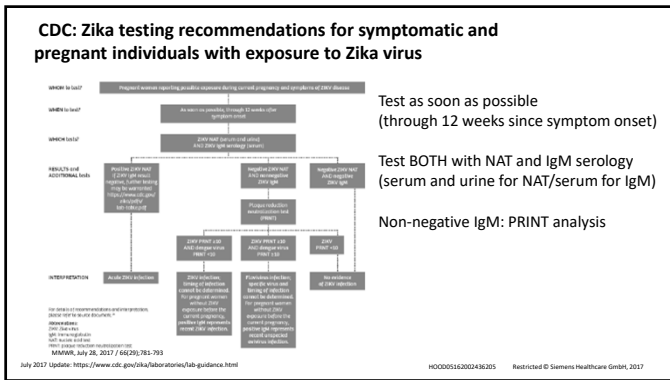
Synopsis: Zika Virus Testing and Outcomes during Pregnancy, Florida, USA, 2016. Emerging Infectious Diseases, Vol. 24, No. 1, January 2018.

Table 2. Laboratory test results of 2,327 pregnant women for Zika virus, Miami-Dade County, Florida, USA, 2016

Laboratory characteristic	Result
IgM positive	102 (4.4)
rRT-PCR-positive	8 (0.3)
Negative	1,999 (85.9)

4.4% of tested samples were IgM-positive
85.9% of samples were negative

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 1, January 2018
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Thanks for attending!

Q&A

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