

# Penicillin to Pills: Oral Options for Early Syphilis

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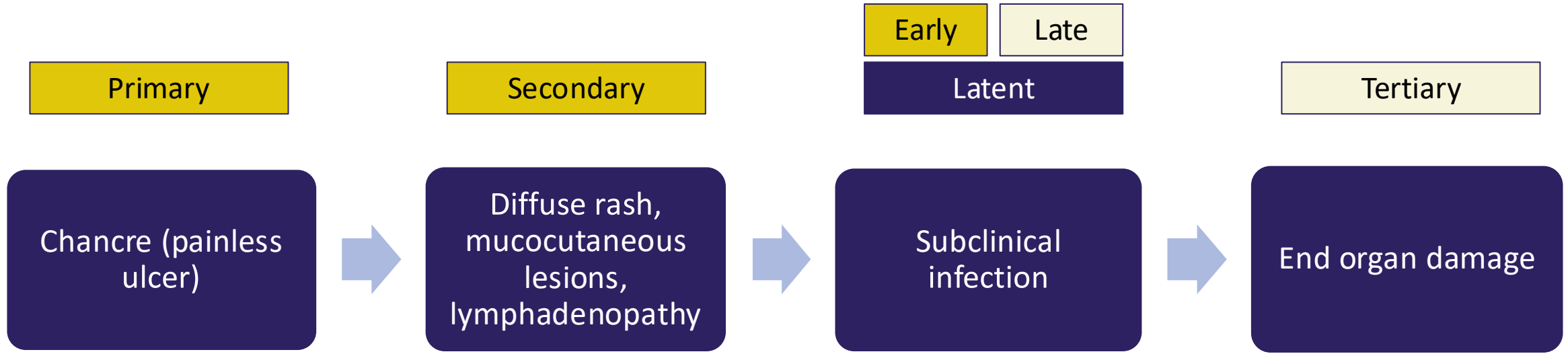
# Disclosures

- I have no financial relationships or conflicts of interest to disclose.
- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

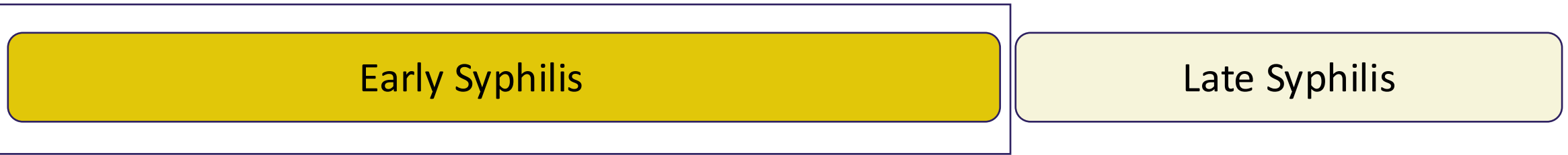
# Background

# Clinical Presentation

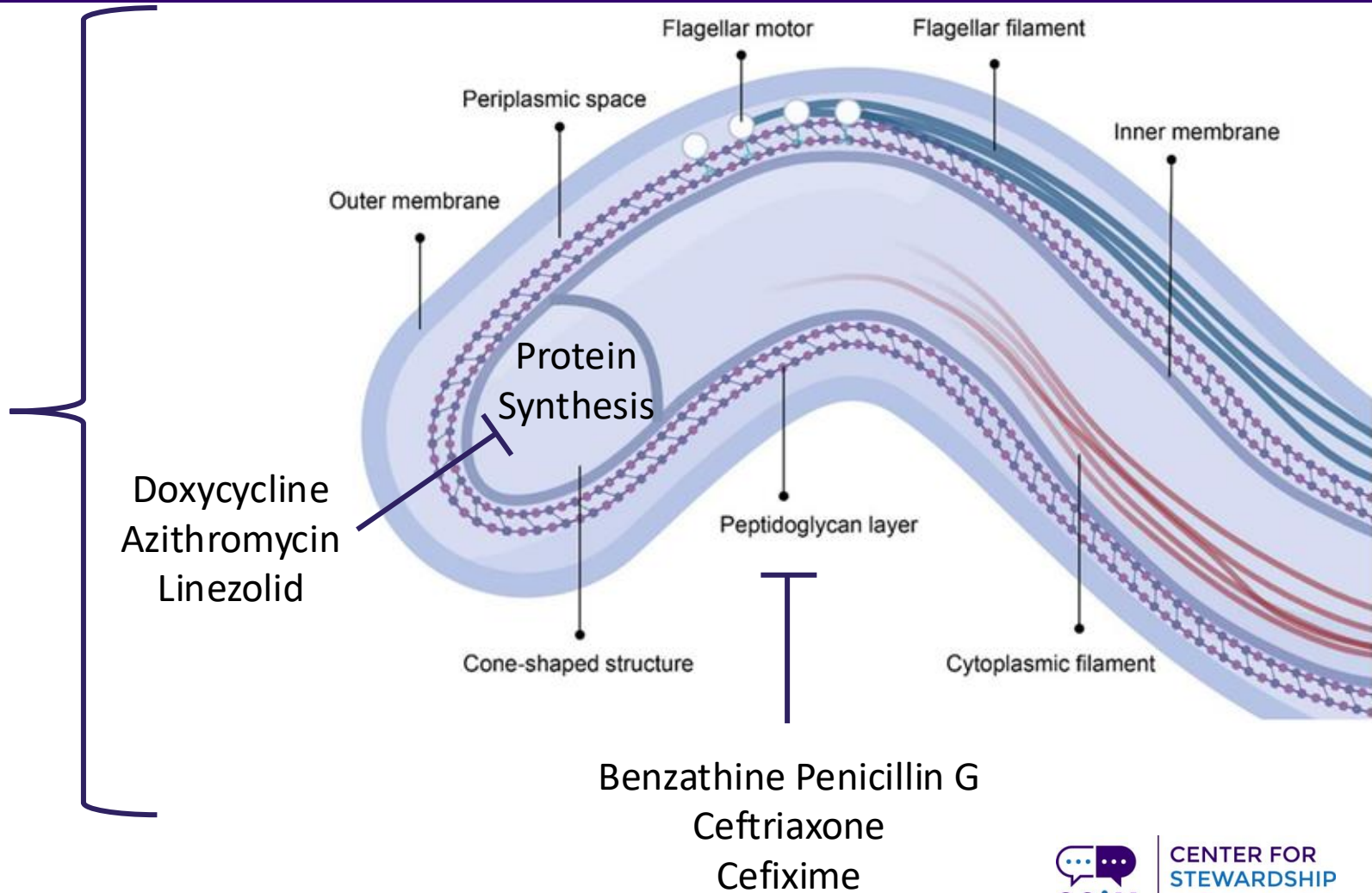
Old terminology



New terminology



# Treponema pallidum



# Diagnostic Tests

## Treponemal Test (TT)

Detect IgM and IgG against *T. pallidum*

### Strength

- Establishes diagnosis

### Limitations

- Cannot monitor treatment response
- Cannot detect re-infection

## Nontreponemal Test (NTT)

Detect antibodies to lipoidal antigens produced in response to *T. pallidum* (RPR, VDRL)

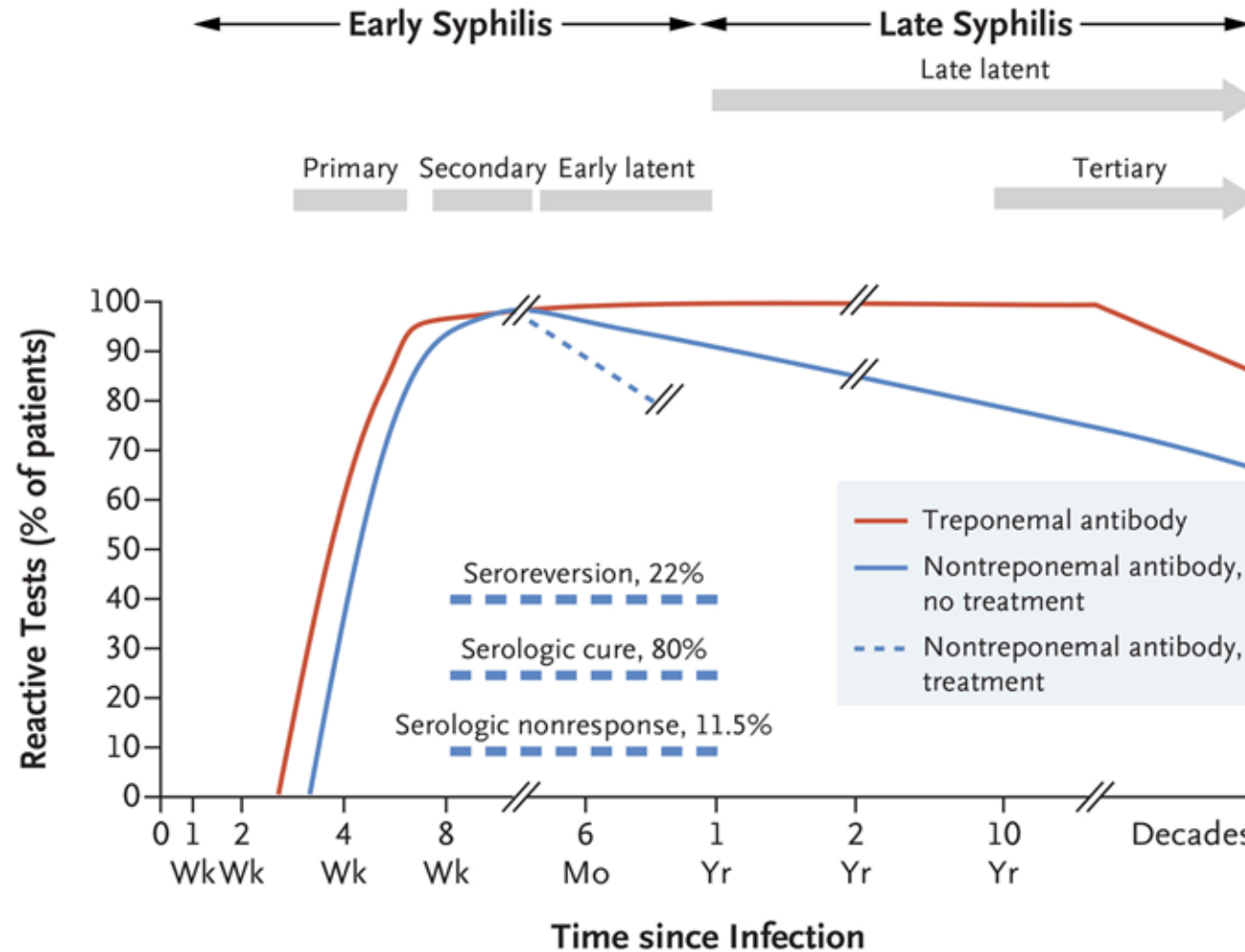
### Strength

- Quantitative titer, can monitor disease activity/treatment response (4-fold decrease at 12 months)

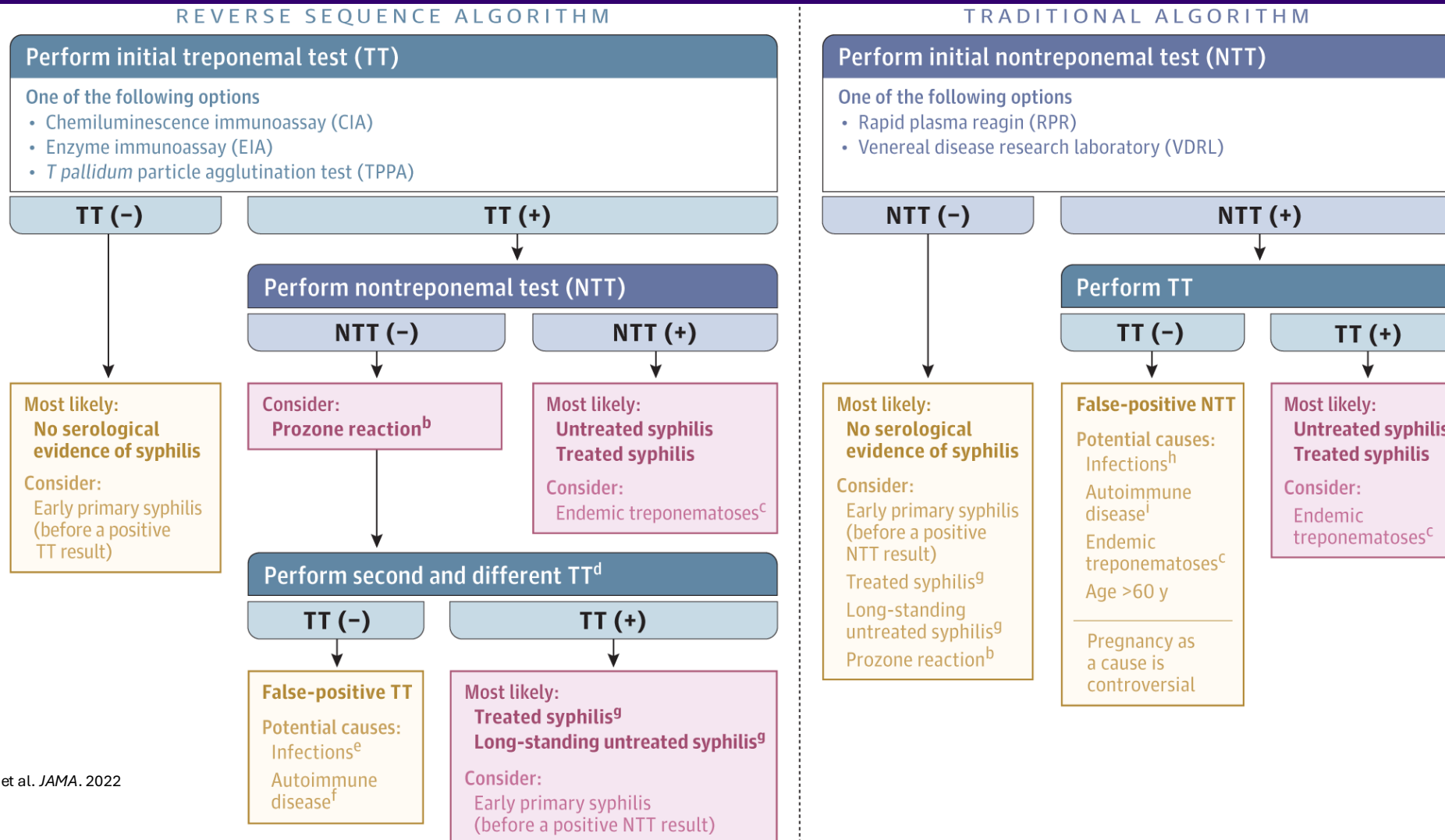
### Limitation

- Prozone phenomenon (false negative)

# Reactive Tests Over Time

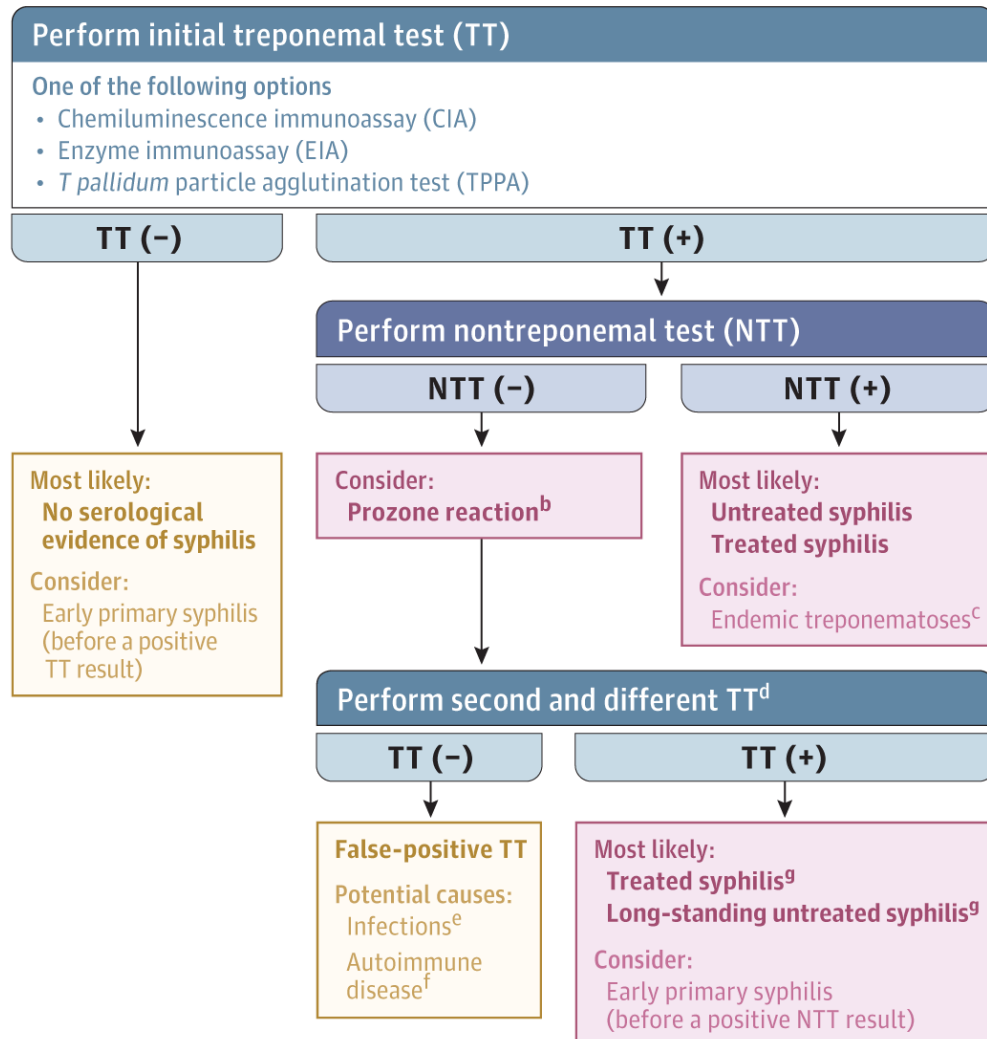


# Traditional vs. Reverse Algorithm



# Example Syphilis Screen

## REVERSE SEQUENCE ALGORITHM



## ! Syphilis Screen

Status: Edited Result - FINAL

Test Result Released: No

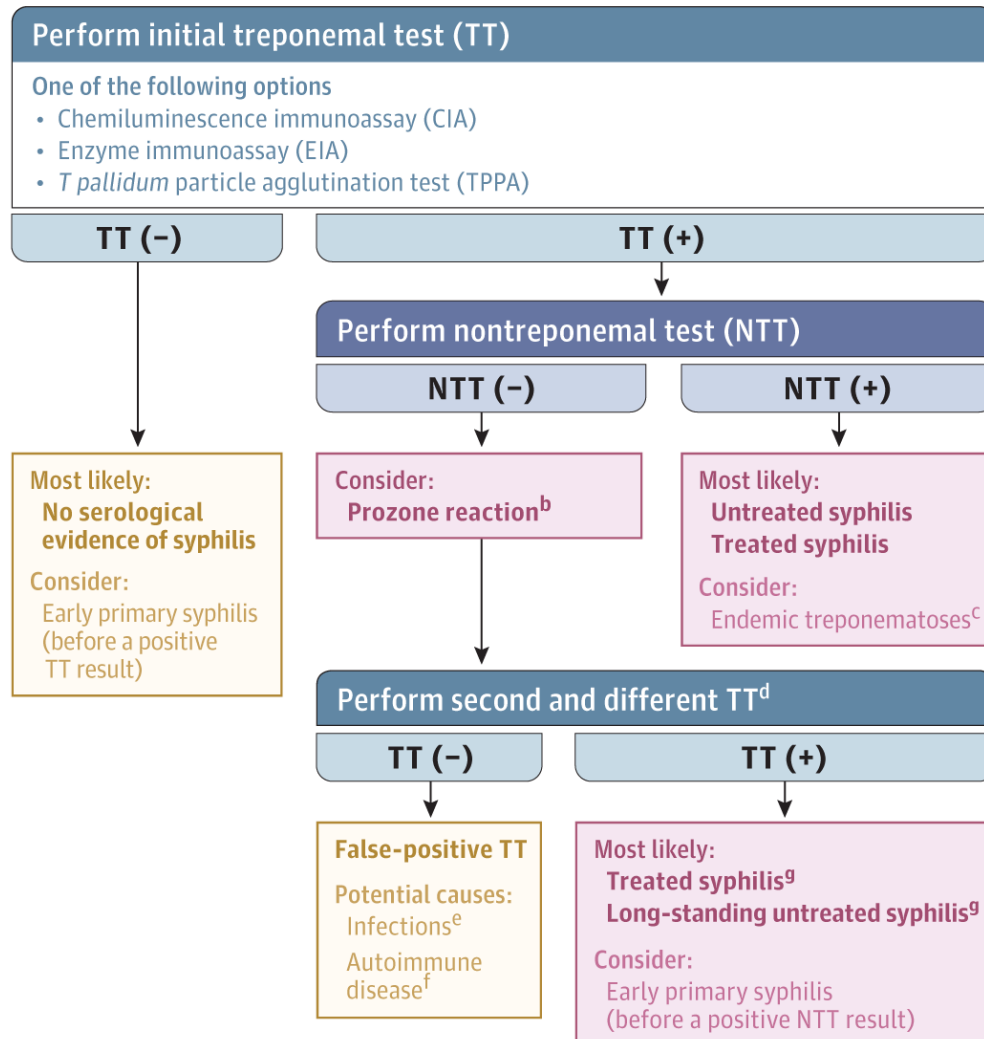
0 Result Notes

**i** Newer results are available. Click to view them now.

Component	4 mo ago
Ref Range & Units (hover)	
Treponema pallidum IgG/IgM Antibody (Bioplex)	
RPR Screen	
Syphilis Screening Status	
Resulting Agency	UWMC Montlake Dept of Lab Med

# Example Confirmation Test

## REVERSE SEQUENCE ALGORITHM



## ⚠ Syphilis Serologic Confirmation (Sendout)

Status: Final result

Test Result Released: No

### 0 Result Notes

ⓘ Newer results are available. Click to view them now.

Component	4 mo ago	Resulting Agency
Ref Range & Units (hover)		
Syphilis Conf Treponemal CMIA, IgG/IgM		Outside Reference Performing Lab
Syphilis Conf RPR Quantitative Titer		Outside Reference Performing Lab
Syphilis Conf Performing Lab	Test(s) performed by Washington State Public Health Laboratories, 1610 NE 150th Street, Shoreline, WA 98155	Outside Reference Performing Lab
Final Syphilis Screening		UWMC Montlake Dept of Lab Med

# Early Syphilis Treatment

## Recommended Regimen

- Benzathine penicillin G (Bicillin L-A) 2.4 MIU IM x1

## Alternative Regimens

- Doxycycline 100 mg PO BID x14 days
- Ceftriaxone 1 g IM/IV daily x10 days

# Poll 1

Is your institution affected by the benzathine penicillin shortage?

A. Yes!

B. No

C. Unsure

# Alternative Oral Agent – Cefixime

## Need for Alternatives

- Shortages in benzathine penicillin G
- Limitations with alternative regimens
  - Ceftriaxone is not an oral option
  - Doxycycline not recommended in pregnancy

## Pilot Study 2021

- Oral cefixime resulted in 87% treatment success

# Cefixime versus benzathine penicillin G for the treatment of early syphilis—a randomized, controlled open label trial

# Study Design

- Open label, randomized control trial
- Conducted in Czech Republic from 7/2021 to 1/2023
- Target sample size for 80% power: 224 participants total
- Inferiority margin: 10% in primary endpoint

# Inclusion & Exclusion Criteria

## Inclusion Criteria

- Adults between 18 and 65 years of age
- Non-pregnant
- Non-breastfeeding
- Laboratory-confirmed early syphilis
- Primary, secondary, early latent VDRL titer  $\geq 1:8$

## Exclusion Criteria

- B-lactam allergy
- Systemic antibiotics 2 weeks before randomization

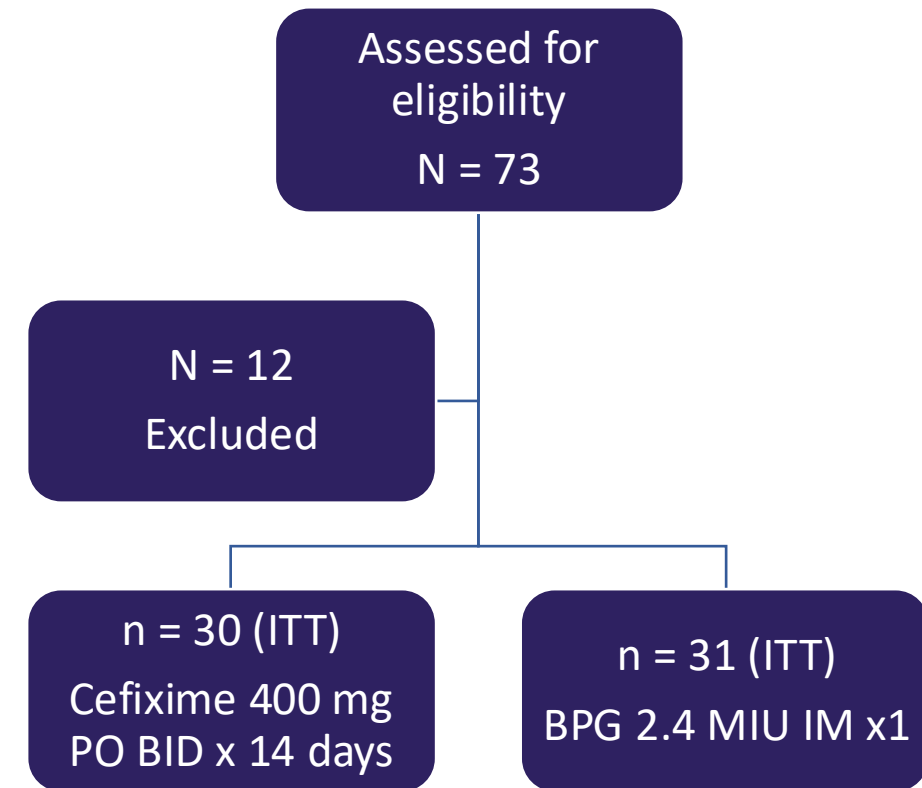
# Methods

## Objective

- To evaluate the efficacy and safety of an oral treatment, cefixime, for early syphilis

## Outcomes

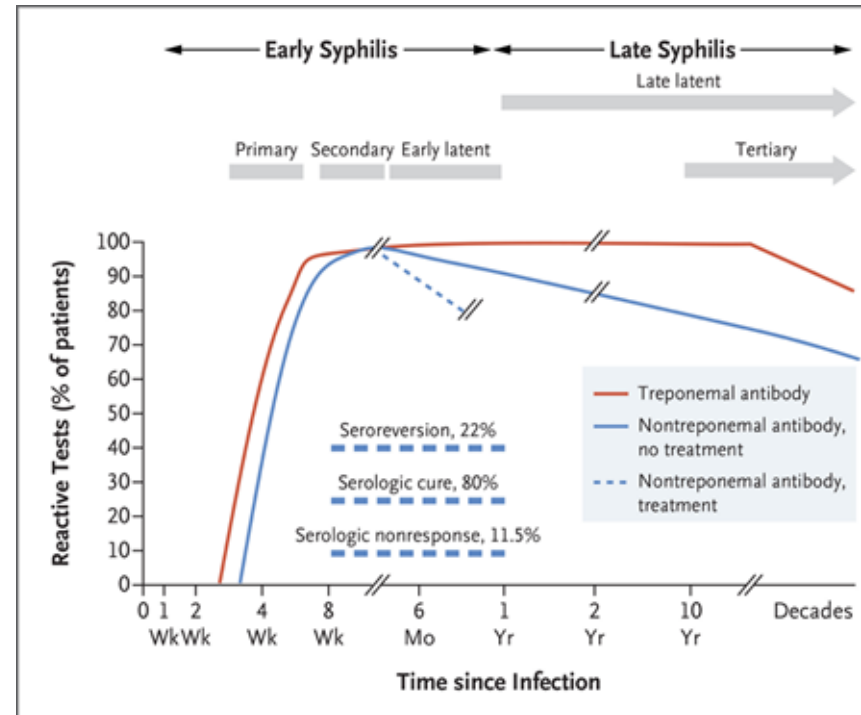
- Primary:  $\geq 4$ -fold decrease in VDRL titer from baseline 3 months after treatment
- Secondary:  $\geq 4$ -fold decrease in VDRL titer from baseline 12 ( $\pm 2$ ) months after treatment



# Poll 2

When would you expect to see a 4-fold decrease in VDRL titer?

- A. 3 months
- B. 6 months
- C. 12 months
- D. > 12 months



# Results – Demographics

Not assessed:  
 1. Renal function  
 2. BMI

**Table 1.** Demographic and clinical characteristics of the study participants

Characteristics	Cefixime 400 mg b.i.d. p.o., 14 days (n=30)	Benzathine penicillin G 2.4 MIU single dose i.m. (n=31)
Gender		
Male	28 (93.3%)	30 (96.8%)
Female	2 (6.7%)	1 (3.2%)
Age (years)		
Mean/median (range)	40.1/42 (27-60)	37.0/38 (24-57)
Sexual orientation		
Heterosexual	3 (10.0%)	6 (19.4%)
MSM	27 (90.0%)	25 (80.6%)
HIV status		
Negative	11 (36.7%)	15 (48.4%)
Positive	19 (63.3%)	16 (51.6%)
Stage of syphilis		
Primary	5 (16.7%)	2 (6.5%)
Secondary	9 (30.0%)	9 (29.0%)
Early latent	16 (53.3%)	20 (64.5%)
Coinfections <sup>a</sup>		
Gonococcal	3 (10.0%)	4 (12.9%)
Chlamydial	1 (3.3%)	6 (19.4%)
Severe adverse event		
No	30 (100.0%)	31 (100.0%)
VDRL titre at baseline		
Median (range)	1:32 (1:8-1:512)	1:32 (1:8-1:256)

b.i.d., two doses per day; p.o., per os; MIU, million units; i.m., intramuscular; MSM, men who have sex with men.

<sup>a</sup>Patients with concomitantly diagnosed gonococcal or chlamydial infection received a single dose of 1 g of azithromycin p.o.

# Results – Outcomes

**Table 2.** Comparison of cefixime 400 mg b.i.d. p.o. for 14 days and benzathine penicillin G 2.4 MIU single-dose i.m. for the treatment of early syphilis

Treatment results	Cefixime	95%CI	Benzathine penicillin G	95%CI	P
Per protocol analysis					
4-fold VDRL titre decrease at 3 months	22/28 (78.6%)	0.59–0.92	27/30 (90.0%)	0.73–0.98	0.29
4-fold VDRL titre decrease at 12 months	28/28 (100.0%)	0.88–1.00	30/30 (100.0%)	0.88–1.00	
Intention to treat analysis					
4-fold VDRL titre decrease at 3 months	22/30 (73.3%)	0.54–0.88	27/31 (87.1%)	0.70–0.96	0.21
4-fold VDRL titre decrease at 12 months	28/30 (86.7%)	0.87–0.99	30/31 (96.8%)	0.83–1.00	0.61

b.i.d., two doses per day, p.o., per os; MIU, million units; i.m., intramuscular; CI, confidence interval; VDRL, Venereal Disease Research Laboratory test.

# Results – Safety

Safety results	Cefixime (n= 30)	95%CI	Benzathine penicillin G (n= 31)	95%CI	P
Serious adverse event	0 (0.0%)	0.00–0.12	0 (0.0%)	0.00–0.11	0.42
Any adverse event	4 (13.3%)	0.04–0.31	2 (6.5%)	0.01–0.21	
Abdominal pain	2 (6.7%)		0 (0.0%)		
Mild diarrhoea	1 (3.3%)		1 (3.2%)		
Headache	1 (3.3%)		0 (0.0%)		
Prolonged injection site pain	0 (0.0%)		1 (3.2%)		

# Author's Conclusion

Cefixime is an effective and safe alternative treatment option for early syphilis

# Poll 3

Based on this study, would you prescribe cefixime?

- A. Yes!
- B. No
- C. Unsure, more data is needed
- D. What even is cefixime?

# Discussion

# Limitations

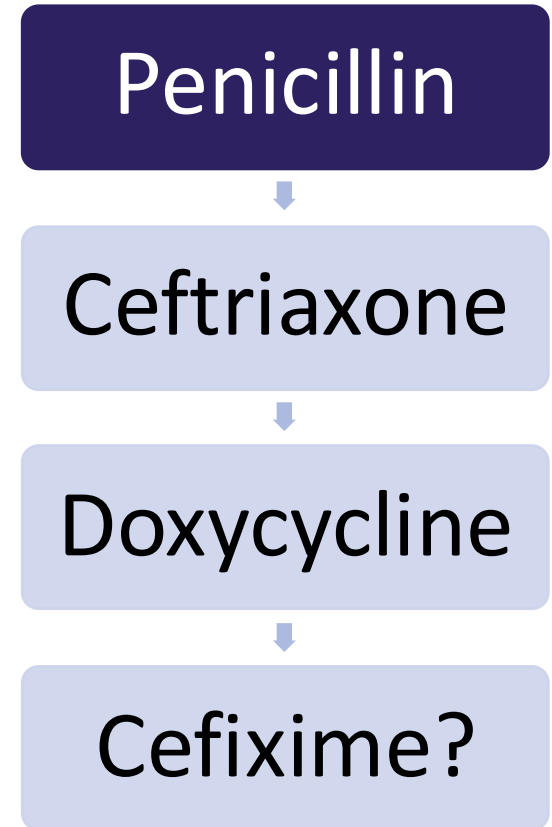
- Underpowered due to lower than anticipated enrollment
- Pregnant people excluded from study
- Duration of therapy – 10 vs. 14 day course
- Azithromycin 1 g for gonococcal or chlamydial coinfections
- Pharmacokinetic parameters
  - Renal dose adjustments (renal function not assessed)
  - BMI not assessed
  - Capsule formulation has reduced drug exposure when taken with food (tablets used in this study)

# Future Directions

- Two large randomized trials in process show 6-month preliminary results of treatment success:
  - Cefixime 89.5%
  - Benzathine Penicillin 96%
  - Doxycycline 100%
- Other oral options?

# Take Home Points

- Penicillin remains first line therapy
- Ceftriaxone and doxycycline remain preferred alternative options
- Cefixime *MAY* be an effective alternative treatment option for early syphilis – pending further data



# Additional Takeaways

- Nursing:
  - Collect accurate history (i.e. allergies, pregnancy, etc.)
- Pharmacy:
  - Ensure correct dosing, frequency, and duration
- Physician:
  - Risk vs. benefit between different treatment options
  - Re-check titers at 3 (HIV+), 6, and 12 months

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# Acknowledgements

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# Questions?