The Diagnosis and Therapy of Syphilis

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Fracastor Syphilis or the French Disease. A Poem in Latin Hexameters

By Girolamo Fracastoro. With a translation, notes, and appendix. By Heneage Wynne-Finch, M.A., and an introduction by James Johnston Abraham, C.B.E., D.S.O., M.A. Cloth. Price, 10/6. Pp. 253, with 10 illustrations. London: William Heinemann, Ltd., 1935.

J Am Med Assoc. 1935;104(25):2292.

"Syphilis sive morbus Gallicus"

--Italian physician Girolamo Fracastoro in 1530

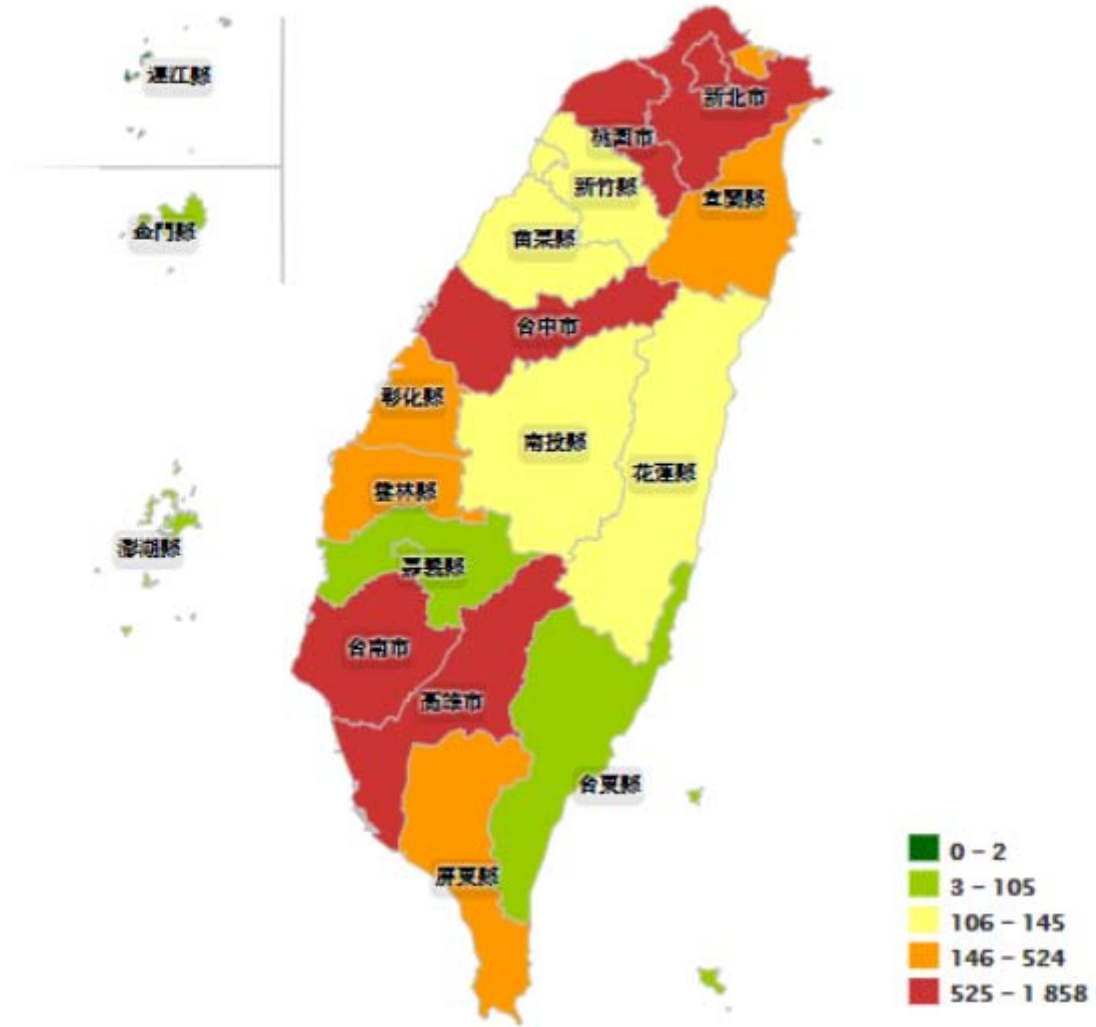
Origins and Outbreak

- Syphilis was a New World disease brought back by Columbus
- French troops besieging Naples in 1494
  - outbreak in European
  - over ten billions death in European
- Spread to China in 16th century

Spirochaetales

- *Leptospira*
- *Borrelia*
  - *Borrelia burgdorferi*
  - *Borrelia recurrentis*
- *Treponema*
  - *Treponema carateum*
  - *Treponema pertenue*
  - *Treponema pallidum*

全國梅毒本土病例及境外移入病例地理分佈(2017年01週-2017年48週)



縣市別	病例數
台北市	1294
台中市	1026
台南市	600
高雄市	1011
基隆市	172
新竹市	119
嘉義市	51
新北市	1858
桃園市	1003
新竹縣	123
宜蘭縣	189
苗栗縣	108
彰化縣	295
南投縣	127
雲林縣	149
嘉義縣	104
屏東縣	290
澎湖縣	43
花蓮縣	141
台東縣	84
金門縣	7
連江縣	2

Treponema pallidum

- Gram-negative bacteria
- Spiral in shape
- length that ranges from 6 to 20 um and a diameter range of 18-20 um
- Obligate internal parasite

  - mammalian host

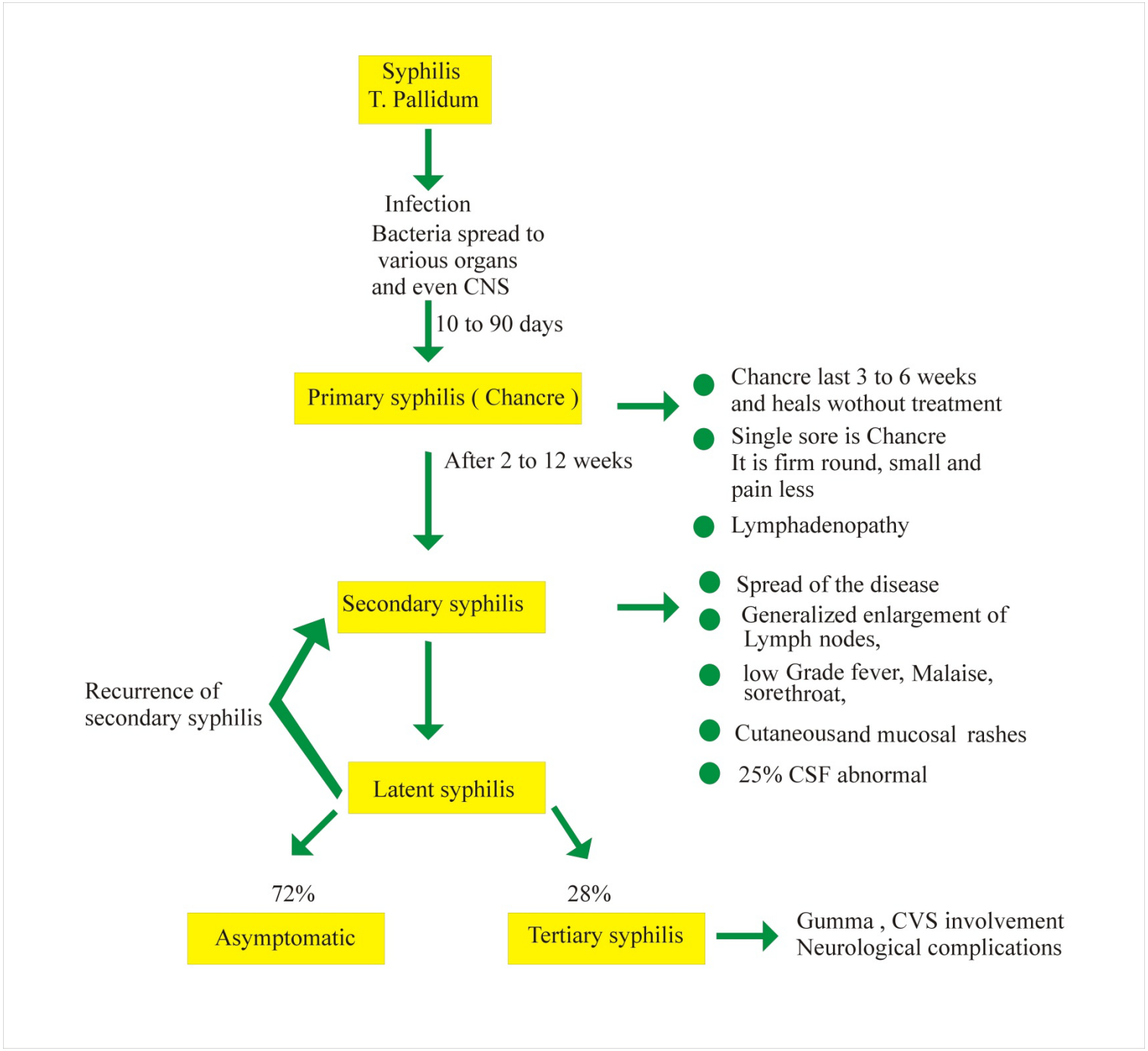
  - human beings as the only host

Pathophysiology

- Treponema pallidum penetrates intact mucous membranes or microscopic dermal abrasions and within hours enters lymphatics and blood to spread throughout the body
- It attaches to the endothelial lining of blood vessels causing inflammation-endarteritis
- Later there can be a hyper-sensitivity response o the organism resulting in gummatous lesions and necrosis

Signs and Symptoms

- Primary syphilis
- Second syphilis
- Tertiary syphilis
- Latent syphilis
- Neurosyphilis


Syphilis
T. Pallidum
Infection
Bacteria spread to various organs and even CNS
10 to 90 days
Primary syphilis (Chancre)
Chancre last 3 to 6 weeks and heals wothout treatment
Single sore is Chancre It is firm round, small and pain less
Lymphadenopathy
After 2 to 12 weeks
Secondary syphilis
Spread of the disease
Generalized enlargement of Lymph nodes,
low Grade fever, Malaise, sorethroat,
Cutaneousand mucosal rashes
25% CSF abnormal
Recurrence of secondary syphilis
Latent syphilis
72%
28%
Asymptomatic
Tertiary syphilis
Gumma , CVS involvement
Neurological complications

Primary syphilis

- Approximately 10–90 days after the initial exposure (average 21 days)
- usually the genitalia, but can be anywhere on the body
- Chancre: **firm, painless skin ulceration**

  -- persist for 4 to 6 weeks and usually heals spontaneously
- Local lymph node swelling
- **Does not leave a scar**

Secondary syphilis

- Approximately 1–6 months (commonly 6 to 8 weeks) after the primary infection
- Systemic manifestations:

  -- malaise

  -- fever

  -- myalgias

  -- arthralgias

  -- lymphadenopathy

  -- rash

Secondary syphilis

- **Macular** lesions symmetrically distributed over the body
- May involve the **palms, soles,** and **oral mucosae**
- Atypical appearances include papular or even pustular lesions
- **Condyloma Lata**
  - painless, highly infectious gray-white lesions
  - in warm, moist sites
- **Alopecia**
  - patchy hair loss of the scalp and facial hair
  - "moth-eaten" appearance

Secondary syphilis

- Rare manifestations
  - acute meningitis
  - hepatitis
  - renal disease
  - hypertrophic gastritis, patchy proctitis, ulcerative colitis, rectosigmoid mass
  - arthritis, periostitis
  - optic neuritis, interstitial keratitis, iritis, uveitis.

Tertiary syphilis

- **Over months to years**
- **Slow inflammatory damage to tissues including nerves and blood vessels**
- **Gummatous syphilis**

  - granulomatous lesions

  - skin, bones, and liver, but may affect any organ

  - noninfectious

Tertiary syphilis

- Cardiovascular complications

  - Syphilitic aortitis, aortic aneurysm, aneurysm of sinus of Valsalva, and aortic regurgitation

- Neurological complication

  - **General paresis of the insane**

    -personality changes, changes in emotional affect, hyperactive reflexes, and Argyll-Robertson pupil

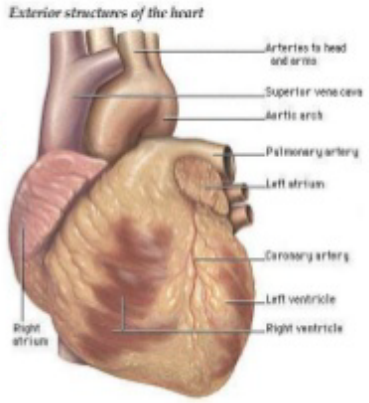
  - Tabes dorsalis

- Gamma

Cardiovascular Syphilis

CARDIOVASCULAR SYPHILIS

- Syphilitic aortitis
- Immune response
- Aortitis ⟹ dilation ⟹ valve incompetence ⟹ aneurysm



Neurosyphilis

- Occur at any stage of syphilis
- 25-35% of patients with syphilis before the advent of antibiotics
- Syphilitic meningitis

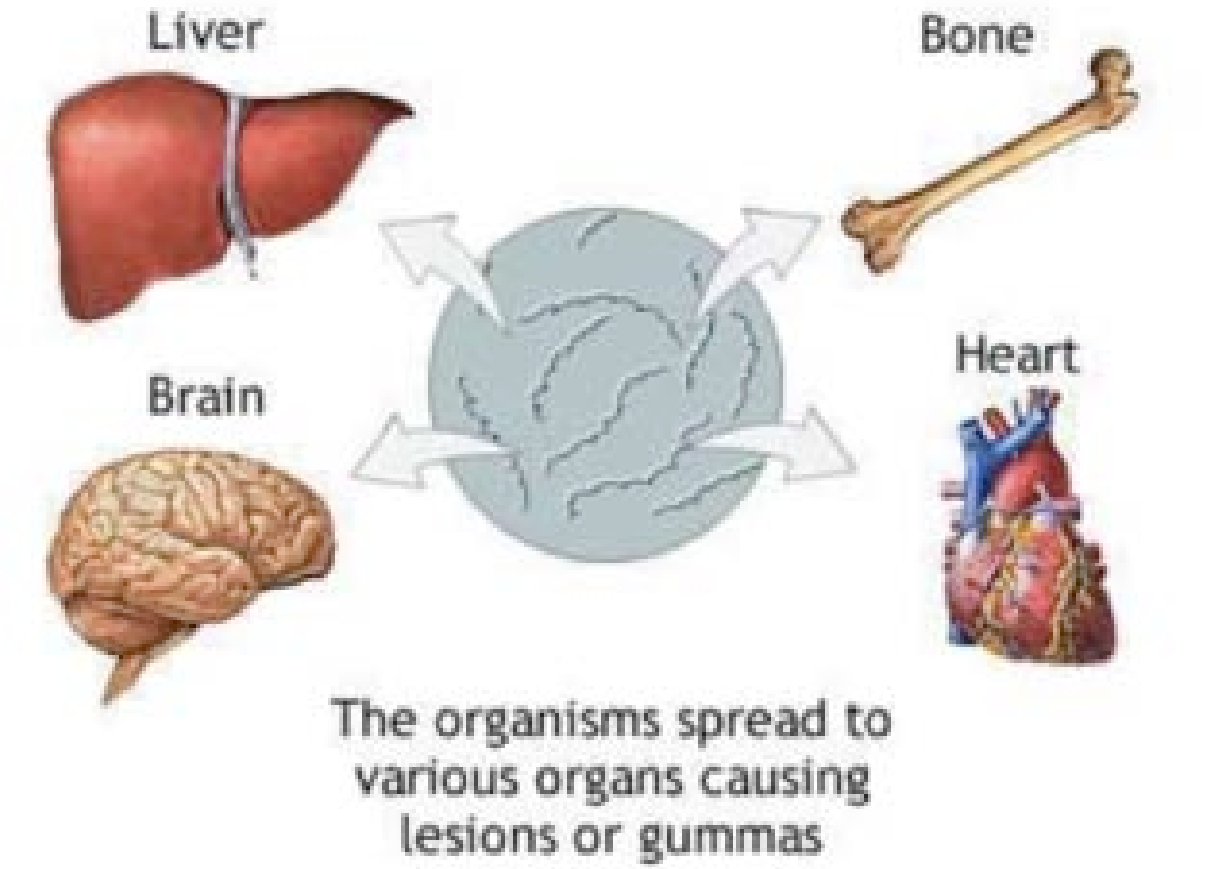
  -headache, meningeal irritation, and cranial nerve abnormalities
- Meningovascular syphilis

  - unilateral numbness, paresthesias, extremity weakness, headache, vertigo, insomnia, and psychiatric abnormalities such as personality changes.
- General paresis of the insane

Neurosyphilis

- Category 1 - Neuropsychiatric (most common manifestations [19]) disorders (psychosis, delirium, and dementia)
- Category 2 - Cerebrovascular accident (acute, focal neurological deficit compatible with a cerebrovascular accident or radiological evidence of stroke)
- Category 3 - Ocular (presentation with uveitis, visual loss, or optic nerve dysfunction)
- Category 4 - Myelopathy (acute, subacute, or chronic dysfunction of the spinal cord, including tabes dorsalis)
- Category 5 - Seizure (presentation with partial seizures, with or without secondary generalization, or myoclonus)
- Category 6 - Brain stem/cranial nerves (signs restricted to the brain stem and cranial nerves)

Gumma


Liver
Bone
Brain
Heart
The organisms spread to various organs causing lesions or gummas
© ADAM, Inc.

Latent syphilis

- Serologic proof of infection without signs or symptoms of disease
- Early latent syphilis

  - syphilis infection within the year
- Late latent syphilis

  - 50%will progress into late stage syphilis
  - 25% will stay in the latent stage
  - 25% will make a full recovery

Diagnosis

- Direct detection of *T. pallidum*
- Nontreponemal Tests
- Treponemal Tests
- Molecular biology-based methods

Direct detection of *T. pallidum*

- Animal inoculation test (since 1907)

  - The oldest method

- Dark-field test (1909)

  - moist lesions containing large number of treponemes

  - primary, secondary, infectious relapsing , early congenital syphilis

- Direct fluorescent-antibody test for *T. pallidum* (DFA-TP)

- Direct fluoresent-antibody tissue test for *T. pallidum* (DFAT-TP)

Nontreponemal Tests

- Wassermann test (1906)
- Venereal Disease Research Laboratory (VDRL) test

  - active antigenic component form beef heart

  - cardiolipin-cholesterol-lecithin antigen
- Rapid Plasma Reagin (RPR) test
- USR
- TRUST

Nontreponemal Tests

- Nontreponemal test antibody titers usually correlate with disease activity
- A fourfold change in titer, equivalent to a change of two dilutions

  - considered a clinically significant difference

. Sensitivity and specificity of nontreponemal tests

Test	% Sensitivity at given stage of infection				% Specificity (nonsyphilis)
	Primary	Secondary	Latent	Late	
VDRL	78 (74–87)[a]	100	95 (88–100)	71 (37–94)	98 (96–99)
RPR	86 (77–100)	100	98 (95–100)	73	98 (93–99)
USR	80 (72–88)	100	95 (88–100)		99
RST[b]	82 (77–86)	100	95 (88–100)		97
TRUST	85 (77–86)	100	98 (95–100)		99 (98–99)

[a] Range of sensitivity or specificity in CDC studies.
[b] RST, reagin screen test.

-- Clinical microbiology, Jan.1995, 1-21

Treponemal Test

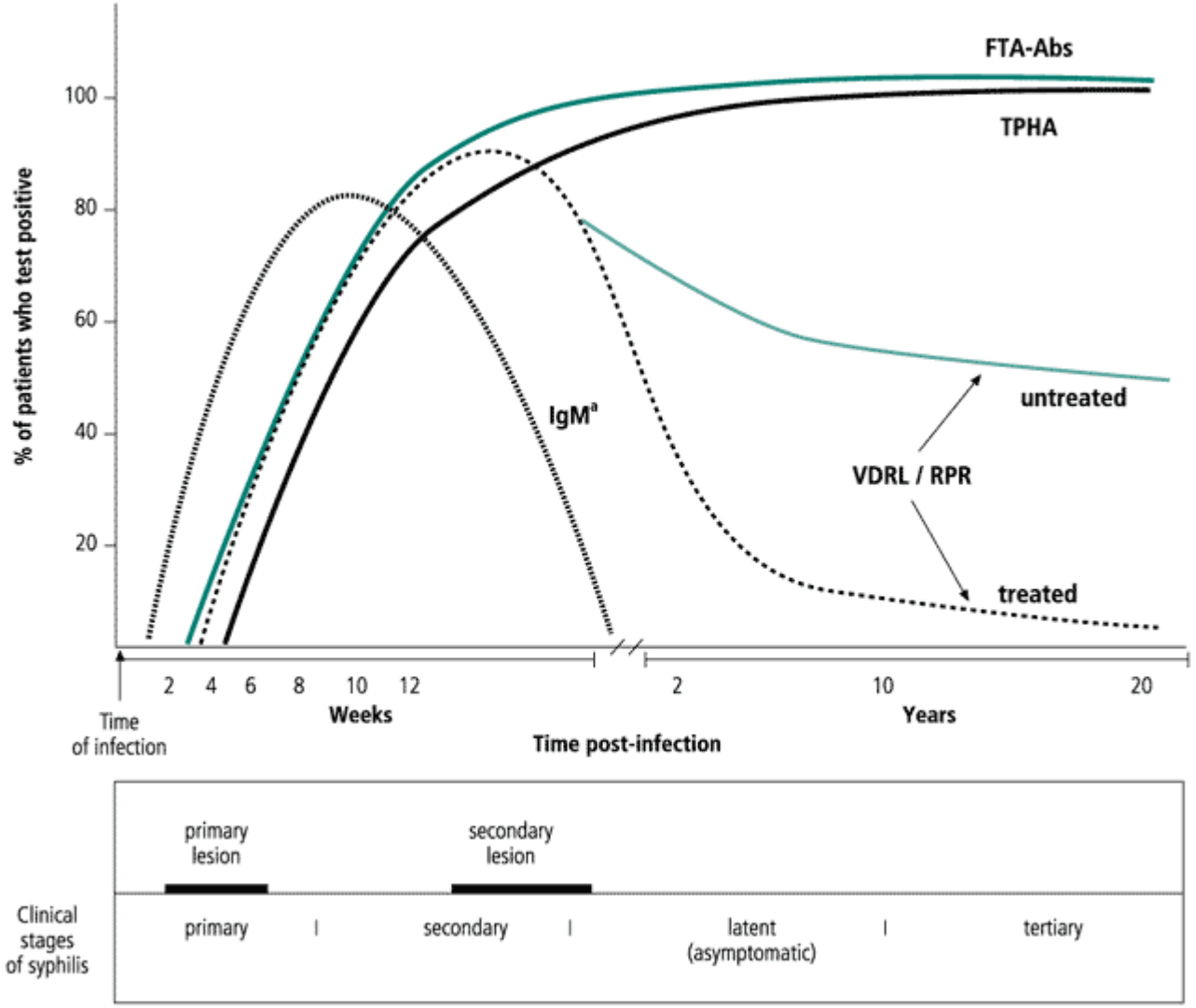
- *T. pallidum* immobilization (TPI) test
- Fluorescent treponemal antibody (FTA) test
- Microhemaggutination assay for antibody to *T. pallidum* (TPHA)

-Treponemal test antibody titers do not correlate with disease activity and should not be used to assess treatment response

Molecular biology-based methods

- DNA Probes
- PCR

Fig. 1. **Common patterns of serological reactivity in syphilis patients**



[a] IgM by ELISA or FTA-ABS 195 or immunoblot

WHO 04.69

Tests (reference)	Sensitivity (%)				Specificity (%)
	Primary	Secondary	Latent	Late	
Nontrepenomal tests					
VDRL[10]	78	100	96	71	98
RPR[10]	86	100	98	73	98
Treponemal tests					
TPHA[11]	86	100	100	99	96
FTA-ABS[10]	84	100	100	96	97
ELISA based assays					
IgG ELISA[12]	100	100	100	—	100
IgM ELISA[13]	93	85	64	—	—
Chemiluminescence assay					
CLIA[14]	98	100	100	100	99

STS: Serological test for syphilis, VDRL: Venereal disease research laboratory, RPR: Rapid plasma regain, TPHA: *Treponema pallidum* hemagglutination assay, FTA-ABS: Fluorescent treponemal antibody-absorption, ELISA: Enzyme-linked immunosorbent assay, CLIA: Chemiluminescence immunoassay

Diagnosis for Neurosyphilis

- CSF leukocyte count
  - usually is elevated (>5 white blood cell count [WBC]/mm3
  - a sensitive measure of the effectiveness of therapy.
- VDRL-CSF is the standard serologic test for CSF
  - highly specific, but insensitive
- CSF FTA-ABS is less specific but highly sensitive
  - a negative CSF FTA-ABS test excludes neurosyphilis

Diagnosis for Neurosyphilis

Indication for lumbar puncture

- neurologic signs or symptoms
- treatment failure
- plans to administer treatment other than penicillin
- a serum reagin titer of greater than or equal to 1:32
- seropositive HIV
- other changes indicative of active syphilis (eg, gumma, aortitis)

Treatment

- *Salvarsan* in 1910 by **Paul Ehrlich**
- Penicillin, is the preferred drug for treatment of all stages of syphilis
- Primary, secondary syphilis and early latent syphilis

  - Benzathine penicillin G 2.4 million units IM in a single dose
- Late latent syphilis or latent syphilis of unknown duration and tertiary syphilis

  - Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1 week intervals
- Neurosyphilis

  - Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days

Jarisch-Herxheimer reaction

- Within the first 24 hours after treatment
- acute febrile reaction frequently accompanied by headache, myalgia, and other symptoms that usually occur
- large quantities of toxins are released into the body as bacteria (typically Spirochetal bacteria) die
- most frequently among patients who have early syphilis
- might induce early labor or cause fetal distress in pregnant women

Penicillin Allergy

- Early syphilis
  - Doxycycline (100 mg orally twice daily for 14 days) and tetracycline (500 mg four times daily for 14 days)
  - Ceftriaxone 1.0 G IV or IM qd for 8-10 days
  - Azithromycin might be effective as a single oral dose of 2 g
- Late syphilis
  - Doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), both for 28 days
- Neurosyphilis
  - ceftriaxone 2 g daily either IM or IV for 10–14 days

Follow Up

- All individuals with syphilis should be tested for other sexually transmitted infections, including HIV.
- Patients who acquire syphilis are at significant risk of reinfection, so recommending regular serological screening for syphilis and providing sexual health pro-motion are essential parts of syphilis management.

Follow Up

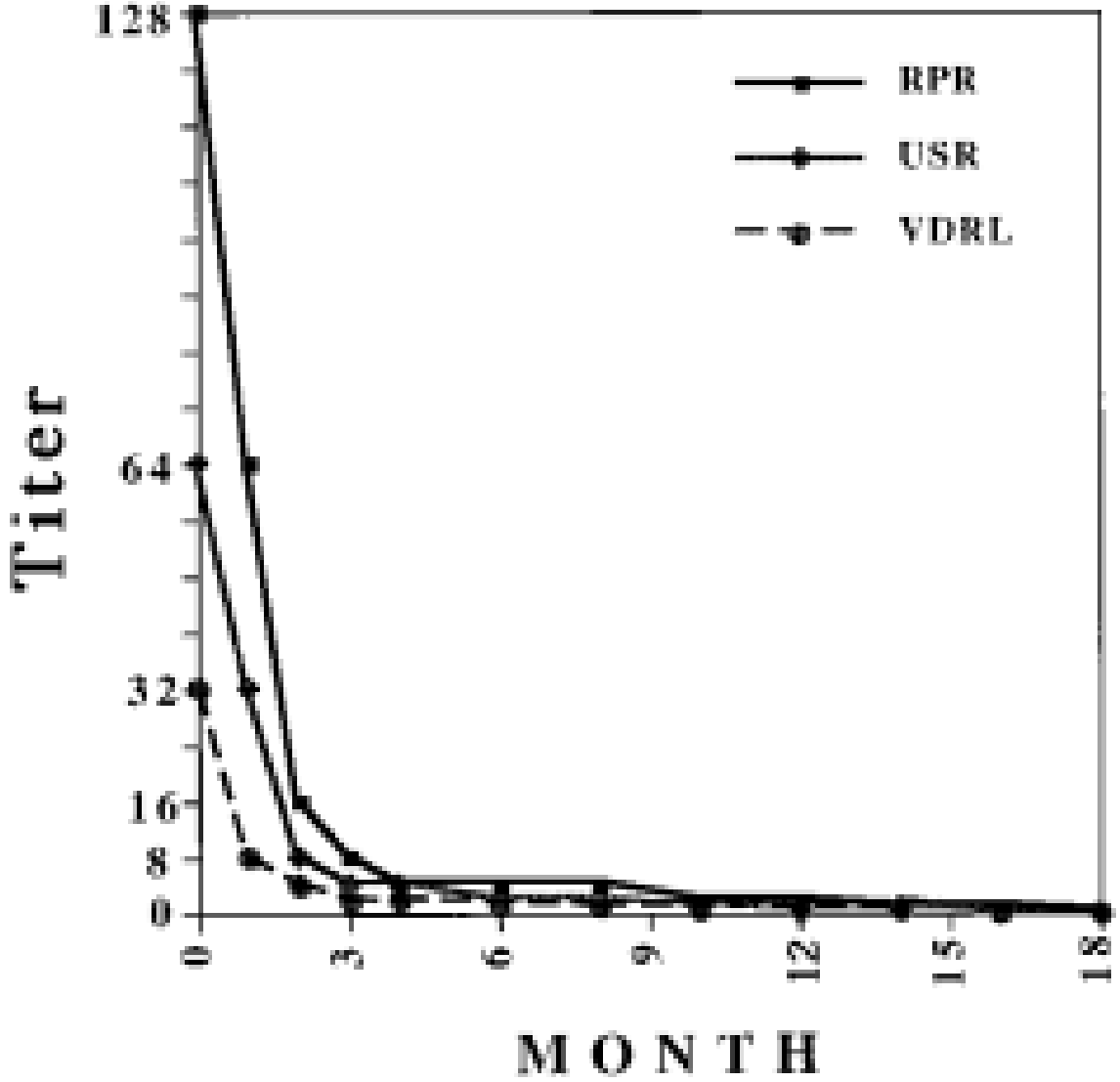
First and second syphilis

- Nontreponemal test titers - 6 months and 12 months after treatment
- Probably failed treatment or reinfection

  - persistent signs or symptoms

  - fourfold increase in nontreponemal test titer
- Probable treatment failure

  - failure of nontreponemal test titers to decline fourfold within 6 months after therapy


128
64
32
16
8
0
Titer
RPR
USR
VDRL
0
3
6
9
12
15
18
MONTH

Follow Up

Latent Syphilis

- Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months.
- Re-treated for latent syphilis

  - titers increase fourfold

  - initially high titer (>1:32) fails to decline at least fourfold within 12–24 months of therapy

  - signs or symptoms attributable to syphilis develop

Follow Up

Neurosyphilis

- CSF examination should be repeated every 6 months until the cell count is normal.
- CSF VDRL-CSF or CSF protein changes more slowly than cell counts
- Re-treatment
  - cell count has not decreased after 6 months
  - CSF is not normal after 2 years

梅毒通報

- 病例定義（Case definition）

（一）通報範圍

１、一期梅毒：符合臨床條件第（1）項及檢驗條件。
２、二期梅毒：符合臨床條件第（2）項及檢驗條件。
３、三期梅毒：符合臨床條件第（3）項及檢驗條件。
４、潛伏性梅毒：無臨床症狀，但符合檢驗條件。

臨床條件

（1）出現一期梅毒臨床症狀，如無痛性潰瘍、硬性下疳等。

（2）出現二期梅毒臨床症狀，如全身性梅毒紅疹、全身性淋巴腺腫、 發燒、頭痛、倦怠、咽喉炎、肌肉關節疼痛、禿髮、扁平濕疣等。

（3）出現三期梅毒臨床症狀，如皮膚梅毒腫、心臟血管性梅毒或神經 性梅毒等 。

- 檢驗條件 具下列任一條件：
- 未曾接受梅毒治療或病史不清楚者，其血清學非特異性梅毒螺旋 體試驗（non-treponemal test）及特異性梅毒螺旋體試驗 （treponemal test）陽性。
- 臨床檢體（病灶滲出液、組織等）以暗視野顯微鏡、螢光抗體檢 驗或核酸檢驗檢測出梅毒螺旋體。
- 腦脊髓液性病研究實驗室試驗（CSF-VDRL）陽性。
- 曾經接受梅毒治療者，其血清學非特異性梅毒螺旋體試驗（nontreponemal test）1效價≧4 倍上升

The End