UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

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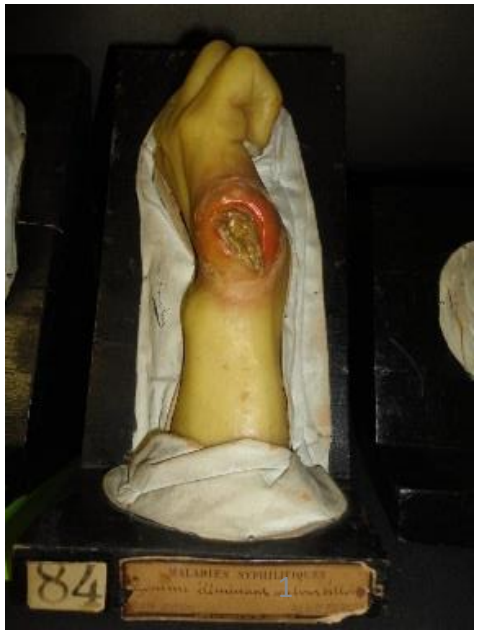
Syphilis
From clinical diagnosis to laboratory confirmation

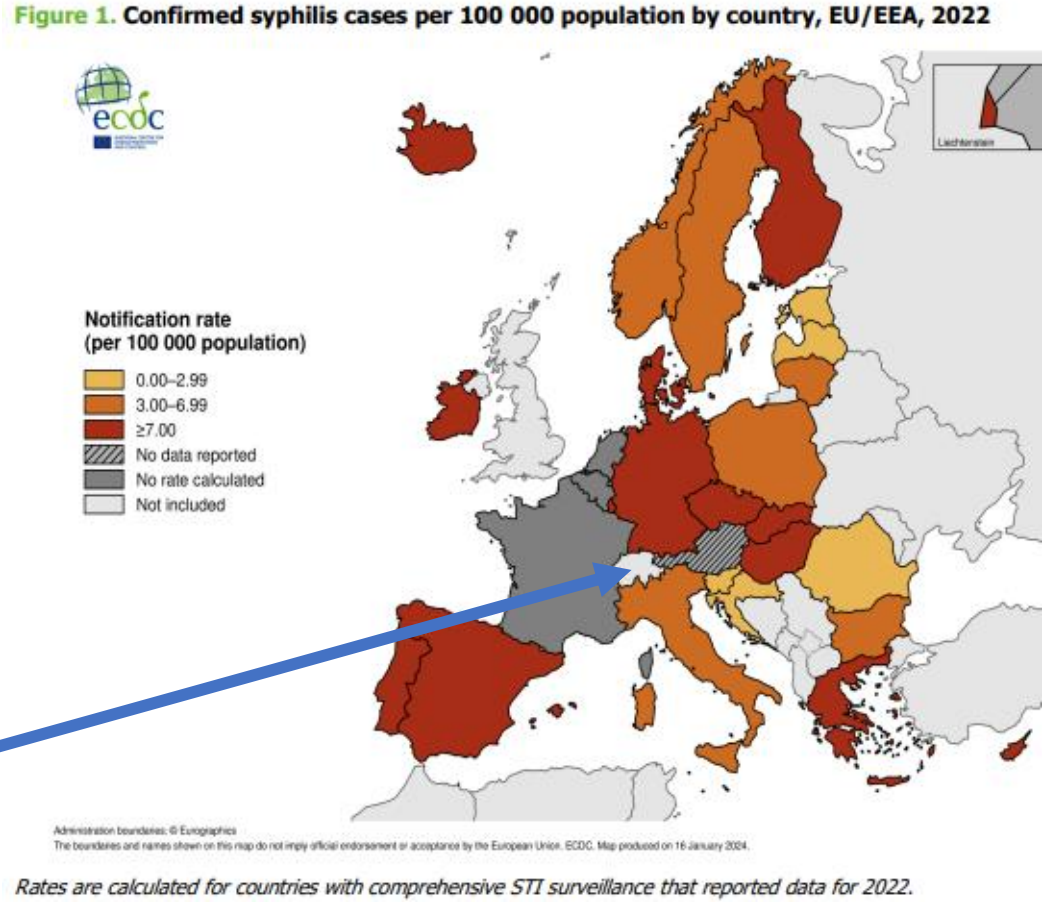
Laurence Toutous Trellu



Syphilis: Epidemiological context

- 8 Millions (2022) World WHO data
- 35 391 in 2022 (ECDC data from 29 countries in Europe: 22% increase compared to 2021. Mean incidence 8.5/100 000
- Switzerland: stable incidence 12,5/100 000 (2,7% increase)

Incidence close to the one from Germany and Denmark



Laboratory and syphilis:Historical development

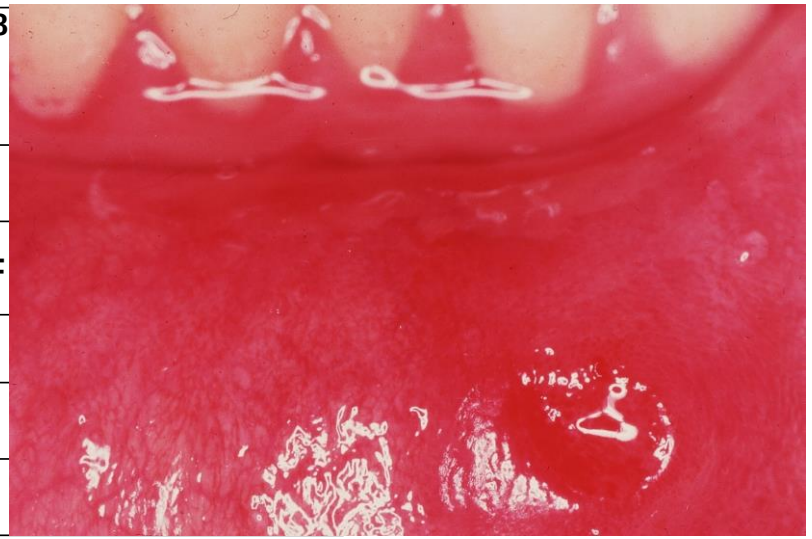
- 1905: spirochete on dark field microscope by Schaudinn
- 1906 Invention of the BWR : Wassermann, Neisser and Bruck ,complement fixation method and immune hemolysis (antigen of luetic organs and blood extracts and antibodies in the blood of patients afflicted with syphilis
- 1945-50: TPHA, VDRL
- 1998: whole genome sequencing by Fraser et al Science
- 2009: PCR and recombinant immunoglobulins applications in human specimen
- 2015 : PCR as a validated diagnosis tool in chancre
- 2018: in vitro cultivation by Edmonson team
- 2023: First antibiogram
- 2020ies: sequencing shows the treponema migration in Human
- Omics era…

Clinical case: primary syphilis

	Unité	Valeurs Réf./Seuil	18.02.2019 PD-USA sgv (*)
Syphilis (dépistage) Treponema anticorps-anti, Ig, EIA	index	< 1	46.2
Syphilis (dépistage) Treponema anticorps-anti, Ig, interprétation (EIA)			POSITIF
Sérologie syphilitique,RPR, qn S-RPR,qn	titre	< 1	NEGATIF
Treponema Pallidum anticorps, IgM S-Treponema Pallidum anticorps, IgM, ql	index	< 0.8	0.17 [A]
Sérologie syphilitique,TPPA,qn S-TPPA,qn	titre	< 80	640 [B]

	Unité	Valeurs	18.02.2019 18:25 frot. ulc. génital (*)	18.02.2019 18:25 frot. urétra(MST) (*)
Amplification Chlamydia trachomatis, par PCR				NEG
Amplification Neisseria gonorrhoeae, par PCR				NEG
Amplification Treponema pallidum (syphilis), par PCR			PRESENT	

	Unité	Valeurs	16.01.2019 sgv (*)	13.09.2018 sgv (*)	24.05.2018 sgv (*)
Syphilis (dépistage) Treponema anticorps-anti, Ig, EIA	index	< 1		3.59	0.09
Syphilis (dépistage) Treponema anticorps-anti, Ig, interprétation (EIA)				POSITIF	NEGATIF
Sérologie syphilitique,RPR, qn S-RPR,qn	titre	< 1	NEGATIF	NEGATIF	
Treponema Pallidum anticorps, IgM S-Treponema Pallidum anticorps, IgM, ql	index	< 0.8		2.32	
Sérologie syphilitique,TPPA,qn S-TPPA,qn	titre	< 80	1'280 [A]	1'280	



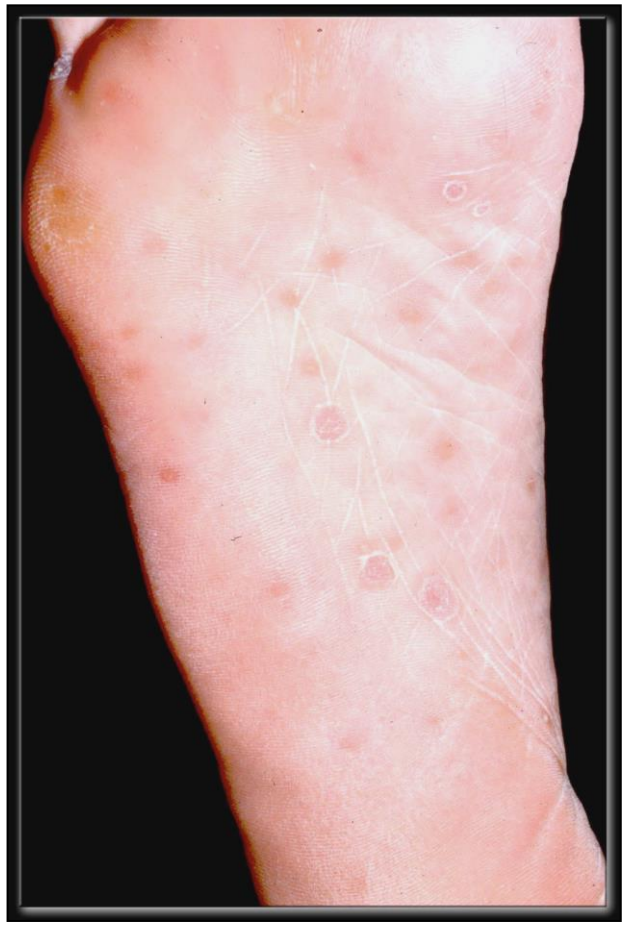
Tardocilline IM

Early treatment: antibodies may never increase or very few

Be care to the false negative non treponemal test:

Repeat the RPR or VDRL in the context of an acute secondary infection to eliminate a prozone phenomenon

Clinical diagnosis



- History + typical presentation you may initiate the treatment and serology will confirm.

Serology = follow-up

RPR or VDRL

Non treponemal test

Syphilis, the Great imitator

- You may miss
- You may forget
- You may be disturbed

History: sexual history

Testing: access/performance

PCR in secondary forms: research purpose

- Genital, anal and oral contaminations
- Positive PCR in many sites (lesions) and fluids
- Several molecular technics (nPCR, qPCR) allow new developments
- LAMP (loop mediated isothermal amplification) just tested in saliva

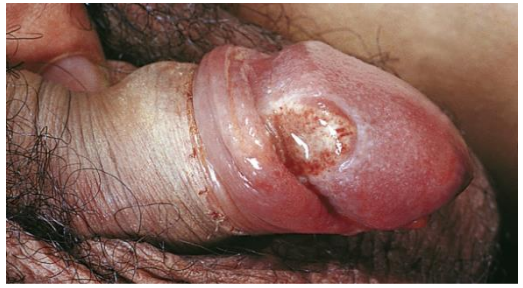
Grillova L PlosOne 2018
Imai K J Clin Microbiol 2024

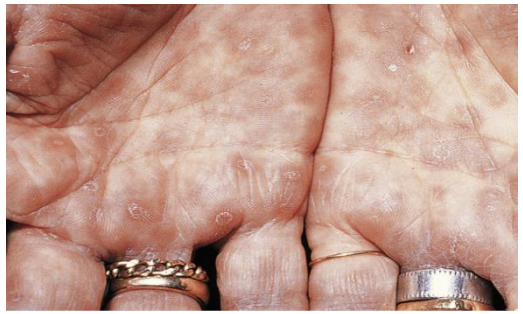
The stage and the test: diagnosis

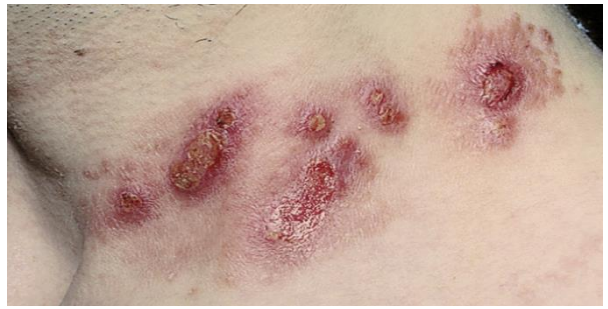
Primary syphilis

Secondary syphilis

Tertiary syphilis







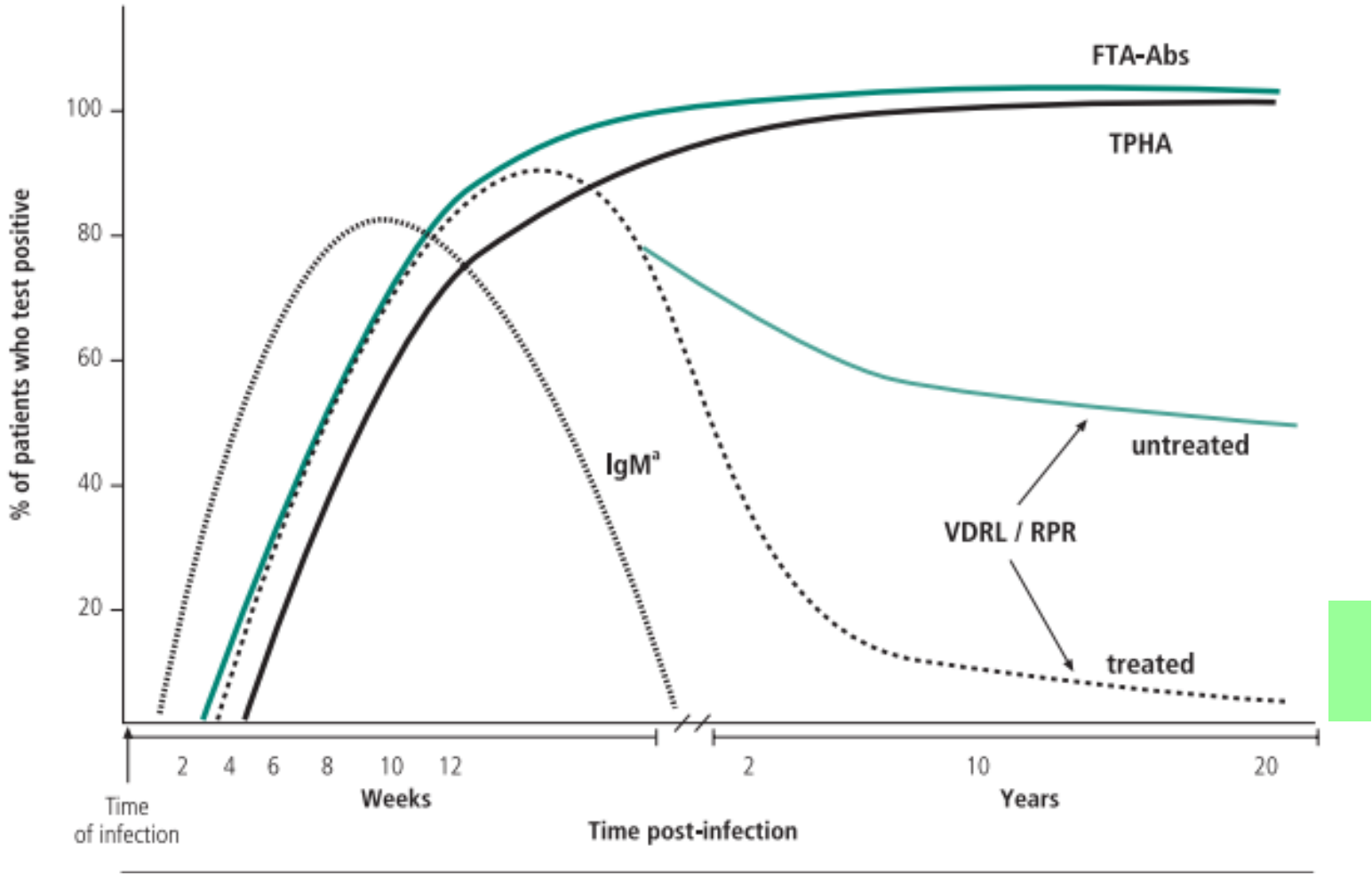
ULCERS

PCR

Serology:
ELISA Ig, IgM
RPR/VDRL
TPPA/TPHA

Antibodies-Serology and follow-up

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



1 2 2-3

Peeling R 2004 Bull WHO

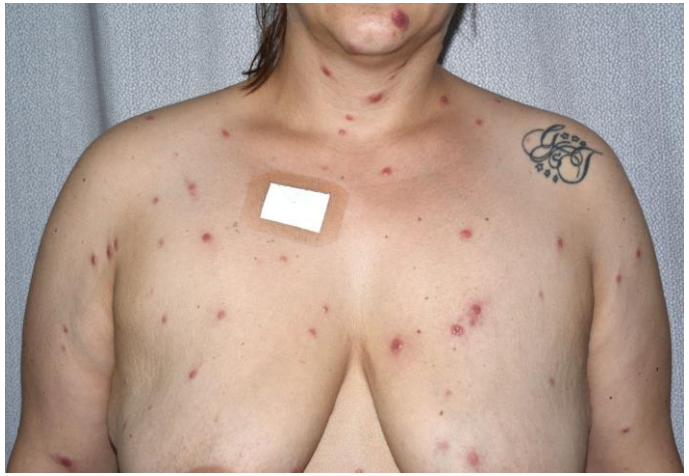
Antibodies testing

- Non treponemal: RPR ou VDRL sensitive and low specificity, follow up
- Treponemal:
  - TPPA/TPHA: Sensitivity, specificity. false positive Borrelia, Hepatitis++ Not used for the follow up
  - Specific anti Treponema pallidum immunoglobulines
    - Automatisation, used to screen
    - Modern TPPA or TPHA, may replace them
    - IgM in early syphilis may help (congenital syphilis)
    - More clinical correlations are needed in severe forms: neurosyphilis, tertiary, mother to child transmission

Yin YP Clin Inf Dis 2013
https://iusti.org/wp-content/uploads/2020/11/2020-Syphilis-guideline.pdf

Clinical case

- Persistant headache,
- Right leg dysesthesia,
- Visual troubles
- Disseminated skin nodules



Clinical case

Syphilis (dépistage)					
Treponema anticorps-anti, Ig, EIA	index	< 1.00			172.00
Treponema anticorps-anti, Ig, interprétation (EIA)					POSITIF
S-RPR,qn	titre	< 1	64 [A]		64 [A]
Lcr-RPR,qn	titre			NEGATIF	
S-TPHA,qn	titre	< 80	20480 [A][B]		81920 [A]
Lcr-TPHA,qn	titre	< 80		NEGATIF	
treponema pallidum, IgG-anti, index de synthèse intrathécale IA	index	<1.7		0.85 [C]	

- Serum and lumbar puncture

- Pleiocytosis
- Proteinorachia

- IV penicillin G treatment

Neurosyphilis diagnosis: clinical and biological challenges

Biological diagnosis of neurosyphilis based on experts consensus

a positive TPHA/TPPA in serum (TPHA/TPPA ≥80) AND neurological signs AND at least 2 positive criteria in CSF examination among:

- a number of white blood cells in > 5 cells /mm3 and / or a number of protein > 0.45 g/l
- a reactive CSF-VDRL/RPR test
- a positive CSF- TPHA/TPPA with a titer >320

Clinical diagnosis is difficult and no single test confirm it

An IgG index CSF/serum is very interesting in neurological forms

CDC/IUSTI recommendations
Alberto C et al Microbiology Spectrum 2022 & STI 2023
Zhang R L et al Nature 2024 28 Dec

Neurosyphilis: next steps

- Diagnosis criteria do not involve ophtalmic and auditive forms
- Very few data on brain lesions: dementia? Gumma?
- Latent forms

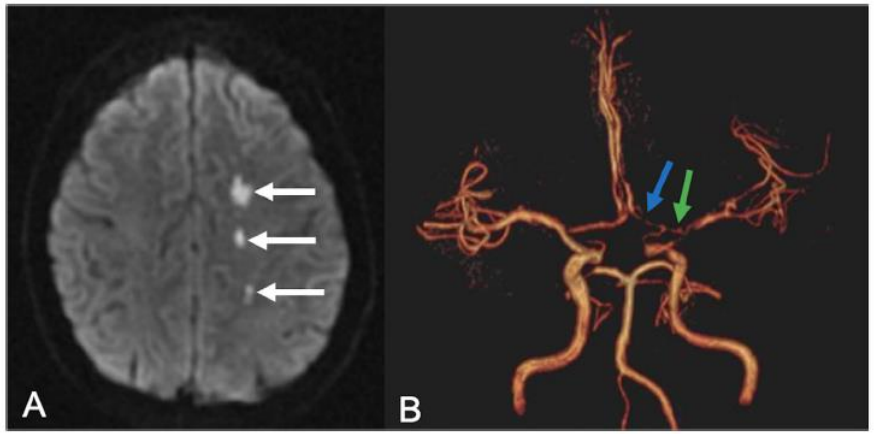


Fig. 5. Meningovascular syphilis, in a 42-year-old HIV-positive man. Brain MRI demonstrated acute infarcts in the left internal border zone, with restricted diffusion (arrows in A). 3D-time-of-flight (TOF) MRA demonstrated narrowing and irregularity in the M1 segment of the left middle cerebral artery (green arrow in B), and in the A1 segment of the left anterior cerebral artery (blue arrow in B). VDRL was positive in the CSF.

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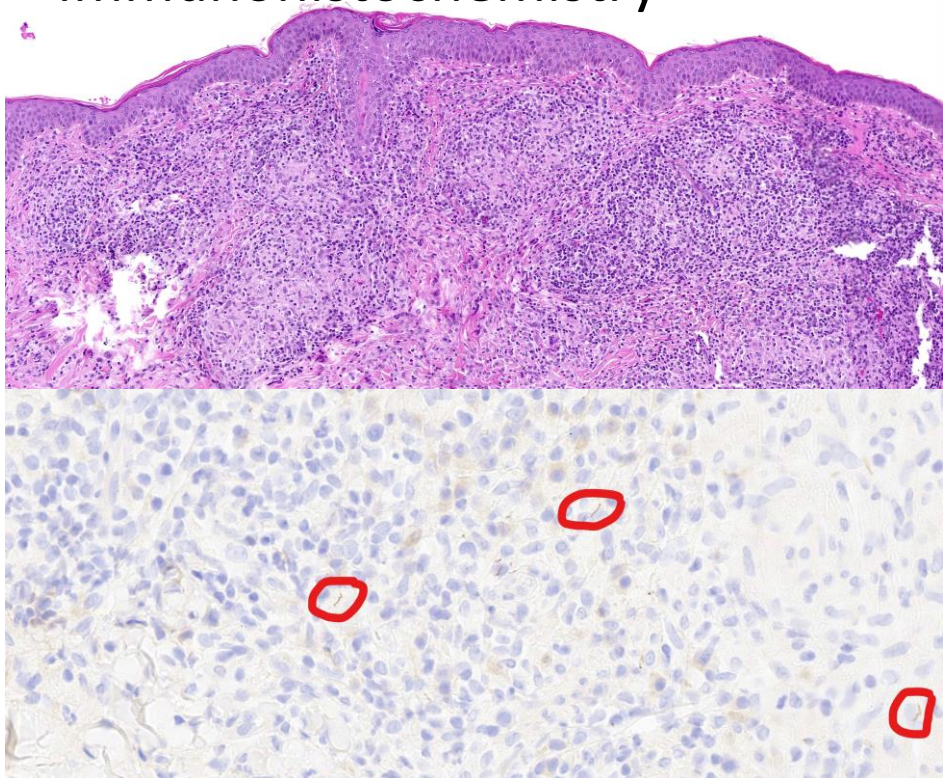
https://archimed.unige.ch/en

Correa D et al. J Neuroradiol 2023

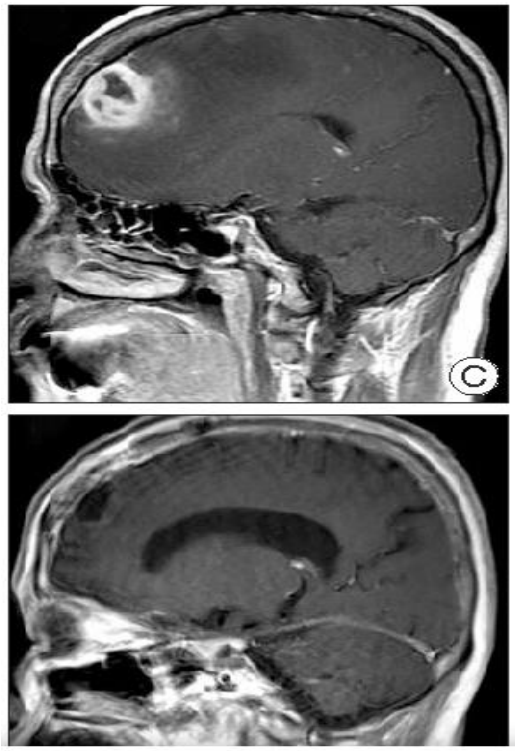
Physiopathology

Histology.
Immunohistochemistry

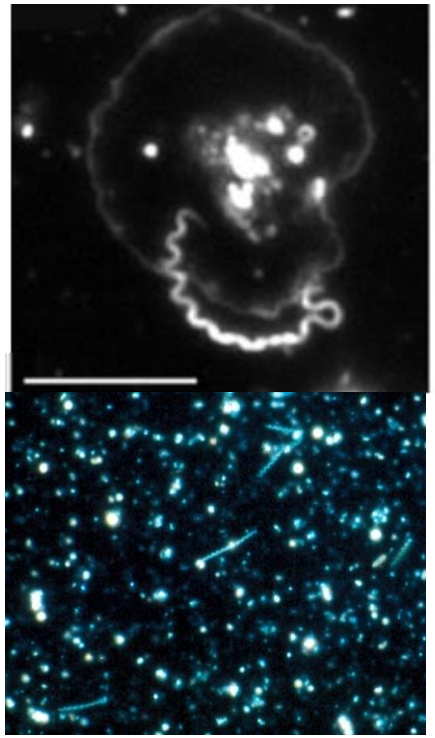


Courtesy: unit of dermatopathology, Geneva Hospital

Radiology



in vitro culture



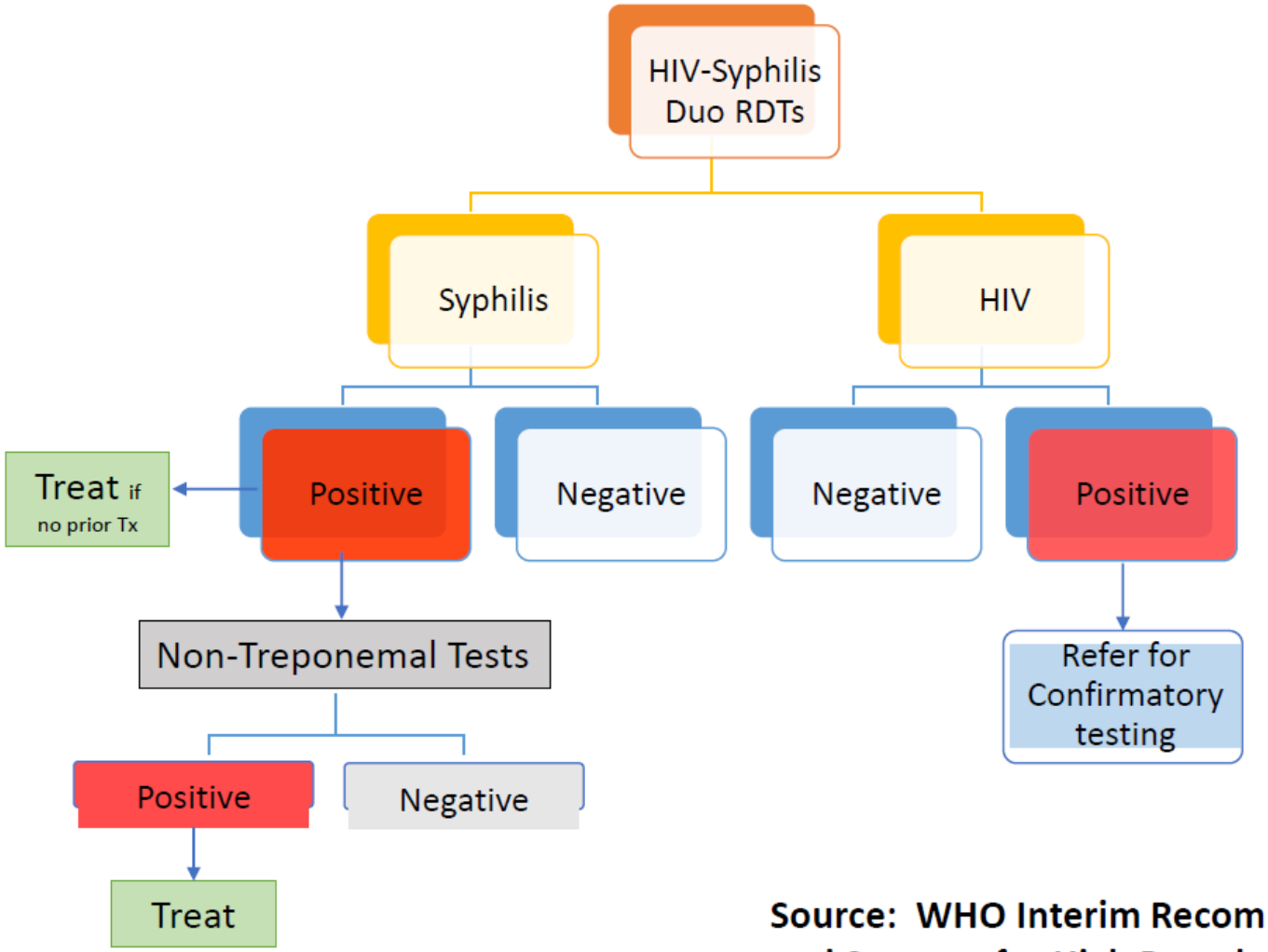
Church et al, plos one 2019
Müller et al, bjd 2011
Ekselius L et al Acta Dermatol 2024

Early screening, frequent screening: **Point of care tests (POC)**

- High developments in STIs
- Many brands delivered on the market
- Various cost: 1 test (50 CHF) 2 to 4 tests (100 CHF)
- Finger drop: whole blood

- Need to be confirm: a close and urgent contact with an healthcare professional is requested

Syphilis Testing and Treatment Algorithm for High Risk Populations



Source: WHO Interim Recommendations for Syphilis Testing and Strategy for High Prevalence Settings (>5%)

courtesy R Peeling, WHO

Conclusion: Syphilis is a modern concern

- Knowledge of typical signs and laboratory tests is mandatory (survival kit) for a good dermatologist.
- Enough practice and centers of reference are needed to understand and optimize treatment in some complexe infections
- Screen in a same time than other STIs and screen sexual partners.
- Many modern high tech biological and imaging developments are ongoing