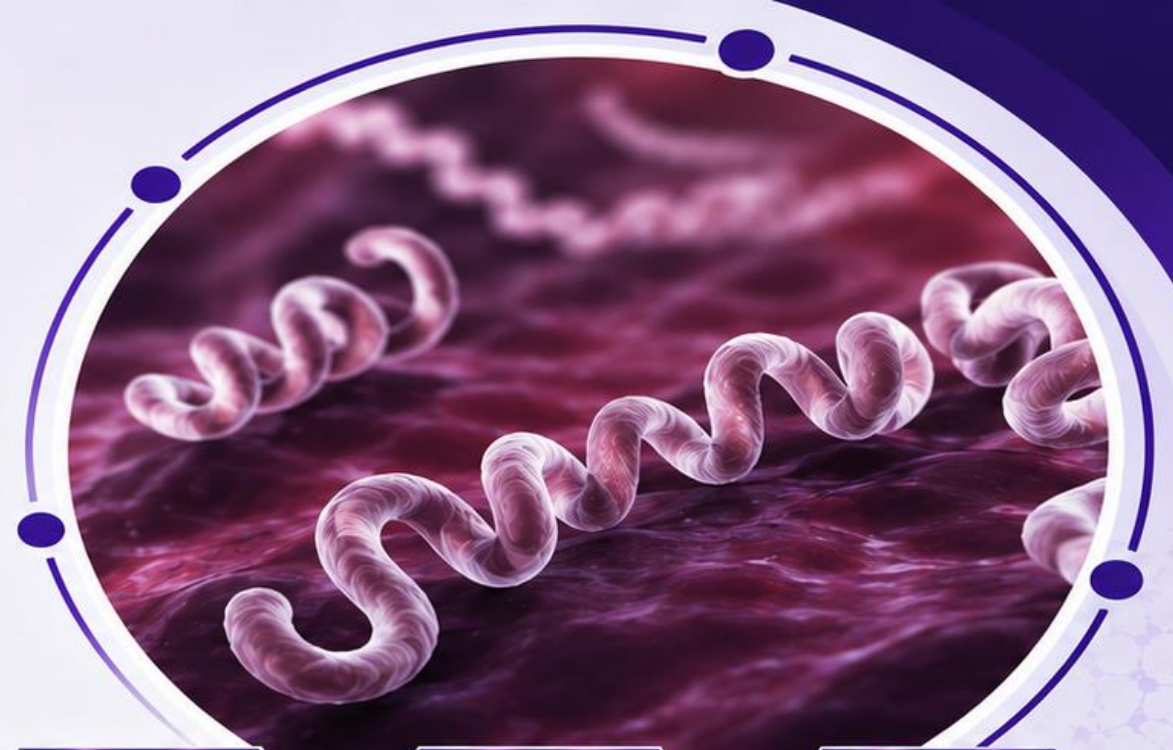


SYPHILIS



— Prof. Ahmed Bouhamidi —



Educational Objectives

- ✓  **Describe** the **epidemiology** worldwide and national of syphilis
- ✓  Explain the **pathophysiology** of *Treponema pallidum*
- ✓  **Diagnose** a primary, secondary, latent and tertiary syphilis
- ✓  Recognize the cutaneous-mucous **manifestations** of the disease
- ✓  Interpret the **serological tests** (treponemal and non-treponemal)
- ✓  Prescribe the appropriate **complementary examinations** according to the stage
- ✓  Plan the **treatment** according to the evolving stage (CDC / IUSTI 2023-2024)
- ✓  Organize clinical and serological **follow-up** post-therapeutic
- ✓  Prevent sexual transmission and organize **sexual partners screening**



Key message: Syphilis is the “**chameleon**” disease — its clinical presentation varies with the stage and the serology, and sometimes it occurs without symptoms.

COURSE OUTLINE

- | | | | | | |
|---|---|------------------------------------|----|---|----------------------------|
| 1 |  | Introduction & epidemiology | 10 |  | Direct diagnosis |
| 2 |  | Microbiology of <i>T. pallidum</i> | 11 |  | Serology & interpretation |
| 3 |  | Physiopathology | 12 |  | Differential diagnoses |
| 4 |  | Primary syphilis | 13 |  | Treatment by stage |
| 5 |  | Secondary syphilis | 14 |  | Post-therapeutic follow-up |
| 6 |  | Latent syphilis | 15 |  | Prevention & partners |
| 7 |  | Tertiary syphilis | 16 |  | Interactive clinical cases |
| 8 |  | Congenital syphilis | 17 |  | Key messages & summary |
| 9 |  | Neurosyphilis | | | |

The history of a multisystem disease



- **Late 15th century:** first epidemic described in Europe (Siege of Naples, 1495), long known as “Neapolitan disease” or “the great pox”



- **1905:** discovery of *Treponema pallidum* by Schaudinn and Hoffmann



- **1906:** introduction of the Wassermann test, first serologic test



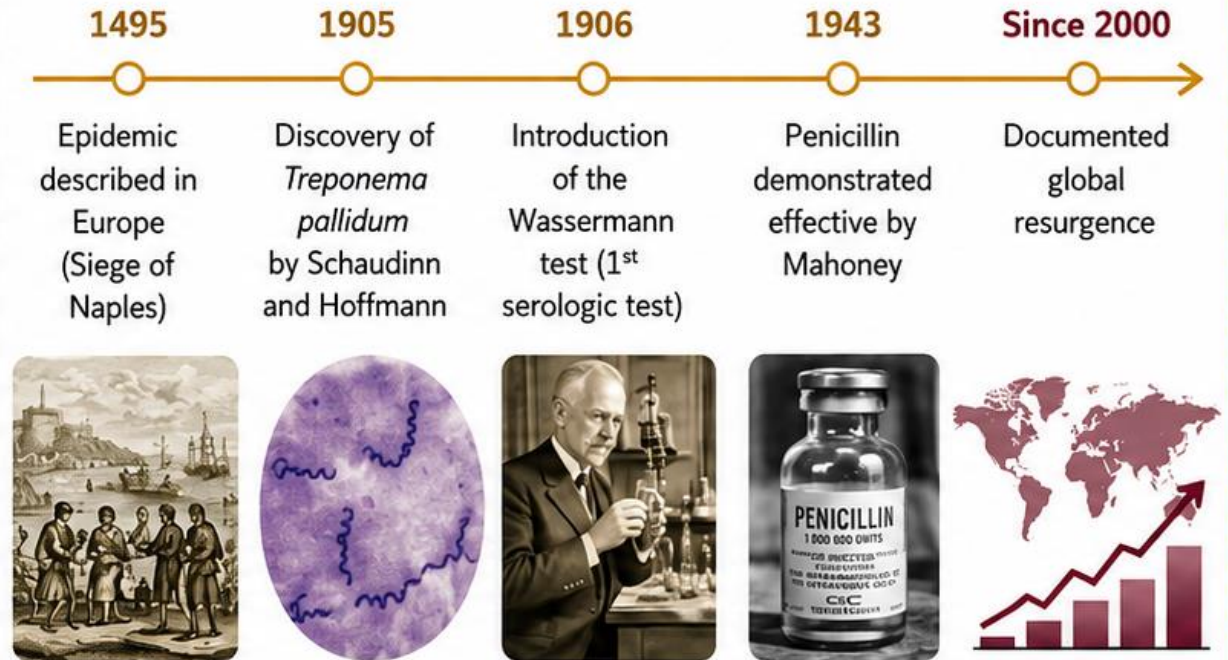
- **1943:** Mahoney demonstrates the efficacy of penicillin — therapeutic breakthrough



- **Since 2000:** documented global resurgence despite simple, effective and inexpensive treatment



Illustrated timeline



Key message: More than a century after the discovery of penicillin, syphilis remains a major public health issue — therapeutic tools alone are not enough to eradicate the disease.

Global epidemiology



- WHO (2023): around **8 million** new cases of syphilis among adults (15–49 years) each year worldwide.



- Particularly high prevalence in **sub-Saharan Africa**, **Latin America** and **Southeast Asia**.



- United States (CDC, 2023): more than **209,000** cases reported, the highest level since 1950.



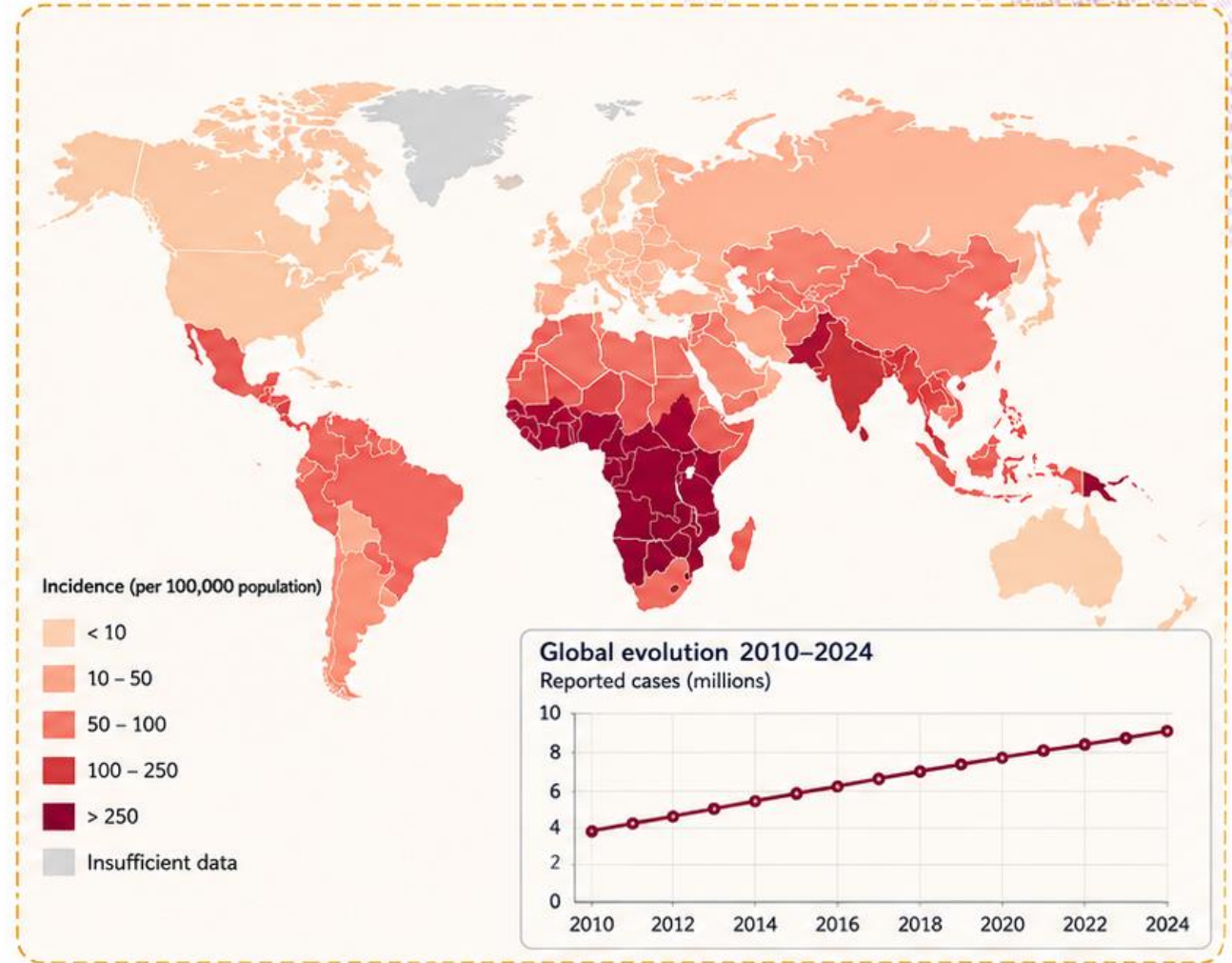
- Europe (ECDC, 2023): continuous increase since 2010, with a predominance among men who have sex with men (**MSM**).



- **Morocco and North Africa**: surveillance data in progress, linked to strengthened STI screening.



- Congenital syphilis: more than **700,000** estimated cases/year worldwide, WHO priority for maternal–fetal elimination.



Key message: Syphilis is not a disease of the past: it affects around 8 million people worldwide each year today.

Epidemic resurgence: what are the drivers?



Relaxation of condom use, particularly since the generalization of PrEP for HIV prevention



Dating apps facilitate the multiplication of sexual partners



Use of psychoactive substances ("chemsex") associated with risky practices



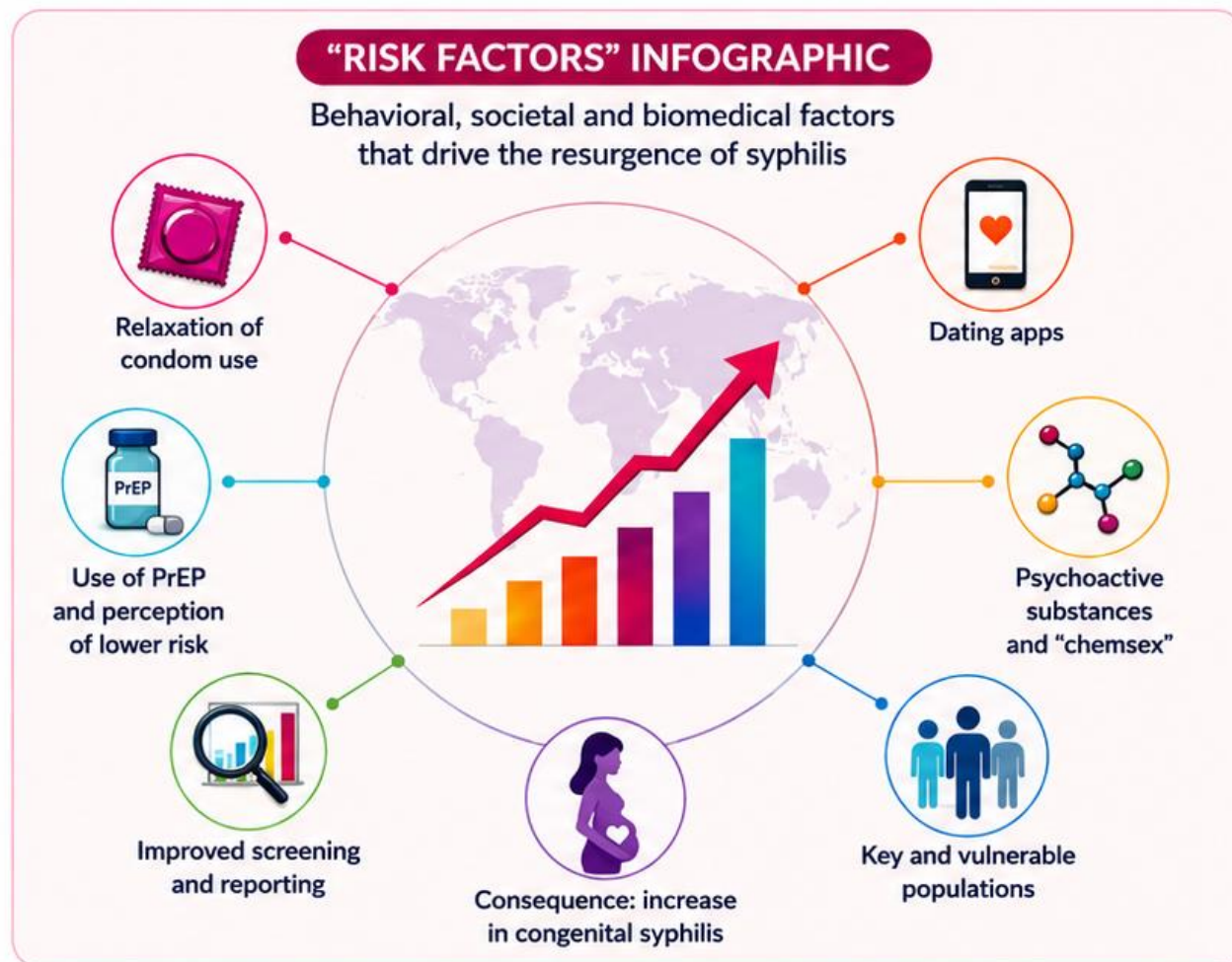
Improved screening and reporting, explaining part of the increase reported



Most affected populations: MSM, people living with HIV, sex workers, and precarious populations



Direct consequence: parallel increase of congenital syphilis in non-screened pregnant women



Key message: The resurgence of syphilis is a behavioral and societal phenomenon as much as a biological one — it calls for expanded and repeated screening.

Treponema pallidum: morphology and biology



Spirochete bacterium, helical, 6 to 15 μm long, 0.1–0.2 μm in diameter



Characteristic motility corkscrew-like, due to periplasmic flagella



Not cultivable in routine in vitro — culture only in specialized research laboratories



Too thin to be seen with Gram staining: requires dark-field microscopy or immunofluorescence



Small genome (~1.14 Mb): strict metabolic dependence on the host



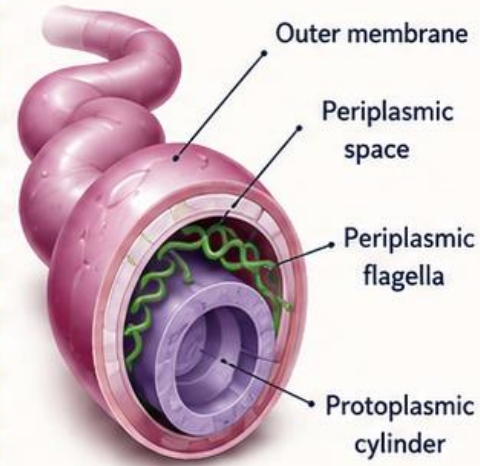
Universal and constant susceptibility to penicillin for over 80 years — no documented resistance



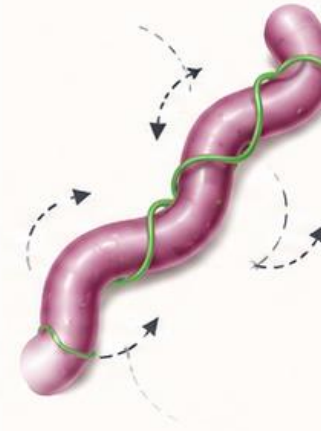
Key message: *T. pallidum* is not seen with Gram staining and cannot be cultured routinely: **direct diagnosis relies on dark-field microscopy, IF or PCR.**

ILLUSTRATIONS

Cross-section of the spirochete



Periplasmic flagella



Corkscrew-like motility

Dark-field microscopy image



Transmission and reservoir



Strictly human reservoir — no animal or environmental reservoir.



Sexual transmission: main route, through direct contact with an infectious mucocutaneous lesion (chancres, syphilides).



Mother-to-child transmission: transplacental route, at any time during pregnancy, with a major risk in recent syphilis.



Blood transmission: exceptional nowadays (transfusion, sharing of injection equipment).



Maximum contagiousness during primary and secondary syphilis (lesions rich in treponemes).

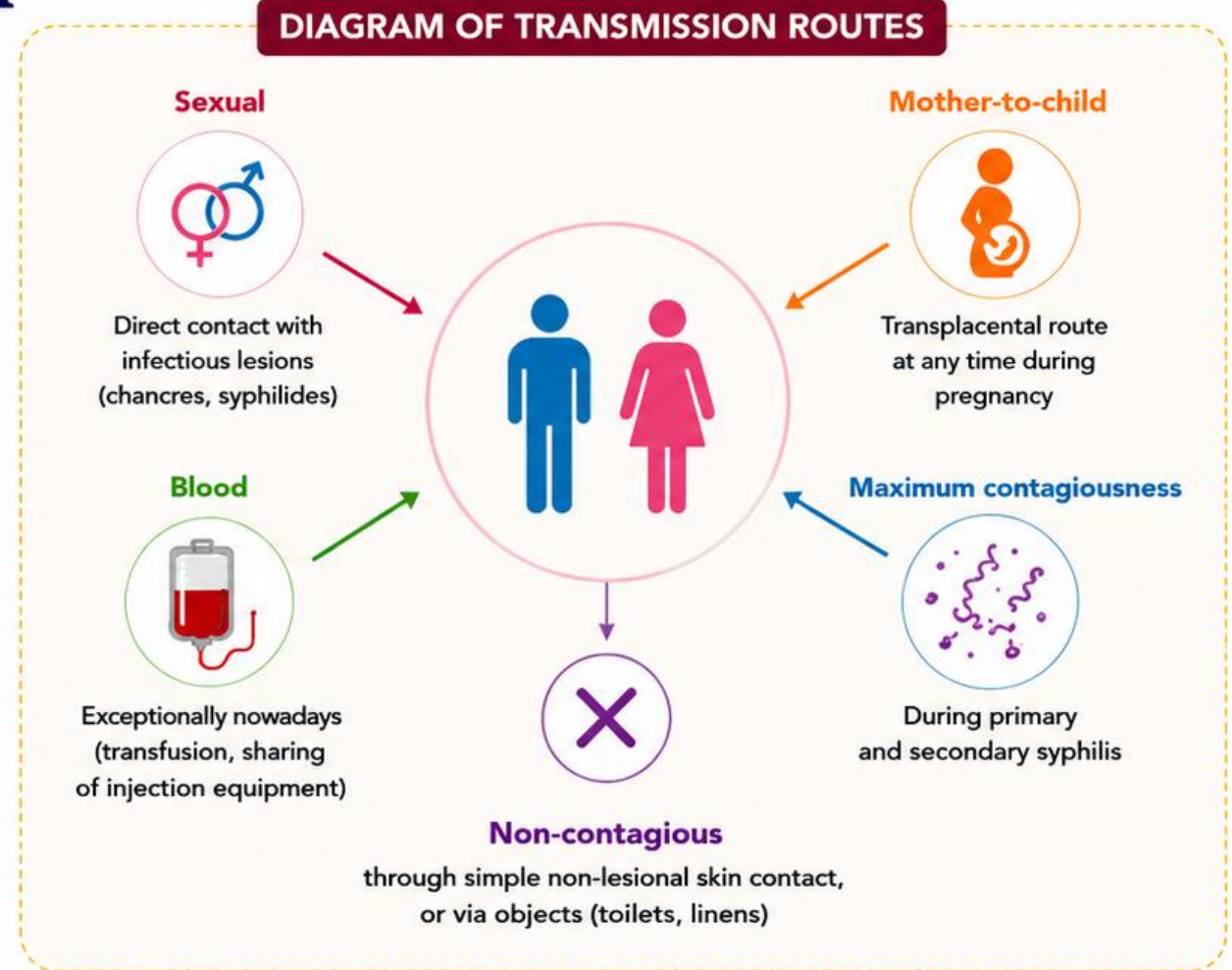


Non-contagious through simple non-lesional skin contact, or via objects (toilets, linens).

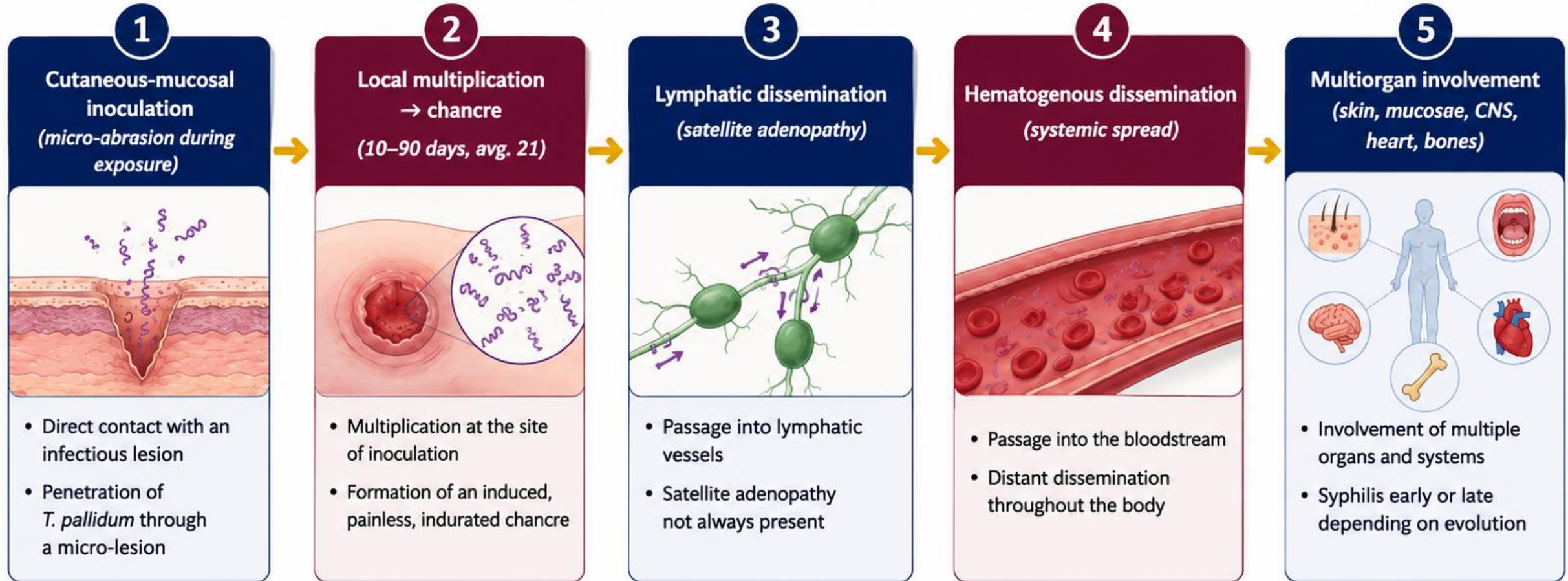


Key message: Maximum contagiousness occurs in the early stages (primary and secondary) — this is why prevention is most urgent.

DIAGRAM OF TRANSMISSION ROUTES



From the entry portal to dissemination



Key message: From the primary stage, *T. pallidum* has already entered the bloodstream — syphilis is therefore a **systemic disease**.

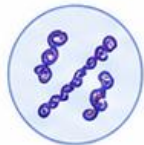
Immune response and natural evolution



Initial cell-mediated immune response (Th1), responsible for the spontaneous healing of the chancre



Antibody production: non-treponemal antibodies (e.g., anti-cardiolipin) and specific treponemal antibodies



Acquired immunity does not sterilize the infection — persistence of quiescent treponemes is possible in tissues



Without treatment, the classic evolution occurs in 3 phases:

Primary



Secondary



Latent

with about one-third of patients progressing to **tertiary syphilis** after several years



Latency corresponds to a serologically active infection that is clinically silent



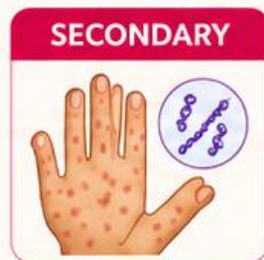
Key message: Without treatment, about one-third of patients will progress to potentially **fatal tertiary syphilis** after several years of clinical silence.

CHRONOLOGICAL TIMELINE OF UNTREATED NATURAL HISTORY



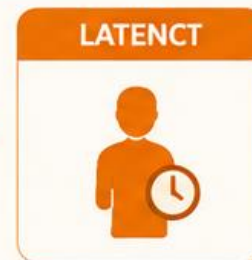
10

Indurated chancre
10–90 days
(median 21 days)



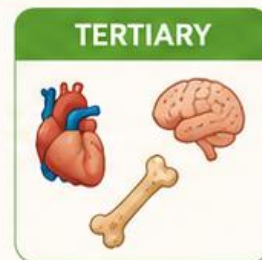
45–160

Eruptions, adenopathies,
mucous patches,
flat condylomata



> 160

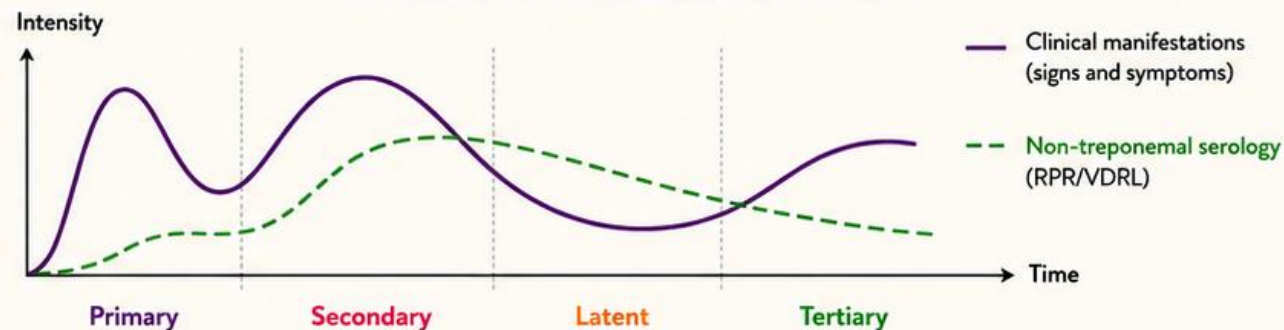
Serologically active
infection, asymptomatic
Duration: years



Years

Cardiovascular, neuro-
syphilis, gummatous
and osseous involvement

CLINICAL AND SEROLOGICAL EVOLUTION



The Syphilitic Chancre



Incubation: 10 to 90 days, with an average of 21 days after exposure.



Typical chancre: a single, painless ulcer with regular borders, a clean base, and firm induration (“cartilaginous” consistency).



Indurated base on palpation — a major clinical diagnostic clue.



Location: genital (glans, balanopreputial sulcus, labia majora/minora, cervix), but also anal or oral depending on sexual practices.



Unilateral regional lymphadenopathy: firm, mobile, painless, non-inflammatory (“syphilitic adenopathy”).

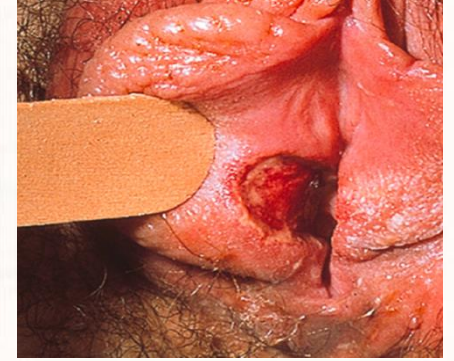


Spontaneous healing within 3–6 weeks, even without treatment — this **does not** mean that the infection **has been cured**.



Key message: Any painless, indurated genital ulcer should prompt syphilis serological testing, even in the absence of a typical chancre.

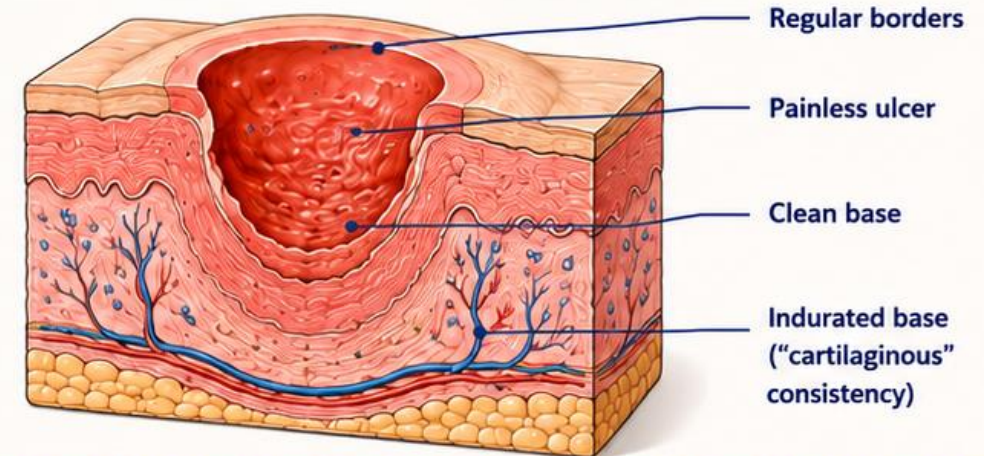
CLINICAL PHOTOGRAPHS



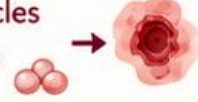
CROSS-SECTIONAL DIAGRAM OF A CHANCRE

CHARACTERISTICS

- ✓ Single and painless ulcer
- ✓ Sharp, regular borders
- ✓ Clean, non-necrotic base
- ✓ Firm indurated base on palpation



Differential diagnosis of the syphilitic chancre

 Condition	 Ulceration	 Pain	 Lymphadenopathy	 Distinctive feature
 Syphilitic chancre (<i>H. ducreyi</i>)	Multiple, with irregular borders 	Very painful 	Inflammatory, fistulized 	Dirty base, purulent 
 Genital herpes (HSV)	Multiple vesicles then erosions 	Painful, burning 	Tender, bilateral 	Recurrent, grouped vesicles 
 LGV (Chlamydia L1-L3)	Often absent or discreet 	Mildly painful 	Large, fistulized (buboes) 	Proctitis context in MSM 
 Donovanosis (<i>Klebsiella granulomatis</i>)	Beefy-red, clean ulcer 	Painless 	Pseudo-buboes, subcutaneous 	Very slow, chronic evolution 
 Aphthous ulcer / Behçet disease	Ulcer with fibrinous base 	Painful 	Absent or minimal 	Recurrent, other locations (oral, ocular, etc.) 



Key message: Painlessness and induration point toward syphilis; however, any genital ulcer requires **systematic serological testing** whatever its appearance.



The syphilitic roseola — first outbreak



Appears 6 to 8 weeks after the chancre
(sometimes with shedding of the chancre).



Macular rash, pale pink, non-pruritic, with ill-defined borders.



Predominantly on the trunk and proximal limbs;
spares the face most of the time.



Discrete, fleeting, often unnoticed by the patient —
hence the term “**flower of the skin**”.



Associated with superficial generalized lymphadenopathy and sometimes **low-grade fever**.



Can be more difficult to recognize on skin of color :
may appear more pigmented, coppery, or sometimes
papular and eczematous.

CLINICAL PHOTOGRAPHS

Roseola on the trunk



Pale roseola



Coppery/papular appearance
on darker skin (phototype V–VI)



Diffuse roseola



Discrete, fleeting exanthem, often unnoticed:
think systematically about secondary syphilis.



Key message: The roseola is discrete and often unnoticed: always think systematically
of **unexplained febrile exanthem** in a sexually active young adult.

Papulosquamous syphilides and flat condylomata



Papulosquamous syphilides: second stage of syphilis, occurs later and is richer in lesions.



Coppery, infiltrated papules, sometimes scaly with a collarette of scale ("Bielt collar").



Highly suggestive palmoplantar involvement: coppery papules with a desquamative collarette.



Flat condylomata (condylomata lata): papulo-hypertrophic lesions in skin folds (genital, perianal), highly contagious.



Mucous patches of the oral and genital mucosa: superficial, painless, whitish erosions, highly contagious.



Syphilitic alopecia: "moth-eaten" or non-scarring, with ill-defined borders, often occipito-temporal.



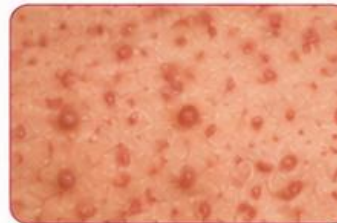
Key message: Papulosquamous palmoplantar involvement in a sexually active young adult is a **highly suggestive dermatological red flag** that should strongly orient toward syphilis.

PAPULOSQUAMOUS SYPHILIDES

Trunk



Back



Face spared



Coppery lesions with Bielt collar



PALMOPLANTAR INVOLVEMENT

Palm



Sole



FLAT CONDYLOMATA

(condylomata lata)

Genital region



Perianal region



MUCOUS PATCHES

Oral mucosa



Genital mucosa



SYPHILITIC ALOPECIA



- ✓ "Moth-eaten", non-scarring
- ✓ Ill-defined borders
- ✓ Location: occipito-temporal

Clinical spectrum of secondary syphilis – overview

 SYSTEM	 MAIN MANIFESTATIONS	 FREQUENCY
 SKIN	Roseola, papulosquamous syphilides, palmoplantar syphilides    	 Very common
 MUCOUS MEMBRANES	Oral and genital mucous patches, condylomata lata  	 Common
 APPENDAGES (HAIR)	“Moth-eaten” alopecia, loss of the lateral third of the eyebrows  	 10–15 %
 LYMPH NODES	Superficial, non-inflammatory generalized lymphadenopathy 	 Very common
 GENERAL	Low-grade fever, asthenia, headache, arthralgia, pharyngitis     	 Common
 ORGANS	Mild hepatitis, glomerulonephritis, uveitis, aseptic meningitis    	 Rare but possible



KEY MESSAGE: Secondary syphilis is a systemic disease: **any unexplained multisystem involvement in a young adult should prompt syphilis serological testing.**

Latent syphilis: early and late



Definition: serologically positive without any suggestive clinical sign.



Early latent syphilis: lasting less than one year (CDC) — possibility of residual sexual infectivity.



Late latent syphilis: lasting more than one year, or of unknown duration — infectivity is almost nil, but persistent risk of maternal-fetal transmission.



The distinction between early and late is based on: date of the last negative test, history of a chancre or recent rash, or an identified contact.

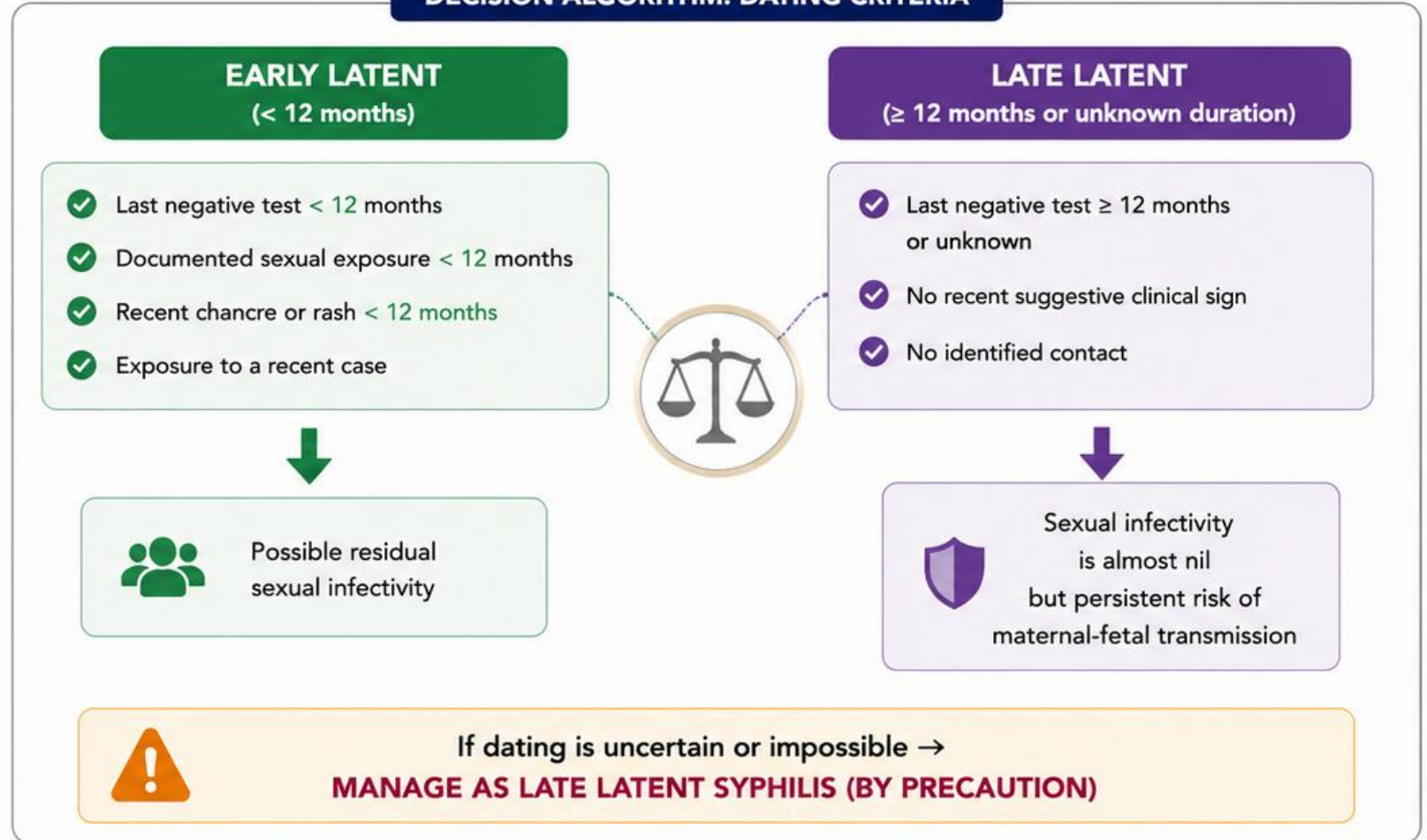


If reliable dating is not possible → always manage as late latent syphilis (precautionary principle).



Diagnosis is exclusively serological: no clinical sign for a positive diagnosis.

DECISION ALGORITHM: DATING CRITERIA



KEY MESSAGE: Uncertainty about dating, the safety rule is to treat all latent syphilis as late latent — a longer regimen, but **without risk of under-treatment**.

Tertiary syphilis: gummas and cardiovascular involvement



Occurs in about 1/3 of untreated patients, after a latency of several years to decades.



Syphilitic gummas: nodules then deep ulcers, indolent, with destructive evolution — skin, bones, liver, mucous membranes.



Cardiovascular syphilis: syphilitic aortitis, ascending aortic aneurysm, aortic insufficiency.



Osseous involvement: periostitis, gummas, bony osteitis.



Not contagious sexually at this stage, but vital prognosis may be affected (risk of aneurysm rupture).



Diagnosis: clinical signs + positive treponemal serology (non-treponemal tests may be negative or weakly positive).

CLINICAL MANIFESTATIONS

SYPHILITIC GUMMAS



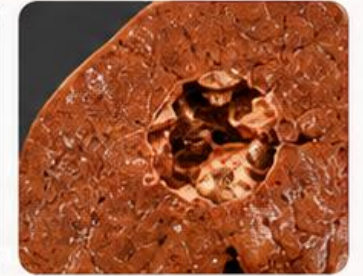
Skin



Oral mucosa



Bone



Liver

CARDIOVASCULAR INVOLVEMENT



Syphilitic aortitis



Ascending aortic aneurysm



Aortic insufficiency

OSSEOUS INVOLVEMENT



Periostitis



Bony gumma



KEY MESSAGE: Tertiary syphilis has become rare thanks to early treatment, but it remains **potentially fatal** due to its cardiovascular complications.

Mother-to-fetus transmission and prenatal diagnosis



Transplacental transmission possible at any time of pregnancy, with greatest risk if maternal infection is recent and untreated.



Possible consequences: fetal death in utero, prematurity, stillbirth, neonatal infection (symptomatic or asymptomatic).



Systematic serological prenatal screening recommended in the 1st trimester (SMS, RPR/VDRL) and repeated in the 3rd trimester in high-prevalence areas.



All pregnant women must be seropositive without delay and treated with benzathine penicillin G adapted to the stage.



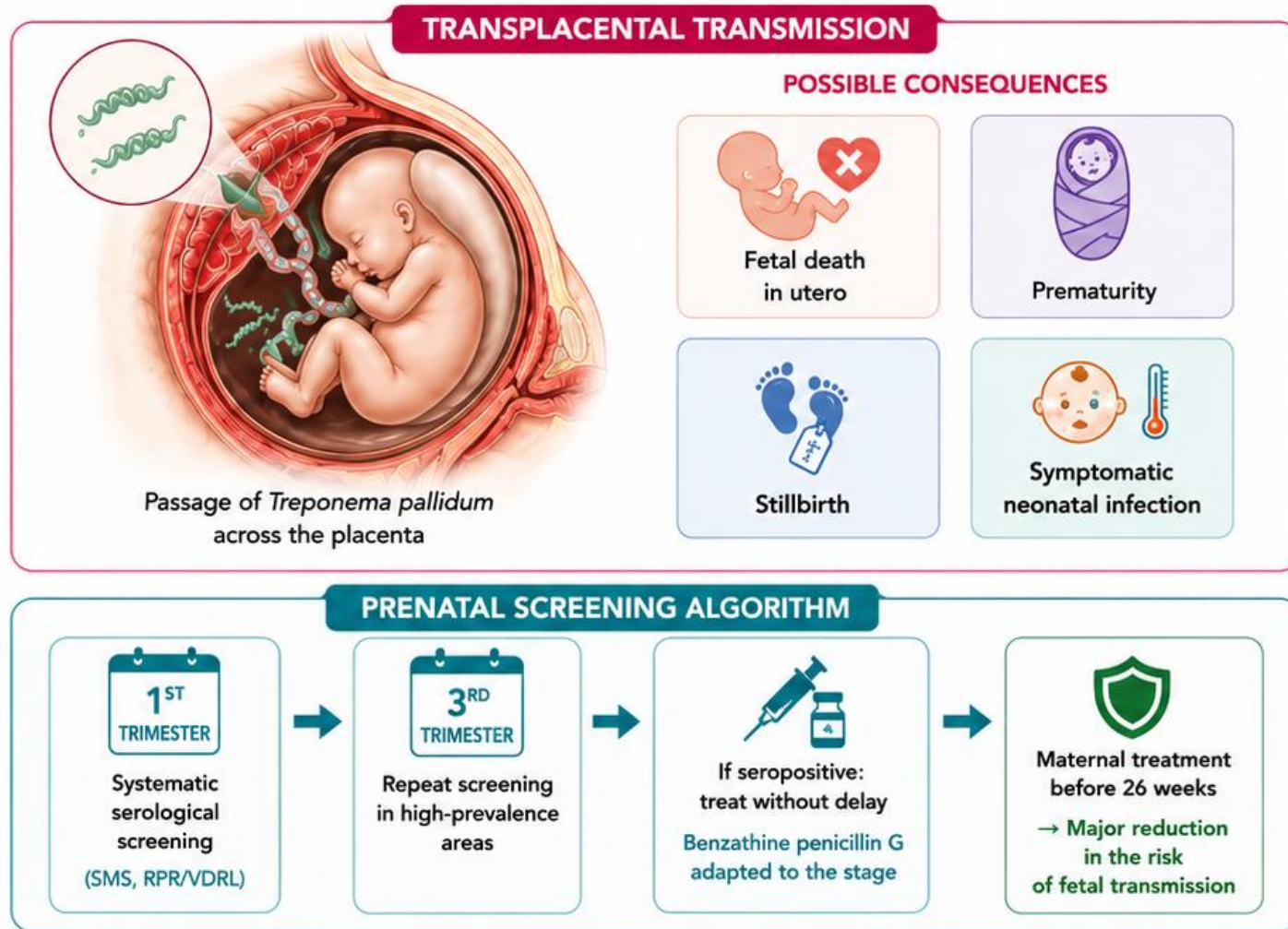
Maternal treatment before 26 weeks of gestation dramatically reduces the risk of fetal transmission.



WHO goal: elimination of mother-to-fetus transmission of HIV and syphilis (EMTCT initiative).



KEY MESSAGE: Congenital syphilis is a disease that is **100% preventable: systematic prenatal screening** and **early maternal treatment** are key.



Early and late clinical forms, prevention



Early form (< 2 years): hepatosplenomegaly, skin eruption, mucous patches, syphilitic rhinitis ("snuffles"), Parrot's pseudoparalysis, anemia, jaundice.



Late form (> 2 years, sequelae): Hutchinson triad (interstitial keratitis, deafness, Hutchinson teeth), saddle nose, saber shin (tibia).



Neonatal diagnosis: comparative mother–infant serology, clinical examination, bone radiographs, PCR if available.



Treatment of the newborn infant: penicillin G IV or IM according to strict neonatal protocol.



Prevention = the winning triad: prenatal screening + early maternal treatment + postnatal serologic follow-up of the infant.



KEY MESSAGE: Syphilitic rhinitis in the newborn and Hutchinson's triad are hallmark signs to recognize in order to never miss a diagnosis of congenital syphilis.

CLINICAL FORMS

EARLY FORM (< 2 YEARS)



Skin eruption



Syphilitic rhinitis ("snuffles")



Parrot's pseudoparalysis



Jaundice

LATE FORM (> 2 YEARS)



Interstitial keratitis



Deafness



Hutchinson teeth



Saddle nose



Saber shin (tibia)

COMPARATIVE OVERVIEW: EARLY VS LATE FORM

EARLY FORM (< 2 YEARS)

- Severe systemic involvement
- Numerous and varied clinical signs
- High risk of early morbidity
- Frequent visceral involvement



LATE FORM (> 2 YEARS)

- Sequelae
- Characteristic stigmata
- Chronic progression
- Possible functional disabilities

PREVENTION: THE WINNING TRIO



Prenatal screening



Early maternal treatment



Postnatal serologic follow-up of the infant

Neurosyphilis: clinical forms



Can occur at ANY stage of the disease, most often **early** — not synonymous with tertiary syphilis.



Early neurosyphilis (weeks to years): meningitis (acute syphilitic meningitis), ocular involvement (uveitis, optic neuritis), otologic involvement (sensorineural hearing loss), meningovascular (stroke in a young adult).



Late neurosyphilis (years to decades): dorsal column involvement (ataxia, lightning pains, Argyll Robertson sign), general paresis (cognitive and psychiatric disorders).



Neurological or ophthalmological symptoms + positive syphilis serology → systematic lumbar puncture.



All ocular or otologic syphilis must be treated according to neurosyphilis protocol, whatever the CSF result.



Lumbar puncture indicated if: neurological or ophthalmological symptoms + positive syphilis serology.



KEY MESSAGE: Neurosyphilis can occur early in its course: any neurological or ocular involvement in a seropositive patient requires a lumbar puncture.

CLINICAL FORMS ACCORDING TO CHRONOLOGY

EARLY NEUROSYPHILIS (WEEKS TO YEARS)

Acute syphilitic meningitis



Headache, fever, stiff neck

Ocular involvement (uveitis, optic neuritis)



Visual loss, pain, photophobia

Otologic involvement (sensorineural hearing loss)



Tinnitus, hearing loss

Meningovascular (stroke in a young adult)



Focal neurological deficit, headache

Other possible involvement



Chronic headache, meningeal syndromes

LATE NEUROSYPHILIS (YEARS TO DECADES)

Dorsal column involvement



Ataxia, lightning pains, areflexia, Argyll Robertson sign, sphincter disorders

General paresis



Cognitive disorders, personality changes, dementia, psychiatric symptoms

Other possible late forms



Tabes dorsalis, optic atrophy, peripheral neuropathy, CNS gumma, myelitis



Perform a lumbar puncture systematically if: neurological or ophthalmological symptoms + positive syphilis serology.

Neurosyphilis: CSF, imaging and treatment

Test	Suggestive result	Interpretation
 Lumbar puncture — cytology	Pleocytosis > 5–10 leukocytes/mm³ (lymphocyte predominance) 	 In favor of active neurosyphilis 
 Lumbar puncture — protein level	Elevated protein > 0.45–0.5 g/L 	 Supportive finding 
 VDRL in CSF	Positive 	 Highly specific but low sensitivity (confirms if +) 
 FTA-ABS / TPHA in CSF	Positive 	 Sensitive but less specific (negative excludes) 
 Brain and spinal MRI	Meningitis, vasculitis, infarcts, atrophy 	 Guides and documents complications 
 Treatment	Aqueous crystalline penicillin G IV, 18–24 million units/day, 10–14 days 	 Only validated regimen (CDC / IDSA) 



KEY MESSAGE: A **positive CSF VDRL** confirms neurosyphilis; a **negative CSF TPHA** helps rule it out — the two tests are complementary.

Direct detection of *Treponema pallidum*



Dark-field microscopy: reference examination of mucosal lesions — allows visualization of motile treponemes in real time.



Limitations: requires a specialized microscope and trained operator; false negatives are common if local antibiotic treatment has been given.



PCR (*Treponema pallidum*): sensitive and specific, detectable on lesion swab; increasingly available and used in clinical practice.



Direct immunofluorescence (DFA-TP): an alternative to dark-field microscopy, more stable for transport.



Skin histopathology (if biopsy performed for another indication): perivascular lymphoplasmacytic infiltrate, visible treponemes with silver stain or by immunohistochemistry.



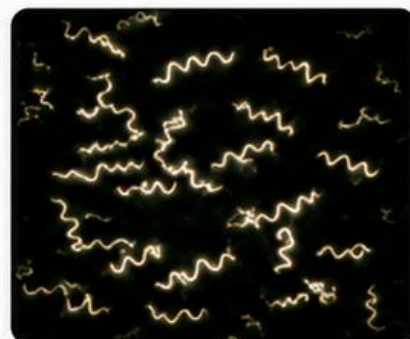
These direct tests are mainly useful in the early stages, before serologic testing becomes positive.



KEY MESSAGE: Direct diagnosis remains important in primary syphilis, a period when serologic tests may still be negative (serologic window).

DIRECT DETECTION OF *TREPONEMA PALLIDUM*

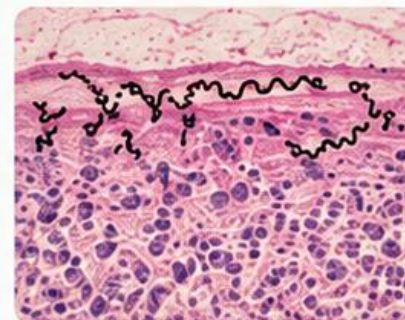
1. DARK-FIELD MICROSCOPY



- Motile treponemes in real time



2. SKIN HISTOPATHOLOGY (silver staining)



- Perivascular lymphoplasmacytic infiltrate
- Visible treponemes



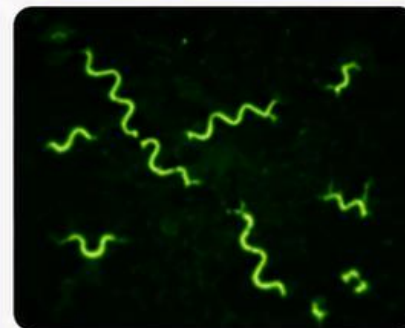
3. PCR (*TREPONEMA PALLIDUM*)



- Sensitive and specific
- Detectable on lesion swab



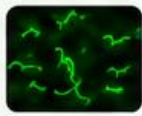
4. DIRECT IMMUNOFLUORESCENCE (DFA-TP)



- Alternative to dark field
- More stable for transport



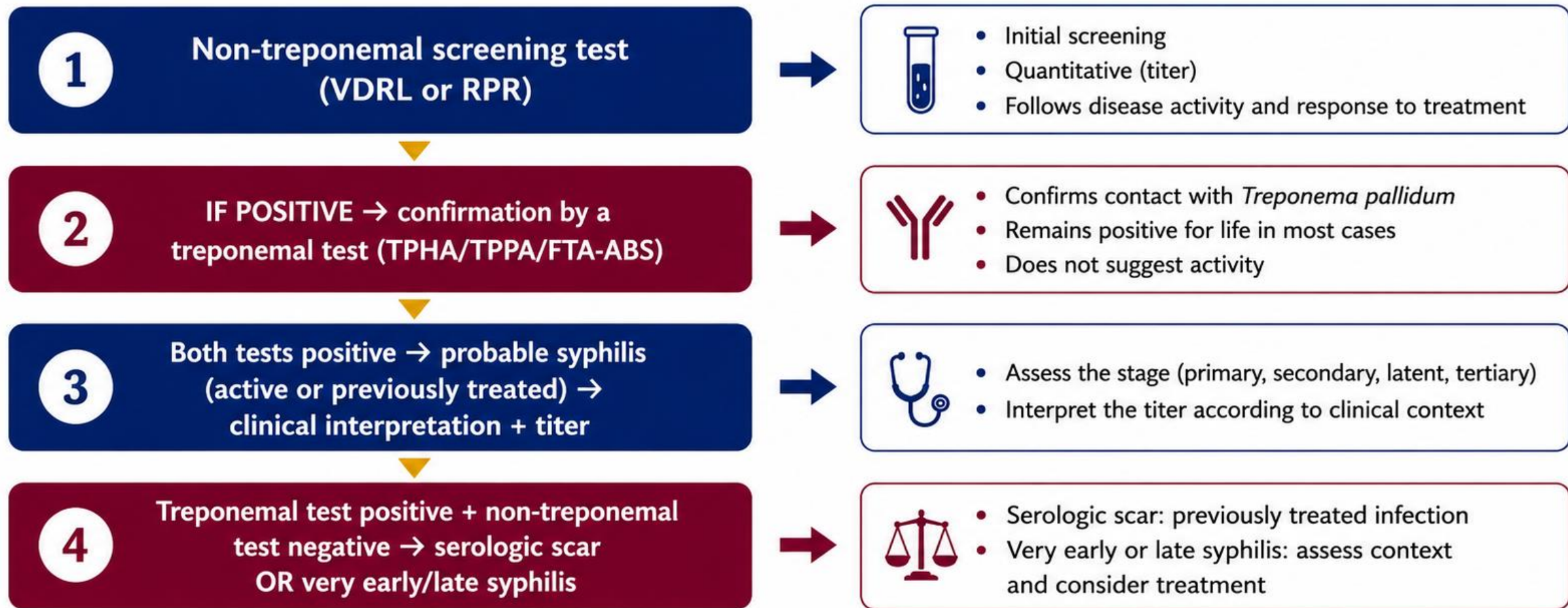
The two families of serologic tests

 NON-TREPONEMAL TESTS Reflect disease activity	Test	Type	Target	Main characteristic
	VDRL 	Non-treponemal	Anti-cardiolipin antibodies 	Quantitative (titer) — correlates with disease activity 
 TREPONEMAL TESTS Confirm infection, often for life	RPR 	Non-treponemal	Anti-cardiolipin antibodies 	Equivalent to VDRL, more widely used in routine (automatable) 
	TPHA 	Treponemal	<i>T. pallidum</i> antigens 	Becomes positive early, remains positive for life in most cases 
	TPPA 	Treponemal	<i>T. pallidum</i> antigens 	More sensitive and specific than TPHA 
	FTA-ABS 	Treponemal	<i>T. pallidum</i> antigens 	Becomes positive earliest (from days 5–10 after chancre) 
	EIA / CIA (automated) 	Treponemal	Recombinant antigens 	Used as first-line test in “reverse algorithm” 



KEY MESSAGE: **Non-treponemal tests** (VDRL/RPR) reflect disease activity; **treponemal tests** (TPHA/TPPA/FTA/EIA) confirm infection, often for life.

Classic serologic algorithm



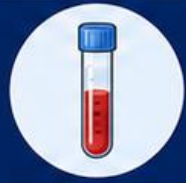
KEY MESSAGE: The classic algorithm starts with a non-treponemal test — simple and inexpensive, but may miss very early syphilis.



Reverse serologic algorithm (“reverse algorithm”)



1. Automated treponemal screening test (EIA/CIA)
— increasingly used as first-line test



2. IF POSITIVE → non-treponemal quantitative test (VDRL/RPR)
to assess disease activity



3. IF BOTH ARE POSITIVE → probable active syphilis,
treat according to the stage



4. Treponemal test positive + non-treponemal test negative →
perform a second treponemal test (TPPA) to resolve



KEY MESSAGE: The reverse algorithm, recommended by the CDC for automated laboratories, detects very early syphilis better but is more likely to produce discordant results to interpret.

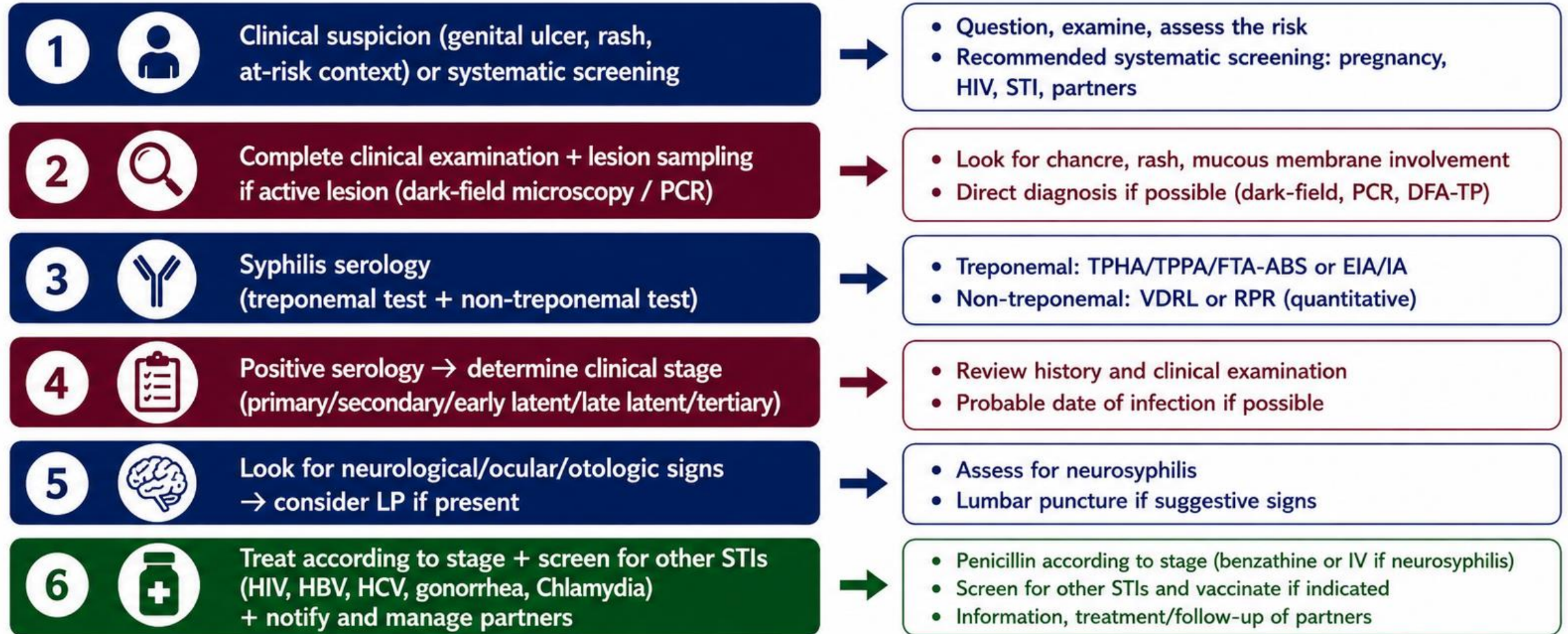
Interpretation According to Clinical Situations

Non-treponemal (VDRL or RPR)	Treponemal (TPHA, TPPA, FTA-ABS or EIA/CIA)	Most Likely Interpretation	Recommended Action
 Negative	 Negative	No evidence of syphilis, or very early syphilis (< 10 days)	 Repeat testing in 2–4 weeks if clinical suspicion persists
 Positive	 Positive	Syphilis, active or previously treated, depending on the clinical context	 Treat according to disease stage; use the non-treponemal titre for follow-up
 Positive	 Negative	False-positive non-treponemal test (pregnancy, autoimmune disease, viral infection, etc.)	 Investigate the cause; perform a second treponemal test
 Negative	 Positive	- Previously treated syphilis (serological scar) - Or very early syphilis - Or late syphilis	 Review history and previous treatment; perform a second treponemal test if needed
 High and rising non-treponemal titre	 Positive	Active syphilis or recent reinfection	 Treat or consider reinfection, particularly if a previous decline in titre had been documented



KEY MESSAGE: No serological result should ever be interpreted in isolation: it must always be correlated with the clinical presentation, patient history, and previous treatment.

Global diagnostic algorithm in the setting of suspected syphilis



KEY MESSAGE: Syphilis diagnosis is a stepwise process: clinical → serology → staging → search for complications → appropriate treatment + screening for other STIs + partner management.

Differential diagnoses of secondary syphilis

Condition	Common features	Distinguishing features
 Pityriasis rosea of Gibert	• Truncal exanthem	• Initial herald patch, oval lesions following cleavage (skin tension) lines, possible pruritus
 Guttate psoriasis	• Diffuse scaly papules	• Thicker scales, post-streptococcal context, absence of Bielt's collarette
 Lichen planus	• Violaceous papules	• Polygonal, pruritic papules, Wickham striae, reticular pattern on mucous membranes
 Drug eruption	• Diffuse exanthem	• History of recent medication, maculopapular eruption, absence of typical palmoplantar involvement
 Acute HIV infection	• Fever, rash, generalized lymphadenopathy	• HIV serology, high viral load; frequent co-infections to investigate systematically
 Behçet's disease / aphthosis	• Mucosal ulceration	• Recurrent bipolar aphthosis, absence of positive treponemal serology



KEY MESSAGE: In the case of any atypical exanthem, palmoplantar or mucosal involvement in a sexually active adult, syphilis serology must be performed systematically.

Treatment According to Stage (CDC 2021 / IUSTI 2023)

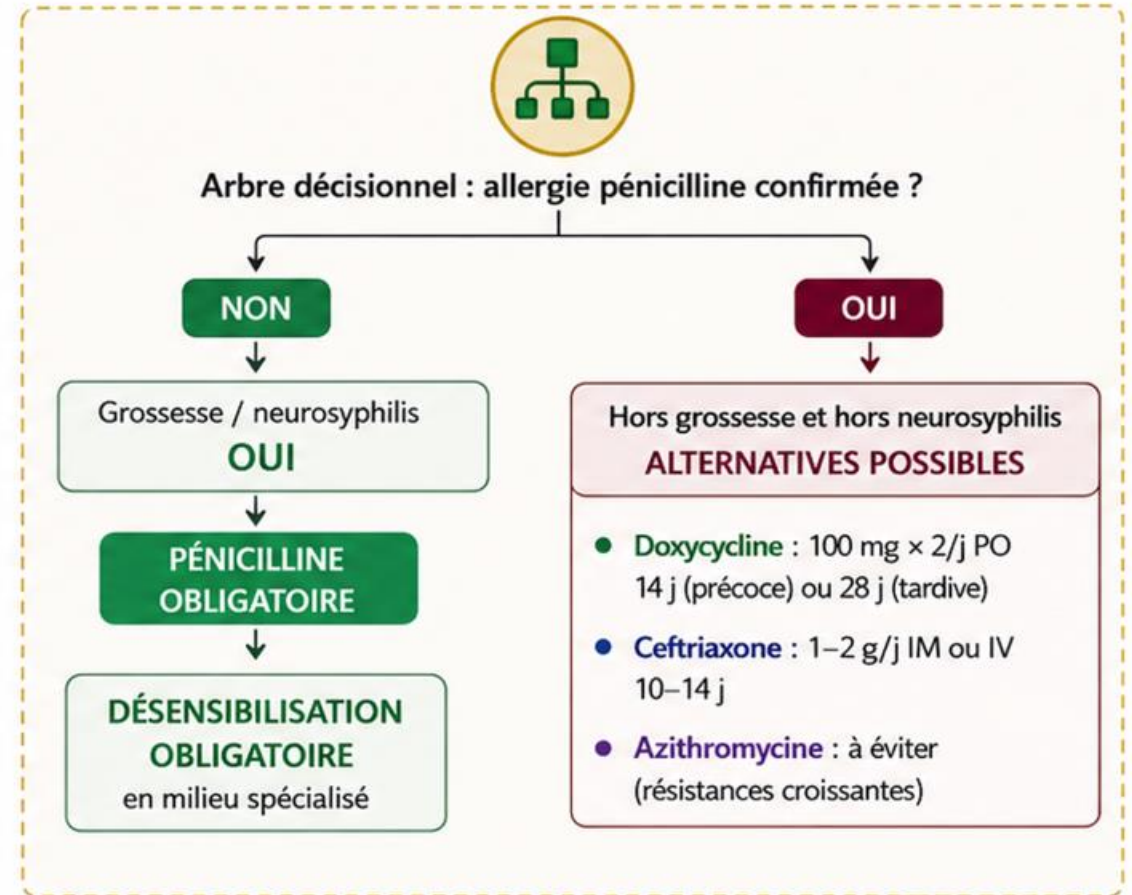
Stage	First-line Treatment	Regimen
 Primary, secondary, early latent	Benzathine penicillin G	 2.4 MU IM, single dose ONLY
 Late latent or latent of unknown duration	Benzathine penicillin G	 2.4 MU IM once weekly for 3 weeks (Days 1–8–15)
 Tertiary (gummas, cardiovascular)	Benzathine penicillin G	 2.4 MU IM once weekly for 3 weeks
 Neurosyphilis (all stages)	Aqueous crystalline penicillin G IV	 18–24 MU/day (3–4 MU every 4 h or continuous infusion) × 10–14 days
 Neurosyphilis (alternative ambulatory)	Procaine penicillin IM + oral probenecid	 2.4 MU/day IM + 500 mg every 6 h PO × 10–14 days



KEY MESSAGE: Benzathine penicillin G remains effective 80 years after its discovery and is the universal first-line treatment for syphilis at all non-neurologic stages.

Allergie à la pénicilline : alternatives et désensibilisation

- Hors grossesse et hors neurosyphilis, alternatives possibles en cas d'allergie documentée à la pénicilline :
 - ➔ **Doxycycline** 100 mg × 2/j PO pendant 14 jours (précoce) ou 28 jours (tardive)
 - ➔ **Ceftriaxone** 1–2 g/j IM ou IV pendant 10–14 jours (alternative, risque d'allergie croisée faible)
 - ➔ **Azithromycine** : à éviter, résistances documentées croissantes de *T. pallidum*
- Chez la femme enceinte et en cas de neurosyphilis : la pénicilline reste **OBLIGATOIRE** — désensibilisation en milieu spécialisé en cas d'allergie vraie
- La désensibilisation orale ou IV est réalisable en quelques heures selon un protocole standardisé, sous surveillance médicale rapprochée



Message clé : Chez la femme enceinte et en neurosyphilis, il n'existe pas d'alternative fiable à la pénicilline : la désensibilisation est la seule option en cas d'allergie vraie.

Special situations: pregnancy and HIV infection



Pregnant woman: treatment is the same according to stage, exclusively with benzathine penicillin G — no valid alternative.



Possible Jarisch–Herxheimer reaction within 24 hours after injection: fever, malaise, uterine contractions — obstetric monitoring recommended.



Treatment < 30 days before delivery: enhanced neonatal monitoring, and treatment of the newborn if indicated.



HIV-positive patient: the same treatment regimens as the general population according to stage.



Increased risk of early neurosyphilis and serologic failure in HIV-positive patients: closer serologic follow-up (3, 6, 9, 12, 24 months).



Lower threshold for lumbar puncture in asymptomatic HIV-positive patients or with low CD4 count and/or uncontrolled viral load.



Summary table: pregnancy/HIV
reference molecule, specific monitoring, serologic follow-up

Situation	Reference drug	Specific monitoring	Serologic follow-up
 Pregnancy	Benzathine penicillin G (all stages)	• Risk of Jarisch–Herxheimer reaction • Obstetric monitoring • < 30 days before delivery: enhanced neonatal monitoring	At 3, 6, 12 and 24 months (and at delivery by stage)
 HIV infection	Same regimens as the general population according to stage	• Increased risk of early neurosyphilis • Risk of serologic failure	At 3, 6, 9, 12 and 24 months



KEY MESSAGE: In pregnant women and in HIV-positive patients, the choice of first-line treatment does not change, but clinical and serologic monitoring must be enhanced.

Therapeutic algorithm for syphilis



1. Confirm clinical and serologic stage ($\pm$ LP if neurologic/ocular/otologic signs)



2. Neurosyphilis? $\rightarrow$ YES: aqueous crystalline penicillin G IV 18–24 million IU/day $\times$ 10–14 days



3. NO, primary/secondary/early latent $\rightarrow$ benzathine penicillin G 2.4 million IU IM single dose



4. NO, late latent/unknown duration/tertiary (non-neuro) $\rightarrow$
benzathine penicillin G 2.4 million IU IM once weekly for 3 weeks



5. Penicillin allergy? $\rightarrow$ pregnancy/neurosyphilis: mandatory desensitization
| other stages: doxycycline or ceftriaxone



6. Systematically treat sexual partner(s) of the last 90 days
(or longer depending on the stage)



KEY MESSAGE: Penicillin G remains the only active principle —
but three different regimens are used depending on the stage: single dose, three injections, or prolonged infusion.

Clinical and Serological Follow-up After Treatment



- **Quantitative serological follow-up (VDRL/RPR)** at 6 and 12 months for early stages; at **6, 12, and 24 months** for late stages.



- **Closer follow-up** (3, 6, 9, 12, and 24 months) is recommended in patients living with **HIV**.



- **Expected treatment response:** at least a **fourfold decrease** in the nontreponemal test titer (**2 dilutions**) within **6–12 months**.



- **Treatment failure or reinfection** should be suspected in cases of:
 - absence of titer decline at 12 months;
 - increase in titer after an initial decline;
 - recurrence or persistence of clinical signs.



- **If treatment failure is suspected:** reassess for possible reinfection, investigate neurosyphilis (lumbar puncture when indicated), check **HIV** status, and retreat according to an appropriate regimen.



- **Treponemal tests (TPHA/TPPA/FTA)** should **NOT** be used for follow-up, as they generally remain positive for life.



KEY MESSAGE: Follow-up should rely exclusively on the quantitative nontreponemal test titer — never on treponemal tests, which generally remain positive for life.

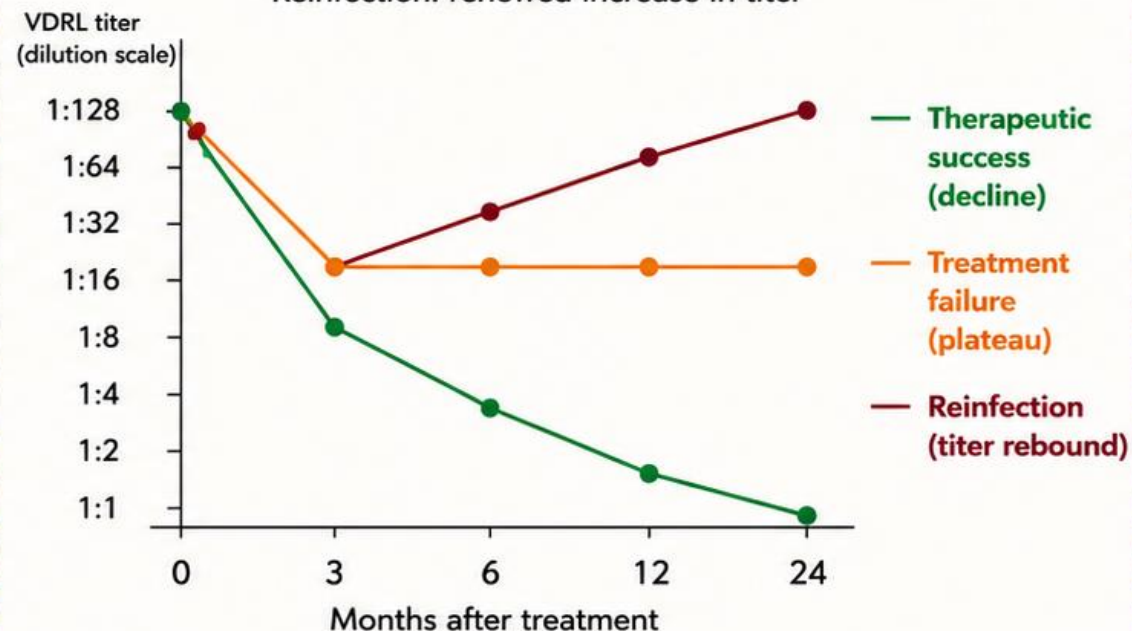


VDRL Titer Trend Over Time:

Therapeutic success: progressive decrease in titer

Treatment failure: plateau

Reinfection: renewed increase in titer



Screening, Prevention and Management of Partners



- **Systematic screening recommended:** pregnant women, blood donors, at-risk populations (MSM, people living with HIV, sex workers), and all STIs.



- **Repeat screening (every 3 to 6 months)** is recommended for populations at high risk of exposure.



- **Condoms reduce risk** but do not eliminate it completely (possible extragenital lesions).



- **Systematic notification and treatment of sexual partners** from the past 90 days (early syphilis) or the past year (late syphilis) prior to symptoms.



- **Presumptive treatment of partner(s) recommended without waiting** for their serology result if the contact is recent.



- **Maternal-fetal prevention:** systematic prenatal screening, and a single intramuscular dose of benzathine penicillin to prevent congenital syphilis.



KEY MESSAGE: Treat an unnotified patient or failing to treat exposed partners leads to immediate reinfection and perpetuates the chain of transmission.



The prevention cascade



1. Screening

Identify early infected individuals



2. Treatment

Stage-appropriate treatment, cure the disease and prevent complications



3. Partner notification

Inform and treat partners to interrupt the chain of transmission



4. Follow-up

Clinical and serological follow-up to confirm response and detect early treatment failure or reinfection

15 key messages to remember



1. Syphilis is caused by *Treponema pallidum*, a non-culturable spirochete, **strictly human-restricted**.



2. From the primary stage, infection is already **systemic** (precoce hematogenous dissemination).



3. Chancre is unique, painless and indurated — but **every genital ulcer must be tested**.



4. Secondary syphilis is the “great imitator”: think **palmoplantar involvement**.



5. Spontaneous healing of lesions **never means cure of the disease**.



6. Latency is a diagnosis based **exclusively on serology**, with no clinical sign.



7. Without treatment, around **1/3 of patients** progress to **tertiary syphilis**.



8. Neurosyphilis can occur **at any stage** — not only in tertiary syphilis.



9. Any ocular or otologic involvement + positive serology = **neurosyphilis** to be treated.



10. Nontreponemal tests (**VDRL/RPR**) follow disease activity; treponemal tests remain positive for life.



11. Aqueous crystalline penicillin G is the **reference treatment** for all non-neurologic stages.



12. **Desensitization is mandatory** in case of penicillin allergy in pregnant women or in neurosyphilis.



13. Follow-up relies solely on the **quantitative nontreponemal titer**, never on treponemal tests.



14. Systematic prenatal screening **prevents all cases** of congenital syphilis.



15. Treat the patient without treating exposed partners leads to **immediate reinfection**.



KEY MESSAGE: Syphilis is a systemic, polymorphic and treatable infection. Diagnosis relies on serology and clinical context; penicillin remains the reference treatment, and partner management is essential to interrupt transmission.

Summary Sheet — Syphilis at a Glance



Agent

Treponema pallidum
(spirochete)



Incubation

10–90 days
(avg. 21 days)



Max. Contagiousness

Primary and secondary
stages



Primary

Painless chancre
+ satellite adenopathy



Secondary

Rash, papulosquamous lesions
of palms and soles, alopecia



Latent

Serology + no clinical signs
(early < 1 year / late > 1 year)



Tertiary

Gummas, aortitis,
aortic insufficiency



Neurosyphilis

Any stage — meningeal/
ocular/otologic early,
tabes/TPG late



Congenital

Rhinitis, hepatosplenomegaly;
early: Hutchinson triad



Serology

Nontreponemal (VDRL/RPR) = active disease; treponemal (TPHA/FTA) = contact for life



Treatment

Benzathine penicillin G 2.4 million IU IM: single dose (early) / × 3 weekly doses (late);
Penicillin G IV 14 days (neurosyphilis)



Follow-up

VDRL/RPR quantitative at 6–12 months (early) or 6–12–24 months (late) —
never use treponemal tests



Key message: Syphilis is a systemic, polymorphic and treatable infection. Diagnosis relies on serology and clinical context; penicillin remains the reference treatment, and partner management is essential to interrupt transmission.

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