biomnis
SPECIALISED MEDICAL PATHOLOGY
Focus
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Biological diagnosis of syphilis in 2009

First identified in the 15th century, syphilis is an infectious disease caused by *Treponema pallidum*. It progresses slowly and its complications take time to manifest themselves.

There are four known subspecies (and many saprophytes) of *Treponema pallidum*:

- *T. pallidum* subsp. *pallidum*, which causes syphilis;
- **and three species** responsible for endemic treponematoses which manifest themselves clinically as skin lesions that are transmitted as early as childhood through direct contact:

  T. pallidum* subsp. *pertenue, which causes yaws (tropical regions);

  ***T. pallidum* subsp. *endemicum*,** which causes bejel (arid regions of Africa and the Middle East);

  T. pallidum* subsp. *carateum, which causes pinta (Mexico, Central America, and South America). Biological techniques (serological tests, PCR, etc.) do not differentiate syphilis from endemic treponematoses.

Biological diagnosis

Direct diagnosis

Direct diagnosis of syphilis is based on placing a fresh sample of primary and secondary lesions (chancre, mucous patches) between a slide and cover slip and examining it under a dark-field microscope to look for mobile treponemes. Indirect immunofluorescence (IIF) may be used if the sample cannot be examined immediately.

Due to its sensitivity and specificity, gene detection by PCR of amniotic fluid is useful in suspected cases of congenital syphilis. In suspected cases of neurosyphilis, the results obtained with cerebrospinal fluid (CSF) samples are inconsistent (false-negative results caused by inhibitors, false-positive results caused by persistence of the genome for some time following treatment).

Indirect diagnosis

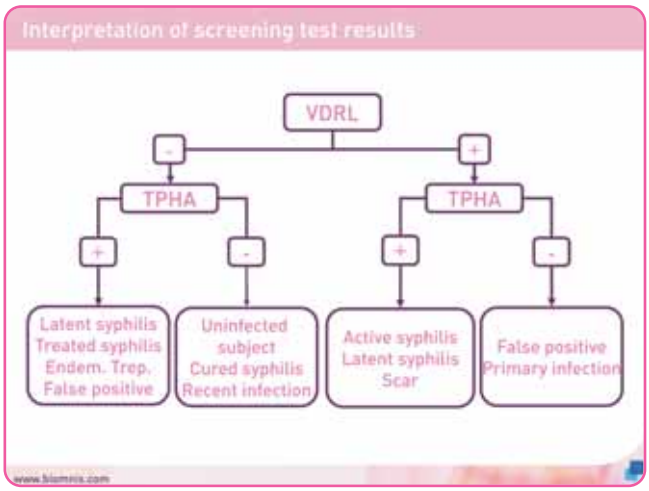
- **Kinetics of the antibodies over the course of untreated syphilis**

  In the primary phase, the IgM antibodies appear early (25-30 days after infection), and the VDRL test results, followed by the TPHA test results, are positive. In the secondary phase, the antibody titre increases and the IgM results remain positive. In the latency phase, the antibody titre drops and the VDRL remains positive/negative. In the tertiary phase, the antibody titre rises again, this time to a variable level.

- **Kinetics of the antibodies over the course of treated syphilis**

  If the disease is treated early (just after chancre formation) the serological test may remain negative. In the primary phase, the antibody titre drops rapidly and disappears in 3-6 months.

  If treatment is started later, the IgM and the VDRL titers drop, but a serological scar persists (TPHA, FTA-ABS +/- VDRL).



- **New diagnosis tools**

	ELISA (several assays available)	"Rapid" tests (several tests available)	Western blot or Dot blot
Benefits	Detect IgG and/or IgM Automatable, early and sensitive	Unitary or "ad-hoc" tests	Confirm specificity Activity marker?
Limits	Qualitative tests Cost	Qualitative tests Performance (being assessed by Afssaps†)	Cost Skills required

† French health products safety agency
†† French schedule of accredited medical procedures

Western Blot (WB) or Immunoblot

These techniques offer two benefits: high sensitivity, particularly during primary infection (before TPHA) and excellent specificity to interference caused by antibodies (cardiolipins, pregnancy, rheumatoid factor, anti-nuclear antibodies, Lyme disease, EBV, etc.).

WB currently differentiates neither serological scars from latent syphilis nor endemic treponematoses from syphilis. It is a sensitive and specific test that is used to confirm positive or equivocal serological results.

Special cases

- **Serological reactions in HIV-positive patients are disrupted.** In most cases, the titres of the specific tests drop as immunosuppression progresses; however, the VDRL titres may be increased by polyclonal stimulation.
- **Neurosyphilis is difficult to diagnose;** the antibody titres in serum and CSF should be compared. A positive VDRL test result with CSF confirms a diagnosis of neurosyphilis.
- **Congenital syphilis:** the risk of maternal-foetal transmission of syphilis is low during the first half of pregnancy but rises after 16 WA (70% if primary syphilis). Interpretation of serological test results is further complicated by the existence of false-positive results caused by pregnancy.

  In the absence of treatment, foetal and perinatal mortality approach 40% and complications are observed in 40% of surviving infants. As a result, treatment must be administered rapidly as soon as the mother tests positive for IgM. IgM are not always present in children infected at birth; their absence does not exclude congenital syphilis. In all cases, the infant must be tested to confirm the absence of potentially transferred maternal antibodies.

HAS 2007 recommendations

HAS (the French National Authority for Health) recommends conducting a treponemal test (TT) (VDRL, RPR) and a non-treponemal test (NTT) (TPHA, TPPA, FTA, ELISA) with titration in the event of positive results followed by confirmation by WB without specifying the indication.

HAS recommends combining several tests as TTs establish the diagnosis of syphilis and NTTs that of active syphilis. Combining two tests increases the screening sensitivity and specificity in low-prevalence populations.

Who should be tested for syphilis?

Syphilis screening should be suggested to the following groups:

- men who engage in unprotected sex with other men (oral sex included);
- sex workers who engage in unprotected sex (oral sex included);
- people who engage in unprotected sex (oral sex included) with sex workers;
- patients diagnosed with or having a history of gonorrhoea, lymphogranuloma venereum or HIV infection;
- people who engage in unprotected sex (oral sex included) with multiple partners per year;
- migrants from endemic countries (Africa, Asia, Eastern Europe, South America);
- newly incarcerated inmates;
- rape victims.

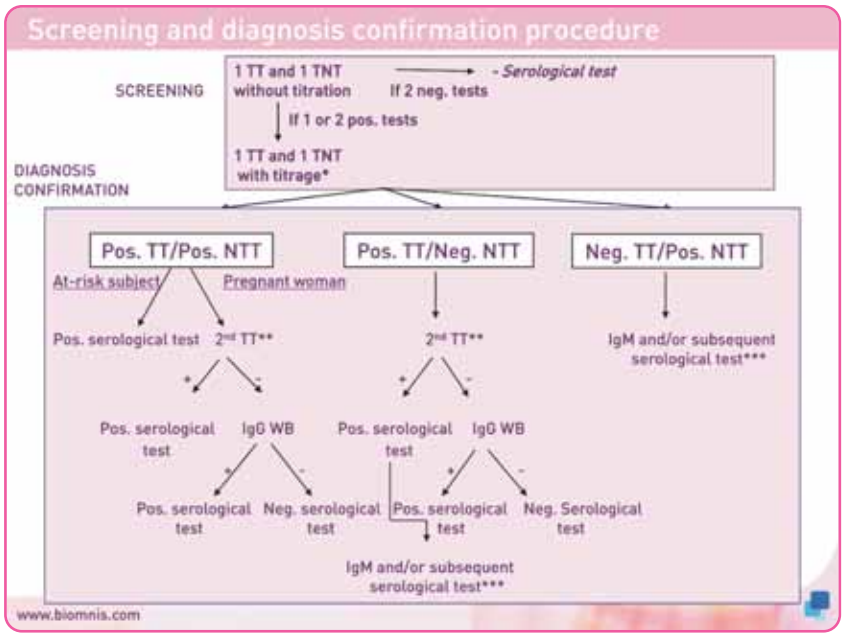
The screening rate for syphilis should be adapted to the frequency of risk exposing behaviours: one-time screening for an occasional case of risk exposure type behaviour to regular screening (at least once a year) in recurring cases of risk exposure behaviour.

In the case of pregnant women, screening must be offered:

- during the first prenatal exam (during the first trimester of pregnancy at best) for all pregnant women;
- during the third trimester if the pregnant woman or her partner have had unprotected sex with a new partner after the first screening; before the 28th week of pregnancy at best;
- before or after delivery if there is no record of serological tests being conducted during pregnancy (check for syphilis serological test results in the obstetrical records of all women before they are discharged from the maternity ward).

Lastly, syphilis screening should be suggested to women with a history of spontaneous abortion or stillbirth.

Screening and diagnosis confirmation procedure



Conclusion

The clinical and biological relationship is fundamental in diagnosing syphilis. If in doubt, do not hesitate to initiate treatment.

Written by Carole Emile, based on an article by Anne Ebel, Biomnis, Paris.