# SYPHILIS

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## Etiology

- Caused by *Treponema pallidum* subsp. *pallidum.*

- *T. pallidum* subsp. *pallidum* causes venereal syphilis, *T. pallidum* subsp. *endemicum* causes endemic syphilis (bejel), *T. pallidum* subsp. *pertenue* causes yaws and *T. carateum* causes pinta.

## Epidemiology

- Infectious syphilis (primary, secondary and early latent stages) is the least common of the three nationally reportable sexually transmitted infections (STIs).[1]

- After achieving rates of 0.4–0.6/100,000 from 1994 to 2000, rates of infectious syphilis rose in 2002 to 1.5/100,000, and preliminary figures for 2004 show projected rates of 3.9/100,000.[1,2]

- The rate of infectious syphilis is increasing in both males and females, but more so in males. In recent years, localized outbreaks of infectious syphilis have been reported in a number of locations worldwide[3, 4] and in Canada, including Vancouver, Yukon, Calgary, Edmonton, Toronto, Ottawa, Montreal and Halifax.[2, 5–7]

- Most of the outbreaks have been related to the sex trade and in men who have sex with men (MSM), but some have been in heterosexual persons not fitting into one of these categories. Some large outbreaks among MSM have been associated with the acquisition of anonymous sex partners through the Internet.[8]

- Syphilis, as with other STIs, increases the risk of acquisition and transmission of HIV.

## Transmission

- The primary mode of transmission is by vaginal, anal and oral sexual contact.[9]

- Kissing, sharing of needles and injection equipment, blood transfusion and accidental inoculation have rarely been reported as routes of transmission.

- Primary, secondary and early latent stages are considered infectious, with an estimated risk of transmission per partner of around 60%.[10] Early latent syphilis is considered infectious because of the 25% chance of relapse to secondary stage.[11]

- The majority of infants with congenital syphilis are infected in utero, but they can also be infected by contact with an active genital lesion at the time of delivery; the risk of transmission is much greater when the mother has untreated primary, secondary or early latent syphilis in pregnancy than if she has late latent syphilis.[12]

**Prevention**

- Results of reactive syphilis tests in a pregnant mother and any treatment history should be provided to the primary caregiver of the newborn infant.

**Manifestations**

**Table 1. Manifestations[9]**

| Stage | Clinical manifestations | Incubation period |
|---|---|---|
| *Primary* | Chancre, regional lymphadenopathy | 3 weeks (3–90 days) |
| *Secondary* | Rash, fever, malaise, lymphadenopathy, mucus lesions, condyloma lata, alopecia, meningitis, headaches, uveitis, retinitis | 2–12 weeks (2 weeks–6 months) |
| *Latent* | Asymptomatic | Early: <1 year<br>Late: ≥1 year |
| *Tertiary* | | |
| Cardiovascular syphilis | Aortic aneurysm, aortic regurgitation, coronary artery ostial stenosis | 10–30 years |
| Neurosyphilis | Ranges from asymptomatic to symptomatic with headaches, vertigo, personality changes, dementia, ataxia, presence of Argyll Robertson pupil | <2 years–20 years |
| Gumma | Tissue destruction of any organ; manifestations depend on site involved | 1–46 years (most cases 15 years) |
| *Congenital* | | |
| Early | Fulminant disseminated infection, mucocutaneous lesions, osteochondritis, anemia, hepatosplenomegaly, neurosyphilis | Onset <2 years |
| Late | Interstitial keratitis, lymphadenopathy, hepatosplenomegaly, bone involvement, anemia, Hutchinson's teeth, neurosyphilis | Persistence >2 years after birth |

**Diagnosis**

*Risk factors*

A diagnosis of syphilis should be considered in the following individuals:

- Those who have had contact with a known case of syphilis.
- Men who have sex with men.
- Commercial sex workers.
- Those with street involvement.
- Injection drug users.
- Those with multiple sexual partners.
- Those with a history of syphilis, HIV and other STIs.
- Those originating from or having sex with an individual from a country with a high prevalence of syphilis; it should be noted that screening for syphilis (using a non-treponemal test) is routinely performed in all immigration applicants to Canada who are older than 15 years.
- Sexual partners of any of the above.

*Symptoms and signs*

- Current or past history of lesions or rash (See Manifestations, above).
- A high proportion of individuals fail to recall a primary chancre.[9]
- Signs and symptoms may be modified in the presence of HIV co-infection.[13]

*Special considerations in pregnant women*

- Given the resurgence of syphilis in Canada, universal screening of pregnant women continues to be important and remains the standard of care in most jurisdictions.
- Screening should ideally be performed in the first trimester and repeated later in pregnancy in women at high risk of acquiring syphilis (See Risk Factors, above).

*Laboratory diagnosis*

- The interpretation of syphilis serology should be made in conjunction with a colleague experienced in this area (see Table 2).
- Every attempt should be made to obtain and document prior history of treatment for syphilis and prior serologic results in order to avoid unnecessary retreatment.

**Table 2. Guide to interpretation of serologic tests for syphilis**

| Test results on blood or serum | | | Most likely condition |
|---|---|---|---|
| **Non-treponemal test: RPR/VDRL** | **Treponemal test: TP-PA** | **Treponemal test: FTA-ABS** | |
| **NR** | **NR** | **R** | Primary syphilis with compatible history/clinical findings |
| **R** *(dilutions can vary)* | **R** | **R** | Infectious syphilis (primary, secondary, early latent), especially if titre >1:8 **OR** Old treated syphilis (especially if titre <1:8) **OR** Follow-up of treated syphilis **OR** In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel |
| **NR** | **R** | **R** | Usually treated syphilis **OR** Late latent of unknown duration if no history of confirmed treatment **OR** In persons from endemic countries, yaws (e.g., Caribbean), pinta (e.g., Central America) or bejel **OR** Early infection (primary syphilis) |
| **R** | **NR** | **NR** | Biological false positive* *(repeat in 3–4 weeks)* |

FTA-ABS=fluorescent treponemal antibody absorbed
NR=non-reactive
R=reactive
RPR=rapid plasma reagin
TP-PA=*T. pallidum* particle agglutination
VDRL=venereal disease research laboratory
*Some causes of false positive serologic tests for syphilis include certain collagen-vascular diseases, pregnancy, injection drug use, etc.

*Specimen collection*

- Dark-field microscopy, DFA/IFA or PCR (For more information on available tests, please contact your local laboratory). To visualize *T. pallidum* from chancres of primary syphilis and some lesions of secondary syphilis (e.g., condyloma lata).
- Dark-field microscopy and direct or indirect fluorescent antibody tests (DFA/IFA) are not reliable for oral/rectal lesions, as non-pathogenic treponemes may be present.

- Polymerase chain reaction (PCR) is available only at specialized laboratories, including the National Microbiology Laboratory.

*Serology*

- Screening for syphilis has traditionally involved the use of non-treponemal tests (NTT) such as rapid plasma reagin (RPR), followed by confirmatory treponemal tests if the NTT is reactive. However, in patients with suspected primary syphilis or late latent syphilis, the NTT may be non-reactive, and it is then appropriate to add a treponemal test to the initial screen or, in the case of primary syphilis, to repeat the NTT after 2–4 weeks. In regions experiencing outbreaks of syphilis, it may be appropriate to screen at baseline with both non-treponemal and treponemal tests.
- The introduction of treponemal tests for IgG/IgM antibodies, such as the treponemal enzyme immunosassay **(**EIA), may provide a more sensitive screening test for syphilis.
- Non-treponemal tests include RPR, venereal disease research laboratory (VDRL) and the toluidine red unheated serum test (TRUST).
- Non-treponemal antibody titres usually correlate with disease activity and are used to monitor response to treatment and assess for reinfection.
- Treponemal tests include the *T. pallidum* particle agglutination (TP-PA), fluorescent treponemal antibody absorbed (FTA-ABS) and EIA to detect IgG and/or IgM antibodies.
- Treponemal tests usually remain reactive for life regardless of treatment, although 15–25% will serorevert if the patient is treated during the primary stage.

*Cerebrospinal fluid*

- Criteria for cerebrospinal fluid (CSF) examination include the following:
  - Presence of neurologic or ophthalmic symptoms or signs.
  - Congenital syphilis.
  - Previously treated patients who fail to achieve an adequate serologic response to treatment.
  - Tertiary syphilis.[14]
  - HIV patients with neurologic symptoms or signs, late latent syphilis, RPR ≥1:32 dilutions, CD4 <350 cells/$\mu$L or treated syphilis with suboptimal decline in VDRL/RPR titre; some experts recommend CSF examination in all cases.[15]
  - Some experts recommend CSF examination in all patients with RPR ≥1:32 dilutions.[15]
- CSF should be tested for cell count and differential, protein, VDRL and/or FTA-ABS.
- CSF-VDRL is highly specific but insensitive.
- CSF FTA-ABS is highly sensitive but non-specific for neurosyphilis; a negative CSF FTA-ABS helps to exclude a diagnosis of neurosyphilis.[14,16–18]
- The diagnosis of neurosyphilis is usually made on a combination of reactive serologic results, abnormalities of CSF cell count or protein or a reactive CSF-VDRL with or without clinical manifestations.

**Management**

*Primary and secondary syphilis*

- Attempt to obtain material from primary or secondary lesions for dark-field microscopy and/or DFA/IFA for *T. pallidum.*
- Ulcers should also be tested for herpes simplex virus and/or chancroid (if epidemiologically appropriate) and/or lymphogranuloma venereum (if epidemiologically appropriate).
- Serology should include both treponemal and non-treponemal tests. Note that both non-treponemal and treponemal tests may be negative in early primary syphilis. Serology should be repeated in 2–4 weeks if they are dark-field or DFA/IFA negative and/or no treatment has been given. If follow-up cannot be assured, it may be appropriate to treat presumptively for primary syphilis.

*Latent syphilis*

- Serology: both treponemal and non-treponemal tests; note that a negative non-treponemal test does not rule out the diagnosis of latent syphilis.
- All patients should undergo a physical examination, including neurologic examination, to evaluate for the presence of signs of tertiary syphilis. Chest x-ray may be appropriate to evaluate for the presence of cardiovascular syphilis (e.g., aneurysm of ascending aorta).
- Lumbar puncture may be appropriate (See Cerebrospinal Fluid, above).
- Treat as appropriate for stage.

*Tertiary syphilis*

- Serology: both treponemal and non-treponemal tests; note that a negative non-treponemal test does not rule out the diagnosis of tertiary syphilis.
- All patients with suspected tertiary syphilis should undergo CSF examination.
  - If CSF is not compatible with a central nervous system (CNS) infection, treat as for late latent syphilis.
  - If CSF is compatible with a CNS infection, treat as for neurosyphilis.

*Congenital syphilis*

- Obtain venous samples from both mother and baby (note that cord blood is not suitable) for serology (treponemal and non-treponemal tests).
  - The interpretation of reactive antibodies in the neonate must take into consideration the maternal history, including stage of syphilis, history of treatment, and syphilis serology results.
- Placenta, neonatal nasal discharge or skin lesions may be examined by dark-field microscopy or DFA/IFA for *T. pallidum.*
- CSF examination should be performed on all infants with suspected congenital syphilis.
- Long-bone x-rays should be performed.

**Treatment**

- Although regimens containing daily IM procaine penicillin for 10–14 days are equally efficacious to regimens containing benzathine penicillin G, the latter are preferred because of better adherence with less frequent dosing.

- Benzathine penicillin G is available in Canada only through provincial/territorial Sexually Transmitted Disease Services, who obtain the drug from non-Canadian pharmaceutical companies through Health Canada's Special Access Program, as the drug is no longer available in Canada.

**Table 3. Treatment**
**(See Table 3.1 below for Summary: Level and Quality of Evidence Indicators)**

| Stage | Preferred treatment | Alternative treatment for penicillin-allergic patients |
|---|---|---|
| All **non-pregnant adults**<br>• **Primary**<br>• **Secondary**<br>• **Early latent** (<1 year duration) | Benzathine penicillin G 2.4 million units IM as a single dose*[19–22] *[A-II; A-III for HIV- infected individuals]* | • Doxycycline 100 mg PO bid for 14 days[23,24] *[B-II]*<br><br>**Alternative agents (to be used in exceptional circumstances)**[†]<br>• Ceftriaxone 1 g IV or IM daily for 10 days[25,26] *[B-II]* |
| **Pregnant women**<br>• **Primary**<br>• **Secondary**[‡]<br>• **Early latent** (<1 year duration) | Benzathine penicillin G 2.4 million units IM as a single dose[*27] *[A-II]* | • There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy; insufficient data exist to recommend ceftriaxone in pregnancy<br>• Strongly consider penicillin desensitization followed by treatment with penicillin *[A-III]* |
| All **non-pregnant** adults<br>• **Late latent** syphilis<br>• **Latent** syphilis of unknown duration<br>• **Cardiovascular syphilis** and other **tertiary syphilis** not involving the central nervous system | Benzathine penicillin G 2.4 million units IM weekly for 3 doses[28,29] *[A-II]* | • Consider penicillin desensitization<br>• Doxycycline 100 mg PO bid for 28 days[24] *[B-II]*<br><br>**Alternative agents (to be used in exceptional circumstances)**[†]<br>• Ceftriaxone 1 g IV or IM daily for 10 days[30] *[C-III]* |
| **Pregnant women**<br>• **Late latent** syphilis<br>• **Latent** syphilis of unknown duration<br>• **Cardiovascular syphilis** and other **tertiary syphilis** not involving the central nervous system | Benzathine penicillin G 2.4 million units IM weekly for 3 doses[31] *[A-II]* | • There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy; insufficient data exist to recommend ceftriaxone in pregnancy<br>• Strongly consider penicillin desensitization followed by treatment with penicillin *[A-III]* |
| **All adults**<br>• **Neurosyphilis** | Penicillin G 3–4 million units IV q 4 h (16–24 million units/day) for 10–14 days[29] *[A-II]* | • Strongly consider penicillin desensitization followed by treatment with penicillin<br>• Ceftriaxone 2 g IV/IM qd x 10–14 days[29,32,33] *[B-II]* |

| | | |
|---|---|---|
| **Congenital syphilis**[34] | *Early (<1 month)*<br>Crystalline penicillin G 50,000 units/kg IV every 12 hours for the first week of life and every 8 hours thereafter for 10 days of total therapy *[A-II]* | |
| | *Late (≥1 month)*<br>Crystalline penicillin G 50,000 units/kg/ IV every 6 hours for 10–14 days *[A-II]* | • If no neurologic involvement and normal CSF: benzathine penicillin G 50,000 units/kg IM (max 2.4 million units) weekly for 3 successive weeks *[B-II]*<br>• No data are available to recommend penicillin alternatives in the case of penicillin allergy |
| Epidemiological treatment of sexual contacts in the preceding 30 days to primary, secondary and early latent syphilis§‖[35] | Benzathine penicillin G 2.4 million units IM as a single dose *[B-II]* | See comment below on Azithromycin ‖ |

*Some experts recommend 3 weekly doses (total of 7.2 million units) of benzathine penicillin G in HIV-infected individuals.
†The efficacy data supporting the use of these agents is limited, and as such they should only be used in exceptional circumstances and when close patient follow-up is assured.
‡Secondary syphilis in late pregnancy (>20 weeks gestation) should be treated with two doses of benzathine penicillin G 2.4 million units given 1 week apart (see note under Pregnancy, below).
§If sexual contact is unreliable or unable to test, then epidemiological treatment should be strongly considered.
‖ ***Azithromycin***
In light of recent reports of failure of azithromycin for the treatment of early syphilis[36] and the rapid development of azithromycin resistance in *T. pallidum*[37, 38], this agent should not be routinely used as a treatment option for early or incubating syphilis unless adequate and close follow up can be ensured, and only in jurisdictions where little to no azithromycin genotypic resistance in *T. pallidum* has been demonstrated. It should be noted, however, that at the present time, very limited Canadian data on the prevalence of Azithromycin resistance in *T.pallidum* is available, with 1 of 47 specimens between 2000-2003 as compared with 4 of 12 specimens from MSM in 2004-2005 collected in Vancouver demonstrating resistance. [38]

## Table 3.1
## Summary: Level and Quality of Evidence Indicators

| **Level** | |
|---|---|
| A | Good evidence (benefit substantially outweighs harm) to support the recommendation |
| B | Fair evidence (benefit outweighs harm) to support the recommendation |
| C | Fair evidence, but too close to justify a general recommendation |
| D | Fair evidence that the recommendation is ineffective (or harm outweighs benefit) |
| I | Insufficient evidence (lacking, poor quality, conflicting) |
| **Quality** | |
| I | Evidence from ≥ 1 randomized control trial |
| II | Evidence from ≥ 1 clinical trial without randomization (cohort, case-control, time-series, dramatic results in uncontrolled experiment) |
| III | Expert opinion |

*Penicillin desensitization*

- Skin testing with the major and minor determinants can reliably identify persons at high risk for penicillin reactions.
- Patients who have a positive skin test to one of the penicillin determinants can be desensitized.
- Oral desensitization is preferable to IV desensitization, as it is safer and less costly.
- Desensitization should occur in a hospital setting as serious allergic reactions, although unlikely, can occur. The whole procedure usually can be completed in 4 hours, after which the first dose of penicillin is given. After administration of the dose, the patient should be observed for at least 1 hour.

**Table 4. Oral desensitization protocol for patients with a positive skin test[39]**

| Penicillin V suspension dose number* | Amount† units/mL | Volume administered (mL) | Units | Cumulative dose (units) |
|---|---|---|---|---|
| 1 | 1,000 | 0.1 | 100 | 100 |
| 2 | 1,000 | 0.2 | 200 | 300 |
| 3 | 1,000 | 0.4 | 400 | 700 |
| 4 | 1,000 | 0.8 | 800 | 1,500 |
| 5 | 1,000 | 1.6 | 1,600 | 3,100 |
| 6 | 1,000 | 3.2 | 3,200 | 6,300 |
| 7 | 1,000 | 6.4 | 6,400 | 12,700 |
| 8 | 10,000 | 1.2 | 12,000 | 24,700 |
| 9 | 10,000 | 2.4 | 24,000 | 48,700 |
| 10 | 10,000 | 4.8 | 48,000 | 96,700 |
| 11 | 80,000 | 1.0 | 80,000 | 176,700 |
| 12 | 80,000 | 2.0 | 160,000 | 336,700 |
| 13 | 80,000 | 4.0 | 320,000 | 656,700 |
| 14 | 80,000 | 8.0 | 640,000 | 1,296,700 |

*Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose, 1.3 million units.
†The specific amount of drug is diluted in approximately 30 mL of water and then administered orally.

**Consideration for other STIs**

- All patients with reactive syphilis serology should be tested for HIV, as this affects treatment and follow-up.
- Testing for other STIs, including chlamydia and gonorrhea, should be performed.
- Genital ulcers should also be tested for herpes simplex virus and/or chancroid and/or lymphogranuloma venereum, depending on epidemiologic risk.
- Immunization against hepatitis B and/or A may be indicated if not already immune.

**Reporting and partner notification**

- Infectious syphilis (primary, secondary and early latent syphilis) is reportable in all provinces and territories and to the Public Health Agency of Canada.
- Non-infectious syphilis (late latent, cardiovascular and neurosyphilis) may be reportable at the provincial/territorial level but is not reportable to Public Health Agency of Canada.
- All sexual or perinatal contacts within the following time periods must be located, tested and treated if serology is reactive.

**Table 5. Partner notification**

| Stage of syphilis | Time period |
|---|---|
| Primary syphilis | 3 months prior to the onset of symptoms |
| Secondary syphilis | 6 months prior to the onset of symptoms |
| Early latent | 1 year prior to the diagnosis |
| Late latent | Assess marital or other long-term partners and children as appropriate |
| Congenital | Assess mother and her sexual partner(s) |
| Stage undetermined | Assess/consult with a colleague experienced in syphilis management |

**Follow-up**

- In the absence of a test of cure, NTTs should be monitored until they are seronegative or at a stable low titre (e.g., 1:4 dilutions).[40]
- See Table 6 for a guide to the monitoring of NTTs.
- See Table 7 for a guide to adequate serologic response (in non-treponemal test, e.g., RPR).[41]

**Table 6. Monitoring of NTTs**

| | |
|---|---|
| Primary, secondary, early latent | 1, 3, 6, 12 months after treatment |
| Late latent, tertiary | 12 and 24 months after treatment |
| Neurosyphilis | 6, 12 and 24 months after treatment |
| HIV-infected (any stage) | 1, 3, 6, 12 and 24 months after treatment and yearly thereafter |
| Babies born to mothers with reactive syphilis serology* | 3 and 6 months after birth; repeat nontreponemal and treponemal tests at 12 and 18 months if remain reactive at 6 months |
| Congenital syphilis* | 0, 3, 6, 12 and 18 months after birth |

*NTT titres should decline by 3 months of age and be non-reactive by 6 months if the infant was not infected. If the titres are stable or increase after 6–12 months of age, the child should be evaluated (including CSF examination) and treated as for congenital syphilis. Passively transferred treponemal antibodies can be present in an infant up to 15 months; a reactive treponemal test after 18 months is diagnostic of congenital syphilis.

**Table 7. Adequate serologic response**

| | |
|---|---|
| Primary | 2-tube* drop at 6 months, 3-tube drop at 12 months, 4-tube drop at 24 months |
| Secondary | 3-tube and 4-tube drop at 6 and 12 months, respectively |
| Early latent | 2-tube drop at 12 months |

*2-tube drop=four-fold drop, e.g., change from 1:32 dilutions to 1:8 dilutions.

- Note that the NTT may revert to non-reactive after treatment or remain at a low steady level (sero-fast); repeat testing is not required if the baseline or follow-up NTT becomes non-reactive, except in HIV-infected individuals.
- A rising NTT after treatment may indicate treatment failure or reinfection. If treatment failure is suspected, further investigation, including CSF examination, may be indicated.
- Patients with neurosyphilis and abnormal CSF examinations should have a lumbar puncture repeated at 6-month intervals after completion of treatment until CSF parameters normalize. CSF pleocytosis is generally the first measure of improvement and should occur over about 6 months.[42] Elevated protein levels, if present, will begin to decline during the first 6 months but can take up to 2 years to return to normal.[43] CSF protein may decline more slowly in patients who are neurologically abnormal compared with those who are neurologically normal.[44] The CSF-VDRL titre should decline (four-fold within a year) if it is initially high, but it may take years to revert to negative.[42] A persistent, low CSF-VDRL titre after a course of treatment may warrant retreatment, but if CSF pleocytosis and elevated protein levels have resolved and serum VDRL titre has not risen, additional treatment is unlikely to be beneficial.[45] All CSF lab parameters normalize more slowly in patients co-infected with HIV.[44] The possibility of treatment failure should be considered if there is clinical progression, increase in RPR/VDRL by ≥2 dilutions or CSF pleocytosis fails to resolve; treatment options for patients with treatment failure should be discussed with a colleague experienced in this area.

**Special considerations**

*HIV infection*

- Persons co-infected with HIV may require a longer course of treatment, as well as closer and longer follow-up.

*Pregnancy*[46]

- All women newly diagnosed with syphilis during pregnancy should receive treatment appropriate to their stage of disease, with the exception of secondary syphilis in late pregnancy, where despite the administration of the recommended penicillin regimen as many as 14% will have a fetal death or deliver infants with clinical evidence of congenital syphilis.[47–49] These cases should therefore be treated with two doses of benzathine penicillin G 2.4 million units 1 week apart, although the effect of this regimen in preventing fetal syphilis is not known.[46]
- Retreatment during pregnancy is not necessary unless there is clinical or serologic evidence of new infection (four-fold rise in a non-treponemal test titre) or history of recent sexual contact with early syphilis.

- Erythromycin is the least effective agent for the treatment of syphilis and does not penetrate the CSF or placental barrier well; it is therefore not recommended in pregnancy.[50, 51]
- If the mother is >20 weeks gestation, an ultrasound should be performed and she should be managed with a obstetrician/maternal-fetal medicine specialist; if fetal abnormalities are identified, the mother should be hospitalized for treatment and fetal monitoring.[52]
- All babies should be assessed at delivery by a pediatrician, and if a maternal non-penicillin regimen was used, consideration should be given to treating the baby empirically for congenital syphilis.

*Congenital syphilis*[53]

- Infected infants are frequently asymptomatic at birth and may be seronegative if maternal infection occurred late in gestation.
- Infants should be treated at birth:
  - If symptomatic.
  - If the infant's non-treponemal titre is four-fold (2 tubes) higher than the mother's.
  - If maternal treatment was inadequate, did not contain penicillin, is unknown or occurred in the last month of pregnancy, or if maternal serologic response is inadequate.
  - If adequate follow-up of the infant cannot be ensured.

*Jarisch-Herxheimer reaction*[54]

- Patients should be made aware of this possible reaction to treatment, especially with penicillin.
- An acute febrile illness with headache, myalgia, chills, rigours generally occurring within 8–12 hours and resolving within 24 hours.
- Common in early syphilis, but usually not clinically significant unless there is neurologic or ophthalmic involvement or in pregnancy where it may cause fetal distress and premature labour.
- Not a drug allergy.
- Can be treated with antipyretics.
- Steroids may be indicated for the management of severe reactions but should be used in consultation with a colleague experienced in this area.

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