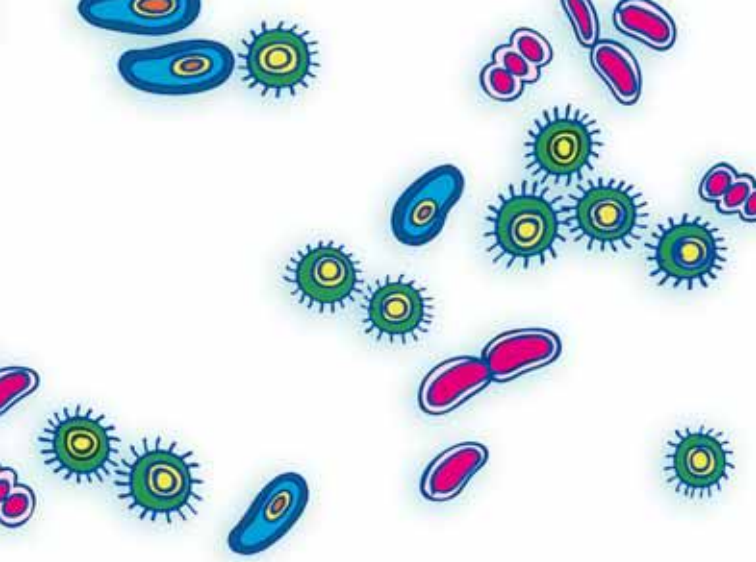




Diagnosis and monitoring
of the main **materno-fetal**
INFECTIONS



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Introduction

- This booklet aims at providing healthcare professionals with a practical, but non-exhaustive, guide for the diagnosis and monitoring of the main infections in pregnant women likely to put the fetus at risk.
- We will examine:
 - when to prescribe tests,
 - what sort of analyses to perform,
 - and how to interpret results.
- Recommendations for screening and disease management can vary from one country to another and although this document cannot cover each local adaptation, it does try to use International guidelines as far as possible.
- Antenatal screening, and more importantly preconception screening, play an essential role in the prevention of vertically transmissible infections. Biological diagnosis is key at all phases of pregnancy as well as for the monitoring of newborns and infants.

Risk of transmission related

	Pregnancy Period	
	1 st trimester	2 nd trimester
Syphilis	●	●
<i>C. trachomatis/N. gonorrhoeae</i>		
<i>Listeria monocytogenes</i>	●	●
Group B <i>Streptococcus</i>		
Rubella virus	●	●
CMV	●	●
Herpes Simplex Virus		
HBV		●
HIV		
Varicella Zoster Virus	●	●
Toxoplasmosis	●	●

● High risk ● Moderate risk ● Low risk

to the time of pregnancy

(Leading to neonatal consequences)

3 rd trimester	Delivery	Newborn
●		
	●	
●		
●	●	
● ○	●	●
● ○	●	
● ○ ○	● ○ ○	●
● ○ ○	● ○ ○	●
●	●	●
●	●	●

5 days before
& HCV
2 days after

○ Higher risk if primary infection ○○ Higher risk if viral load is high

Bacteria, viruses or parasites contracted by the mother (with or without any consequences for her) represent a risk to the fetus. Transmission occurs through the amniotic or hematogenous pathway, during the delivery or after (close contact, breast feeding...).

The most frequently found organisms and the related pathologies are described in the following chapters.

Route of vertical transmission

Based on and adapted from Infections in Pregnant Women, Gilbert GL, MJA 2002, Vol 176: 229-236

Pathogen/Disease	Intrauterine	Perinatal (genital)	Perinatal (hematogenous)	Post-natal
Syphilis	++	--		
<i>Chlamydia trachomatis</i>		++		
<i>Neisseria gonorrhoeae</i>		++		
<i>Listeria monocytogenes</i>	++		+	
<i>Group B Streptococcus</i>	--	+	++	
Rubella virus	++			
Cytomegalovirus*	++	++	++	+
Varicella Zoster virus	+		++	
Parvovirus B19	++			
Herpes Simplex virus*	--	++	++	
Hepatitis B virus	--	++	++	+
Hepatitis C virus	--		++	
HIV	+		++	+
Toxoplasmosis	++		+	

Intrauterine transmission: via the transplacental route (hematogenous or amniotic)

Perinatal transmission: shortly before onset of labour or during delivery via hematogenous or genital route

Postnatal transmission: breastfeeding (exclude nosocomial infections)

++ : important risk

+ : low risk

-- : rare but possible

* : higher risk during primary infection

Syphilis



Infectious agent: *Treponema Pallidum*

Strictly human and pathogen, sexually transmissible.

The WHO reports an estimated 12 million new cases of syphilis annually worldwide, with more than 90% in developing countries.

Prevalence among pregnant women:

in developed countries: 1/10,000.

Clinical symptoms for the mother

The natural course of syphilis is usually characterized by three phases:

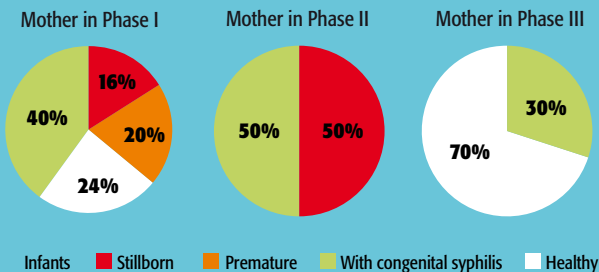
- Primary infection: local with chancre and regional lymph nodes.
- Secondary phase: 10 weeks after primary infection, muco-cutaneous lesions and mild fever and malaise.
- Latent phase: approximately 10 years
- Tertiary phase: cardiovascular and neurological complications

Clinical symptoms for the fetus/newborn

Regardless of the stage of infection of the mother before pregnancy, infection with *Treponema pallidum* can cause congenital syphilis in newborns if passed through the placenta. The risk of infection of a newborn to an untreated mother in phase I or II is 50%.

Transmission occurs essentially in the second half of pregnancy and can lead to preterm delivery, stillbirth or spontaneous abortion.

Untreated syphilis during pregnancy: the phases and their consequences among infants



Congenital Syphilis

Cutaneous and mucosal lesions (palmar and plantar syphilds), bone and joint manifestations, hepatic and pancreatic involvement, ocular manifestations, anemia, neurological lesions.



Biological diagnosis

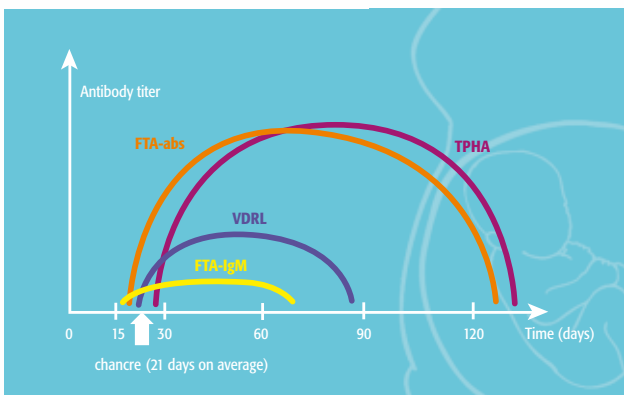
Which test should be prescribed ?

	Screening of the Mother	Confirmation tests	Diagnosis and Monitoring of the Mother	Diagnosis and Monitoring of Newborns
VDRL/ RPR				
TPHA / MHA-TP				
EIA IgG & IgM				
Western blot				
FTA-Abs				
EIA IgM / SPHA IgM				
DGM			Chancere	

Serological tests:
 VDRL: Venereal Disease Research Laboratory
 RPR: Rapid Plasma Reagin
 TPHA: *Treponema pallidum* Hemagglutination Assay
 MHA-TP: Microhemagglutination-*Treponema pallidum*
 EIA: Enzyme-Linked Immunoassay
 SPHA: Solid Phase Hemadsorption Assay
 FTA-abs: Fluorescent Treponemal Antibody Absorption Test

Microbiological tests:
 DGM: Dark Ground Microscopy

Antibody Kinetics Graph



Treatment and Prevention

Long-acting Penicillins: one injection for the mother, and one “booster injection” 1 week later; 10-day treatment for the newborn.

Group B Streptococcus

Group B *Streptococcus* (GBS) remains a leading cause of infection in neonates with associated high morbidity and mortality.

It is responsible for 50% of neonatal bacterial infections.

The bacterium

Streptococcus agalactiae is part of the normal vaginal and rectal flora present in 10 to 25% of pregnant women.

Clinical symptoms for the mother

GBS colonization can be transient, chronic or intermittent.

Most infected pregnant women have no symptoms associated with genital tract colonization.

GBS infection may cause urinary tract infections, prematurely ruptured amniotic membrane, pyelonephritis, chorioamnionitis and endometritis.

Newborns contract GBS during gestation or from the mother's genital tract during labour and delivery.

Several factors can increase transmission: previous Strepto B infection, instrumental delivery, prematurity, GBS bacteriuria during pregnancy.

Clinical symptoms for the newborn

Early-onset GBS disease (80%) occurs within the first week of life, with purpura fulminans sepsis, pneumonia or meningitis.

Late onset (20%) infections can appear between the first week of life and the age of 3 months (average 1 month).

Infection is due to horizontal transmission and symptoms are usually fever with bacteremia and meningitis.

Biological diagnosis

- Prenatal screening (35-37 weeks gestation): culture based tests using vaginal and/or rectal specimens. Selective culture media enable isolation and identification from 18-24 hrs to 48 hrs.
- Neonates: blood culture, Cerebro Spinal Fluid culture (CSF), miscellaneous specimen collections: pharyngeal, auricular, meconium, gastric aspiration (gastro-intestinal content).





Molecular tests take less time than culture but are still too long (around 1 hour) and their use is limited by:

- the need for having skilled technicians 24hrs a day, 7 days a week.
- the high cost

Treatment and Prevention

GBS screening & maternal intrapartum antibiotic therapy are currently considered to be the most effective strategy to decrease the incidence of GBS infections in newborns.

In 1996, the CDC published guidelines for the prevention of perinatal group B streptococcal disease. In their revised Guidelines (CDC, 2002, 2010), many of the recommendations remain the same but they include some key changes.

This strategy is followed or locally adapted by most industrialized countries.

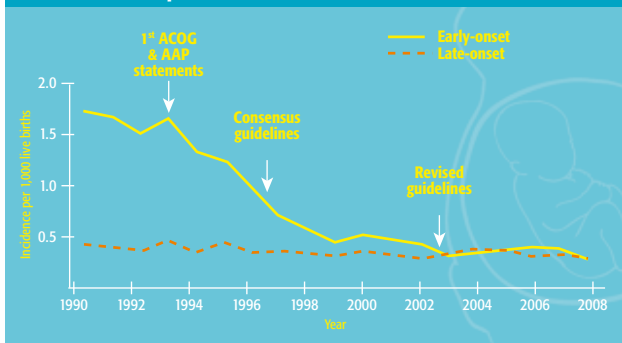
The CDC guidelines (2010) recommend:

- **UNIVERSAL PRENATAL SCREENING** for vaginal and rectal GBS colonization of all pregnant women at 35–37 weeks' gestation, based on a large retrospective cohort study of a strong protective effect of this culture-based screening strategy relative to the risk-based strategy.

Intrapartum antibiotic prophylaxis for positive women.

Penicillin remains the first-line agent for this prophylaxis, with amoxicillin being an acceptable alternative.

Incidence of early- and late-onset invasive group B streptococcal (GBS) disease - Active Bacterial Core surveillance areas, 1990-2008, and activities for prevention of GBS disease



Source : Jordan HT, *et al.* *Pediatr Infect Dis J.* 2008;27:1057-64

Abbreviations: ACOG = American College of Obstetricians and Gynecologists

AAP = American Academy of Pediatrics

CDC = Centers for Disease Control and Prevention

Listeria

Infectious agent

Listeria monocytogenes: Gram-positive bacilli (ubiquitous), present in the environment and animals. Infections occur mainly in fragilized populations (the elderly, immunocompromised patients or pregnant women). They are rare but severe (total mortality rate 25-30%). Maternal transmission occurs via contaminated food.

Clinical symptoms for the mother

Mild, flu-like illness with gastro-intestinal symptoms, fever and muscle aches.

Maternal contamination to the fetus occurs through the placenta (bacteremia in the mother)

Clinical symptoms for the fetus/newborn

Listeriosis is rare but often causes congenital infection: increase in pre-term labour/ premature birth/ still birth, spontaneous abortion in the first 4 months, neonatal sepsis or meningitis with an associated mortality rate of 50%.

Early onset neonatal listeriosis: during the 4 first days of life, mainly in premature newborns: severe septicemia (mortality rate 50%).

Late onset neonatal listeriosis: up to 10 days after birth, mainly meningitis.

Biological diagnosis

- For the mother: blood culture (for any type of fever without explanation).
- For the newborn: blood culture, CSF culture, miscellaneous collections: pharyngeal, auricular, meconium, gastric aspiration (gastro-intestinal content).

Typing can be used for epidemiological purposes.

Treatment and Prevention

- Prevention: well cooked food, avoid unpasteurized milk and soft cheese, smoked food (fish...), clean raw vegetables. Safe food handling and storage, hand washing.
- Treatment: Ampicillin is the treatment of reference. It can be associated with aminoglycosides. The minimum therapy is 15 days in pregnant women.

Listeria monocytogenes is resistant to cephalosporins.





Other bacteria presenting a risk for newborns and for which biological examinations are recommended for the mother

Clinical Indication	Type of Specimen	Bacteria	Risk for the Fetus/Newborn
At risk for Sexual Transmissible Diseases: multiple partners or STD in partner	Vaginal - cervical	<i>N. gonorrhoeae</i> & <i>C. trachomatis</i>	Conjunctivitis; pneumonia for the newborn (<i>C.trachomatis</i> only)
Cervicitis - vaginitis	Vaginal cervical-rectal	<i>Trichomonas vaginalis</i>	Chorioamniotitis, prematurity
Bacterial vaginosis or history of vaginosis	Vaginal	<i>Gardnerella vaginalis</i> , <i>Mycoplasma hominis</i> , etc.	Chorioamniotitis, prematurity
Premature rupture of the membranes	Vaginal	SGB, <i>E. Coli K1</i> , Enterobacteria, <i>H. influenza</i> , <i>S. aureus</i> <i>S. pneumoniae</i>	Prematurity, sepsis
History of risk of pre-term labour	Vaginal (at the beginning of pregnancy)	<i>Gardnerella vaginalis</i> , <i>Mycoplasma hominis</i> , <i>Ureaplasma urealyticum</i>	Prematurity sepsis
Unexplained fever	Blood	Listeria	Abortion, sepsis, meningitis
Urinary Tract Infection with negative culture	Vaginal	Listeria	Fetal growth restriction prematurity



To find out more on cervico-vaginal infections consult our specific clinician booklet.



Vaginal infections are asymptomatic in 50% of cases

Cytomegalovirus

CMV is one of the world's most widespread infections, with prevalence of the virus from 40% to 90% depending on the country.

Congenital CMV infections are found in 0.1 to 1% of births.

Infectious agent

CMV belongs to the herpes virus family, is strictly human, usually with low pathogenicity, except in immunocompromised patients or fetuses.

Clinical symptoms for the mother

Primary infection in pregnant women is 1-4%. It is associated with a 30-70% transmission rate to the fetus depending on the stage of pregnancy. It causes more complications than a simple re-infection.

The disease is generally silent or with only a mild fever (mononucleosis-like illness).

Transmission occurs through the hematogeneous pathway during pregnancy, perinatally through contact with maternal blood or vaginal secretions, or post-natally through breast feeding.

Clinical symptoms for the fetus/newborn

The majority of infected newborns present no clinical symptoms.

30 to 70 % of fetuses will be infected depending on the stage of pregnancy. 5 to 10 % of them will be symptomatic at birth:

psychomotor and mental retardation, hepatitis, thrombocytopenia, bronchitis, mononucleosis syndrome and deafness.

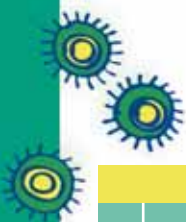
The severity of the anomaly is less if induced by secondary infection (re-infection or re-activation).

90% of the asymptomatic cases will have normal development and 10% may develop late disorders (mainly deafness).

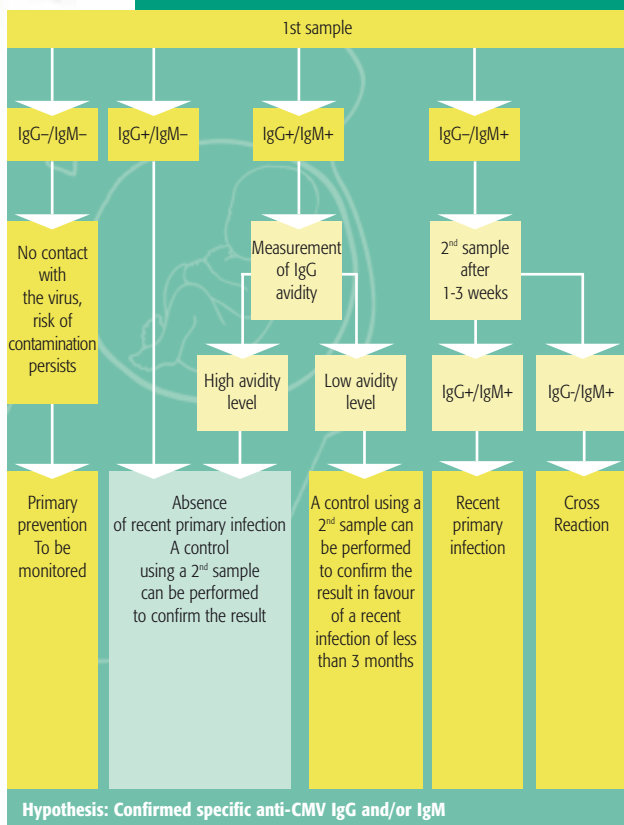
Biological diagnosis

- **Mother:** Serology testing can indicate past infection. The appearance of IgM when monitoring previously IgG-negative pregnant women may indicate the beginning of seroconversion. The appearance of IgG must be confirmed using a 2nd sample collection. Low anti-CMV IgG avidity demonstrates primary infection whereas high avidity excludes primary infection. It is recommended that a second sample be collected to control the result.
- **Fetus:** Prenatal diagnosis includes viral culture and/or molecular testing using amniotic fluid, 6 weeks after seroconversion and after the 21st week of gestation.
- **Newborns:** Diagnosis of congenital infection is based on molecular testing or viral culture performed using urine/saliva samples within the first 2 weeks after birth. The presence of specific IgM indicates congenital infection, but their absence does not rule out infection.





Serological diagnosis of a CMV infection



* IgM, usually persists for several months except in some cases when it is ≤ one month.

Treatment and Prevention

No effective *in utero* treatment has been approved for congenital CMV infection.

For this reason, prevention measures are essential:

Avoid contact with urine or saliva from young children, wash hands carefully after these types of contact, avoid tasting feeding-bottles or food when feeding babies or children, do not share toiletries used for childcare, avoid kissing children directly on mouth and any contact with biological liquids such as tears...

Varicella-Zoster



Infectious agent

Varicella-zoster virus (VZV) belongs to the *Hesperiviridae* family. It has two clinical expressions:

- Varicella (Chickenpox) is the primary infection, usually benign for children but potentially severe for adults, immunocompromised patients or newborns. It is one of the most contagious infections. 90 to 95% of adults are immune.
- Herpes zoster (shingles) is the reactivated form of latent VZV infection. Varicella during pregnancy carries a high risk of maternal complications and a risk of transmission for the fetus. Due to the high rate of adult immunity (more than 90%), the disease is pretty rare (5-7 cases/10 000).

Clinical symptoms for the mother

Varicella is responsible for higher morbidity and mortality in adults including pregnant women, the most severe and frequent complication being pneumonia, with 10% mortality rate if no treatment is administered.

Maternal herpes zoster infection is not clinically different from infection in non-pregnant women.

Clinical symptoms for the fetus/newborn

Transmission rates of varicella through the placenta or at delivery (5 days before, 2 days after) are less than 10% and 25-50%, respectively.

- *In utero* infection: before 20-24 weeks of gestation the risk of abnormality is approximately 2%; congenital malformations (skin lesions, musculoskeletal, ocular and CNS abnormalities), herpes zoster during the first year of life. After 24 weeks, mainly cutaneous lesions and herpes zoster during the first year of life.
- Neonatal infection: contamination at delivery leads to potentially severe varicella.

Herpes zoster in pregnant women has no consequence for the fetus.

Biological diagnosis

- Maternal: in case of difficult diagnosis, molecular methods are used on vesicle samples. Serological IgM & IgG tests can also be performed.
- Fetal: molecular tests using amniotic fluid, 6 weeks after seroconversion and after the 21st week of gestation.

Prevention

- Specific immunoglobulins can be given by injection to the mother but efficacy is uncertain.
- Vaccination before pregnancy of non-immune women.

Treatment

- Systematic treatment of the mother in case of severe maternal varicella, regardless of time of onset during pregnancy: antiviral therapy. If near to term, after therapy wait until the maternal immunoglobulin antibody rises before allowing delivery.
- Provide antiviral therapy and immunoglobulins for the newborn if perinatal varicella.

Hepatitis B virus



Infectious agent

HBV is a DNA virus in the *Hepadnaviridae* family.

Worldwide, 1/3rd of the population has been in contact with the virus and 400 million cases have evolved to become chronic HBV carriers.

Prevalence of chronic carriers among the population varies from <1% in developed countries to 20 % in developing countries.

70% of chronic carriers are located in Asia.

Mother-to-child transmission accounts for 5% of the infected Asian population.

HBV is the tenth cause of mortality mainly related to hepatocarcinoma.

The disease is 50-100 times more infectious than HIV and is transmissible through multiple routes: blood, saliva, unsafe injections, sexual contact, perinatal.

Mother to child transmission

Most perinatal transmissions (85–95%) result from intrapartum exposure to contaminated blood and genital tract secretions.

The frequency of transplacental transmission varies depending on the viral load which is usually indicated by the presence of HBe Ag and the time of HBV infection during pregnancy. It is about 10% if HBe Ag is absent, but 90% if HBe Ag is present.

Clinical symptoms for the mother

When symptomatic during the acute phase, HBV clinical pattern is: flu-like symptoms (sickness, nausea, vomiting, anorexia, fatigue), followed by jaundice, white stools and dark urine.

Chronic carriers are usually asymptomatic and mainly detected during routine blood test or at complicated cirrhosis stages.

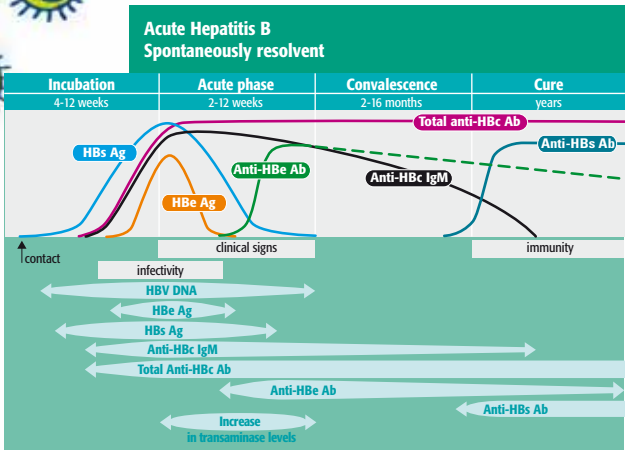
Clinical symptoms for the fetus/newborn

Usually clinically asymptomatic, HBV infection in children evolves toward chronic carriage in 95% of cases if no preventive measures are taken at birth.

Biological diagnosis for pregnant women

All pregnant women should be tested for HBV during pregnancy by screening for HBsAg. If the mother is identified as a HBV carrier, she should be closely followed-up to determine the stage and activity of the disease, and referred to a liver specialist.

Antibody evolution profile



Treatment and Prevention

Cesarian sections have not been found to prevent HBV transmission from mother to child. To protect the baby from HBV infection, preventive measures should be planned for the delivery.

Breast feeding is safe if the newborn is vaccinated.

Currently, antiviral treatment is not recommended during pregnancy but can be considered depending on the risk of further liver damage.

Newborns from infected mothers are treated with specific HBV immunoglobulin and vaccinated within the first 12 hours of life.

The complete HBV vaccine series (2 doses at 1 and 6 months of age) should be performed.

Note: HBV vaccine is not contraindicated during pregnancy.

Hepatitis C virus



Infectious agent

HCV is a single-stranded RNA virus belonging to the *Flaviviridae* family.

HCV infection is estimated to represent 170 million chronic carriers worldwide.

The world prevalence of chronic HCV infections is estimated to be around 3% of the whole population and was found to be similar in pregnant women. Frequency ranges from 0.5 to 19% and depends on the endemic HCV rate in the geographical area concerned (0.5 to 3% in developed countries and up to 19% in Egypt) and behavioural risk factors (IVD users).

Mother to child transmission

HCV is transmitted from about 2-8% of infected women to their infant. The hepatitis C viral load within the maternal blood influences the probability of vertical transmission to the infant. Transmission increases substantially with concomitant HIV infection (from 5-15%). The delivery method, as for HBV, does not reduce the risk of transmission. Breastfeeding is safe unless the nipples bleed or crack.

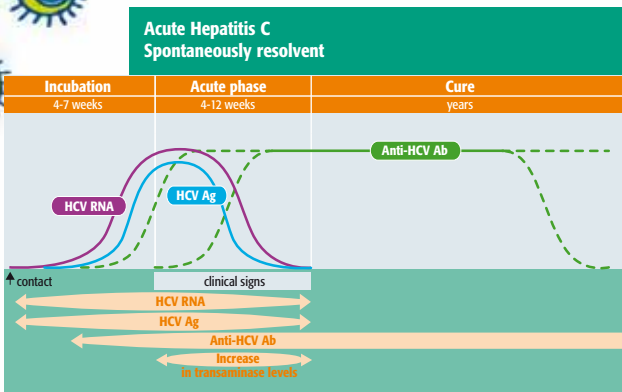
Clinical symptoms and clinical course

HCV infection usually remains asymptomatic and evolves to chronicity in 85% of cases.

In pregnant women, the natural course of HCV infection during pregnancy is a significant reduction in ALT levels during the 3rd trimester with an increase during the post-partum period. It is interesting to note that the viral load increases in this period and is not correlated with the ALT level reduction but with liver damage. Invasive investigation of liver disease in HCV positive pregnant women should be postponed until after delivery.

In children, as for other hepatitis viral infections, HCV infection is asymptomatic.

Antibody Evolution Profile



Biological diagnosis

Pregnant women belonging to an at risk population (i.e. exposed to unsafe injections or transfusions) should be tested for HCV by screening for HCV Ab.

In babies, RNA detection is used as their mothers' antibodies are passively passed on to them during pregnancy and persist until 18 months of age. However, it can take several months after birth for the RNA virus level to be high enough to be detected, therefore repeated testing during the first year of the baby's life is often necessary.

Treatment and Prevention

Experience of treatment in children is limited.

If the **infected woman** is undergoing antiviral treatment, pregnancy should be discouraged due to the teratogenic effect of ribavirin.

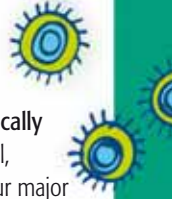
When chronic HCV infection is diagnosed for the first time during pregnancy, administration of treatment should be postponed.

Current treatment for HCV infection is effective in about 90% of acute cases and 50% of chronic cases, depending on the genotype.

The medication used is ribavirin combined with alpha-interferon or pegylated interferon.

No vaccination is available. A large number of mutant viruses known as quasi-species are generated during virus replication. These quasi-species pose a major challenge with respect to immune-mediated control of HCV and may explain the variable clinical course and the difficulties in vaccine development.

Hepatitis E



Infectious agent

Hepatitis E virus (HEV) is the major etiological agent of **enterically transmitted** non-A, non-B hepatitis worldwide. It is a spherical, non-enveloped, single stranded RNA virus and up to now, four major genotypes (I to IV) have been described.

HEV infection mainly occurs through large outbreaks in developing countries where the hygiene level is low.

Distribution according to geographical areas is not yet well established and seroprevalence varies from 5-25%. It is the most frequent cause of clinical hepatitis in adults mainly in South-East & Central Asia and India. In India, the seroprevalence is low below 10 years of age and reaches a plateau at 40% for 16-25 year olds. In the Middle-East and Africa, HEV is the second most commonly found hepatitis infection after HBV.

Clinical symptoms

In the acute phase, the disease cannot be distinguished from other viral hepatitis cases in terms of clinical symptoms. However, it is usually not severe and usually resolves within a few weeks.

There is no risk of chronic disease.

Signs and symptoms typically appear within 2 weeks to 2 months after exposure to HEV. About 40% of people infected with HEV become ill.

The main characteristics of HEV is the frequency of fulminant forms which lead to fatal outcomes (on average 1%).

Pregnant women are particularly at risk with a 20% mortality rate when primary infection occurs during the 3rd quarter of pregnancy. For children, HEV infection is a major cause of fulminant hepatitis.

Biological diagnosis

Diagnosis is performed by detecting HEV IgM at the beginning of the disease, given that IgG's are also present at this stage.

Treatment and Prevention

There is no treatment nor vaccine available against HEV infection. Treatment is usually focused on relieving signs and symptoms.

Parvovirus B19

Although responsible for benign infections in adults and children, Parvovirus B19 can be at the origin of severe fetal infections.

Infectious agent

Parvovirus B19 belongs to the *Parvoviridae* family and is the only parvovirus which can be transmitted to humans. Its pathogenicity stems from its cytopathic effect on reticulocytes in bone marrow.

40 to 60 % of adults have become immunized to this virus.

Infection with Parvovirus B19 is generally non-symptomatic or gives a rash and moderate fever in young children (erythema infectiosum or Fifth disease).

Clinical symptoms for the mother

The materno-fetal transmission rate is estimated to be between 25 - 30%. Transmission usually occurs through respiratory secretions and the majority of pregnant women are contaminated by young children but are non-symptomatic in 25% of cases.

The infection is usually suspected when abnormalities are detected during ultrasound scan examination, or by the presence of a red facial rash (often termed as "slapped-cheek" syndrome) with arthralgia, or severe anemia, or from known contact with an infected child.

Clinical symptoms for the fetus/newborn

When primary infection occurs before the 20th week of gestation, there is an estimated 2-10% risk that Parvovirus B19 can cause fetal death, with or without hydrops fetalis. Severe anemia leads to heart failure, but also direct myocardial disorders. If the newborn survives hydrops fetalis, then generally there are no sequelae.

Biological diagnosis

Mother: After contact of the pregnant woman with an infected child, or in the case of clinical symptoms or abnormal ultrasound examination, the diagnosis of Parvovirus B19 infection is based on the presence of IgG and IgM. IgM appear 15-20 days after viral contact, but may have already disappeared at the time of the abnormal ultrasound examination. A negative IgG result excludes infection.

Newborn: Etiological monitoring of hydrops fetalis using amniotic fluid and/or fetal blood is performed using the direct detection of viral DNA.

Treatment

Regular monitoring using ultrasound scan examination of hydrops fetalis can, depending on the level of fetal anemia, lead to ex-sanguineous transfusion.

HIV

Infectious agent

HIV is an enveloped virus, belonging to the *Retroviridae* family (sub-family: *Lentivirinae*).

It has a tropism for CD4+ lymphocytes and monocytes and has three enzymes which are required for multiplication.

Clinical symptoms for the mother

- Primary HIV infection: possibly fever ($\geq 38^{\circ}\text{C}$), asthenia, adenopathy, skin rash, myalgia, arthralgia, cephalgia and pharyngitis. These symptoms disappear rapidly and spontaneously.
- Asymptomatic carrier phase: if no anti-retroviral treatment is given, the average incubation period for AIDS is estimated to be 8 years.
- AIDS: different symptoms appear, indicating clinical deterioration such as chronic fever, weight loss, diarrhea, oral candidiasis, herpes zoster. At the same time, biological analysis will reveal immunosuppression shown by the presence of CD4 lymphopenia ($< 200/\text{mm}^3$). The development of opportunistic infections (pneumocystosis, toxoplasmosis, mycobacteria infections, severe cytomegalovirus infections, etc.) and cellular proliferation (Kaposi's Sarcoma, B-cell lymphoma, cervical cancer, etc.) mark the progression to full-blown AIDS.

Mother to child transmission

HIV can be transmitted from mothers to infants during three periods: prenatal (rare), peri-natal (the most frequent), and post-natal (through breastfeeding).

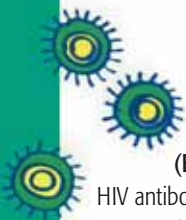
Clinical symptoms for the fetus/newborn

HIV does not increase the risk of malformation and unspecific signs of the disease are usually not present at birth and appear during the first few months of life after infection.

Without treatment there are two forms of infection:

- A fast evolutive disease, with AIDS clinical symptoms (mainly encephalopathy, hematological disorder) present during the first year of life. Without any efficient treatment, death will occur in less than 4 years.
- The most common form progresses more slowly: complications are lymphoid interstitial pneumopathy and dilated cardiomyopathy. After 1 year the progression to death is variable.





Biological diagnosis

Identification of HIV antibodies using **immuno-enzymatic (ELISA) tests**. Such detection methods are effective because HIV antibodies are produced continuously and are detectable as early as several weeks after infection (on average 22 days). Serological testing is also practical to perform. Most antibody assays detect both HIV-1 and HIV-2 antibodies.

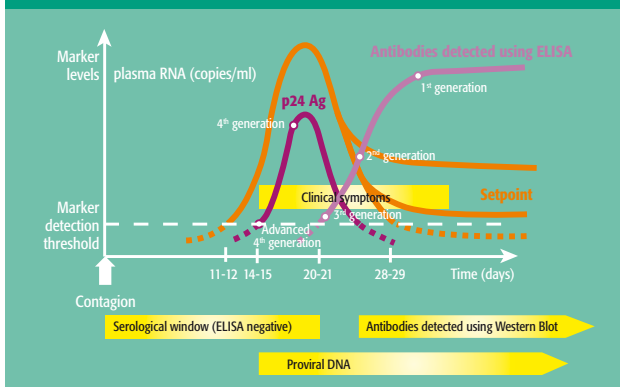
4th generation tests (HIV1 p24 antigen and antibodies) reduce the serological window for the detection of HIV-1 by approximately one week when compared to 3rd generation tests (antibodies alone).

4th generation "advanced" tests enable the differentiation between antibody and antigen signals.

Rapid, single-use tests are slightly less sensitive and specific than ELISA tests. However, as these tests are easy-to-use and do not require sophisticated equipment, they lend themselves well to use in emergency situations and in areas where testing using sophisticated techniques is not feasible.

A confirmation test is absolutely necessary in cases of positive results: Western Blot or immunoblot and re-confirm positivity using a new blood collection. It is strongly recommended to use tests that distinguish between HIV-1 and HIV-2, as the viral load progression and therapeutic choices may be different depending on the virus.

Kinetics of viral markers during the early stages of infection



(See also bioMerieux's specific clinician booklets: "Interpretation algorithms for 4th generation HIV serology tests" and "Diagnosis and monitoring of HIV infection".)

Biological follow-up of pregnant women and newborns

Biological monitoring of HIV infection is essentially based on CD4+ lymphocytes and viral load (quantification of plasma viral RNA). These tests are usually performed every 6 months if the CD4 count is $> 500/\text{mm}^3$ and every 3 to 4 months if the CD4 count is between $200-500/\text{mm}^3$. Given that the Hepatitis B (HBV) and C (HCV) viruses are important co-morbidity factors, screening for possible co-infection with one of these two viruses should also be carried out.

Treatment and prevention

Antiviral Therapy (ART) should be given at the end of the 2nd quarter to reduce perinatal transmission, or earlier if viral load is high. Breast feeding is contraindicated.

ART is recommended for the newborn until 6 weeks of age.

Vertical transmission in industrialized countries is now rare due to the use of antiretroviral therapy and alternative feeding methods as well as delivery by caesarean section (approximately 1-2% compared to 15-30% when no preventive measures are taken).

Early Infant Diagnosis (EID)

Infants can be tested for HIV using molecular biology techniques as early as six weeks of age. However, this requires taking a blood sample that must be kept refrigerated during transport to a testing facility. Recently, a new technology, known as the Dry Blood Spot (DBS), has emerged that facilitates blood sample collection and allows molecular testing to be performed on small spots of dried blood. DBS are easy to prepare and can be stored and transported to testing facilities without refrigeration. This simple technology can lead to more rapid treatment for infants with HIV.



Rubella

Rubella is a short-lived viral infection, generally mild and benign in adults and children. Severe consequences can occur when women are infected during pregnancy.

The incidence of Congenital Rubella syndrome (CRS) is between 1 and 10 cases for every 100,000 births, and more in some countries.

Infectious agent

Rubella virus is part of the *Togaviridae* family, gender Rubivirus.

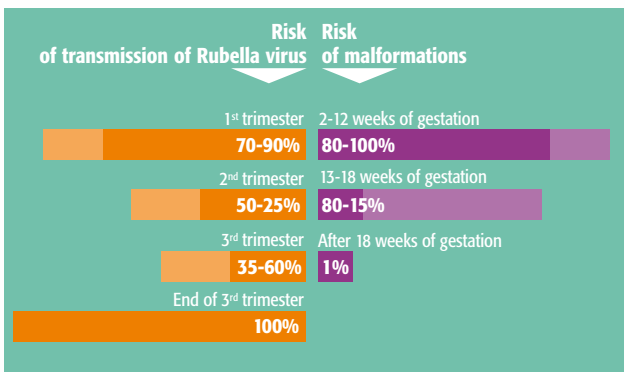
Clinical symptoms for the mother

Clinical symptoms appear after the incubation phase of 13-20 days, and are characterized by lymphadenopathy, maculopapular rash and fever.

In some cases, there is arthralgia (30% of adults), encephalitis (1 case out of 10 000) with good prognosis and thrombocytopenia. After a primary infection, adults have long-term immunity, but sometimes, it is possible to have a new infection. The incidence of this type of re-infection during pregnancy is not known.

Congenital Rubella

The rate of transmission is variable depending on fetal age at the onset of contamination.



Congenital Rubella Syndrome (CRS): low birth weight, ocular disorders, deafness, cardiac malformation, and mental retardation.



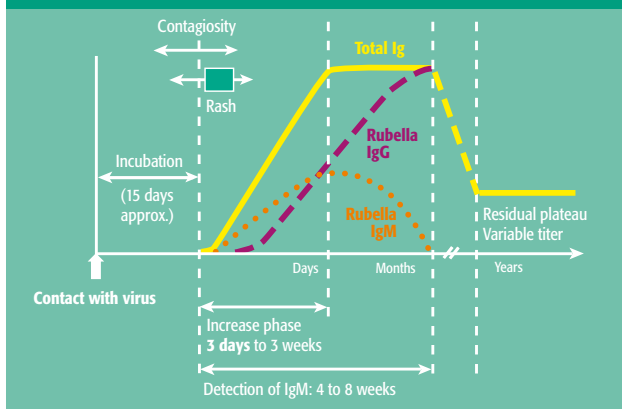
Biological diagnosis

• **Mother:** Given the severe complications which can result from Congenital Rubella, it is important to determine the immune status of women of childbearing age, preferably before pregnancy, to vaccinate those who are seronegative. If no determination has been performed prior to conception, it should be carried out as soon as pregnancy is confirmed to ensure monitoring of women who are not immune.

Carry out an IgM assay in the following cases:

- possible contact with the disease,
 - if clinical symptoms suggest primary infection,
 - seroconversion or if raised IgG levels are observed during systematic checks.
- **Fetus:** Prenatal diagnosis involves detection of IgM in fetal blood and/or viral RNA in amniotic fluid using molecular testing, 6 weeks after seroconversion and after the 21st week of gestation.
- **Newborn:** IgM indicate the presence of congenital infection.

Kinetics of antibodies during rubella infection



Treatment and prevention

As there are no active antiviral drugs for Rubella it is essential to vaccinate the general population to prevent Congenital Rubella Syndrome. Vaccination should certainly be given to women, but also to men since they are also vectors of the disease.

The incidence of Congenital Rubella Syndrome (CRS) remains between 1-10 cases for every 100 000 births (more in some countries).

Efficient vaccination can easily prevent this.

Herpes Simplex Virus

Infectious agent

Herpes Simplex Virus (HSV) is part of the *Herpesviridae* family.

This neurotropic DNA virus has a capsid and an envelope.

Both HSV type 1 and HSV type 2 cause genital herpes.

Congenital herpes infection is rare (4/100 000 live births in the US), but severe: mortality is 50%.

Clinical symptoms for the mother

HSV can be transmitted at term to neonates from mothers with primary or initial genital herpes. In 90% of cases, genital herpes is acquired by cervical or lower genital contact at delivery (the risk is about 50% in cases of primary infection, but less than 4% in case of maternal recurrence, 1/1000 if history of genital herpes without visible lesions). Transplacental passage is rare.

In 66% of cases, the mother has no symptoms or no known history of genital herpes (up to 20% of women may be seropositive for HSV2, but this figure is highly variable depending on the country).

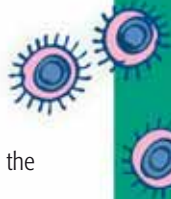
Clinical symptoms for the fetus/newborn (clinical features of neonatal infection)

- Disseminated forms: the disorder may appear at birth or up to 7 days after birth. Symptoms are very often non-specific: lethargy, convulsions, dyspnea, jaundice, fever... In the absence of vesicular rash (50% of cases), diagnosis is difficult. Central nervous system lesions are present in half the cases diagnosed. Even with antiviral treatment, mortality is high (50%) and in the survivors there are severe sequelae.

Localized forms:

- Central nervous system: meningo-encephalitis
- Eye, skin and mouth: conjunctivitis, keratitis and occasionally chorioretinitis, vesicular lesions, gingivo-stomatitis

50% of neonatal infections are not associated with any known history of genital herpes



Biological diagnosis

- Virus isolation is the reference method: for genital specimens in the mother and several specimens in the newborn (skin lesions, urine, pharynx, eyes...).
- Molecular tests are the method of choice for CSF specimens, since they are more rapid and more sensitive than viral culture.

Treatment and Prevention

- History of genital herpes in the pregnant woman and her partner.
- Virological confirmation of suspected genital lesion in pregnant women.
- Genital examination at the beginning of delivery, when there are no clinical symptoms.
- Caesarian delivery only if genital lesions are present at the time of birth.
- Prevention using condoms when the partner has a history of genital herpes.
- Antiviral treatment for genital herpes.

Impact of maternal genital herpes on neonatal herpes

(from F. Denis, in *Virus transmissibles de la mère à l'enfant*)

Maternal Status	Frequency in Mothers of Infected Children	Risk of Herpes for the Child	Recommendation
Primary infection in pre-partum (or in the previous month)	rare	++++ 75%	Cesarian Treat using ACV
Recurrence in pre-partum (or in the past few days)	+	++ 2 – 5%	Cesarian
History of genital herpes (mother or her partner)	++	+ 1/1000	Birth canal after Betadine®. Isolation of HSV only at full term. If +, decide whether to implement ACV for child
No sign of genital herpes	+++ Two thirds of cases	± 1/10 000	Do nothing, Protection against STD



Toxoplasmosis

Infectious agent

Toxoplasma is an obligate intracellular protozoan parasite and is very prevalent in humans (in some countries 50% of the population is infected). Toxoplasmosis is generally very mild in the immunocompetent host, but can be severe in immunosuppressed patients and fetuses.

The parasite infects most warm-blooded animals, including humans, but the primary host is the feline (cat) family. Animals are infected by eating infected meat, through contact with cat feces, or by transmission from mother to fetus. The most common means of transmission to humans is raw or undercooked meat, or raw vegetables.

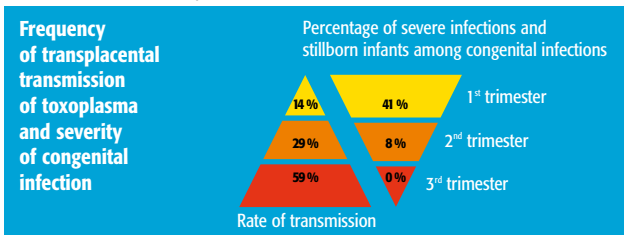
Clinical symptoms for the mother

Toxoplasmosis causes usually mild or no illness, or a flu-like illness. Most of the time, healthy people who have been infected do not know their status.

When the immune system is depressed, it can cause encephalitis and neurological disease and can affect the heart, liver, and eyes (chorioretinitis).

Clinical symptoms for the fetus/newborn

Transmission to the fetus is the result of transplacental transmission of toxoplasma during the acute phase of the disease. The frequency and severity of fetal infection is dependent on several factors, including the date of onset of the maternal infection, the virulence of the parasite strain, the quantity of the inoculum and the quality of the mother's immune response.



Most congenital toxoplasmic infections are asymptomatic at birth; clinical symptoms may appear later. Consequences of congenital toxoplasmic infection can be severe: death *in utero*, hydrocephaly, microcephaly, encephalitis, intracranial calcification, chorioretinitis, blindness, convulsions, psychomotor and/or mental retardation.

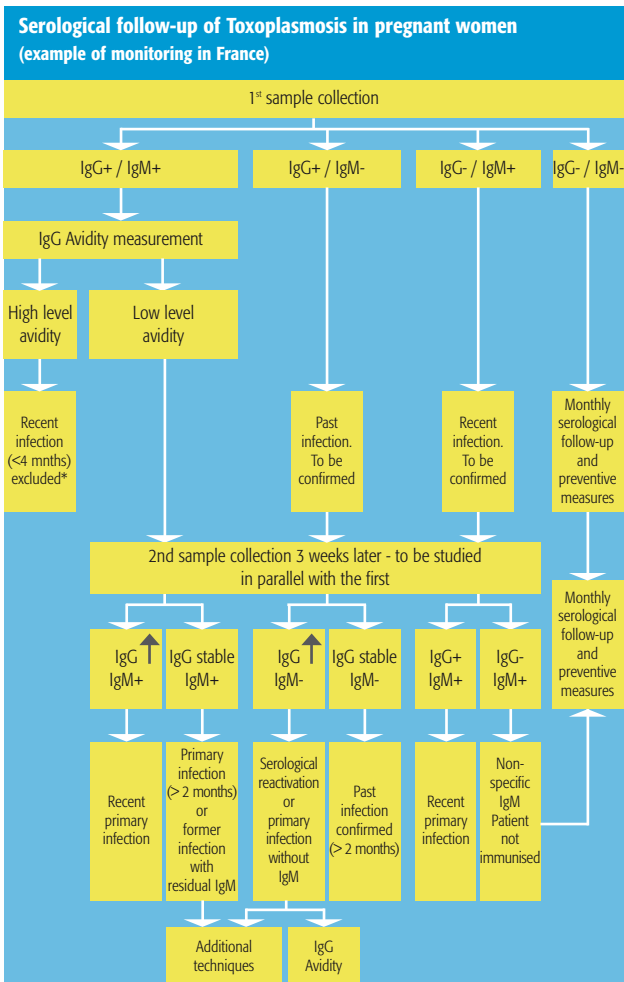
Biological diagnosis

Diagnosis of Toxoplasmosis is based essentially on the detection of specific immunoglobulins (IgM and IgG).

Acute infection acquired during pregnancy is diagnosed by detecting seroconversion in patients who were previously identified as being negative, or by a significant rise of the antibody titer detected in two sequentially tested samples.

The possibility of recent infection is ruled out by measuring the IgG avidity.

Other reference tests or very sensitive tests are also useful such as the Dye test (Reference test for IgG detection using live toxoplasma), ISAGA test (agglutination test specific to IgA or IgM), molecular tests using amniocentesis or plasma samples from newborns.



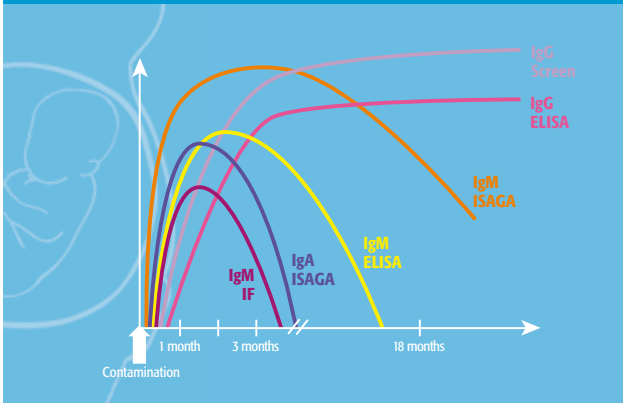
* according to product package insert or manufacturer's recommendations



Important notes for toxoplasmosis serology

- Positive reactions are easier to interpret when performed early in pregnancy.
- Seroconversion is defined by the appearance of IgG; confirmation should be performed using a 3rd sample collection.
- A 3-week interval between 2 sample collections is necessary to confirm IgG titer stability; but 10 to 15 days can sometimes be sufficient to detect an increase.
- The presence of IgM is rare in cases of reactivation.
- Right from the 1st sample, an avidity index (IgG) can exclude most of the recent infections.
- However, low avidity (IgG) usually persists for many months.
- Checking for clinical symptoms and the use of additional techniques (differential agglutination, IgA detection...) may be necessary to accurately date infection.

Antibody kinetics during toxoplasmosis infection



Treatment and Prevention

Treatment of the mother: spiramycin until delivery.

If fetal infection is proven or strongly suspected: pyrimethamine + sulfonamides + folinic acid, as a replacement for spiramycin.

Treatment of infected infants: whether or not there are any clinical symptoms: pyrimethamine and sulfonamides for at least one year.

Prevention: when seronegative, several measures are essential:

- Avoid contact with cat litter or earth that is potentially soiled and wear gloves when handling it.
- Cook meat well, avoid meat that has been marinated, smoked or grilled. Choose fish or poultry when eating out. Toxoplasma is killed when meat is frozen.
- Wash raw vegetables well or avoid.
- Wash hands after touching any soiled items or instruments that have been in contact with these elements.

Questions/Answers

1. When confirming pregnancy for a young woman, her toxoplasmosis screening test is found to be: IgM antibody positive, IgG antibody positive. Which additional test should be performed?

Perform an avidity test and another IgG test after 2 to 3 weeks, to confirm or exclude primary infection.

2. What is a toxoplasmosis IgG Avidity test? What is it used for?

IgG avidity corresponds to the capacity of the antibodies to link with antigens. In recently acquired infections, the IgG avidity level is low, whereas in the case of a former infection, the avidity level may be low or high. A high avidity level can help to exclude a recent infection, but a low avidity level cannot confirm recent infection.

3. A 29 year old pregnant woman (15 weeks gestation) was in contact with an infant with chickenpox. She does not know her immune status. What would you do?

- IgG antibody testing to check her immune status: the probability of being immune to varicella is high in the Northern hemisphere (> 90%).
- If IgG are negative, there is a risk of primary infection. If primary infection is confirmed, the risk of abnormalities in the fetus is less than 2%. In this case, post-exposure antiviral therapy, such as acyclovir may be prescribed (or administration of specific immunoglobulins). Pregnant women with clinical symptoms are generally hospitalized (risk of pneumonia).

4. An 8-month pregnant woman has an isolated fever (> 38°C) for 2 days. Which diagnostic tests do you recommend ? What else would you do?

- These symptoms can be linked to many different causes. Priority testing should be given to: pyelonephritis, Listeria and malaria (depending on case history) since they can be treated.
- Viruses can often also be the cause. However, depending on the virus, and given the late stage of pregnancy, no specific treatment is generally necessary.

5. When confirming the pregnancy of a young woman she informs you that her partner has a history of genital herpes. What would you do ?

The risk of genital herpes is mainly at the end of pregnancy. Condoms are recommended to avoid transmission. Serology is not necessary.

6. When screening for HBV in a 6-month pregnant woman, HBs Ag is found to be positive. What other biological analyses would you perform ?

- Viral load: will be positive in the presence of active viral replication, with a major risk of viral transmission during delivery: a double dose of immunoglobulins will be necessary for the newborn, in addition to the vaccination.
- HBe IgM: to determine the disease status: positive if acute hepatitis.

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HIV

- 4th generation screening tests
 - Vironostika® HIV Ag/Ab
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- "Advanced" 4th generation screening tests
 - VIDAS® HIV DUO ULTRA
- Determination of p24 antigen
 - VIDAS® HIV P24 II
 - VIDAS® HIV P24 II Confirmation
- Determination of HIV viral load
 - NucliSENS Easy Q® HIV-1 v2.0
- Rapid test
 - VIKIA® HIV 1/2

Hepatitis

- | | |
|---|---|
| Hepatitis A <ul style="list-style-type: none">VIDAS® HAV IgMVIDAS® anti-HAV Total | Hepatitis B <ul style="list-style-type: none">VIDAS® HBs Ag UltraVIDAS® HBs Ag Ultra ConfirmationVIDAS® Anti-HBs Total QuickVIDAS® Anti-HBc Total IIVIDAS® HBc IgM IIVIDAS® HBe-Anti HBeHepanostika® HBs Ag Ultra (microplates)Hepanostika® HBs Ag Ultra Confirmatory (microplates)Hepanostika® Anti-HBc Uni-form (microplates)VIKIA® HBs Ag (rapid test) |
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Rubella

- VIDAS Rub IgG II
- VIDAS Rub IgM

CMV

- VIDAS® CMV IgG
- VIDAS® CMV IgM
- VIDAS® CMV IgG Avidity

Varicella

- VIDAS Varicella-Zoster IgG

Toxoplasmosis

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| <ul style="list-style-type: none">VIDAS® TOXO IgG IIVIDAS® TOXO IgMVIDAS® TOXO COMPETITIONVIDAS® TOXO IgG Avidity | <ul style="list-style-type: none">TOXO ISAGA IgATOXO ISAGA (IgM detection)TOXO SCREEN DATOXO SPOT IF™ |
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Syphilis

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| Screening tests <ul style="list-style-type: none">TREPANOSTIKA™ TP Recombinant (microplates)TPHA 100RPR NOSTICON II | Confirmation Test <ul style="list-style-type: none">FTA/ABS |
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Other tests

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| Chlamydiae <ul style="list-style-type: none">VIDAS® Chlamydia | Chagas disease <ul style="list-style-type: none">ELISA cruzi (microplates – CE marked)Chagatek™ (microplates)*TESA cruzi (immunoblot - confirmation test)** |
| Herpes Simplex Virus <ul style="list-style-type: none">NucliSENS Easy Q® HSV 1/2 | |

* not CE-marked

** not CE-marked, Research Use Only (RUO) outside Brazil

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Culture-based Tests

	Pre-plated culture media	Identification and Susceptibility testing	
		VITEK® 2	API®/ATB™/ Slidex®
Anaerobes	Schaedler + sheep blood	ANC identification card	API® 20 A RAPID™ ID 32 A ATB™ ANA (CLSI** and EUCAST*)
Enterobacteriaceae & Non-Enterobact	Mac Conkey BCP EMB	GN identification card	API 10 S API 20 E RAPID 20 E API 20 NE ID 32 E RAPID ID 32 E ID 32 GN ATB G- (CLSI and EUCAST) ATB UR (CLSI and EUCAST) ATB PSE (CLSI and EUCAST) RAPID ATB E (CLSI) RAPID ATB UR (EUCAST)
<i>Gardnerella vaginalis</i>	Gardnerella Columbia or Trypcase soy + sheep blood	NH identification card GP identification card	API 20 STREP API CORYNE RAPID ID 32 STREP
<i>Haemophilus</i>	Haemophilus Chocolate Chocolate agar + PolyViteX	NH identification card	API NH ATB HAEMO (CLSI and EUCAST)
Listeria	Columbia CNA or Trypcase soy + sheep or horse blood		API LISTERIA
Mycoplasma	A7 Mycoplasma		Mycoplasma IST 2

	Pre-plated culture media	Identification and Susceptibility testing	
		VITEK [®] 2	API [®] /ATB [™] / Slidex [®]
<i>Neisseria gonorrhoeae</i>	Chocolate + PolyViteX VCAT3 Chocolate agar + PolyViteX Gonoline DUO 2	NH identification card	API NH
<i>Staphylococcus</i>	chromID [™] S. aureus Mannitol salt agar	GP identification card	API STAPH ID 32 STAPH Slidex [®] Staph Plus ATB STAPH (CLSI and EUCAST)
<i>Streptococcus</i>	Columbia CNA or Trypcase soy + sheep or horse blood	GP identification card	API 20 STREP RAPID ID 32 STREP Slidex Strepto Plus ATB STREP (CLSI and EUCAST) ATB ENTEROC (CLSI)
<i>Streptococcus</i> Group B	Enrichment: Todd Hewitt broth with antibiotics chromID Strepto B Granada broth	GP identification card	API 20 STREP RAPID ID 32 STREP Slidex Strepto Plus ATB STREP (CLSI and EUCAST)
Yeasts (<i>Candida albicans</i>)	chromID [™] Candida Sabouraud chloramphenicol gentamycin	YST identification card	API CANDIDA API 20 C AUX ID 32 C ATB FUNGUS 3 (CLSI and EUCAST)

Other identification tests

Chlamydiae
Chlamydia direct IF

* CLSI[®] : Clinical Laboratory Standards Institute - EUCAST: European Committee on Antimicrobial Susceptibility Testing



Clinical booklets: Diagnosis and monitoring of HIV infection
Diagnosis and monitoring of viral hepatitis



Patient flyers: Toxoplasmosis, Rubella, CMV

**More educational tools are available.
Contact your local representative for more details.**

**The information in this booklet is given as a guideline only
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It in no way binds bioMérieux S.A. to the diagnosis established
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