BORRELIOSIS

1 Relapsing fever

1.1 Relapsing fever, summary

- Spiral shaped bacteria, transmitted by ticks (endemic) or lice (epidemic)
- Recurrent fever, rash, hepatosplenomegaly, red eyes, haemorrhagic diathesis, muscular pain, coughing, confusion, neurological complications
- Thick film test positive, esp. in beginning of attack
- Treatment with penicillin or tetracyclines (e.g. vibramycin)

1.2 Recurring fever, general

Borrelia sp. are very thin, spiral shaped bacteria. They are larger, longer and have looser coils than treponemes or leptospires. They are responsible for major diseases, including recurrent or relapsing fever. In 1868 the German Otto Obermeier identified the microorganisms during an epidemic in Berlin. The pathogenic potential was demonstrated in 1874 by Gregor Münch, who inoculated himself with *Borrelia recurrentis* and survived the subsequent relapsing fever. The French microbiologists Sergent and Foley identified the body louse as the vector. The British pathologist Joseph Dutton (famous because of *B. duttoni*) discovered an alternative vector: the soft tick *Ornithodoros moubata*. He injured himself while performing an autopsy on a patient who had died from borreliosis and died himself from relapsing fever. During his research into East Coast fever in East Africa, the famous Robert Koch discovered that transovarial transmission took place in these ticks. Charles Nicolle and co-workers established that *Borrelia recurrentis* disappeared from the intestine of the louse 24 hours after a blood-meal, to appear again suddenly in the haemolymph of the insect after 6-8 days. These data were refined and improved later. Once inside the stomach, the bacteria change shape and will resemble small balls with a granular content. Instead of being a degenerated form, this could represent a survival mechanism for this bacterium. This should be studied further. Experimental animals such as rats and mice can be inoculated successfully. *Borrelia recurrentis* can be on chicken embryos and, since 1994, also in-vitro.

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There are two types of borreliosis: relapsing fever, louse-borne borreliosis (*Borrelia recurrentis*) and tick-borne borreliosis (*Borrelia duttoni* and many other varieties, depending on the geographical region). The bacteria are morphologically identical. The name “tick-borne borreliosis” sometimes causes confusion, as *Borrelia burgdorferi* is also transmitted by ticks, but

this organism does not cause relapsing fever.

1.3 Louse-borne borreliosis

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In the epidemic form of borreliosis the bacterium *Borrelia recurrentis* is transmitted by lice. The vector is the common body louse (*Pediculus humanus corporis*). [The body louse is also the vector of epidemic typhus and of *Bartonella quintana*. This insect is not to be confused with the pubic louse (*Phthirus pubis*)]. The head louse (*P. h. capitis*) hardly ever plays a part in transmission. There is no transovarial transmission of *Borrelia recurrentis* in the louse. Humans are the reservoir of the disease.

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The louse is infected by sucking blood at the time the patient has an outbreak of fever. At this time the levels of bacteria in the blood are at their highest. The bacteria penetrate the insect's intestine and multiply in the haemolymph ["blood"] of the louse. The bacteria do not penetrate the salivary glands. The disease is not transmitted by the bite itself. If an infected louse is crushed on the skin when scratching, the bacteria can penetrate into the skin. Lice do not like high temperatures and will readily leave a person who has a fever. In the event of poor hygiene and close physical contact between people, lice can pass from a sick person to a healthy person.

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The disease is rare but can occur all over the world. Epidemics occur in conditions of poor hygiene, overcrowding and malnutrition, such as in floods, mass migration, earthquakes, concentration camps and refugee camps, war, and in the slum districts of large towns. Body lice multiply rapidly and a population can increase by 11% per day. Infection is more frequent in the cold months. People live closer together then, wear more clothes, so there are more lice and consequently more transmission. Mortality can be very high (30 to 80%). Between 1910 and 1945 there were 7 large epidemics in Africa, Eastern Europe and Russia, with 15 million cases and 5 million dead.

1.4 Endemic relapsing fever

This is a sporadic, endemic disease in a number of areas, caused by *Borrelia duttoni* and related bacteria. The vectors are soft ticks (*Ornithodoros* sp.). There is often a striking adaptation between the vector and bacteria. For example *Ornithodoros hermsii, O. parkeri* and *O. turicata* transmit *Borrelia hermsii, B. parkeri* and *B. turicata* respectively (USA). In West Africa *O. erraticus* is responsible for the transmission of *B. hispanica*. In Central, Eastern and Southern Africa *Ornithodoros moubata* is the main vector (*B. duttoni*). These latter ticks infect

people through their saliva and through coxal fluid. It is mainly an infection of rodents. These animals are the principal reservoir. Because the bacterium in ticks passes from one generation to the next by transovarial transmission, the ticks themselves also form a reservoir. People can be infected by ticks, for example when walking through grass or bushes. In Central Africa there is a domestic variety whereby the ticks live in cracks in the mud huts and are therefore more likely to bite humans. The people who are infected are then the main reservoir. Ticks can live for a number of years (exceptionally up to 15 years), unlike lice (a maximum of 2 months). They can survive for a long time without a blood-meal. Mortality in man is lower with tick-borne borreliosis (2 to 5%) than with the epidemic form. The local population builds up immunity from repeated infections; they usually have a mild form. The bacteria can cross the placenta to the foetus.

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Over the course of an infection in a single human host, *Borrelia* sp. regularly display antigenic variation, mainly by changing various surface proteins ("variable large proteins and variable small proteins"). We currently know of 4 genetic mechanisms that the causative agent uses to enable this to take place. (1) There can be a change in the transcription site (an active gene is inactivated and a gene that is not active is activated, without the DNA having to change place). (2) Gene conversion. An active gene is removed from its locus and replaced by another that in turn will become active. (3) DNA rearrangement by recombination and rearranging of the sites of the active and the inactive genes. (4) Multiple point mutations in an active gene.

1.5 Relapsing fever, clinical data

After an incubation period of 4 to 14 days (1 week on average), the patient suddenly develops a violent fever (39° to 41°C). This is accompanied by a high bacteriaemia: 10^{6-8}/ml. The concentration of bacteria is so high that they can be detected with the thick film test or a thin blood smear (in "normal" Gram-negative bacteriaemia the concentration of bacteria is much lower). The patient suffers from headache, muscular pain and pain in the joints. There is often a dry cough and dyspnoea, which can be quite severe. The patient sometimes suffers from abdominal pain and diarrhoea. The patient is frequently jaundiced. The spleen, the liver and the lymph nodes are often swollen. Neurological abnormalities occur. The conjunctivae are often red. Sometimes (in 4 to 50% of cases) there is a discrete rash, which usually appears when the first fever peak subsides. Diffuse intravascular coagulation (DIC) and thrombocytopenia, petechiae and haemorrhaging can occur, e.g. epistaxis (nose bleeds). Sometimes ($^1/_3$) a considerable leukocytosis can be present, but leukopenia can also occur. The cerebrospinal fluid can contain an increased number of lymphocytes (mainly in endemic tick-borne borreliosis). The fever suddenly disappears after 2 to 8 days, on average after 5 days. This is usually accompanied by an aggravation of the symptoms, hypotension and

sometimes death. The prognosis is worse with louse-borne borreliosis, when there is manifest jaundice, hypotension and high bacteriaemia (which can be objectivated in a thin blood mear). There is high neonatal mortality (50%).

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The first febrile episode is followed by a period of 3 to 30 days (on average 9 days) without fever. In 60% of patients this is followed by a second febrile period, which is somewhat less severe than the first and also lasts for a shorter time (on average 2 days). This can be repeated a number of times: maximum 4 times in case of louse-borne borreliosis, maximum 11 times in case of tick-borne borreliosis. This characteristic explains why it is called “relapsing fever”.

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Complications are meningo-encephalitis, with as sequelae facial paralysis, deafness and paralysis of the eye muscles (mainly endemic tick-borne borreliosis). [Most spirochaetes are neurotropic]. Myocarditis and abortion may also occur. If a pregnant woman has relapsing fever, she has about a 50% chance of going into labour.

1.6 Relapsing fever, diagnosis

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The clinical signs and symptoms are not specific, apart from the recurrent bouts of fever. At the beginning of a febrile episode bacteria are found in the blood. These very thin spiral shaped bacteria (0.5μm) can be seen in an unstained unfixed preparation because of their typical mobility. They can also be stained with Giemsa and Wright stain. Staining with Diff-Quik (xanthene thiazine stain) is an alternative. They are found between the red blood cells. The fact that the bacteria can be seen in peripheral blood is explained by the very high density of the bacteria.

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The differential diagnosis includes many febrile conditions, including malaria, typhoid fever, hepatitis, amoebic hepatic abscess, leptospirosis, septicaemia, arbovirosis, rickettsial diseases (can also be transmitted by lice and ticks).

1.7 Relapsing fever, treatment

Tetracyclines are the first choice, e.g. doxycycline. A single administration is often sufficient. Alternatively, erythromycin can be given. In the case of louse-borne borreliosis, in ± 90% of patients a spectacular deterioration in the symptoms is seen 1 to 3 hours after starting therapy: headache and muscular pain, tremor, very high fever, tachypnoea, tachycardia and initial hypertension. This is followed shortly after by excessive perspiration and hypotension and sometimes shock. This is a so-called “Jarisch-Herxheimer” reaction, which usually lasts 6

to 12 hours. This reaction rarely occurs (1%) with tick-borne borreliosis. The reaction was first described in syphilis patients who were being treated with mercury chloride or penicillin. It can also occur when treating other infections caused by intracellular bacteria (such as *Brucella*, Q fever), but is quite rare. It has a mortality rate of about 5%. It is thought that it develops from various substances being released from the destroyed bacteria, together with high concentrations of certain cytokines (e.g. TNF alpha, IL-6 and IL-8). Steroids are not effective in preventing the reaction. The patient must be kept under close supervision (bed rest, IV infusion). Penicillin is less frequently associated with Herxheimer reactions, but is less effective (often further recurrences).

1.8 Relapsing fever, prevention

There is no vaccination and no lasting immunity after a patient has had the infection. In the case of an epidemic (louse-borne borreliosis), mass delousing is often carried out (2 x with an interval of 2 weeks), for example in refugee camps. This is based on the use of insecticides and hot sterilisation (boiling and washing) of clothes.

2 Lyme disease

2.1 Lyme disease, general

The disease is named after the town of Lyme in Connecticut, USA, where in 1975 a large number of children developed a disease that resembled juvenile rheumatoid arthritis. The infection occurs in America, Europe, Australia and Asia (China, Japan and Korea). It is not known to have spread to other parts of the world (insufficient data) and there are no confirmed cases from the southern hemisphere. In Europe and North America it is the most common human disease that is transmitted by ticks. The disease is caused by *Borrelia burgdorferi*. The bacterium was identified in 1982. There are at least 11 different genomic species. The current taxonomic classification recognises *B. burgdorferi* sensu stricto, *B. gariniii, B. afzelii, B. valaisiana, B. lusitaniae* (Portugal, Tunisia), *B. bissetti* (?), *B. andersoni, B. sinica* (China). *B. turdii, B. tanuki* and *B. japonica* exist in Japan. *B. garinii* and *B. afzelii* do not occur in the USA, but they do exist in Europe. The strains in Europe are very heterogeneous, unlike those in the USA. This makes serological diagnosis difficult. There are differences in terms of virulence and organotropism. For example *B. afzelii*, with its main reservoir in pheasants, is more frequent in people with skin disorders (e.g. acrodermatitis), while *B. garinii*, with a rodent reservoir, is more often associated with neuroborreliosis. *B. burgdorferi* s.s. is found more frequently in people with articular symptoms. In 1999 it was established that many

people in one particular area of the USA develop a typical erythema chronicum migrans after a tick bite, but routinely test negative for Lyme. It could be that other -still undiscovered- bacteria are involved. Ticks can simultaneously be infected with more than one species of *Borrelia*.

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Borrelia are thin, spiral-shaped motile bacteria. There are 7 to 11 flagellae in the periplasmic space. They are wrapped around the cell and attached to the poles. This arrangement allows the bacteria to stay motile in a viscous medium in which other bacteria would be quickly immobilised (see Reynold's number).

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Although many bacteria have a circular chromosome and may contain a number of plasmids, the genetic structure of *Borrelia burgdorferi* is quite unusual. The genome of these bacteria consists of a 950 Kbp linear chromosome and an additional 500,000 bp (base pairs) spread over 9 small linear and 12 circular plasmids. The entire genome has been mapped. The genes that code for the main outer wall proteins (outer surface proteins, namely OspA, OspB, OspC and OspD) are found on plasmids. These proteins are genetically variable and play a part in the pathogenesis. *Borrelia* that are found in the tick's stomach carry OspA on their membrane. When the tick takes blood the bacteria are activated and migrate to the salivary glands. It is then that the production and expression of OspA is reduced and that of OspC is increased. This may be important for vaccination (see below). Similarities between a specific part of OspA and LFA-1 (lymphocyte function-associated antigen), a protein present on some human cells, might explain the origin of autoimmune problems in chronic Lyme disease.

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Borrelia species and geographical distribution

B. afzelli	Europe and parts of Asia
B. garinii	Europe and parts of Asia
B. burgdorferi ss	Europe and North America
B. bissettii	Slovenia and North America
B. andersoni	North America
B. valaisiana	Central Europe, UK, Ireland
B. lusitaniae	Portugal, Tunesia
B japonica	Japan
B. turdii	Japan
B. tanuki	Japan
B. sinica	China

2.2 Lyme disease, transmission

The bacteria are transmitted by so-called hard ticks. A tick has to be present for a fairly long period (several hours) before bacteria are introduced in the bite. In Europe the disease is transmitted by *Ixodes ricinus*, in Asia by *Ixodes persulcatus*. [These ticks are also a vector of FSSE / RSSE tick encephalitis]. In the eastern part of North America they are transmitted by *Ixodes scapularis* (includes the former *I. dammini*) and in the western part of North America by *Ixodes pacificus*. [*Ixodes scapularis* is also a vector for babesiosis and for human granulocytic ehrlichiosis]. It is possible that the seabird tick *Ixodes uriae* might carry borrelia across the world.

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European ticks successfully inoculate the host much more quickly and more often than their American counterparts. In Europe transmission is thought to take place in 50% of cases if the tick has been present for 16 hours. This rises to 100% after 48 hours, but not every transmission results in disease. Certain bird ticks can also be carriers of *Borrelia burgdorferi* and play a part in spreading it over large geographical distances. It is quite possible that other vectors will be identified in future. With the known tick vectors there is transstadial transmission (from egg to larva to nymph to adult). Transovarial transmission has been described but seems to be very inefficient (most infected eggs die early). This means that bites by tick larvae are do not lead to infection with *Borrelia.* [However, larvae of *Ixodes ricinus* can transmit European Spring-Summer encephalitis virus.] The bacteria have also been found in warble flies, horseflies and mosquitoes, but these insects do not appear to play a significant role in transmission. Contact transmission has been described in mice (through the urine).

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The enzootic cycle is complex. The tick larvae that are responsible for transmission prefer to feed near the ground, on rodents such as mice, while nymphs and adult ticks usually wait for a larger host on higher vegetation at a height of 40-70 cm. While they are waiting they spread their front legs (“questing”). In the north-east and central northern parts of the USA there is efficient transmission between tick larvae and tick nymphs and white-footed mice *(Peromyscus leucopus*). In the Southeast of the USA the nymphs prefer to suck the blood of lizards. The adults prefer to feed off deer (white-tailed deer, *Odocoileus virginianus*). The increase in the deer population in the late 20th century accelerated the Lyme epidemic in these areas. The bacteria can also infect dogs, birds, squirrels, hedgehogs and rabbits, and some of these animals can also play a part in the transmission chain. In northern California and Oregon the vector ecology is rather different. The spirochaete is maintained in nature by rats (“dusky-footed wood rat”) and *Ixodes neotomae* ticks. These ticks do not bite people. Although nymphs of *Ixodes pacificus* bite people, they prefer to feed off lizards, which cannot be infected by the bacteria. Transmission to people can only occur if *I. pacificus* nymphs have fed by chance on infected rats and then bite a person. Rodent populations can fluctuate a great deal from year

to year. One of the factors involved here is the food supply for these small animals, such as acorns and seeds. These in turn are affected by the weather and the rainfall in any given season. Some enzootic cycles include ticks that rarely or never suck people's blood. These quiet foci have no direct implications for people but demonstrate the complexity of the ecological niche occupied by these bacteria. Birds such as blackbirds, robins and pheasants can be infected and these play a part in the complex cycle. If the temperature falls below –10°C or rises above 30°C, the mortality rate of the ticks increases. Although ticks like high humidity (80-100%), they avoid open water. The low, dense vegetation in woods and along footpaths reduces to some extent marked fluctuations in humidity (buffer effect).

2.3 Lyme disease, clinical

A "complete, classic" presentation of the disease is very unusual in day-to-day clinical practise. The disease has dermatological, neurological, cardiological and rheumatological components. It is characterised at first by skin rash (erythema migrans) where the tick has bitten. This painless non-itching rash, spreading slowly in a circle, occurs in about 75% of patients, usually after a little more than a week (range 3 to 31 days). In Lyme disease, there is a typical time interval between the tick bite and the appearance of the rash. If a skin reaction develops immediately or during the first 24 hours after a tick bite, it is usually the result of an allergic or toxic reaction, not a borrelial infection. The rash is sometimes confused with urticaria, a reaction to an insect bite, tinea corporis or streptococcal cellulitis. Routine laboratory tests do not show signs of inflammation at this stage. Regional lymphadenopathy occurs in slightly less than half of patients. Even without treatment the rash disappears after 3 to 4 weeks. Later, similar but usually smaller annular lesions can occur elsewhere on the skin. This indicates that the bacteria have disseminated. After a variable interval, intermittent joint pains and arthritis (usually in large joints such as the knee), neurological complications and invasion of the heart occur. Invasion of the myocardium can lead to conduction abnormalities. Cardiac symptoms and electrocardiogram abnormalities usually disappear within 3-6 weeks, but complete heart block can be fatal. Luckily this is very rare. Localised borrelial lymphocytoma (previously called lymphadenosis benigna cutis) is a solitary bluish-red swelling, measuring up to a few centimeters in diameter. It tend to appear on earlobes and nipples. There is a dense infiltration with lymphocytes (esp. B-lymphocytes). Acrodermatitis chronica atrophicans is a rather frequent chronic skin manifestation of Lyme borreliosis. It tends not to resolve spontaneously. It is most often located on the extensor sites of the hands and feet. Initially the lesion is usually unilateral; later on it may become symmetrical. The lesion(s) enlarge(s) slowly over months to years. There is an important lymphocyte and plasma-cell infiltration of the dermis. Clinically, it is sometimes confused with vascular insufficiency. Neuroborreliosis can result in many different symptoms, but pain due to radiculoneuritis is common. Meningoradiculioneuritis is also known as Bannwarth's syndrome (syn. Garin-Bujadoux-Bannwarth syndrome). Isolated

peripheral neuritis also occurs. Cranial nerves can be affected, especially the facial nerve (paralysis on one or both sides). Borrelial lymphocytic meningitis can lead to mild to very severe headache. There will be lymphocytic pleiocytosis in the liquor, with a normal or slightly raised protein level. There can be features of disseminated encephalomyelitis which might resemble multiple sclerosis.

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Other symptoms such as eye damage (conjunctivitis, keratitis, choroiditis, optic neuritis), parotitis and myositis can also occur but are rare. Intermittent occurrence of joint disorders separated by periods in which the patient is free of symptoms can occur in a number of patients. *Borrelia burgdorferi* can be transmitted through the placenta to the foetus, with serious consequences. If antibodies are produced after the infection, they provide substantial protection against re-infection.

2.4 Lyme disease, diagnosis

Diagnosis is based on the patient's previous medical history and a clinical examination, backed up with serology, Western Blot or PCR. Production of IgM is at its greatest ± 3-6 weeks after infection and IgG is produced a little later. Serodiagnosis is therefore not sensitive in the early phase after the bite. These antibodies remain present for years with a titre that falls only very slowly. In the acute phase, serology can therefore still be negative. If possible, an uncertain or positive serology should be followed by a Western Blot (higher specificity). Culturing of the bacteria is possible and very specific, but is difficult and not very sensitive (e.g. Barbour-Stoenner-Kelly medium, with a generation time of 12 hours). The bacteria can be detected in biopsies using silver stains and immunofluorescence. The sensitivity and specificity of the laboratory tests need to be improved further. The Lyme urine antigen test is not reliable.

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Antigen mixtures can be used for serological diagnosis, but some test kits are based on monospecific antigens (e.g. 41-kD flagellin). In view of the differences in antigen composition in the *B. burgdorferi* complex, this latter test is less reliable in Europe than in the USA. In addition to antigenic variation, various cross-reactions with antigens of other, more or less related bacteria, make the serological interpretation difficult. Antibody production is inhibited if antibiotics are administered shortly after infection (before the 4th week).

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A number of studies indicate that overdiagnosis and overtreatment of Lyme disease is common. This can result in various problems, including mental fixation on the disease. On the other hand, underdiagnosis should be avoided, but at present there is no ready solution to this dilemma.

2.5 Lyme disease, treatment

Treatment of the early stages consists of 2 to 4 weeks vibramycine, amoxycillin or cefuroxime axetil (Zinnat®). Macrolides are only the fourth choice. Vibramycine is preferred since it is also active against erhlichia, bacteria which can be co-transmitted during a tick bite and which are not sensitive to beta-lactam antibiotics. Ceftriaxone (Rocephine®) 2 gram per day IV for 2 to 4 weeks is the treatment of choice in the later stages, but is much more expensive. Pregnant women and immunodeficient patients with early symptoms such as erythema migrans might also benefit from parenteral treatment, although at present there are not sufficient data. Cefotaxime (Claforan®) or penicillin G in high doses are alternatives. There are a number of patients (up to 10%) who do not respond to the therapy. In this situation, an association with HLA-DR4 and HLA-DR2 has been described. Here the symptoms will drag on due to an auto-immune mechanism and sometimes also due to the persistence of *B. burgdorferi* in the lesions. The molecule OspA is very similar to a human protein (LFA-1), which could give rise to auto-immunity in people who have the variant HLA-DRB1*0401. Patients who display persistent pain and tiredness after adequate treatment of Lyme disease do not improve more often after prolonged treatment with antibiotics than a placebo group.

2.6 Lyme disease, prevention

Avoid tick bites by keeping clear of grass and bushes, wear clothes that cover the body, use agents that repel ticks (repellents with permethrin or DEET), examine your skin after walking in the country and remove ticks quickly. A tick is best removed by carefully grasping it around the base near the mouth, and pulling it out gently without squeezing it flat. It is probable that by squeezing it flat a large quantity of bacteria will penetrate into the skin.

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There are data suggesting that after a single dose of 200 mg of vibramycin within 72 hours of the tick bite, the risk of infection is reduced by almost 90%. However, more study on this strategy is required.

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There is a whole cell vaccine for dogs. Vaccines based on recombinant OspA (a bacterial protein present in tick saliva) have been evaluated in the USA for use in people (Imulyme® and LYMErix®). Because just about every strain of *B. burgdorferi* contains a variant OspC, a vaccine based on OspC would certainly have to be multivalent. On the other hand, OspA is only expressed in the tick's gastrointestinal system. OspA has virtually no antigenic variation. A vaccine based on OspA acts by immobilising or killing the spirochaetes in the tick, even before OspA is replaced by OspC. The purpose is to prevent the disease. It is unlikely that the administration of the vaccine itself can trigger Lyme-like symptoms, but this needs to be investigated further. Preliminary results of randomised, placebo-controlled studies were

promising. After three injections, 90-100% of the young people displayed a protective immune response. In older people (>65 years) this was clearly less efficacious. The antigens that occur in Europe are different from those found in America and a different vaccine composition will be needed. Since the time that the vaccine has become licenced (1998) and available in the USA, there has been little interest of the general public, leading to the withdrawal of the vaccine from the market for commercial reasons in early 2002.

3 Borrelia vincenti

It is not clear whether this bacterium is itself a pathogen or whether it is present as a saprophyte in necrotic material. The bacteria can, unlike the other *Borrelia*, be cultured in an anaerobic environment. In combination with certain anaerobic bacteria (fusobacteria = anaerobic Gram-negative “fusiform bacteria”) this bacterium is suspected of causing ulcerative damage in the:

- throat: Plaut-Vincent’s angina. This results in a major throat infection with localised necrosis. DD diphtheria of the throat, local anthrax or plague.
- gums: Trench mouth or Vincent’s stomatitis, a necrotising and ulcerative gingivitis of the cheek. This occurs in malnourished children and sometimes after herpes simplex.
- Cheeks / lips: Cancrum oris (noma) is characterised by pain and very important tissue destruction. Treatment consists of penicillin, correct nutrition and treatment of any underlying disorder (e.g. kala-azar, etc). Plastic surgery will be needed.
- scrotum: Gangrene of the scrotum (Fournier’s gangrene).
- skin: Painful (in the acute stage), purulent, foul-smelling ulcers, mainly on the legs or feet (phagedenic or tropical ulcer). Ulcers such as this can drag on for years or sometimes heal spontaneously. In some patients a spinocellular carcinoma develops which is invasive locally and can metastasise to the local lymph nodes. Treatment consists of penicillin and metronidazole. Local wound cleaning, antiseptics and non-adhesive dressings are important. Dry dressings should be avoided because they prevent the forming of new epithelium (when the dressing is removed the new cells are pulled off).

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Note on Spirochaetes

Spirochaetes are very thin, spiral shaped organisms. There are a number of species. The bacteria take their name from various sources: *Borrelia* (after the French bacteriologist Amédée Borrel), leptospires (meaning "fine coils"), treponemes ("turning, drilling"). Spirilla are usually classified separately. As yet there is no definitive nomenclature for the various subspecies.

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Summary of Spirochaetes:

Borrelia: 6 to 10 μm in length. 5 to 10 very irregular coils. The various species are morphologically identical.

- *B. recurrentis*: louse-borne borreliosis
- *B. duttonii, B. hispanica, B. persica* and others: tick-borne borreliosis
- *B. burgdorferi*: Lyme disease
- *B. vincenti*: Tropical ulcer, Plaut-Vincent's angina, Cancrum oris, Fournier's scrotal gangrene, Trench mouth (necrotising ulcerative gingivitis)

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Leptospira: 6 to 20 μm in length. Very fine coils and two terminal hooks.

- *L. interrogans* : among others, Weil's disease

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Treponema: 5 to 24 μm in length. Corkscrew-shaped, 8 to 20 coils.

- *T. pallidum*: syphilis, bejel (non-venereal syphilis)
- *T. pertenue:* framboesia
- *T. carateum*: pinta

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Sometimes confused with spirochaetes:

- *Spirillum*: short (2 to 4 μm), thick and regular
- *Spirillum minus*: Sodoku or rat bite fever

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Insufficient data as yet:

- *Brachyspira* sp. and *Serpulina* sp.: bacteria thought to be responsible for so-called intestinal spirochaetosis.