”A good story”
Ebola

WHO November 2014:
13,241 cases – 4,950 death
Lyme Borreliosis - Distribution

- Most common vector borne infection in Europe and US
- Occurs throughout the northern hemisphere
Lyme Borreliosis

Incidence

Europe:
- 20-35 cases / 100,000 inhabitants / year
  
  *Willking et al., Ticks tick borne dis 2014*

Denmark:
- App. 80 cases of neuroborreliosis reported / yr
- *MIBA*: App. 250 *Bb* intrathecal antibody synthesis / yr
Age distribution
Neuroborreliosis

Figur 1. Aldersfordeling af 160 anmeldte tilfælde af neuroborreliose, 2011-2012
Seasonal distribution of NB

Hansen and Lebech. Brain 1992
Vector & Agent

- Principal vector:
  - *Ixodes ricinus* species complex

- Etiological agent:
  - *Borrelia burgdorferi* sensu lato
Ixodes ricinus

Tick bite
<table>
<thead>
<tr>
<th>Stadium 1</th>
<th>Erythema migrans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stadium 2</td>
<td>Multiple erythema migrans</td>
</tr>
<tr>
<td></td>
<td>Lymphadenosis benigna cutis</td>
</tr>
<tr>
<td></td>
<td>Neuroborreliosis</td>
</tr>
<tr>
<td></td>
<td>Carditis</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
</tr>
<tr>
<td>Stadium 3</td>
<td>Acrodermatitis chronica atrophicans</td>
</tr>
<tr>
<td></td>
<td>Chronic neuroborreliosis</td>
</tr>
<tr>
<td></td>
<td>Chronic arthritis / Antibiotic-resistant arthritis</td>
</tr>
</tbody>
</table>
## Spectrum
### US - Europe

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>American LNB</th>
<th>European LNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative <em>Borrelia</em> subspecies</td>
<td><em>B. burgdorferi</em> sensu stricto</td>
<td>Mostly <em>B. garinii</em>, occasionally <em>B. afzelii</em></td>
</tr>
<tr>
<td>LNB as a percentage of all Lyme cases</td>
<td>&lt;10%</td>
<td>&gt;35%</td>
</tr>
<tr>
<td>Multiple erythema migrans lesions</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Painful radiculitis</td>
<td>Rare (&lt;10%)</td>
<td>Common (&gt;50%)</td>
</tr>
<tr>
<td>“Aseptic” meningitis presentation</td>
<td>Majority</td>
<td>Minority</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>VII, very rarely others</td>
<td>Usually VII, but can include others</td>
</tr>
<tr>
<td>Associated chronic skin manifestation (lymphocytoma or ACA)</td>
<td>Never</td>
<td>Not rare</td>
</tr>
<tr>
<td>Associated with Lyme arthritis</td>
<td>Common</td>
<td>Almost never</td>
</tr>
<tr>
<td>Chronic encephalomyeloradiculois</td>
<td>Very rare (&lt;0.1% of LNB)</td>
<td>More frequent, but unusual (&lt;3% of LNB)</td>
</tr>
<tr>
<td>Intrathecal antibody production</td>
<td>Minority of cases</td>
<td>Common (&gt;50%)</td>
</tr>
</tbody>
</table>

ACA—acrodermatitis chronica atrophicans.

*Table: Differences between European and American LNB*
### B. burgdorferi sensu lato species complex

18 genomic species – 8 human pathogenic

<table>
<thead>
<tr>
<th>Genomic type</th>
<th>Geographic</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. burgdorferi sensu stricto</td>
<td>US, Europe</td>
<td>EM, arthritis, carditis, neuroborreliosis</td>
</tr>
<tr>
<td>B. garinii</td>
<td>Europe, Asia</td>
<td>EM, <strong>neuroborreliosis</strong> (arthritis)</td>
</tr>
<tr>
<td>B. afzelii</td>
<td>Europe</td>
<td>EM, ACA, neuroborreliosis</td>
</tr>
<tr>
<td>B. spilmanii</td>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>B. bavariensis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baranton et al., Int. J. Syst. Bacteriol 1992; Stanek et al., Lancet review 2011
*Ixodes ricinus* in DK

**Distribution - infection rate**

Infection rate of *Bb* sensu lato: 15.5%

- *B. afzelii*: 64%
- *B. garinii*: 57%
- *B. lusitaniae*: 27%
- Mixed infections: 64%

*Mostrup Jensen, KVL, 2000*  
*Vennestrøm, Parasitology, 2008*
Transmission process - Establishment of infection

- Tick deposits spirochetes into the skin
- Disseminate through blood or tissue planes to other location e.g. joints, nervous system or distant tissue
- Risk of hematogenous/tissue dissemination is *Bb* strain depended

*Lagal et al., Microbes and Infection 2006*
**B. burgdorferi:** Routes to the nervous system

- **Hematogenous**
  - Bloodstream → cerebral and spinal vessels
  - Integrin attachment → diapedesis through endothelium

- **Transneural migration**
  - Empirical observation: radicular pain and paresis show a topographical association to the site of entry (tick bite or erythema migrans)
    
    *Hansen K, Lebech Brain 1992 / Christen HJ 1994*

    Demonstration of *Bb* in the facial nerve in a rat model

    *Eiffert 2004*

- Bb is a tissue based (= extracellular matrix) - not an intracellular organism
Erythema migrans

- Tick bite recalled by 70%
- Incubation time:
  7-14 days (3 days-4 months)
- Symptomatic complaints: 50%
Diagnostic in EM

- Culture positive in skin biopsies in 40-50%
- PCR positive in skin biopsies in 65-85%
- Serology only positive in 47-60%
- Antibody testing is due to a low diagnostic performance of tests not necessary
- EM is a clinical diagnosis

*Hansen et al, Jclin Microbiol, 1989
Steere et al., CID, 2008*
Neuroborreliosis in children

- 35% of patients with NB ≤ 15 years

- Clinical picture:
  - Lymphocytic meningitis
  - headache, weight loss, low grade fever, slight neck stiffness
  - Monosymptomatic motor paresis
  - facial palsy

- Severe radicular pains rare
- Limb pareses rare (2%)
CASE 1:

**Expositioner:**
Intet flåtbid – muligt erythema migrans

**Lumbalpunktur:**
Sp-leucocytter = 160 mill./ml (95% mono)
Sp-protein= 0,85 g/l

Intrathecal *Bb*-antistof index: IgG 3, IgM 24

Ceftriaxone/Doxycyklin 14 dage
Fuld restitution
Lyme neuroborreliosis

- Tick bite recalled by 25%;

- EM recalled by 50%

- Onset 3 weeks after EM (1-16 weeks)

- EM has usually disappeared
Main features of European Neuroborreliosis

**Pain:**
- Increases with age
- Often mimics other root syndromes
- Nocturnal exacerbations
- Worst axially in the back – between shoulder blades
- Duration 2 – 12 wks
- Independent of physical activity
- May mimic many other conditions

**Paresis:**
- Asymmetrically in onset, distribution, severity
- Cranial nerve VII (60%), VI (5%), III (1%)
- Limb paresis exclusive in 10-20%
## Evolution of second stage neuroborreliosis

<table>
<thead>
<tr>
<th>Event</th>
<th>Latency in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tickbite</td>
<td>3 (0-16)</td>
</tr>
<tr>
<td>Erythema migrans</td>
<td>21 (5-90)</td>
</tr>
<tr>
<td>Sensory radiculitis</td>
<td>15 (1-99)</td>
</tr>
<tr>
<td>First paresis</td>
<td>7 (1-30)</td>
</tr>
<tr>
<td>Last paresis</td>
<td></td>
</tr>
</tbody>
</table>

*Hansen and Lebech, Brain 1992*
Clinical picture
Lyme neuroborreliosis

- **Bannwarths syndrome**
  - + radicular pains; + paresis
  - Adults: 61%
  - Children: 3.6%

- **Lymphocytic meningoradiculitis**
  - + radicular pains; - paresis
  - Adults: 25%

- **Lymphocytic meningitis**
  - - radicular pains; - paresis
  - Adults: 5%
  - Children: 27%

- **Acute peripheral facial palsy**
  - - radicular pains; + paresis
  - Adults: 55%

References:
- Hansen Lebech, Brain 1992
- Christen, HJ et al., Acta Pædiatrica 1993
Difference in clinical spectrum children - adults

- Head – neck region
  the predominant site of tick bites in children

- Nearly all cases with tick bite in the head shows ipsilateral facial palsy – direct invasion of affected nerve / inflammatory edema injure the nerve in canalis facialis

- NB without cranial neuritis occurred more frequently following a tick bite in the trunk or extremities
Facial palsy in Lyme neuroborreliosis

- 40-50% of LNB patients have facial palsies
  Oschmann et al. J Neurol 1998

- <2% of "idiopathic" Bell’s palsies are due to Borrelia burgdorferi
  Kuiper et al. Arch Neurol 1992

- ~30% of facial palsies in children however are due to Borrelia burgdorferi
  Christen et al. Acta Paediatr suppl 1993
Acute facial palsy in children: How often is it LB?

- 115 children admitted for acute peripheral facial palsy
- Stavange Hospital 1996-2004
- 75 (65%) diagnosed as Lyme borreliosis
- CNS inflammation was demonstrated in all but 1 of the children
- Sp-leuco > 5 mill./ml

Tveitnes et al. Scand J Inf Dis 2007
Blood and CSF findings
Neuroborreliosis

Blood:
- Routine tests as WBC ESR etc: no value
- Predictive value of a positive a-Bb antibody test 10 -25%
- Titer kinetics on consecutive samples
- Disease duration > 3 months: anti Bb Ig positive

CSF:
- Lymphocytic pleocytosis 150 cells/µl (20-1000)
- 98 % mono (77-100)
- Spinal protein concentration ↑
- Bb-specific intrathecal antibody production present
  < 3 weeks disease duration: 85%
  > 6 weeks disease duration: 100%
How to differentiate NB from aspetic meningitis in children?

- Cross-sectional study
- Compared patients with NB – enteroviral meningitis

**TABLE 1. Characteristics of Children With Lyme and Enteroviral Meningitis (Univariate Analysis)**

<table>
<thead>
<tr>
<th></th>
<th>Lyme (N = 24)</th>
<th>Enteroviral (N = 151)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yr)</td>
<td>10.5 (4.1–16.9)*</td>
<td>5.5 (0–17.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median symptom duration (d)</td>
<td>12 (2–42)*</td>
<td>1 (0–7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median headache duration (d)*</td>
<td>7.5 (0–42)</td>
<td>2 (0–7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neck signs and symptoms*</td>
<td>17/24 (71%)</td>
<td>62/83 (75%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Cranial neuropathy*</td>
<td>17/24 (71%)</td>
<td>0/151 (0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seizure</td>
<td>0/24 (0%)</td>
<td>7/151 (5%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Photophobia (by history or on examination)*</td>
<td>5/12 (42%)</td>
<td>52/74 (70%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Erythema migrans rash (by history or on examination)</td>
<td>6/24 (25%)</td>
<td>0/151 (0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Papilledema</td>
<td>6/13 (46%)</td>
<td>0/21 (0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Presentation June–September</td>
<td>21/24 (88%)</td>
<td>131/151 (87%)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Shak et al, Pediatric Inf Dis J, 2005
How to differentiate NB from aseptic meningitis in children?

**TABLE 2. Cerebrospinal Fluid Findings in Children With Lyme and Enteroviral Meningitis (Univariate Analysis)**

<table>
<thead>
<tr>
<th></th>
<th>Lyme (N = 24)</th>
<th>Enteroviral (N = 151)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count per mm$^3$</td>
<td>73 (23–122)$^\dagger$</td>
<td>118 (42–284)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>1 (0–4)</td>
<td>47 (24–77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mononuclear cells (%)$^\ddagger$</td>
<td>98 (96–100)</td>
<td>52 (23–74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total protein (mg/dL)</td>
<td>76 (34–104)</td>
<td>47 (33–78)</td>
<td>0.14</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>50 (45–55)</td>
<td>58 (50–65)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Shak et al, Pediatric Inf Dis J, 2005
Antibiotic therapy
Lyme neuroborreliosis

- Active neuroborreliosis responds to antibiotic therapy
- The principle drugs are:
  - Penicillin G i.v.
  - Ceftriaxon i.v.
  - Doxycyclin p.o.
- \( Bb \) has never been shown to be resistant to these drugs
- No evidence that penicillin is less effective than ceftriaxon
- No evidence favoring treatment >14-21 days
- Lack of treatment response should lead to a diagnostic reevaluation

*IDSA guidelines, CID, 2012
EFNS, 2010
Recovery in neuroborreliosis

Follow-up 3-5 years:

- Facial paresis ~15-20% sequelae
- Limb paresis ~ 25% slight sequelae
- 15% may experience constitutional symptoms or pains for wks – mths
- 15-20 % may have permanent residual weakness
- 88%-95% resumed daily activity

- Majority of symptoms are subjective
- Duration of symptoms > 6 weeks before diagnosis, high WBC in CSF risk factors

Berglund et al, Scand J inf Dis 2002
Neuropsychological Profile of Children after an Episode of Neuroborreliosis

- A total of 20 children between 6 -16 years with an episode of LNB at least 4 month before neuropsychological testing
- 20 healthy controls.
- Children with LNB had cranial nerve palsies or meningoencephalitis, pleocytosis in CSF (leukocytes > 10 cells/µL) and/or an intrathecal synthesis of antibodies for *B. burgdorferi*.

- Neuropsychological deficits resulting from LNB in childhood are rare. Most children had a good cognitive, emotional, and behavioral outcome.

_Zotter et al., Neuropediatrics 2013_
Post treatment follow-up in Lyme neuroborreliosis

- Declining CSF inflammation
- Bb specific antibody measurement in serum - CSF ?
- Lack of treatment response should lead to a diagnostic reevaluation
- Upon convalescence - no protective immunity
Laboratory diagnosis of Lyme Borreliosis

- **Direct methods**
  - *In vitro* cultivation (BSK)
  - PCR

- **Indirect methods**
  - Serological assays
    - ELISA
    - Sonicate antigen
    - Flagellum antigen
    - C6 peptide
  - Western blot
Laboratory diagnosis of LNB
Culture - PCR

Direct methods

- *Bb* culture from CSF 5-10% - highest within first 2 weeks

- PCR diagnostic sensitivity < 25% - highest within first 2 weeks

- *Bb* specific PCR at SSI since 2014

Laboratory diagnosis of Lyme Borreliosis

**Indirect methods**
Serological assays
  - ELISA
    - Sonicate antigen
    - Flagellum antigen
    - C6 peptide
  - Western blot

**US CDC recommrnded**:
  - 2-tier approach
  - Sonicate ELISA
  - Western Blot

Questionable value of WB in Europe due to:
- significant Bb strain heterogeneity
- ∉ accepted, standardized ”WB reading rules” in Europe.
Main problems of Lyme Serology

- Weak and slow onset of the Bb specific antibody response

<table>
<thead>
<tr>
<th>Neuroborreliosis</th>
<th>IgG</th>
<th>IgM</th>
<th>IgG+M</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 weeks</td>
<td>58%</td>
<td>65%</td>
<td>80%</td>
</tr>
<tr>
<td>2-5 weeks</td>
<td>81%</td>
<td>60%</td>
<td>95%</td>
</tr>
<tr>
<td>&gt;6 weeks</td>
<td>100%</td>
<td>47%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- Lack of specificity of the test antigen → cross reactions → "false positives"

- Persistence of the antibody response after Bb exposure
  seroprevalence ↑
  inability to discriminate between actual inf - previous exposure

Steere et al., CID, 2008; Wormser et al. CID, 2008
Predictive value of a positive Bb specific intrathecal antibody test

Table 4
B. burgdorferi specific intrathecal antibody test; Statens Seruminstitut 1990 - 1991

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>1991</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests performed</td>
<td>1676</td>
<td>2080</td>
<td>3756</td>
</tr>
<tr>
<td>Positive patients</td>
<td>52</td>
<td>73</td>
<td>125</td>
</tr>
<tr>
<td>LNB I</td>
<td>49</td>
<td>65</td>
<td>114</td>
</tr>
<tr>
<td>LNB II</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

LNB I  Patients with actual neuroborreliosis
LNB II Patients with previous neuroborreliosis

A War Over Lyme Disease: The debate about how to treat this illness has patients raging--and doctors losing their licenses.

November 13, 2000 | France, David

Stalking Dr. Steere Over Lyme Disease

By DAVID GRANN  Published: June 17, 2001

.....As the world's foremost expert on the illness, however, Steere did not believe many of them had Lyme disease at all, but something else -- chronic fatigue or mental illness or fibromyalgia -- and he had refused to treat them with antibiotics.

.....and in turn, hordes of patients had started to stalk him. They showed up at his public engagements, holding signs that read "How many more will you kill?" and "Steer Clear of Steere!" They depicted him in the media as a demon, worse than the spirochetes, the tick-borne bacteria that they claimed inhabited their bodies and that, because of his restrictive diagnosis, they could not eliminate...
Practice Parameter: Treatment of nervous system Lyme disease (an evidence-based review)
Report of the Quality Standards Subcommittee of the American Academy of Neurology

A Critical Appraisal of “Chronic Lyme Disease”

Henry M. Feder, Jr., M.D., Barbara J.B. Johnson, Ph.D., Susan O’Connell, M.D.,
Eugene D. Shapiro, M.D., Allen C. Steere, M.D., Gary P. Wormser, M.D.,
and the Ad Hoc International Lyme Disease Group

Perspectives on “Chronic Lyme Disease”

Phillip J. Baker, PhD
American Lyme Disease Foundation, Lyme, Connecticut
"Post-LB syndrome"

- Patients who have had well-documented Lyme disease

- Remain symptomatic for many months to years after completion of appropriate antibiotic therapy (Fatigue, musculoskeletal pain, difficulties in concentration)

- Controversy: Chronic Lyme disease is caused by persistent infection with *B. burgdorferi*
Post Lyme Syndrom og ”Chronic Lyme Disease”

Argumenter for negativ Lyme serologi trods kronisk sygdom

- insensitive testsystemer
- forudgående antibiotisk behandling
- kronisk borrelia infektion i sig selv supprimerer det humorale immunrespons
- Borrelia gemmer sig i ”immunologically privileged sites” fx hjernen
- intracellulær lokalisation af B.burgdorferi
"Post Lyme Syndrome”
Randomized controlled therapy trials

  pt. med tidligere LB oftest EM og fortsatte symptomer efter behandling
  n=78 seropositive  n=51 seronegative
  randomiseret til: 30 dage i.v. ceftriaxon + 60 dage p.o. doxycyclin vs. placebo
  efter 3 og 6 mdr: symptommæssigt Medical outcome study + SF36 rating
  → ≠ signifikant forskel

- **Kaplan et al. Neurology 2003**
  samme pt population og studie som ovenfor
  efter 3 og 6 mdr: neuropsykologisk testning depressions- rating → ≠ signifikant forskel

- **Krupp et al. Neurology 2003**
  pt. med udtalt fatigue og tidl behandlet LD
  n=55
  randomiseret til: 28 dage i.v. ceftriaxon vs. placebo
  efter 6 mdr: fatigue rating kognitiv testning SF36 rating → ≠ signifikant forskel
**B. burgdorferi** persistens – okkult infektion i CNS?


Usandsynlig fordi:

- ingen objektive kliniske CNS deficit
- ingen inflammation i CSF (6/129)
- ingen Bb specific intrathecal antistofsyntese (8/129)
- negativ PCR og dyrkning i CSF (0/129)
- ingen effekt af selv langvarig antibiotika behandling
- ingen specifikke abnorme strukturelle fund ved cerebral MR (4/27 → MS)

Morgan K et al. Flair amd magnetization transfer imaging of patients with posttreatment Lyme disease syndrome. Neurology 2001
"Post-LB syndrome"

- No evidence to indicate that symptoms are caused by persistent infection with *B. burgdorferi*
- No effect of prolonged courses of antibiotics
- Such treatment can be associated with serious adverse events
- Seronegative is unexpected in patients with late Lyme borreliosis

*Feder HM et al., N Engl J Med, 2008*
Mere end 200 danske patienter tager årligt til Augsburg
Hvilke test tilbyder de:

The following lab tests are necessary for Lyme disease:

- Borrelia IgG and IgM EIA
- Borrelia IgG and IgM Blot
- Lyme Elispot LTT
- Lyme CD 57+ cells
- Borrelia-DNA-PCR
Natural Killer Cell Counts Are Not Different between Patients with Post-Lyme Disease Syndrome and Controls

Adriana Marques, Margaret R. Brown and Thomas A. Fleisher

Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, and Immunology Service, Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, Maryland

Received 16 April 2009/Accepted 1 June 2009

It has been reported that patients with “chronic Lyme disease” have a decreased number of natural killer cells, as defined by the CD57 marker. We performed immunophenotyping in 9 individuals with post-Lyme disease syndrome, 12 who recovered from Lyme disease, and 9 healthy volunteers. The number of natural killer cells was not significantly different between the groups.

The lymphocyte transformation test for the diagnosis of Lyme borreliosis has currently not been shown to be clinically useful


Clinical Microbiology and Infection
Unvalidated tests available as of 2013 include:

- Capture assays for antigens in urine
- Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- In-house criteria for interpretation of immunoblots
- IgM or IgG tests without a previous ELISA/EIA/IFA
Does Symptomatic Improvement While on Antibiotic Therapy Confirm the Diagnosis of Lyme Disease?

- Other infections, if present, can respond to the same antimicrobials.

- In blinded, placebo-controlled trials of patients with persisting symptoms, improvement occurred in up to one third of placebo-receiving individuals.

- Many of the antimicrobials used have a broad range of anti-inflammatory actions.
Proponents of prolonged treatment have created a self-reinforcing logical construct.

- If patients improve after prolonged treatment, this is taken as validation of the diagnosis.
- If the patient's condition does not improve, this is interpreted as evidence that the infection is treatment resistant.
- If the patient worsens, this is interpreted as a Herxheimer reaction.
Vaccine (LYMEnrix)

- A recombinant OspA-based vaccine has been registered in the US

- The vaccine was retracted 2002 – not profitable

- Clinically unproven public concern regarding vaccine induced arthritis

- Antibiotic-refractory Lyme arthritis - HLA-DRB1 molecules that bind epitopes of OspA_{163-175}
- Multivalent vaccine OspA1-5
- Vaccine induced antisera biologically active
- Kill strains of 5 Bb strains
- Prevent LB throughout Asia, Europe, and US
- Few side effects
Lyme borreliosis
Prevention

- Awareness
- Removal of ticks
- Recognition of signs
- Antibiotic therapy