



7 Foruroligende Udtalelser *fra Sundhedsstyrelsen*

ved Borrelia dialog-mødet 2016

v/ Alex Holmstedt

foretræde, Sundheds og Ældreudvalget 2016.11.29



Gitte Kronborg
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afd. Hvidovre Hospital

*sagkyndig repræsentant
for Sundhedsstyrelsen*

I USA har de kun en
type **Borrelia**.

Foruroligende Udtalelse nr. 1/7

Gitte Kronborg: I USA har de kun **en type Borrelia**.

”I North Amerika kan findes **syv arter** af LB-gruppe (Lyme Borreliose) spirochæter...”

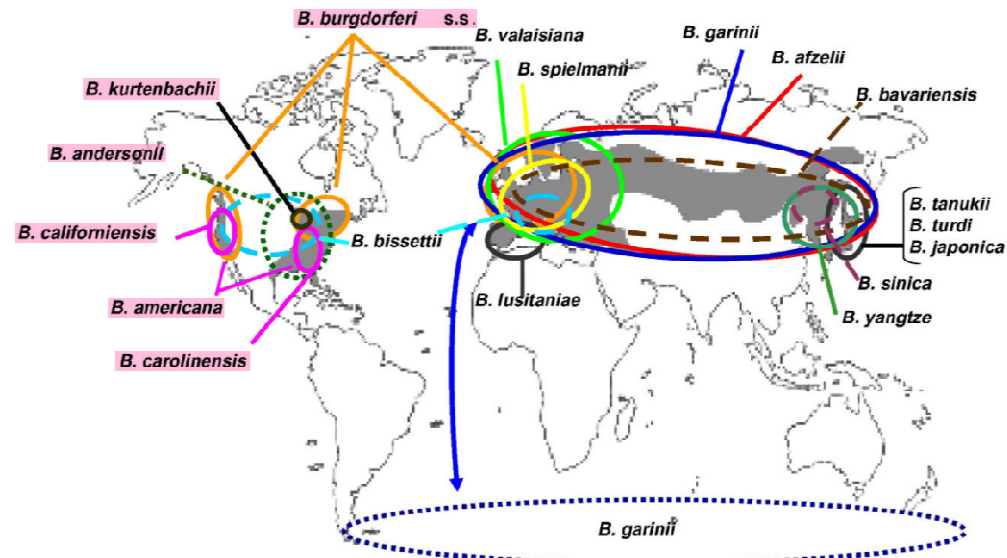


Figure 4.
Map showing the global distribution of the LB species. The shaded areas show the distribution of tick vectors. **Seven species of LB group spirochetes are found in North America**, eight species in Europe, and eight species in Asia, two species overlap in the Old and New Worlds, three in Europe and Asia (see text for details).

Ref.: Population genetics, taxonomy, phylogeny and evolution of *Borrelia burgdorferi* sensu lato - Gabriele Margos et al., *Infection, Genetics and Evolution*, Journal, 2011 October [Link](#)



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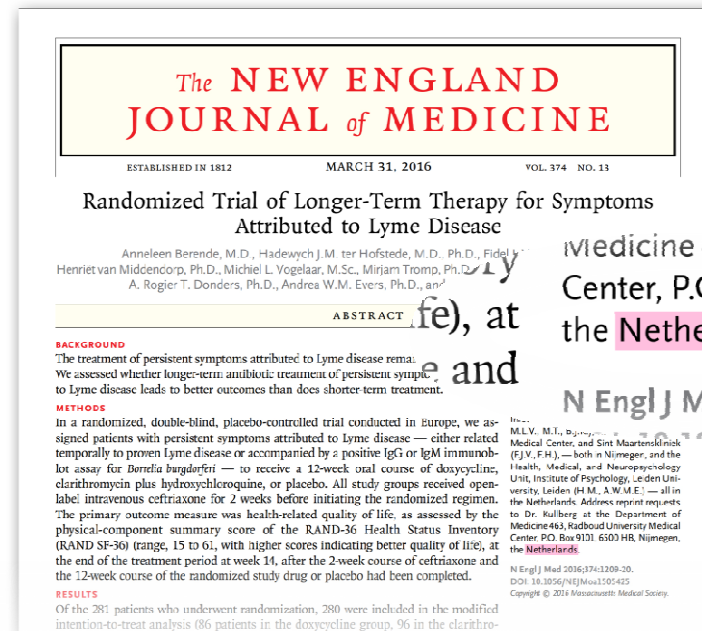
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Her er et nyt **norsk**
studie om effekten af
længerevarende
antibiotika-behandling.

Foruroligende Udtalelse nr. 2/7

Gitte Kronborg: Her er et nyt **norsk** studie om effekten af længerevarende antibiotika-behandling.

”Nederlands.”
[Holland]



medicine 463, Kauberg
Center, P.O. Box 9101, 6500
the Netherlands.

N Engl J Med 2016;374:1209-20

Ref.: Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease - Anneleen Berende et al., The New England Journal of Medicine, March 31 2016 [Link1](#) , supplerende: [Link2](#) [Link3](#) [Link4](#) [Link5](#)



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...nå ok, **Hollandsk.**
I studiet indgik en stor
gruppe som **alle havde**
haft **Neuroborreliose.**

Foruroligende Udtalelse nr. 3/7

Gitte Kronborg: I studiet indgik en stor gruppe som **alle havde** haft **Neuroborreliose**.

”Udelukkelseskriterie 3:
Individer med en formodet
Neuroborreliose-diagnose”

| | |
|---------------------------|--|
| | immunoblot ^{1,2,3}), regardless of prior ELISA IgG/IgM screening results |
| 3 | Subjects must sign a written informed consent form |
| Exclusion criteria | |
| 1 | Subjects with a known history of allergy or intolerance to tetracyclines, macrolides, hydroxychloroquine, or ceftriaxone |
| 2 | Subjects who have had more than 5 days of antimicrobial therapy with activity against <i>B. burgdorferi</i> within the previous 4 weeks |
| 3 | Subjects with a presumed diagnosis of neuroborreliosis (CSF pleiocytosis or intrathecal antibody production) for which intravenous antimicrobial therapy is required |
| 4 | Subjects with a known diagnosis of HIV-seropositivity or other immune disorders |

Ref.: Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease - Anneleen Berende et al., The New England Journal of Medicine, March 31 2016 [Link1](#) , supplerende: [Link2](#) [Link3](#) [Link4](#) [Link5](#)

Foruroligende Udtalelse nr. 4/7



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**Ingen deltagere i
studiet, oplevede
forbedringer.**

Foruroligende Udtalelse nr. 4/7

Gitte Kronborg: *Ingen* deltagere i studiet, *oplevede forbedringer* (af længerevarende behandling).

Af studiets 280 deltagere, **all med vedvarende symptomer**, havde **250 eller 89%** modtaget ”**passende**” Borreliose antibiotika behandling...

| | | | |
|---|---------|---------|---------|
| Acrodermatitis chronica atrophicans¶ | 0 | 1 (1) | 2 (2) |
| Meningoradiculitis | 1 (1) | 9 (9) | 5 (5) |
| Previous antibiotic treatment — no. (%) | 75 (87) | 86 (90) | 89 (91) |
| Duration — days | | | |
| Median | 40 | 30 | 31 |
| Interquartile range | 27–57 | 21–44 | 20–59 |

”Passende” iflg. officielle retningslinjer...

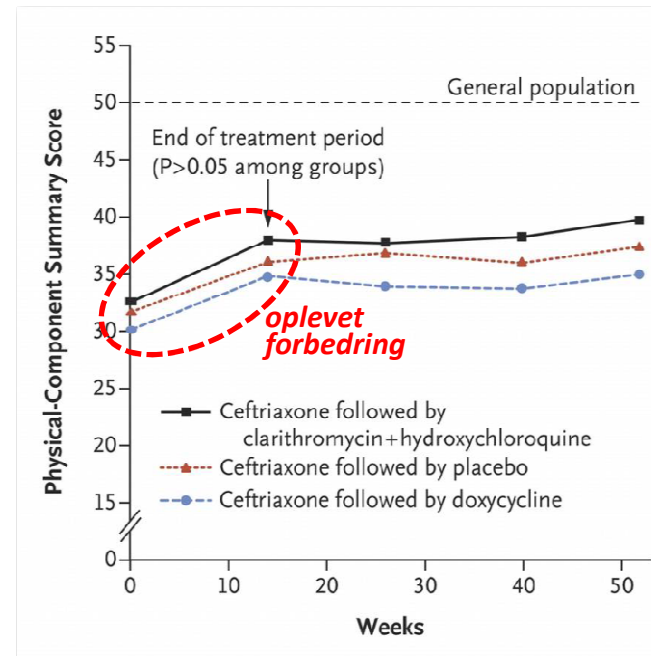
Ref.: Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease - Anneleen Berende et al., The New England Journal of Medicine, March 31 2016 [Link1](#) , supplerende: [Link2](#) [Link3](#) [Link4](#) [Link5](#)

Foruroligende Udtalelse nr. 4/7

Gitte Kronborg: **Ingen** deltagere i studiet, **oplevede forbedringer** (af længerevarende behandling).

Alle deltager i studiet **oplevede forbedringer** efter 2 uger med Ceftriaxon...

Ceftriaxon er intravenøs antibiotika



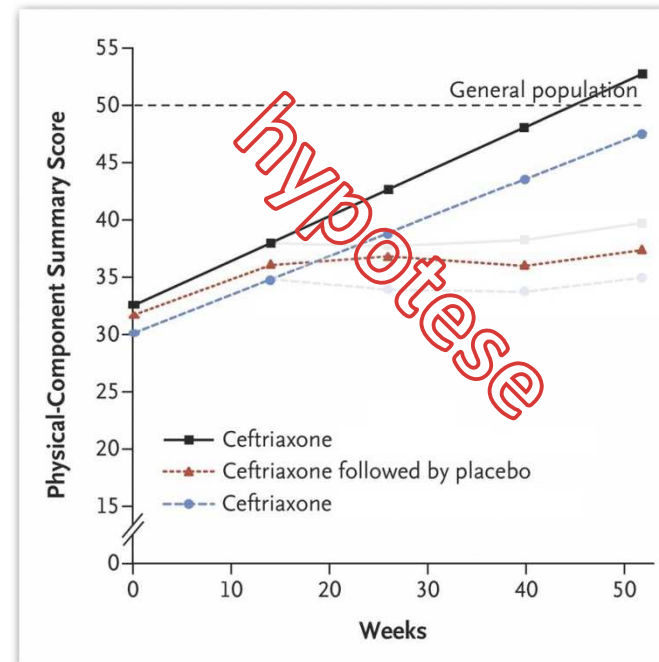
Ref.: Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease - Anneleen Berende et al., The New England Journal of Medicine, March 31 2016 [Link1](#) , supplerende: [Link2](#) [Link3](#) [Link4](#) [Link5](#)

Foruroligende Udtalelse nr. 4/7

Gitte Kronborg: **Ingen** deltagere i studiet, **oplevede forbedringer** (af længerevarende behandling).

Muligt udfald ved forlænget
behandling med Ceftriaxon...?

Hypotetisk graf-eksempel...



Ref.: Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease - Anneleen Berende et al.,
The New England Journal of Medicine, March 31 2016 [Link1](#) , supplerende: [Link2](#) [Link3](#) [Link4](#) [Link5](#)



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Danske flåter overfører
primært **Borrelia** men
enkelte steder også
TBE.

Foruroligende Udtalelse nr. 5/7

Gitte Kronborg: Danske flåter overfører **primært Borrelia** men enkelte steder også TBE.

”Antal positive puljer ...
testet i ... Danmark:

Anaplasma p.

Candidatus N. m.

Spotted fever grp.

Rickettsia h.

Babesia d.

Babesia v.”

Table 3 | Number of positive pools of ticks out of the 47 tested, for two sites in France, Denmark, and the Netherlands using the microfluidic tool (BioMark™ system).

| | Number of positive pools (out of 47 tested) | | | | | |
|-------------------------------------|---|---------------|---------------|--------------|----------------------|---------------|
| | France | | Denmark | | The Netherlands | |
| | Murbach F1 | Wasselonne F2 | Vestskoven D1 | Grib Skov D2 | Duin en Kruidberg N1 | Austerlitz N2 |
| <i>Borrelia</i> spp. | 32 | 33 | 47 | 40 | 38 | 44 |
| <i>B. burgdorferi</i> sensu stricto | 0 | 1 | 31 | 29 | 14 | 6 |
| <i>B. garinii</i> | 5 | 8 | 19 | 36 | 20 | 17 |
| <i>B. afzelii</i> | 13 | 17 | 46 | 32 | 20 | 36 |
| <i>B. valaisiana</i> | 1 | 1 | 13 | 11 | 6 | 1 |
| <i>B. spielmanii</i> | 1 | 1 | 10 | 17 | 3 | 1 |
| <i>B. miyamotoi</i> | 22 | 10 | 13 | 2 | 20 | 27 |
| <i>Anaplasma phagocytophilum</i> | 8 | 12 | 4 | 45 | 10 | 19 |
| Candidatus N. mikurensis | 13 | 2 | 10 | 2 | 28 | 41 |
| Spotted fever group | 46 | 46 | 44 | 47 | 45 | 32 |
| <i>Rickettsia helvetica</i> | 46 | 46 | 44 | 46 | 45 | 32 |
| <i>Babesia venatorum</i> (sp. EU1) | 2 | 3 | 14 | 5 | 0 | 9 |

Bold values represent pathogens detected at least in one site.

Ref.: Population genetics, taxonomy, phylogeny and evolution of *Borrelia burgdorferi* sensu lato - Gabriele Margos et al., *Infection, Genetics and Evolution*, Journal, 2011 October [Link](#)

Foruroligende Udtalelse nr. 6/7



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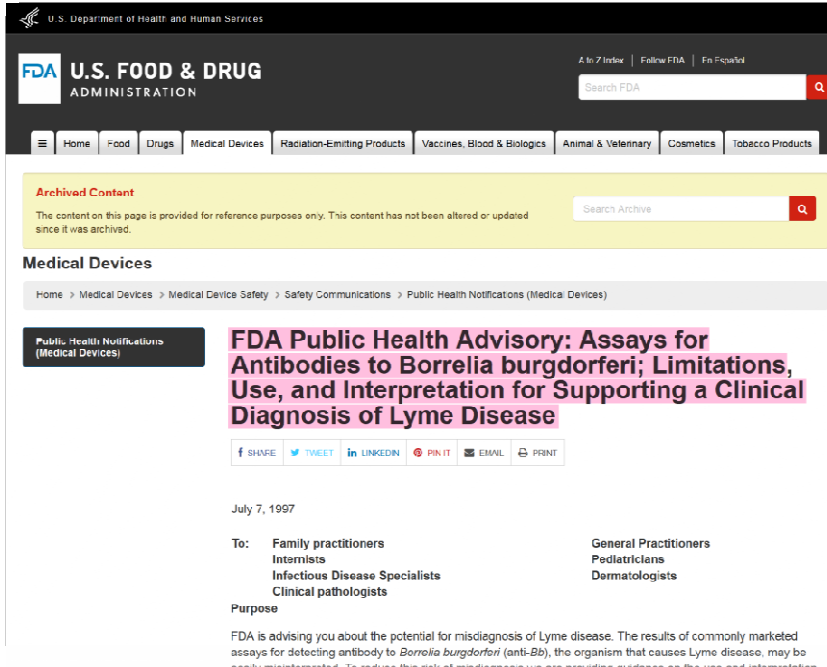
Bakterien er svær at
finde, så vi kigger
efter antistoffer,
antistoffer er svære
at finde – det er
problemet.

Foruroligende Udtalelse nr. 6/7

Kåre Mølbak: ... vi kigger efter antistoffer, **antistoffer er svære at finde** — det er problemet.

”FDA Folkesundheds Advarsel:
Prøver for antistoffer mod
Borrelia b.; Begrænsninger,
brug og Tolkning til Støtte
for Klinisk diagnose af
Borreliose”

FDA, 1997 ...



The screenshot shows the FDA website interface. At the top, it says "U.S. Department of Health and Human Services" and "U.S. FOOD & DRUG ADMINISTRATION". There is a search bar and navigation tabs for Home, Food, Drugs, Medical Devices, Radiation-Emitting Products, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, and Tobacco Products. Below this is an "Archived Content" section with a search bar. The main content area is titled "Medical Devices" and shows a breadcrumb trail: Home > Medical Devices > Medical Device Safety > Safety Communications > Public Health Notifications (Medical Devices). The main heading is "FDA Public Health Advisory: Assays for Antibodies to *Borrelia burgdorferi*; Limitations, Use, and Interpretation for Supporting a Clinical Diagnosis of Lyme Disease". Below the heading are social media sharing icons for Facebook, Twitter, LinkedIn, Pinterest, Email, and Print. The date is "July 7, 1997". The "To:" list includes Family practitioners, Internists, Infectious Disease Specialists, Clinical pathologists, General Practitioners, Pediatricians, and Dermatologists. The "Purpose" section states: "FDA is advising you about the potential for misdiagnosis of Lyme disease. The results of commonly marketed assays for detecting antibody to *Borrelia burgdorferi* (anti-Bb), the organism that causes Lyme disease, may be easily misinterpreted. To reduce this risk of misdiagnosis we are providing guidance on the use and interpretation."

Ref.: FDA Public Health Advisory: Assays for Antibodies to *Borrelia burgdorferi*;
Limitations, Use, and Interpretation for Supporting a Clinical Diagnosis of Lyme Disease, July 7 1997 [Link](#), supplerende: [Link](#)

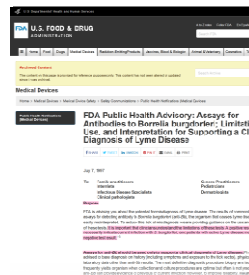
Foruroligende Udtalelse nr. 6/7

Kåre Mølbak: ... vi kigger efter antistoffer, **antistoffer er svære at finde** — det er problemet.

”Formål: **Det er vigtigt, ... at forstå begrænsningerne af disse tests. Et positivt resultat betyder ikke nødvendigvis aktuel infektion ... og patienter med aktiv Borreliose kan have et negativt testresultat.**

Prøver for anti-Bb bør kun anvendes til at støtte en klinisk Borreliose- diagnose.

FDA, 1997 ...



Infectious Disease Specialists
Clinical pathologists

Dermatologists

Purpose

FDA is advising you about the potential for misdiagnosis of Lyme disease. The results of commonly marketed assays for detecting antibody to *Borrelia burgdorferi* (anti-Bb), the organism that causes Lyme disease, may be easily misinterpreted. To reduce this risk of misdiagnosis we are providing guidance on the use and interpretation of these tests. It is important that clinicians understand the limitations of these tests. A positive result does not necessarily indicate current infection with *B. burgdorferi*, and patients with active Lyme disease may have a negative test result.¹

Assays for anti-Bb should be used only to support a clinical diagnosis of Lyme disease. Physicians are advised to base diagnosis on history (including symptoms and exposure to the tick vector), physical findings, and laboratory data other than anti-Bb results. The most definitive diagnostic procedure, biopsy and isolation in culture,

Ref.: FDA Public Health Advisory: Assays for Antibodies to *Borrelia burgdorferi*;

Limitations, Use, and Interpretation for Supporting a Clinical Diagnosis of Lyme Disease, July 7 1997 [Link](#), supplerende: [Link](#)

Foruroligende Udtalelse nr. 6/7

Kåre Mølbak: ... vi kigger efter antistoffer, **antistoffer er svære at finde** — det er problemet.

”Patogenese: **Borrelia b. ... har flere måder, hvorpå den undviger immunsystemet, ... Resultaterne tyder på, at Borrelia. b. dermed låner en praktisk "regnfrakke" fra flåten, der beskytter mod immunreaktioner. ...**”

Borrelia klaringsrapporten 2. Udgave 2014...

immunreaktion=
antistof



Patogenese

Klinisk Lyme borreliose synes primært at ramme mennesker, mens det naturlige reservoir af værts i naturen, såsom rådyr, mus og fugle, formentlig enten ikke udvikler sygdom eller måske mild

beskrevet i USA (23-25). I visse tilfælde etableres langvarige infektioner (fx acrodermatitis chronica atrophicans) på trods af et stærkt humoralt og cellulært immunrespons.

B. burgdorferi s.l.* har flere måder, hvorpå den undviger immunsystemet, fx resistens mod komplement ved at binde værtsens komplement kontrolproteiner. *B. burgdorferi s.l.* binder endvidere værtsens plasminogen, som omdannes til plasmin, et stærkt proteolytisk enzym, som kan nedbryde fibrin og fibronectin (ekstracellulær matrix). Dette bidrager til spredningen af *B.

en og/eller bakteriemeninge i mus har også vist korrelation. Dette er også tilfældet hos mus, der var immune efter tidligere *Borrelia* infektion. Omvendt har man kunnet hæmme *Borrelia* infektionen i mus, når musene blev inficeret af Salp15-depleterede flåter. Resultaterne tyder på, at *B. burgdorferi* dermed låner en praktisk "regnfrakke" fra flåten, der beskytter mod immunreaktioner. Der opdages stadig nye facetter af det komplekse samspil mellem flåt, vært og bakterie, og mange detaljer i patogenesen er ikke belyst endnu. Billedet kompliceres yderligere af stor genetisk og geografisk variation. Det er typisk, at molekylærbiologiske detaljer, som fx op- og nedregulering af

Ref.: Lyme Borreliose, Klinik, diagnostik og behandling i Danmark 2. udgave, Dessau et al., Februar 2014

[Link1](#), supplerende: [Link2](#)

Foruroligende Udtalelse nr. 6/7

Kåre Mølbak: ... vi kigger efter antistoffer, **antistoffer er svære at finde** — det er problemet.

”Kommercielle testkits til påvisning af Borreliose: en meta-analyse af test nøjagtighed”

Kritisk gennemgang af ELISA og Western Blot tests fra 18. november 2016...

International Journal of General Medicine Dovepress
open access to scientific and medical research

Open Access Full Text Article ORIGINAL RESEARCH

Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy

This article was published in the following Dove Press journal:
International Journal of General Medicine
18 November 2016
Number of times this article has been viewed

Michael J Cook¹
Basant K Puri²

¹Independent researcher, Dorset, UK; ²Department of Medicine, Hammersmith Hospital, Imperial College London, London, UK

Abstract: The clinical diagnosis of Lyme borreliosis can be supported by various test methodologies; test kits are available from many manufacturers. Literature searches were carried out to identify studies that reported characteristics of the test kits. Of 50 searched studies, 18 were included where the tests were commercially available and samples were proven to be positive using serology testing, evidence of an erythema migrans rash, and/or culture. Additional requirements were a test specificity of ≥85% and publication in the last 20 years. The weighted mean sensitivity for all tests and for all samples was 59.5%. Individual study means varied from 30.6% to 86.2%. Sensitivity for each test technology varied from 62.4% for Western blot kits, and 62.3% for enzyme-linked immunosorbent assay tests, to 53.5% for synthetic C6 peptide ELISA tests and 55.7% when the two-tier methodology was used. Test sensitivity increased as dissemination of the pathogen affected different organs; however, the absence of data on the time from infection to serological testing and the lack of standard definitions for “early” and “late” disease prevented analysis of test sensitivity versus time of infection. The lack of standardization of the definitions of disease stage and the possibility of retrospective selection bias prevented clear evaluation of test sensitivity by “stage”. The sensitivity for samples clas-

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Ref.: Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy, Cook and Puri, 18 November 2016 [Link1](#), supplerende: [Link2](#)

Foruroligende Udtalelse nr. 6/7

Kåre Mølbak: ... vi kigger efter antistoffer, **antistoffer er svære at finde** — det er problemet.

”Figur 9: Test-følsomhed versus udgivelsesår.”

4% gennemsnitlig øgning af test-følsomhed over 20 år, 1996-2016...

Udgivelsesår for dokumentation der beviser de forskellige test kits følsomhed...

Ref.: Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy, Cook and Puri, 18 November 2016 [Link1](#), supplerende: [Link2](#)

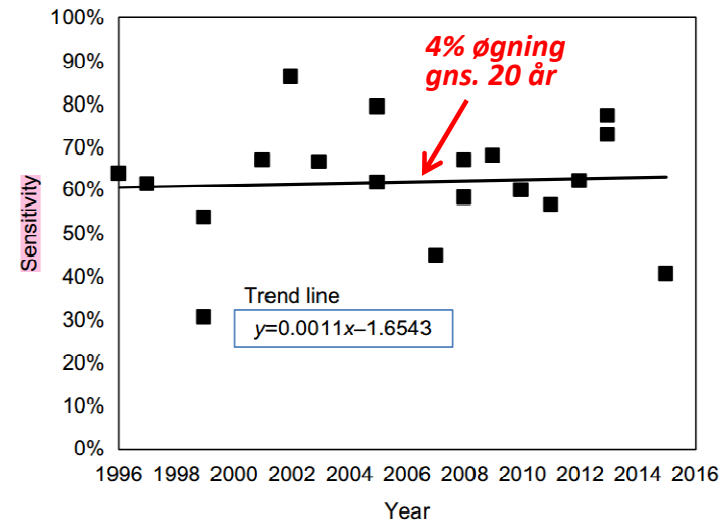
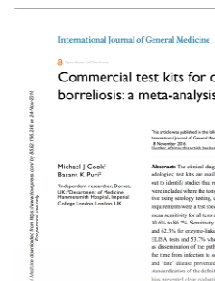


Figure 9 Test sensitivity versus year of publication.

Foruroligende Udtalelse nr. 6/7

Kåre Mølbak: ... vi kigger efter antistoffer, **antistoffer er svære at finde** — det er problemet.

” ... følsomheden fastsat for testene ved disse prøver forventes at være tæt på 100%. Det er ikke tilfældet, som påvist i denne analyse.

Følsomheden ... var så lav som 7%. Den gennemsnitlige følsomhed for alle testkits ... var 60%, ”

Ref.: Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy, Cook and Puri, 18 November 2016 [Link1](#), supplerende: [Link2](#)



diagnosis of the disease”.

Conclusion

All studies included in this analysis used test samples that were predefined as positive for LB infection either by a prior serological test that was positive, or a clinical record showing a history of an EM rash, or culture confirmed, or a combination of these. **Based on this, the sensitivity determined for the tests with these samples would be expected to be close to 100%. This is not the case, as has been demonstrated in this analysis.**

The sensitivity of an individual test was as low as 7.4%. The mean sensitivity of all test kits with all samples was 59.5%, and ranged from 30.6% to 86.2%.

The technologies with the highest sensitivity were WB, with a mean sensitivity of all test kits of 62.4% and ELISA

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Tragisk at patienter
tager til udlandet
og fastholdes i en
Borrelia-diagnose —
når de måske fejler
noget andet.

Foruroligende Udtalelse nr. 7/7

*Kåre Mølbak: **Tragisk at patienter tager til udlandet og fastholdes** i Borrelia-diagnose...*



Hønen eller ægget...

...så syge skatteborgere
søger altså ikke hjælp, i
udlandet, fordi de muligvis
fastholdes i forkerte
diagnoser — af et "gratis"
sundhedsvæsen..?

Foruroligende Udtalelse nr. 7/7

*Kåre Mølbak: **Tragisk at patienter tager til udlandet og fastholdes** i Borrelia-diagnose...*

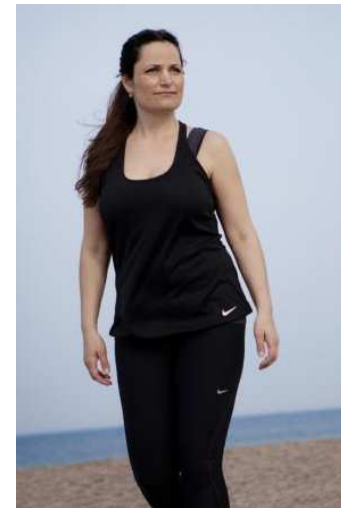
Information:

»Ingen i Danmark troede på mig«

Sadet Daniels fik i 2006 diagnosen stress ...

I Tyskland fik hun konstateret borrelia, ...

»... For første gang i hele forløbet følte jeg, at man tog mig seriøst. Og behandlingen var ekstremt effektiv. ... «”



Sadet Daniels

Ref.: »Ingen i Danmark troede på mig«, Information, 3. maj 2010 [Link1](#)

Foruroligende Udtalelse nr. 7/7

*Kåre Mølbak: **Tragisk at patienter tager til udlandet og fastholdes** i Borrelia-diagnose...*

Information:

»Jeg fik at vide, at det nok var psykisk«

”»Jeg har kun mødt læger, der har kigget mistroisk på mig ... «

... Men på en tysk privatklinik blev hun testet positiv. Her blev hun også behandlet ...
Og Louise Ankerstjerne vurderer selv, at hun er i klar bedring”



Louise Ankerstjerne

Ref.: »Jeg fik at vide, at det nok var psykisk«, Information, 16. april 2016 [Link1](#)

Foruroligende Udtalelse nr. 7/7

*Kåre Mølbak: **Tragisk at patienter tager til udlandet og fastholdes** i Borrelia-diagnose...*

BT:

**Thomas Uhrskovs datter bare sov og sov,
men lægerne ville ikke teste for Borrelia –
så tog de til Tyskland**

”Familien havde allerede besøgt syv forskellige læger, og selv om Sally udviste klassiske borrelia-symptomer var der ikke nogen af lægerne, der var parat til at teste hende.”



Thomas Uhrskov
om hans datter Sally

*Ref.: Thomas Uhrskovs datter bare sov og sov, men lægerne ville ikke teste for Borrelia - så tog de til Tyskland, BT
8. oktober 2016 [Link1](#) , supplerende: [Link2](#)*



...7 Foruroligende Udtalelser...

**...tiden går, også for udiagnosticerede
og underbehandlede
Borreliose-patienter...**

Tak for opmærksomheden