A Vaccine against Borreliosis When and how?

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Conflict of Interest Statement

Received honoraria for lectures, consultancies and as principal investigator in studies from:

Abbott, Baxter, Boehringer Ingelheim, Crucell, GSK, Hoffmann LaRoche, Intercell, Medicago, Novartis Vaccines, Pfizer, r-biopharm, Sanofi, MSD Sharp & Dohme, Sekizui-Virotech, Sigma Tau, Takeda, Themis Bioscience, Valneva

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New Scientist

INSIGHT 29 March 2017

Lyme disease is set to explode and we still don't have a vaccine

A new prediction says 2017 and 2018 will see major Lyme disease outbreaks in new areas. This could lead to lifelong health consequences, so where's the vaccine?

Tick tock
Mike Peres/Custom Medical Stock Photo/SPL

By **Chelsea Whyte**

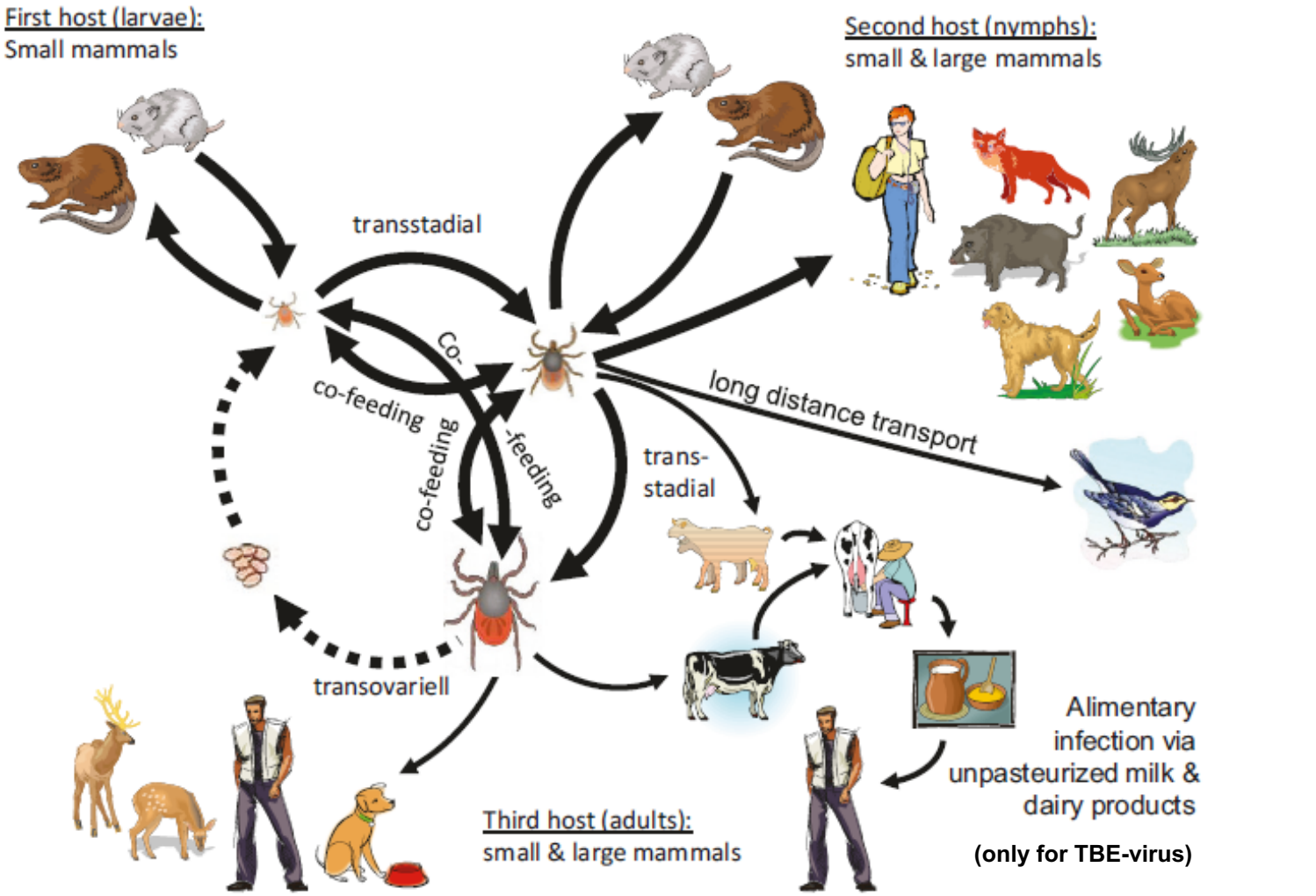
BY THE time he had finished his walk through the woods in New York state, Rick Ostfeld was ready to declare a public health emergency. He could read the warning signs in the acorns that littered the forest floor – seeds of a chain of events that will culminate in an unprecedented outbreak of Lyme disease this year.

Since that day in 2015, Ostfeld has been publicising the coming outbreak. Thanks to a changing climate it could be one of the worst on record: the ticks that carry the disease have been found in places where it has never before been a problem – and where most people don't know how to respond. The danger zone isn't confined to the US: similar signs are flagging potential outbreaks in Europe. Polish researchers predict a major outbreak there in 2018.

LYME - Chronology

Year of discovery	Tick-borne diseases symptoms described ...
1883	first known case of **Acrodermatitis chronica atrophicans** (ACA) (Buchwald A, 1883)
1900 - 1909	**Erythema chronicum migrans** (Afzelius A, 1910; Lipschütz B, 1914) Ixodiasis = tick fever **Spirillum-detection** Six **ACA-cases presented** at dermatologic meeting / Stockholm = **bites caused by ticks**/ insects
1913	**Tick-paralysis** intoxication?
1922	**Meningopolyneuritis** = Paralysie par les tiques
1914 **1930 - 1937** **1931** **1940** **1948**	**Far-East (Taiga) Encephalitis** – cases described **Russian Spring-Summer-Encephalitis** = RSSE (Zilber LA, 1939) **„Meningitis serosa epidemica“** in Austria (Schneider H. 1931) **Kumlinge Disease** at Aaland Islands (Oker-Blom N, 1956) **„European“ TBE** in Czechoslovakia (Krejci J, 1949)
1941	**Meningoradikulitis** (Bannwarth) = „rheumatic“? (Bannwarth A, 1941)
1951	**Meningitis** in case of Eryth. chr. migrans (Hellerström) (Delank HW, 1989)
1970s	Physicians in **New England** identified groups of children in an **area** around **Lyme**, **CT**, who had an unusual rash and associated arthritis
1975	**Lyme-disease** (Steere AC et al, 1977)
1981	**Etiology of Borrelia** in case of Lyme-disease (Burgdorfer W et al, 1982)*B. burgdorferi* spirochetes related to the illness were identified in the gut of ticks (Willy Burgdorfer) (named in honour to Amédée Borrel)
1982	**U.S. CDC-surveillance program started**

Life Cycle of ticks (*Ixodes ricinus*)



Dobler G, Gniel D, Petermann R, Pfeffer M; Epidemiology and Distribution of Tick-Borne Encephalitis; Wiener Med .Wochenschr. 2012; 162:230-238

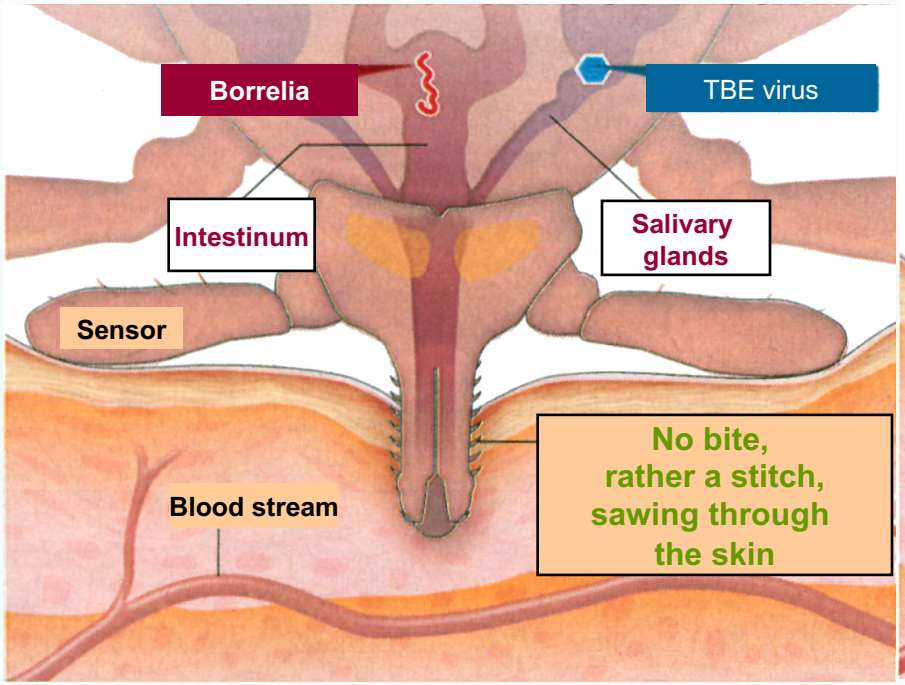
Transmission of Borrelia

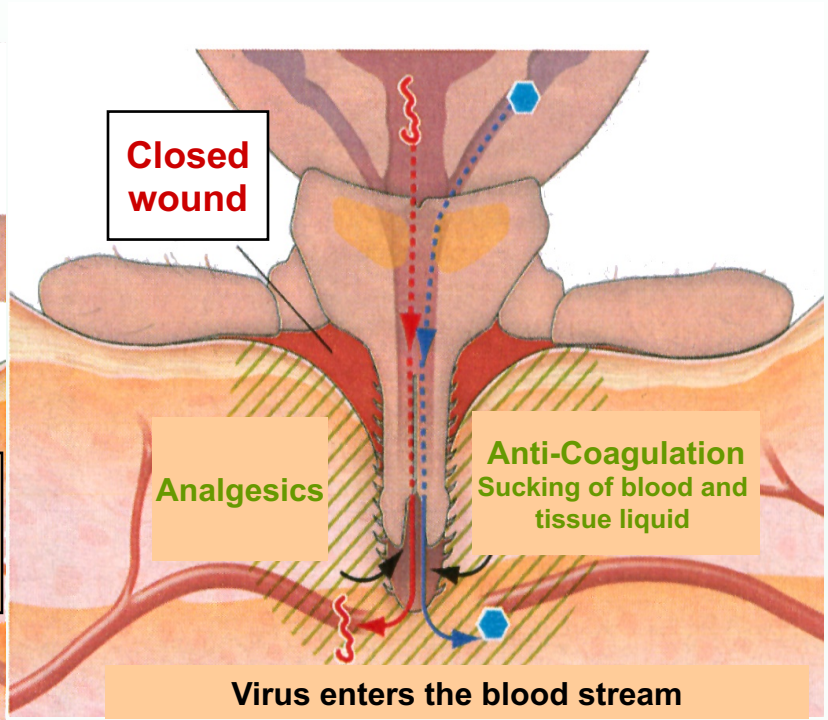
- Borreliae live in the gut of the ticks (several hundreds)
- Microbes and proteins can persist in the gut of ticks, where no digestion occurs[1]
- Transmission of the borreliae starts 36-48 hours after feeding
- When a nymph engorges upon a host, densities of over 100,000 bacteria per nymph are reached

[1] Wickramasekam et al. Emerg. Infect. Dis 14, 1273-1275 (2007)

How does infection occur?

Tick bite Infection

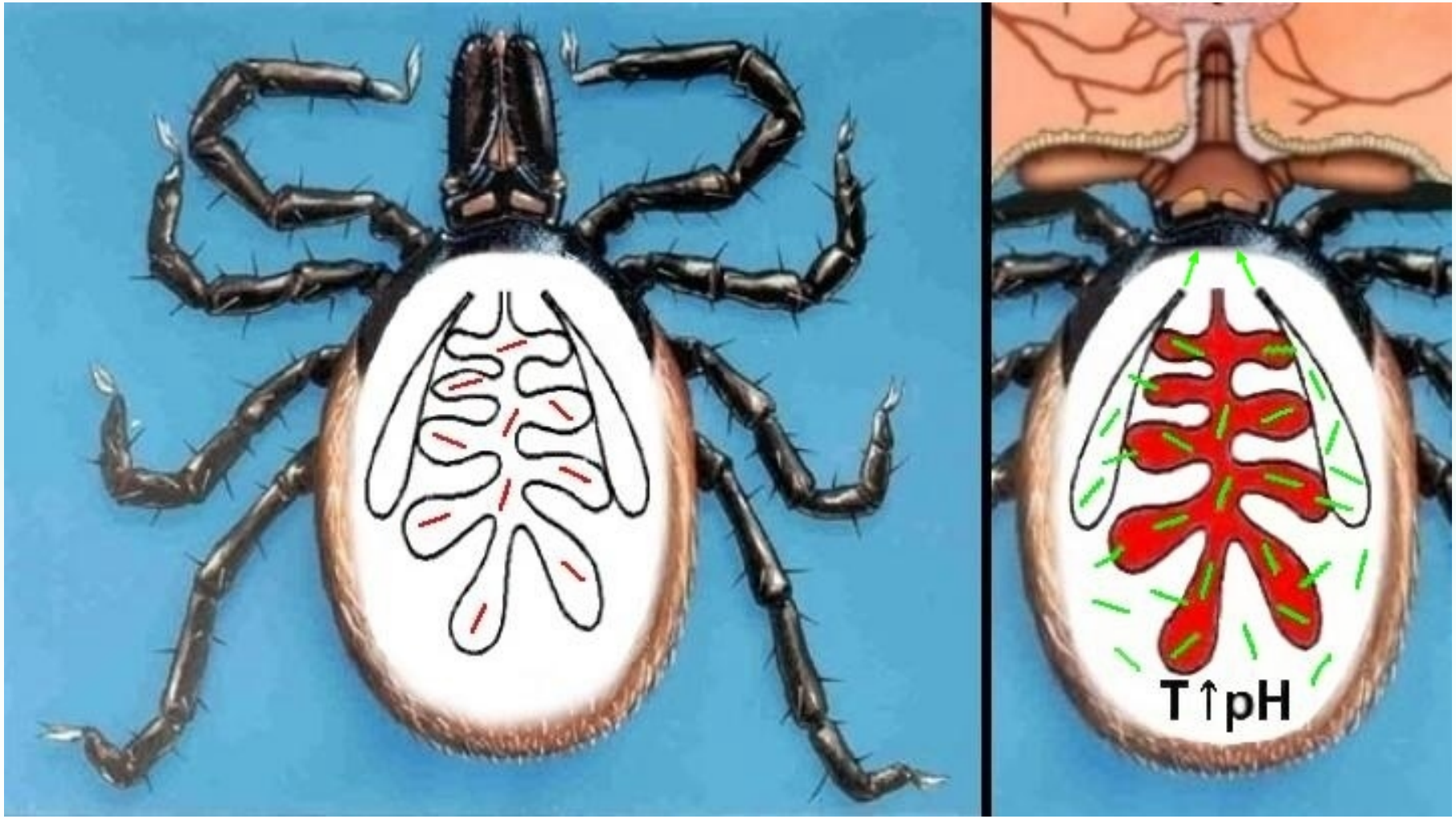




Mind: Duration of tick bite, Analgesics, Anti-Coagulation…..

Source: Apotheken Umschau, 74-75, Juni 2005

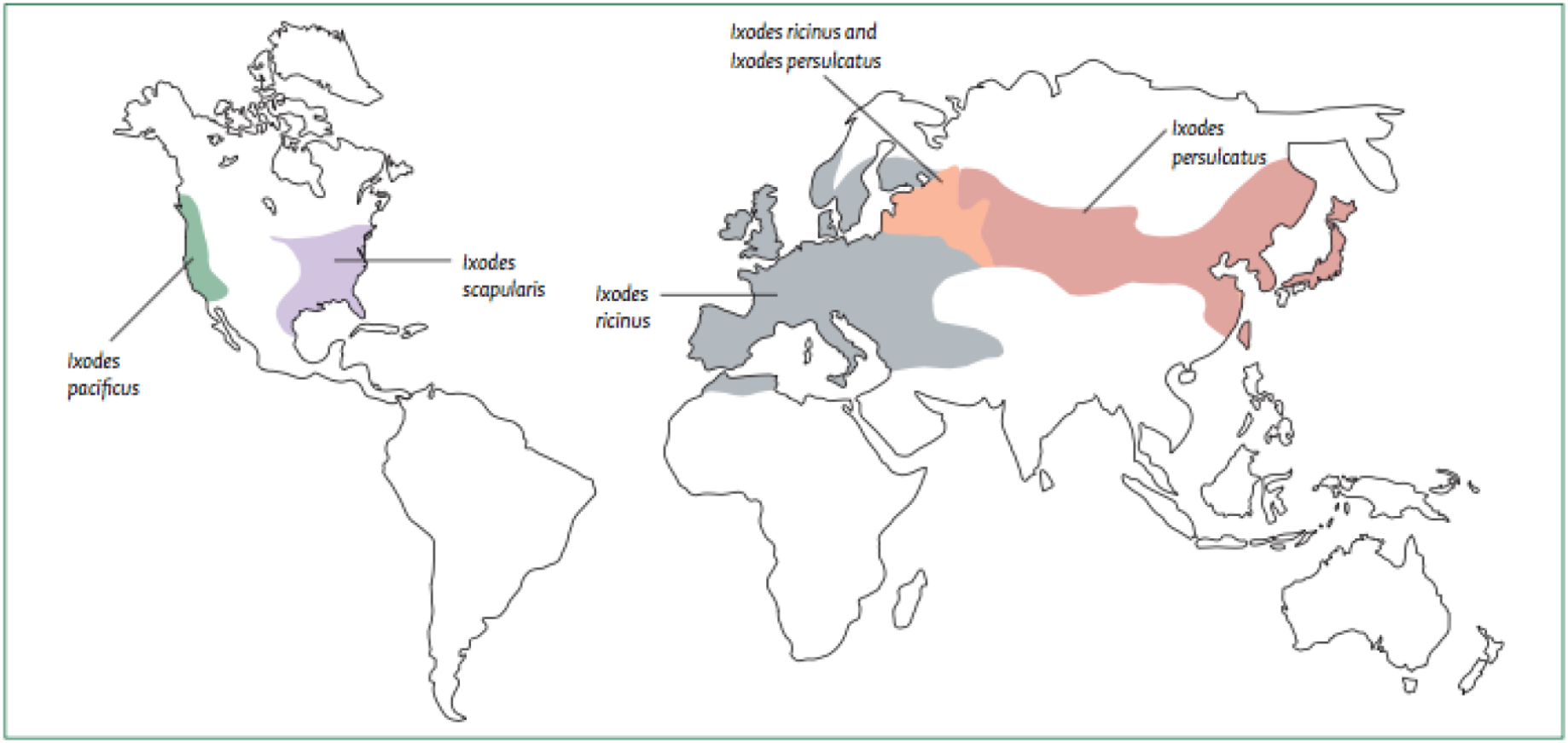
Activation of Borrelia spp. in the tick: antigenic switch from OspA to OspC



OspA

OspC

Distribution of Vectors for Borrelia spp.

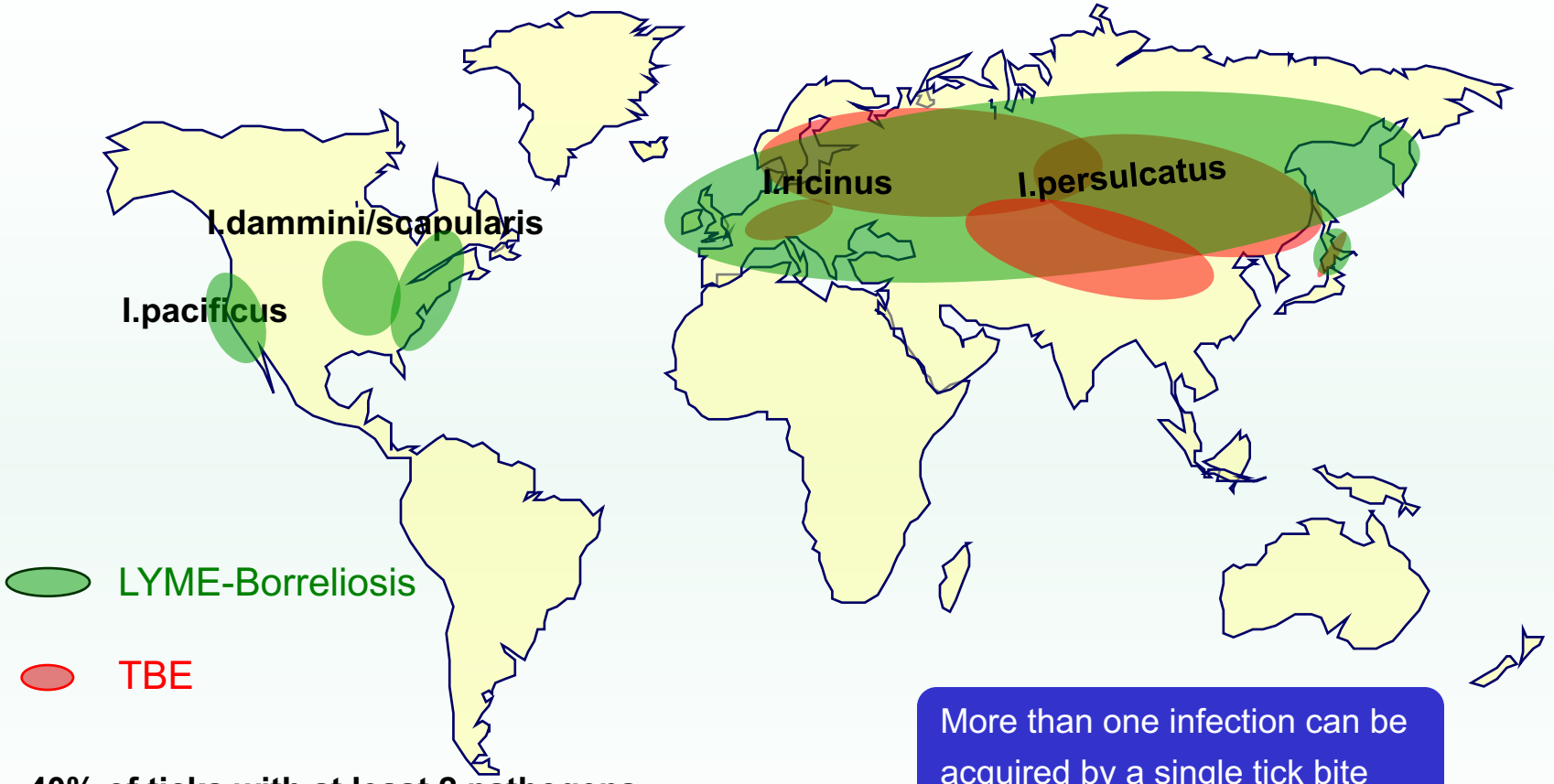


- Main vector in Europe is *Ixodes ricinus*
- Main vector in the Eastern part of the US is *Ixodes scapularis*, in the West *Ixodes pacificus*

Stanek et al - Lancet 2012; 379: 461–73

LYME and TBE worldwide

distributed by Ixodes (I.) ticks



More than one infection can be acquired by a single tick bite

40% of ticks with at least 2 pathogens

Double (and more) infections have been detected:

***Borrelia burgdorferi* + TBE +**

Sun Yi et al. Acta Parasitol. Med. Entomol. Sin. 14, 231-240 (2007);
Map: D.Gniel, 2012

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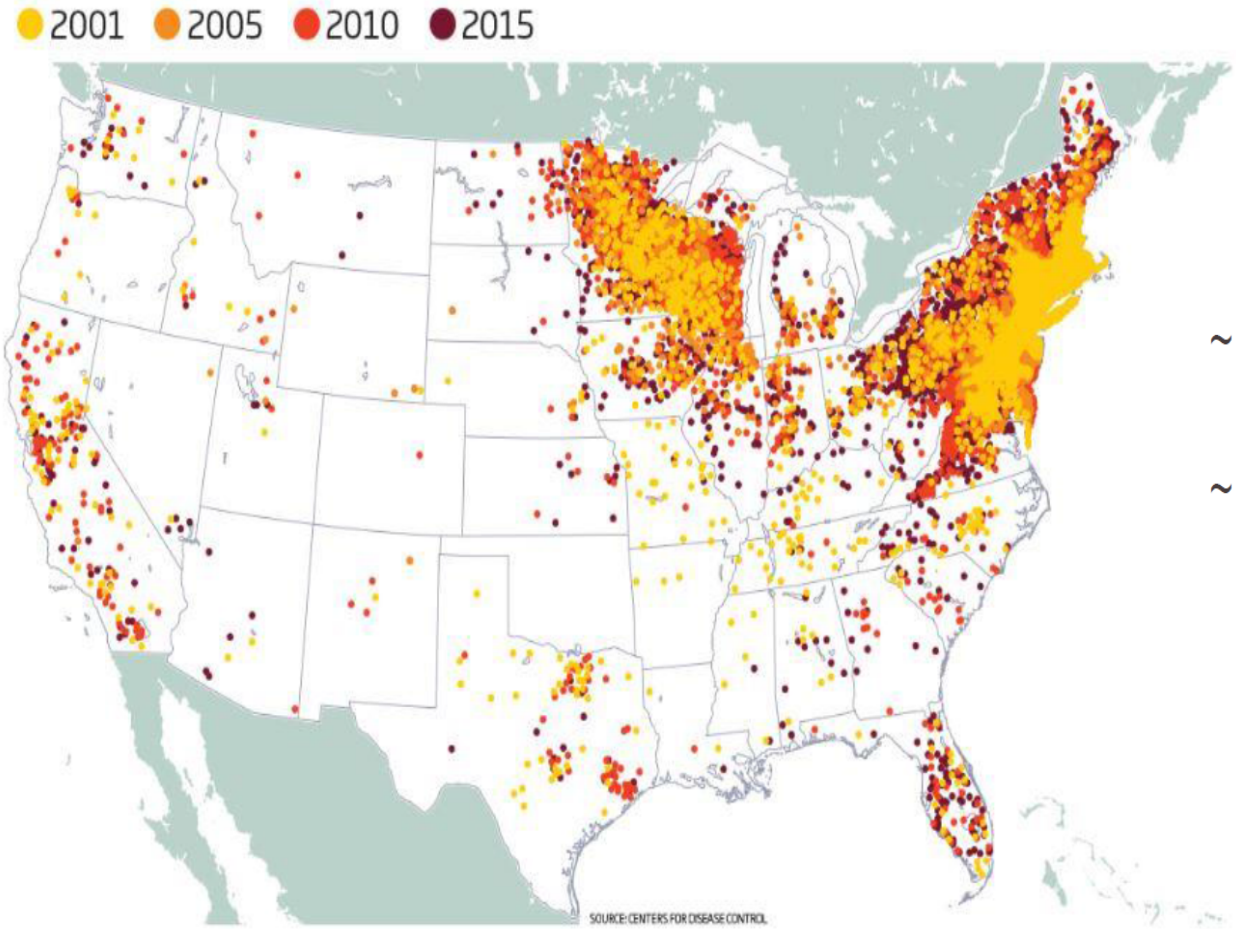
Disease spread in the United States[1]



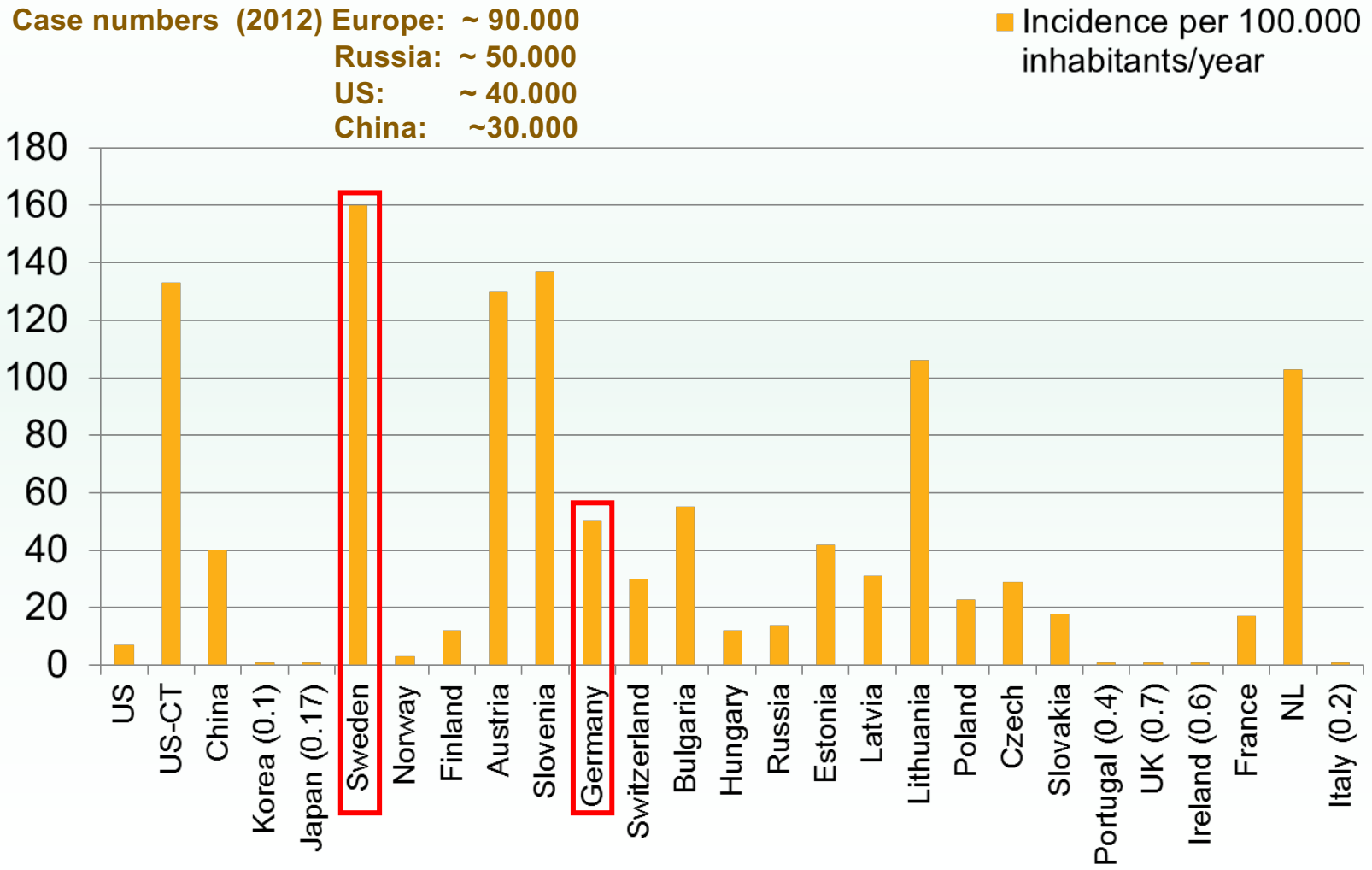
~ 300,000 cases in US (p.a.)[2]

~ 200,000 cases in EU (p.a.)[3]

1 Centers for Disease Control and Prevention; **2** https://wwwnc.cdc.gov/eid/article/21/9/15-0417_article; **3** Estimated from available national data. Number largely underestimated based on WHO Europe Lyme Report as case reporting is highly inconsistent in Europe and many LB infections go undiagnosed; ECDC tick-borne-diseases-meeting-report

Comparative Incidence of LYME-Borreliosis

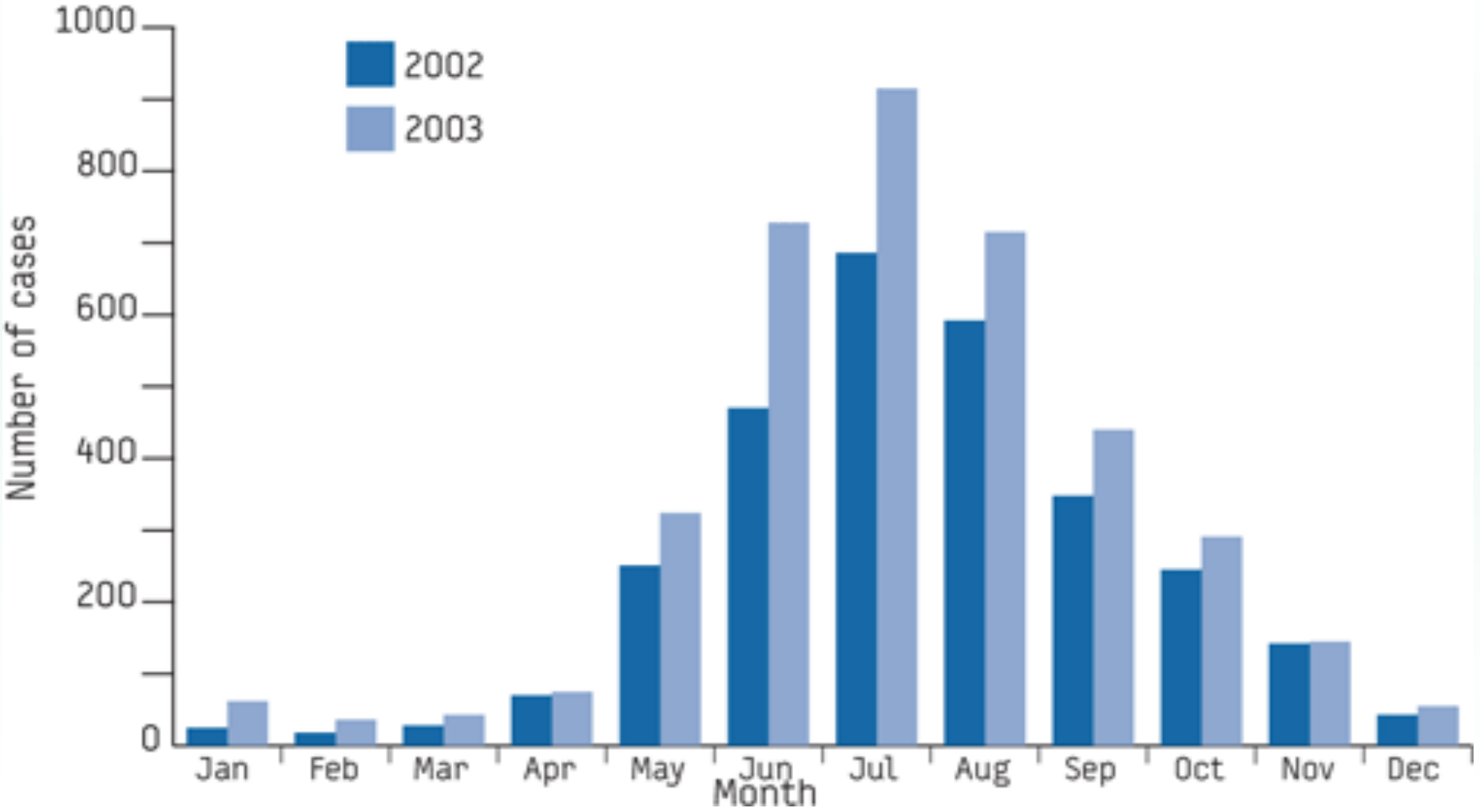
(average past 20 years)



Source : ECDC 2014

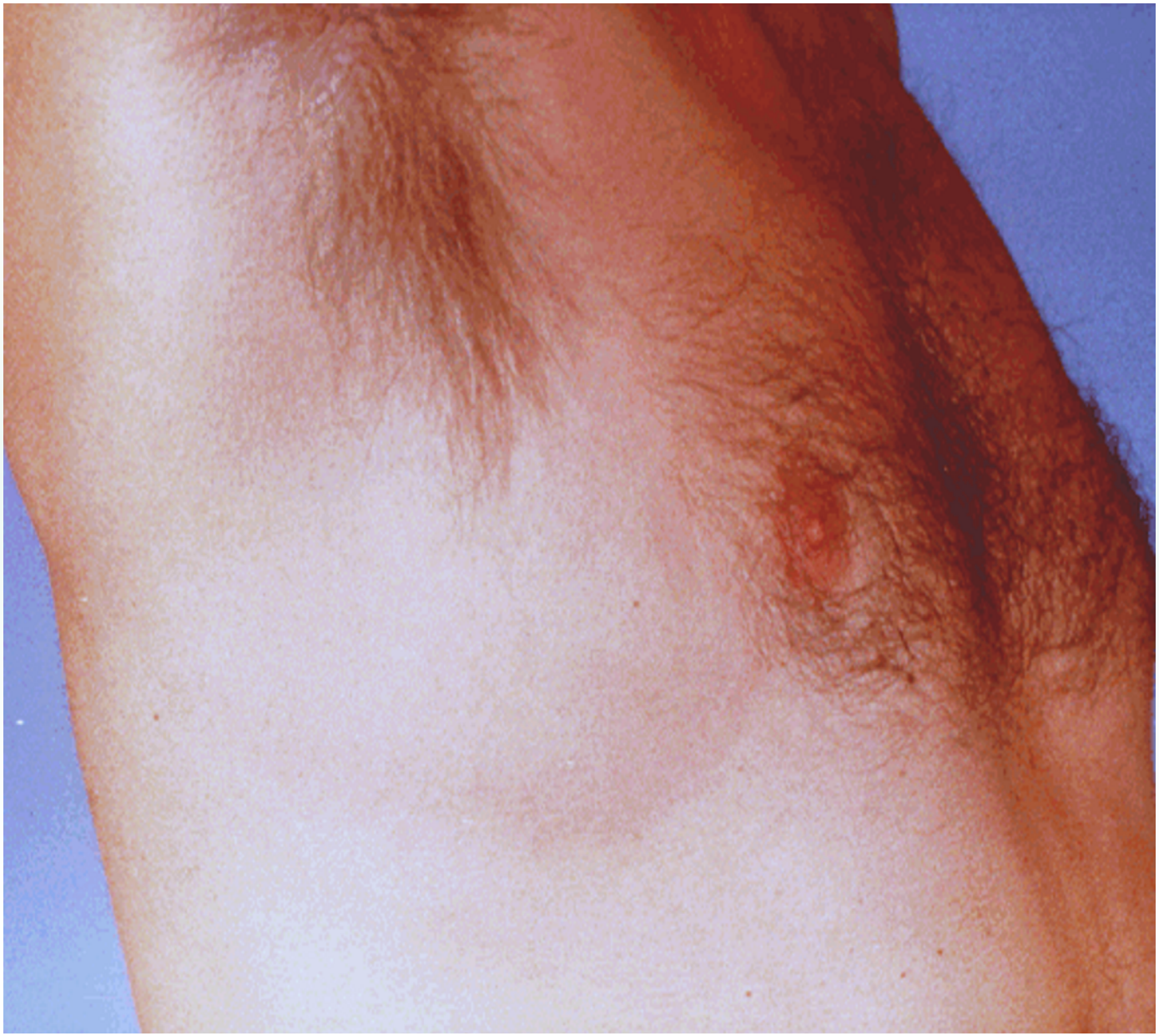
FIGURE 3

Date of illness onset of Lyme borreliosis – 6 East German states, (2002 n=3 019 cases, 2003 n=3 968 cases)

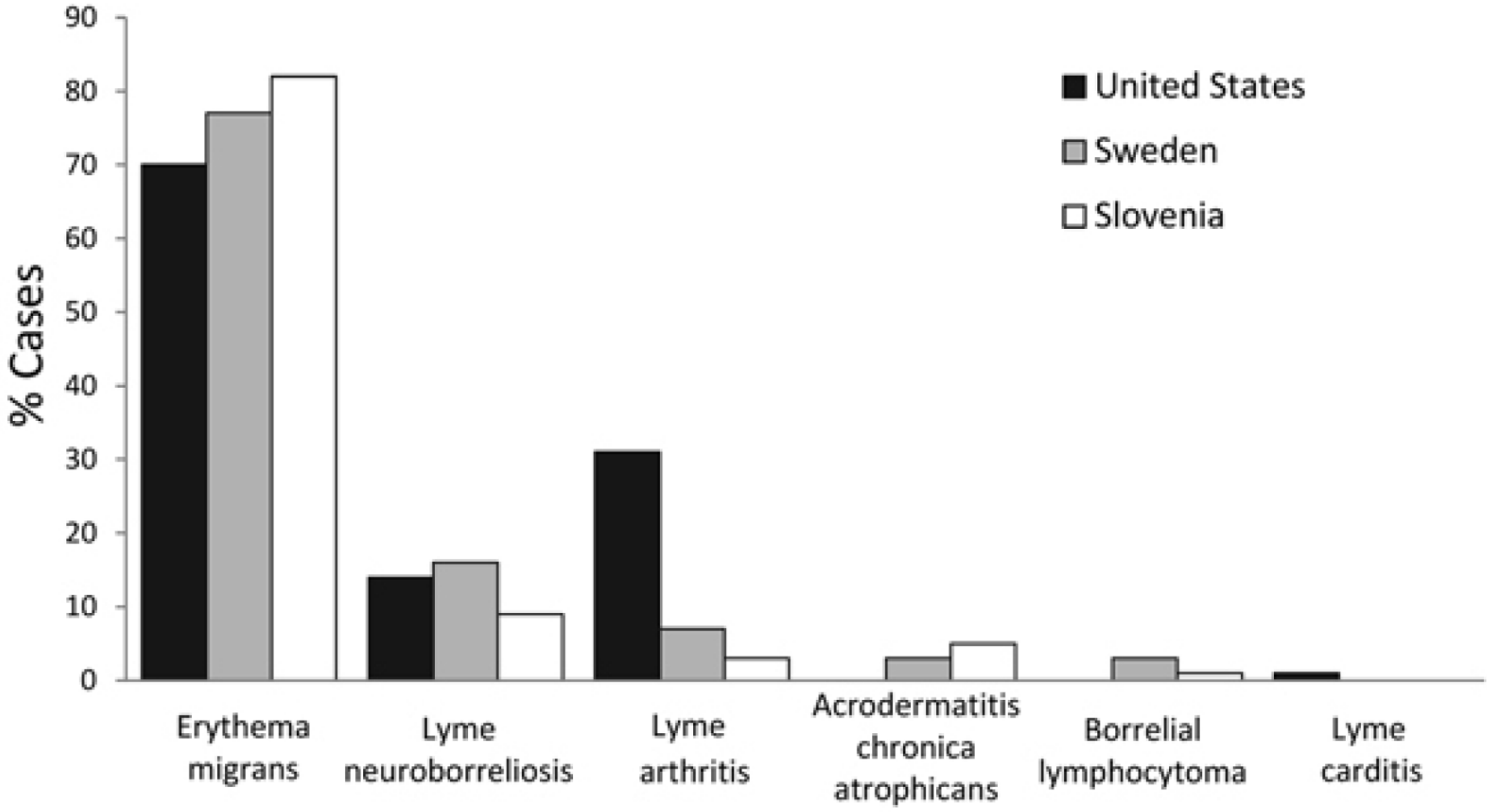


Source : RKI 2006

Lyme Disease: Erythema migrans



Lyme Disease: Different Clinical Manifestations



Markowicz (2015)

Patients with Borreliosis expresss Anti-OspC and Anti-FlaB, but not Anti-Osp-A

Humoral immune response to *B. burgdorferi* antigens among 39 patients with EM

Assay and antigen	Antibody response by ELISA during phase[a]								
	IgM			IgG			IgM or IgG		
	Acute	Conv	*P*	Acute	Conv	*P*	Acute	Conv	*P*
ELISA									
B. burgdorferi lysate	14 (36)	30 (77)	<0.001	5 (13)	23 (59)	<0.001	16 (41)	36 (92)	<0.001
FlaB	12 (31)	15 (38)	0.6	10 (26)	21 (54)	0.02	18 (46)	28 (72)	0.04
OspC	18 (46)	30 (77)	0.01	15 (38)	22 (56)	0.09	24 (62)	34 (87)	0.02
OspA	3 (8)	2 (5)	1.0	3 (8)	3 (8)	1.0	6 (15)	5 (13)	1.0
Any of the above antigens	23 (59)	36 (92)	0.001	21 (54)	32 (82)	0.01	28 (72)	37 (95)	0.01
Two-test approach[b]	11 (26)	26 (67)	<0.001	2 (5)	4 (10)	0.7	13 (33)	29 (74)	<0.001

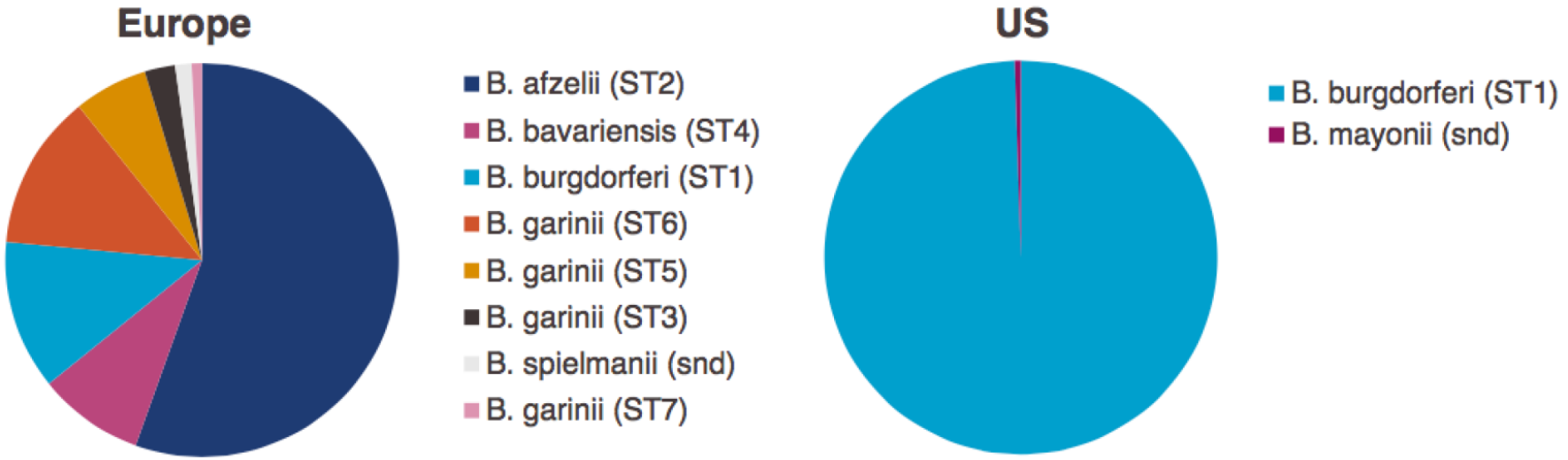
[a]Acute- and convalescent (Conv)-phase samples of patients with EM were tested by ELISA for IgM and IgG responses to borrelial antigens. Except for *P* values, results are presented as number (percent) of samples testing positive.

[b]ELISA and Western blotting.

Vaz et al. Infect Immun 2001:69;7437-7444

Prevalent Borrelia strains in the US and in Europe

- **Analysis of US CDC statistics** and 595 European* (16 countries) LB-patient isolates**
  - US: LB is caused almost exclusively by *B. burgdorferi* s.s. (ST1)
    - The novel species *B. mayonii* rarely causes LB in US*** (prevalence and incidence to be watched)
  - Europe: *B. afzelii* (ST2) is the most common causative agent of LB
    - *Borrelia* belonging to OspA ST1 to ST6 are responsible for almost all European LB cases



* Data from German National Reference Centre for *Borrelia* at the Bavarian Health and Food Safety Authority (Germany) and Baxter have been summarized.
** Centers for Disease Control and Prevention. *** Pritt et al., Lancet. Infect. Dis. 2016. Snd; Serotype not determined

Borrelia species by geography and disease

	relative distribution in %		**OspA**
	Europe	USA	**serotype**
B. Burgdorferi (sensu stricto)	9,3%	100,0%	**1**
B. afzelii	64,5%	-	**2**
B. garinii	25 %	-	**3-7**

The three species are summarized to *B. burgdorferi* sensu lato complex

Leading symptoms for Lyme Disease:

Europe: Neuroborreliosis + Acrodermatitis

U.S.: Arthritis

OspC-mediated immune response does not offer protection

Mechanism of OspA-mediated protection:

In unfed ticks: *B. burgdorferi* s.l. present in tick mid-gut express OspA

During blood meal

- Uptake of OspA-antibodies from OspA-immunized host
- Binding of antibody to spirochetes in the tick mid-gut
  - Killing through bactericidal antibody
  - Antibody blocks attachment to receptors on tick gut epithelium
- Failure of spirochetes to migrate into salivary glands
- Transmission to the OspA immunized host is blocked

Implications for OspA vaccines

- Dependence on high concentration of circulating antibodies for protection

Two OspA vaccines in the past

Smith Kline Beecham

LYMErix

30µg OspA 1

+ aluminium hydroxide

phase III: 10,936 persons[1]

months 0, 1, 12

efficacy:
after 2 doses 83%
after 3 doses 100%

marketed in Dec. 1998

(15-70 years of age)

Pasteur Merieux Connaught

ImuLyme

30µg OspA

No adjuvant

phase III: 10,305 persons[2]

months 0, 1, 12

efficacy:
after 2 doses 68%
after 3 doses 92%

marketed : never

[1]Steere A. et al. N. Engl. J. Med 339, 209-215 (1998)
[2]Sigal L.H. et al. N. Engl. J. Med 339, 216-222 (1998)

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Reactogenicity of LYMErix®

Symptoms	Vaccine (%)	Placebo (%)	*P* Value
Related or Possibly Related to Vaccination			
Local (Injection Site)			
Soreness	24.1	7.6	<.001
Redness	1.8	0.5	<.001
Swelling	0.9	0.2	<.001
Systemic			
Early (≤30 Days)			
Arthralgia			
Headache			
Myalgias			
Fatigue			
Achiness			
Flu-like symptoms			
Fever			
Chills			
Upper respiratory tract infection			
Totals			
Late (>30 Days)			
Arthralgia			
Totals	4.1	3.4	.06
Unrelated to Vaccination			
Early	27.1	27.9	.37
Late	53.3	52.6	.48

From Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme disease with recombinant *Borrelia burgdorferi* outer-surface lipoprotein A with adjuvant. *N Engl J Med*. 1998;339:209–215, copyright Massachusetts Medical Society.

Arthritis

- From December 1996 through August 2000, during the first 19 months after licensure, approximately 1.4 million doses of LYMErix®

…) were

…tients)

…nd OspA

…immunity in a subgroup of these patients was not suggestive of a vaccine-induced process

Market withdrawal in 2002 amid increasing

- **controversial activities of lyme activists,**
- **media coverage,**
- **fears of vaccine side effects,**
- **and declining sales**

Lathrop et al. Vaccine. 20:1603 2002
Ball et al. Arthritis Rheum. 60:1179 2009

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Baxter:
Safety and immunogenicity of a multivalent OspA vaccine - Phase1/2

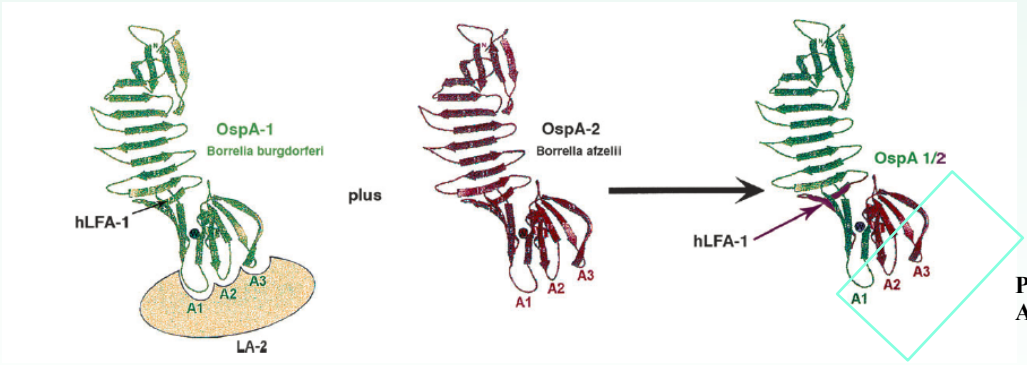
LYME-Vaccine Details:

3 recombinant (chimeric) Osp A antigens (protective epitopes):

Osp A-1 – OspA-2 (B. burgdorferi sensu stricto – B. afzelii)
Osp A-5 – OspA-3 (both B. garinii)
Osp A-6 – OspA-4 (B. garinii and B. bavariensis)

The hypothetical risk of T-cell cross-reactivity (molecular mimicry of OspA-1 with human LFA1) has been eliminated with the replacement of the putative cross-reactive OsPA-1 epitope with the corresponding OsPA-2 sequence

OspA T-cell epitope mimicking human Leukocyte Function-associated Antigen 1 (hLFA-1) sequence



Protective Antibody

The resulting rOspA molecule contains the first of the three surface exposed loops recognized by protective Mab LA-2 (green color). The second and third loops recognized by LA-2 are replaced by equivalent sequences from serotype 2 molecule (red color).

Livey I et al. Clin. Infect. Dis, 2011; 52 (Suppl. 3): S266-S270

A New Approach to a Lyme Disease Vaccine

Ian Livey,[1] Maria O'Rourke,[1] Andreas Traweger,[1] Helga Savidis-Dacho,[1] Brian A. Crowe,[1] P. Noel Barrett,[1] Xiaohua Yang,[3] John J. Dunn,[2] and Benjamin J. Luft[3]

[1]Vaccines Research and Development, Baxter Innovations GmbH, Biomedical Research Center, Orth an der Donau, Austria; [2]Biology Department, Brookhaven National Laboratory, Upton; and [3]Department of Medicine, State University of New York at Stony Brook, Stony Brook, New York

A single recombinant outer surface protein A (OspA) antigen designed to contain protective elements from 2 different OspA serotypes (1 and 2) is able to induce antibody responses that protect mice against infection with either *Borrelia burgdorferi sensu stricto* (OspA serotype-1) or *Borrelia afzelii* (OspA serotype-2). Protection against infection with *B burgdorferi ss* strain ZS7 was demonstrated in a needle-challenge model. Protection against *B. afzelii* species was shown in a tick-challenge model using feral ticks. In both models, as little as .03 μg of antigen, when administered in a 2-dose immunization schedule with aluminum hydroxide as adjuvant, was sufficient to provide complete protection against the species targeted. This proof of principle study proves that knowledge of protective epitopes can be used for the rational design of effective, genetically modified vaccines requiring fewer OspA antigens and suggests that this approach may facilitate the development of an OspA vaccine for global use.

Table 2. Immunization with rOspA 1/2 Protects against Infection with Tick-Transmitted *B. afzelii*

		No. of positive samples				Infecting *Borrelia* sp.	
Treatment[a]	Dose[b]	SC	PCR	Culture	Total[c]	*B. afzelii*	Other *Borrelia* sp.
Control	0	10/14	11/14	10/14	11/14	11/11	None
OspA 1/2	0.10	1/16	1/16	0/16	1/16	0/1	*B. garinii*
OspA 1/2	0.03	1/16	2/16	2/16	2/16	0/2	*B. garinii, B. valaisiana*

NOTE. SC, seroconversion

[a] C3H/HeJ mice received 2 different lots of rOspA 1/2 antigen in a 2-dose regimen.

[b] μg rOspA 1/2 antigen, formulated with .2% $Al(OH)_3$ (w/v), per mouse.

[c] Number of animals deemed infected (see Results for details).

Safety and immunogenicity of a novel multivalent OspA vaccine against Lyme borreliosis in healthy adults: a double-blind, randomised, dose-escalation phase 1/2 trial

	OspA serotype 1*	OspA serotype 2†	OspA serotype 3‡	OspA serotype 4§	OspA serotype 5‡	OspA serotype 6‡
Surface-binding antibodies						
Baseline (n=49)	12 (9–17)	3 (3–3)	13 (13–13)	3 (3–4)	7 (6–8)	8 (6–8)
28 days after third dose (n=46)	77 (50–117)	38 (26–57)	767 (582–1012)	11 (9–15)	38 (29–50)	25 (17–36)
Immediately before booster (n=33)	26 (18–39)	7 (5–9)	34 (27–43)	4 (3–5)	17 (13–21)	11 (9–13)
28 days after booster (n=33)	1239 (837–1834)	466 (314–692)	3928 (3072–5021)	115 (77–172)	429 (307–598)	377 (268–531)
Borreliacidal antibodies						
Baseline (n=49)	35 (28–43)	28 (25–32)	ND	33 (25–42)	31 (24–41)	33 (26–43)
28 days after third dose; n=46)	131 (85–201)	101 (70–145)	ND	65 (46–92)	52 (38–73)	152 (89–260)
Immediately before booster (n=33)	58 (39–86)	34 (27–42)	ND	37 (28–49)	32 (25–41)	49 (32–75)
28 days after booster (n=33)	889 (634–1248)	654 (470–909)	ND	706 (459–1085)	228 (158–329)	774 (454–1319)

Data in parentheses are 90% CI. The killing assay could not be done for *Borrelia garinii* expressing OspA serotype 3 because of their inherent complement sensitivity. ND=not done. **Borrelia burgdorferi* sensu stricto. †*Borrelia afzelii*. ‡*B garinii*. §*Borrelia bavariensis*.

Table 4: Antibody titres for specific OspA serotypes induced by the 30 µg adjuvanted formulation capable of binding to the surface of and killing *Borrelia* spp

University of Vienna, Vienna, Austria (M Zeitlinger MD, Prof M Müller MD, Prof H Kollaritsch MD, M Paulke-Korinek MD); **and Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany** (M Esen MD, Prof P G Kremsner MD)

formulations induced substantial mean IgG antibody titres against OspA serotypes 1–6 after the first three vaccinations (range 6944–17 321) and booster (19 056–32 824) immunisations. The 30 µg adjuvanted formulation induced the highest antibody titres after the booster: range 26 143 (95% CI 18 906–36 151) to 42 381 (31 288–57 407).

Interpretation The novel multivalent OspA vaccine could be an effective intervention for prevention of Lyme borreliosis in Europe and the USA, and possibly worldwide. Larger confirmatory formulation studies will need to be done that include individuals seropositive for *Borrelia burgdorferi* sensu lato before placebo-controlled phase 3 efficacy studies can begin.

Clinical and Vaccine Immunology p.

A Novel Multivalent O
and Immunogenic in a
Borrelia burgdorferi Se

Nina Wressnigg,[a] P. Noel Barrett,[b] Eva-Mari
Brian A. Crowe,[b] Ian Livey,[b] Thomas Dvoral
Peter G. Kremsner,[f] Tomas Jelinek,[g] Roland

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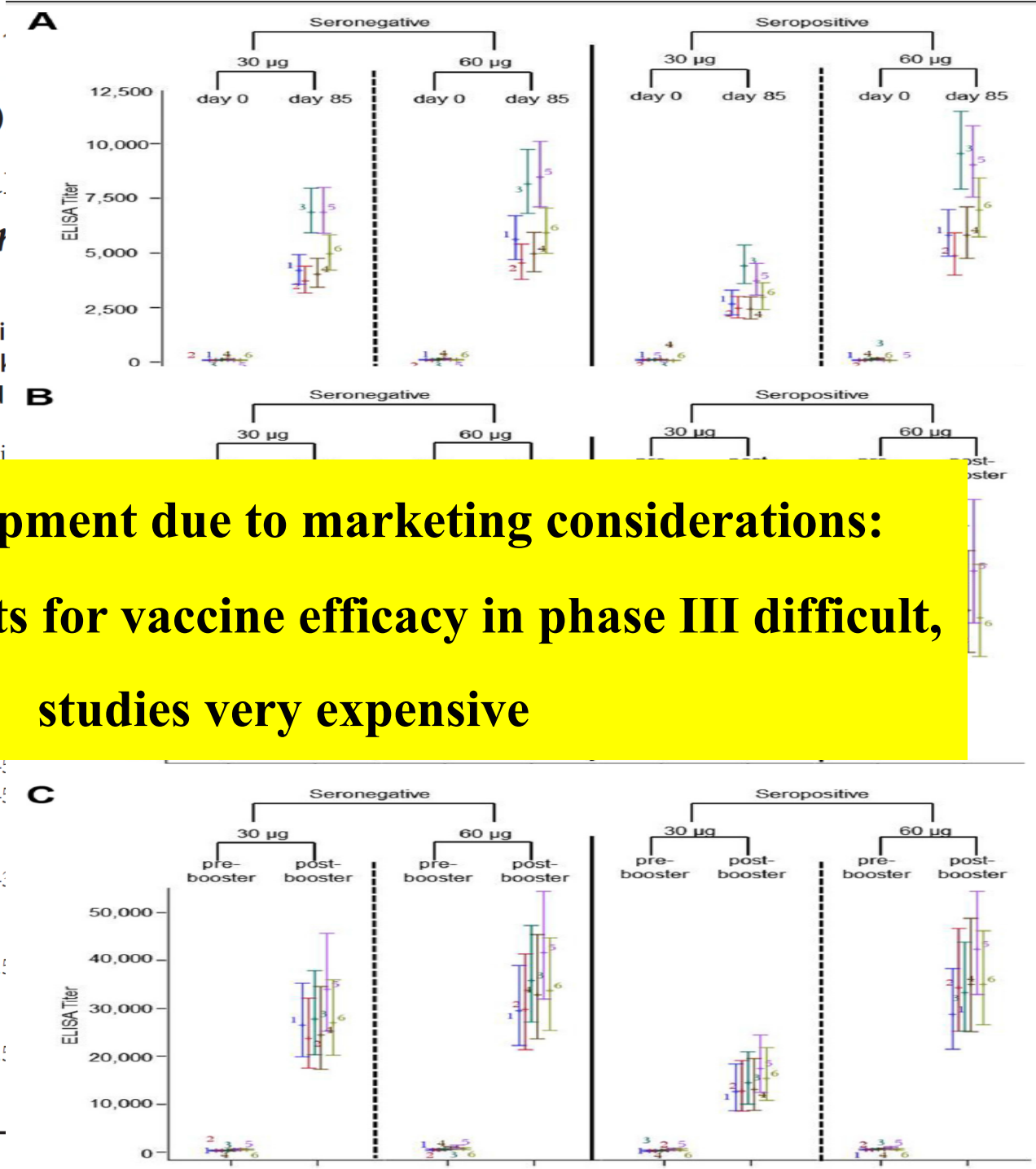
TABLE 2 Participants with solicited injection si

Reacti	
Local r	
Any	
Swe	
Indu	
Red	
Injection site pain	42 (41.6, 33.3–5
Tenderness	50 (49.5, 40.9–5
Systemic reactions	
Any	30 (29.7, 22.3–3
Malaise	5 (5, 2–10.1)
Fatigue	8 (7.9, 4–13.8)
Headache	12 (11.9, 7–18.5
Nausea	1 (1, 0.1–4.6)
Vomiting	0 (0, 0–2.9)
Myalgia	12 (11.9, 7–18.5
Arthralgia	2 (2, 0.4–6.1)
Fever (>38.0°C)	0 (0, 0–2.9)

[a] CI, confidence interval.



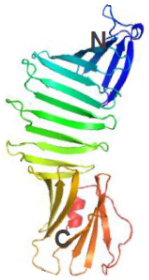
Stop of development due to marketing considerations:

Clinical endpoints for vaccine efficacy in phase III difficult, studies very expensive

VLA15 – Design

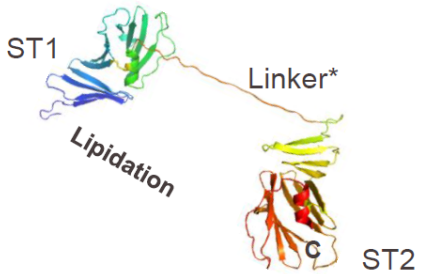
Product based on three engineered proteins with or w/o Alum

Full-length OspA



Truncated stabilized OspA monomer

Stabilized OspA monomers representing 6 serotypes joined with a linker to 3 heterodimers



* linked with a 21 amino acid linker derived from two N-terminal loops of OspA-ST1 (aa 65-74, aa 42-53)

Focus on C-terminal region of OspA

- Epitope LA-2 (OspA-ST1) correlates with protective immunity after vaccination[2]
- Truncated OspA monomers are stabilized through introduction of disulfide bonds
- T-cell epitope mimicking hLFA-1 sequence replaced by respective region from ST2[1]

3 heterodimers targeting major OspA-serotypes[1]

- 3 heterodimers target the most relevant *Borrelia* OspA serotypes (ST1- ST6) in Europe and US
- 3 proteins reduce industrialization complexity
- Lipidation and Alum-adjuvantation increase immunogenicity in mice

1 Comstedt et al. 2014, PLoS One 9:e113294; Comstedt et al. 2015, Vaccine 33:5982-8 **2** Golde et al. Inf. Imm 1997

Slide taken from:
T. Lingelbach. Developing a vaccine against Lyme disease.
Presentation at World Vaccine Congress Washington, 4 APR 2018

Valneva's Lyme vaccine candidate (VLA15)
Summary

- Multivalent, protein subunit-based vaccine – intended for global reach
- Based on *Borrelia* Outer Surface Protein A (OpsA), expressed by the bacteria when present in a tick
  - › Vaccine design allowed elimination of epitope with homology to hLFA-1
- Only active clinical Lyme vaccine program to date
- FDA Fast Track designation granted[1]

- Positive Phase 1 interim results reported[2]
- Pre-clinical data showed that VLA15 has the potential to provide protection against the majority of *Borrelia* species pathogenic for humans[3]
- Phase 2 currently expected to commence in H2/2018

1 http://www.valneva.com/download.php?dir=News_2018&file=2018_03_22_Valneva_2017_FY_Results_PR_EN.pdf; 2 http://www.valneva.com/en/investors-media/news;
3 http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0113294

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Valneva's Lyme disease vaccine candidate (VLA15)

Target Product Profile

Indications	▪ **Prophylactic active immunization against Lyme disease in individuals ≥ 2 years of age in US and Europe**
Dose and Administration	▪ Route of administration: Intramuscular injection ▪ Recommended dose: Best formulation of 3 heterodimers (ST 1/2, 4/3, 5/6) with or without Alum ▪ Dosage schedule: Month 0-1-2 (alternative schedule: Month 0-2), first booster after 1 year, further booster after 3-5 years (3 years for elderly)
Dosage Form	▪ Single dose syringe (2-8°C)
Contraindications	▪ Hypersensitivity to any component of the vaccine
Adverse Reactions	▪ Comparable to intramuscularly injected Alum adjuvanted vaccines
Target Population/ Target Groups	▪ Individuals at risk who live in endemic areas ▪ People who plan to travel to endemic areas to engage in outdoor activities (e.g., hiking) ▪ People at risk with prior history of Lyme disease, since infection with *Borrelia* may not confer protective immunity

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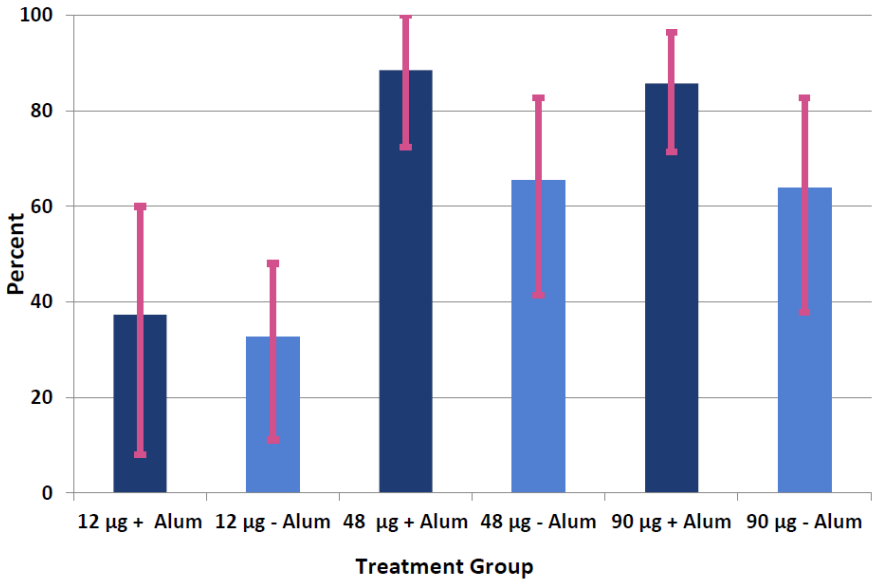
Phase 1 study (VLA15-101) – Immunogenicity

SCR for Highest Adjuvanted Dose Group between 71.4% and 96.4%

Seroconversion Rates (SCR)

Average* Seroconversion Rate by Treatment Group, Day 84



*Average = Arithmetic Mean of SCRs against individual Serotypes 1-6 (Rate of subjects with ≥4-fold increase in OspA-specific IgG)
** Error Bars represent highest / lowest individual Serotype SCR for treatment group

Key results

- OspA specific IgG antibody responses induced in all treatment groups and against all OspA serotypes
- Significant difference in response between the lowest adjuvanted dose group and the two highest ones
- Alum-adjuvanted treatment groups more immunogenic compared to non-adjuvanted groups in same dose levels
- No significant dose response between 48µg and 90µg. Day 56 data indicate better kinetics of immune response at higher dose levels
- Highest dose considered for further development***

*** Further dose optimization will be considered

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VLA15 Lyme vaccine candidate

A Potential for a Correlate of Protection Strategy?

- Antibodies against the LA-2 epitope were correlated with a protective response in humans[1]. In the LYMErix Phase 3 vaccine trial, the LA-2 equivalent antibody titers were significantly lower in subjects that were breakthrough cases and developed Lyme disease
- A correlate of protection against *B. burgdorferi* was established based on OspA IgG ELISA titers[2]. Titers of 700 to 1,400 ELISA units/mL provided 70% to 95% sensitivity, allowing differentiation between vaccine failure and success, and are predictive for protection
- The ability of OspA antibodies to inhibit *Borrelia* growth was reported to be predictive for protection in humans[3]
  - › Growth inhibition strongly correlated with OspA ELISA results

Valneva will actively seek ways to collaborate with regulatory authorities in order to potentially accelerate the path to licensure through a correlate of protection-based pivotal Phase 3 immunogenicity trial

1 Steere et al. NEJM 1998; 339:209-215, **2** Parenti et al. 1998 Abstract in annual meeting of the Infectious Diseases Society of America, **3** Luke et al. JID 2000; 181:1062-8

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Conclusions

- ✓ An effective vaccine against borreliosis is needed
- ✓ Probably OspA-vaccine necessary
- ✓ Antigen with potential for global efficacy identified
- ✓ Immunogenicity proven
- ✓ Association with arthrits rejected / not proven
- ✓ High antibody titers for efficacy needed

  (frequent boosts necessary?)
- ✓ Determination of endpoints for protective efficacy difficult
- ✓ Further studies needed: Phase III very long and expensive
- ➢ Technical way to effective vaccine probably identified,

  marketing and public need to be convinced


Thank you