

TICK-BORNE DISEASE
DIAGNOSIS SHOULD
NOT BE LIMITED TO
JUST LYME DISEASE

A LOOK AT THE
BIGGER
PICTURE !

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Evaluating polymicrobial immune responses in patients suffering from tick-borne diseases

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Periodontal diseases



20 – 50 %¹

Global population

500¹

Microbial species

19 - 44 %¹

Risk cardiovascular

Respiratory diseases



50 – 400²

Million worldwide

50 - 200³

Microbial species

90 %⁴

Risk diabetes

Mosquito -
borne



29 – 40 %^{5, 6}
Global population

Symbiosis⁷
Same microbial species

Immunosuppression⁸
Meningitis

Tick -
borne



0.3 – 2.4⁹
Million worldwide

?
Microbial spectrum

?
Likelihood

Borrelia spirochete species

Borrelia burgdorferi

Borrelia afzelii

Borrelia garinii

Tick-borne co-infections

Babesia microti

Bartonella henselae

Brucella abortus

Ehrlichia chaffeensis

Rickettsia akari

Tick-borne encephalitis virus

Borrelia spirochete species

Borrelia burgdorferi

Borrelia afzelii

Borrelia garinii

Tick-borne co-infections

Babesia microti

^{10, 11, 12}

Erpingtonella henselae

Brucella abortus

Ehrlichia chaffeensis

Rickettsia akari

tick-borne encephalitis virus

4 to 60 %

Co-infection rate

Borrelia spirochete species

Borrelia burgdorferi

Borrelia afzelii

Borrelia garinii

4 to 60 %

Co-infection rate

Tick-borne co-infections

Babesia microti

Bartonella henselae

Brucella abortus

Ehrlichia chaffeensis

Rickettsia akari

tick-borne encephalitis virus

Borrelia species persistent forms

Borrelia burgdorferi

Borrelia afzelii

Borrelia garinii

Opportunistic microbes

Chlamydia pneumoniae

Chlamydia trachomatis

Coxsackievirus

Cytomegalovirus

Epstein-Barr virus

Human parvovirus B19

Mycoplasma pneumoniae

Mycoplasma fermentans

Borrelia spirochete species

Borrelia burgdorferi

Borrelia afzelii

Borrelia garinii

4 to 60 %

Co-infection rate

Tick-borne co-infections

Babesia microti

Bartonella henselae

Brucella abortus

Ehrlichia chaffeensis

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tick-borne encephalitis virus

Borrelia species persistent forms

Borrelia burgdorferi

Borrelia afzelii

Borrelia garinii

Opportunistic microbes

Chlamydia pneumoniae

Chlamydia trachomatis

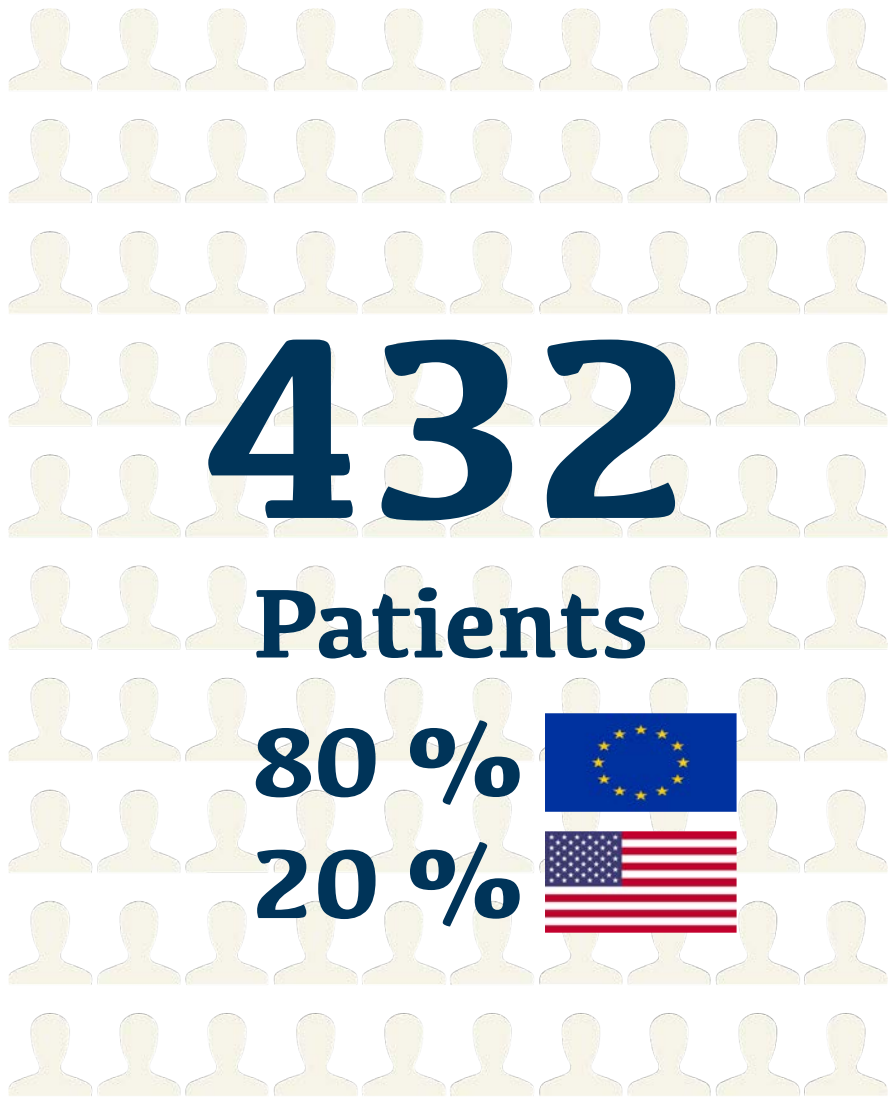
Coxsackievirus

Tick-borne diseases are exceptionally polymicrobial in nature ?

Human parvovirus B19

Mycoplasma pneumoniae

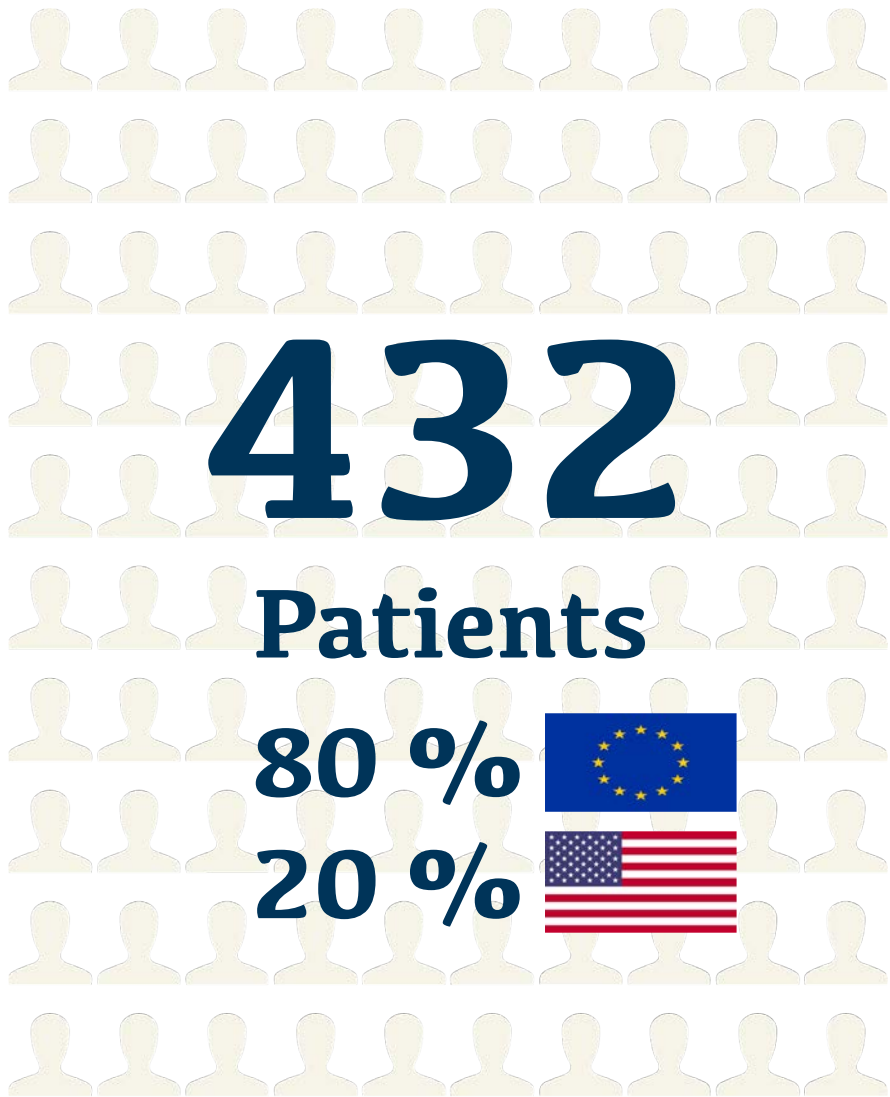
Mycoplasma fermentans



20 Microbes

<p>Borrelia spirochete species</p> <ul style="list-style-type: none"> <i>Borrelia burgdorferi</i> <i>Borrelia afzelii</i> <i>Borrelia garinii</i> 	<p>Tick-borne co-infections</p> <ul style="list-style-type: none"> <i>Babesia microti</i> <i>Bartonella henselae</i> <i>Brucella abortus</i> <i>Ehrlichia chaffeensis</i> <i>Rickettsia akari</i> Tick-borne encephalitis virus
<p>Borrelia species persistent forms</p> <ul style="list-style-type: none"> <i>Borrelia burgdorferi</i> persistent form <i>Borrelia afzelii</i> persistent form <i>Borrelia garinii</i> persistent form 	<p>Opportunistic microbes</p> <ul style="list-style-type: none"> <i>Chlamydia pneumoniae</i> <i>Chlamydia trachomatis</i> Coxsackievirus Cytomegalovirus Epstein-Barr virus Human parvovirus B19 <i>Mycoplasma pneumoniae</i> <i>Mycoplasma fermentans</i>





*Centers for Disease Control and Prevention (CDC)

** Infectious Disease Society of America (IDSA)

*** CE/ IVD/FDA marked test kits for non-Borrelia microbes

* CDC Acute

* CDC Late

* CDC Negative

** PTLDS

*** Immunocompromised

*** Unspecific

*** Healthy

IgM response to

More than 1 microbe

Only 1 microbe

No response



IgG response to

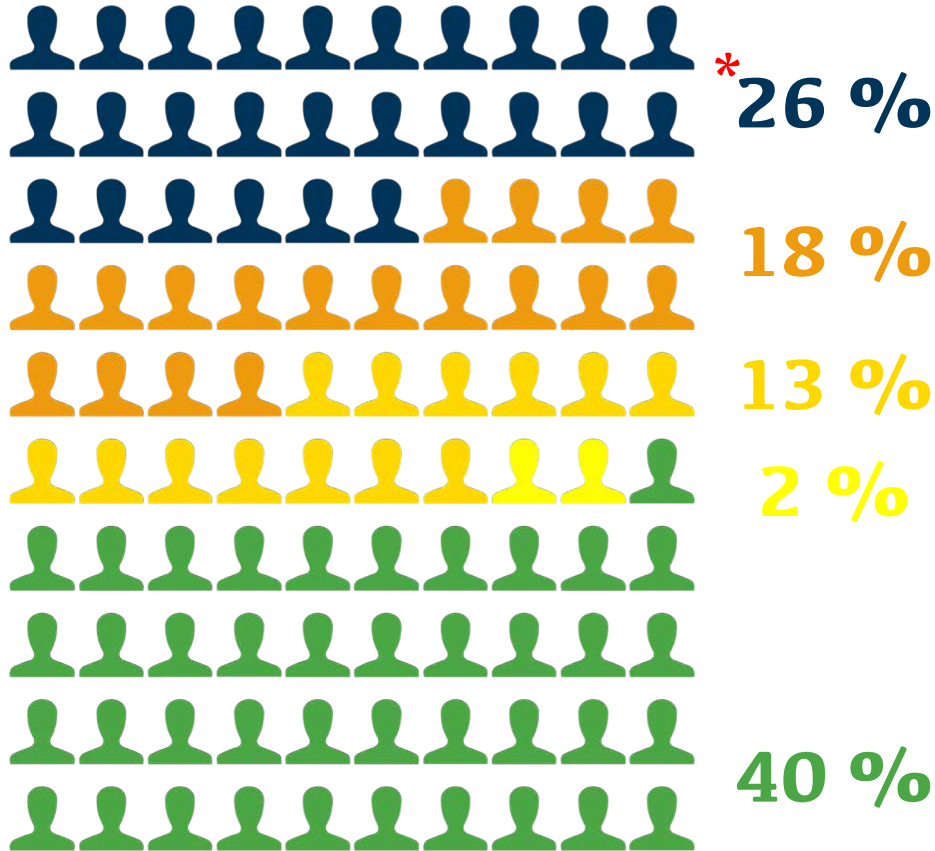
More than 1 microbe

Only 1 microbe

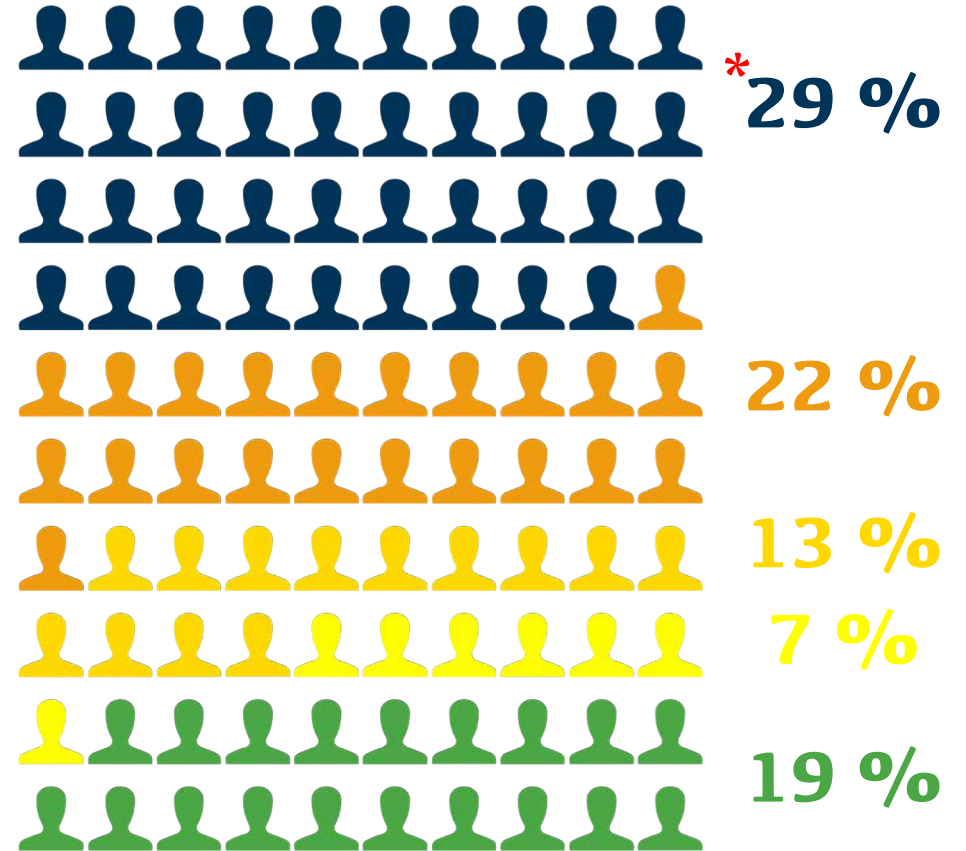
No response



IgM response to



IgG response to

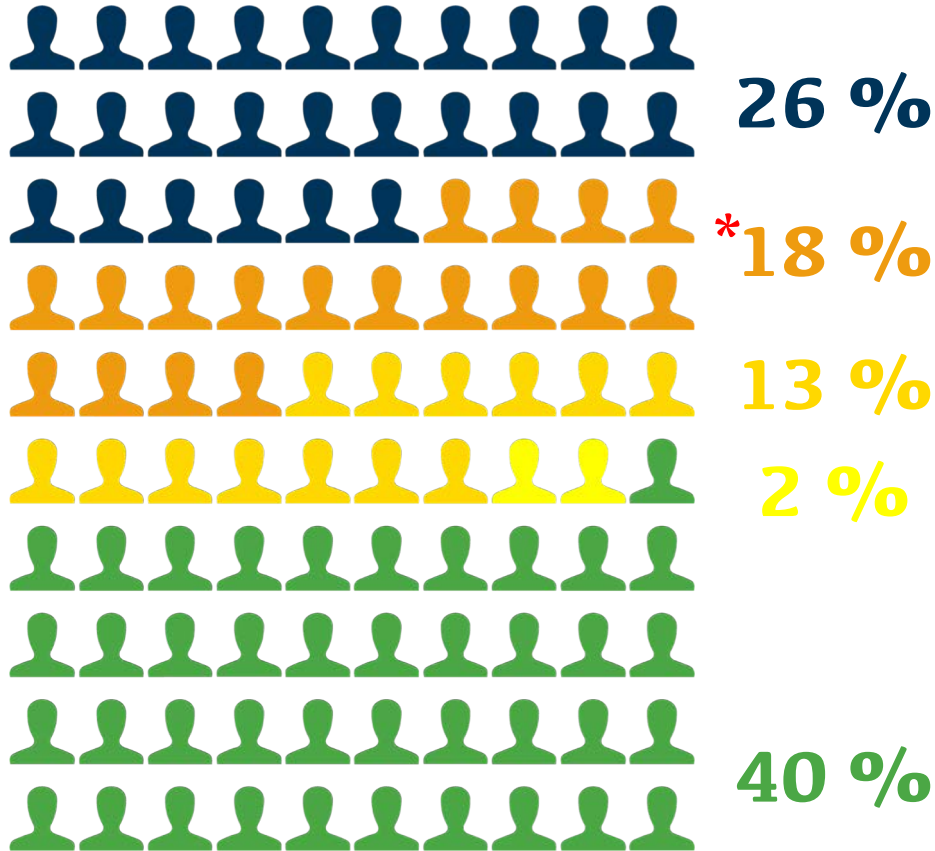


IgM response to

Borrelia spirochete and persistent forms

Other TBD microbes Borrelia persistent form

Borrelia spirochete form No response

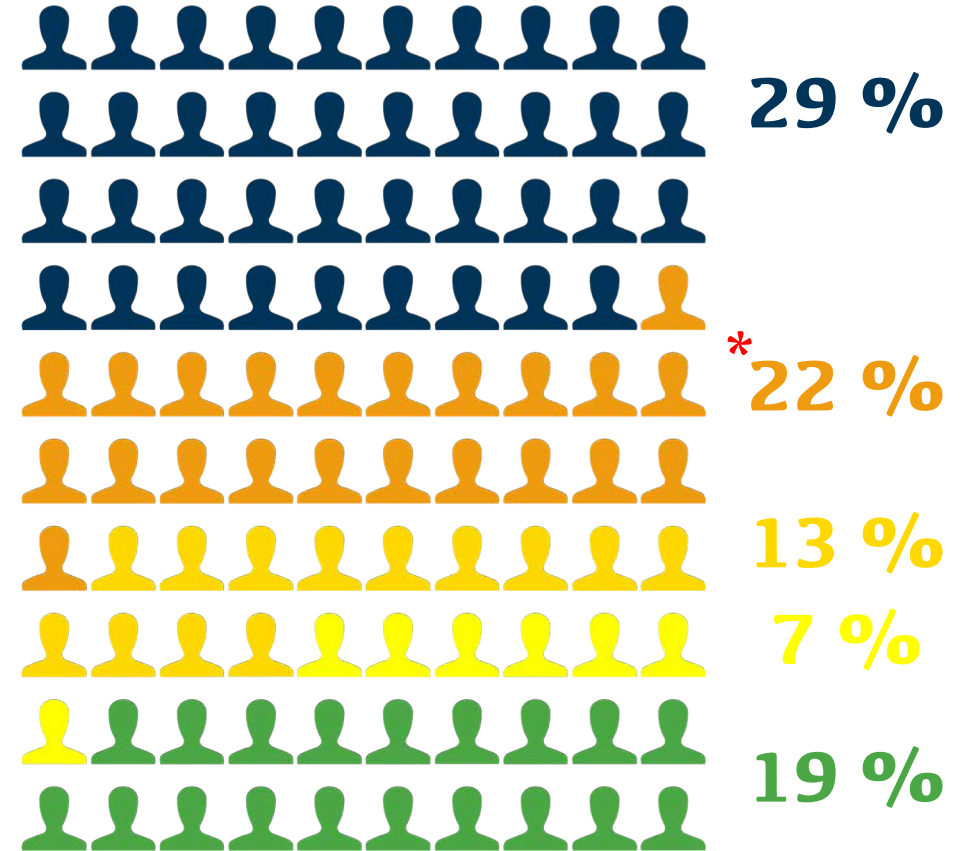


IgG response to

Borrelia spirochete and persistent forms

Other TBD microbes Borrelia persistent form

Borrelia spirochete form No response



IgM response to

Borrelia spirochete and persistent forms

Other TBD microbes Borrelia persistent form

Borrelia spirochete form No response



13 %

2 %

IgG response to

Borrelia spirochete and persistent forms

Other TBD microbes Borrelia persistent form

Borrelia spirochete form No response



13 %

7 %

IgM response to

Borrelia spirochete and persistent forms

Other TBD microbes Borrelia persistent form
Borrelia spirochete form No response

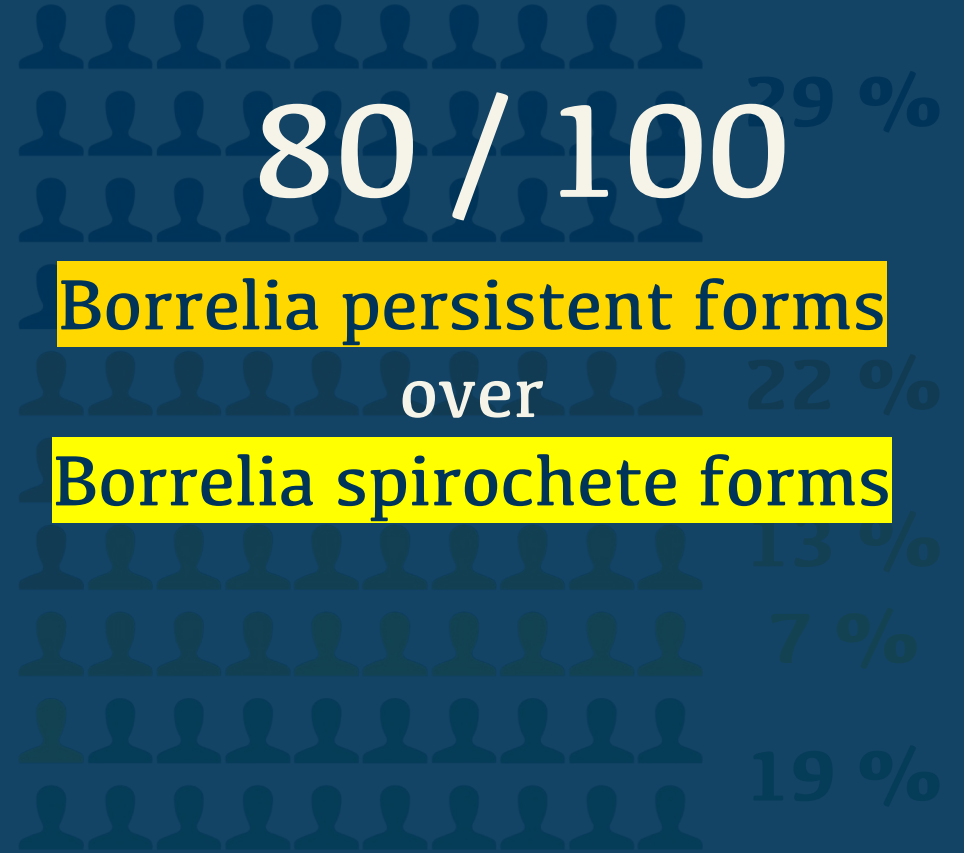


40 %

IgG response to

Borrelia spirochete and persistent forms

Other TBD microbes Borrelia persistent form
Borrelia spirochete form No response



80 / 100

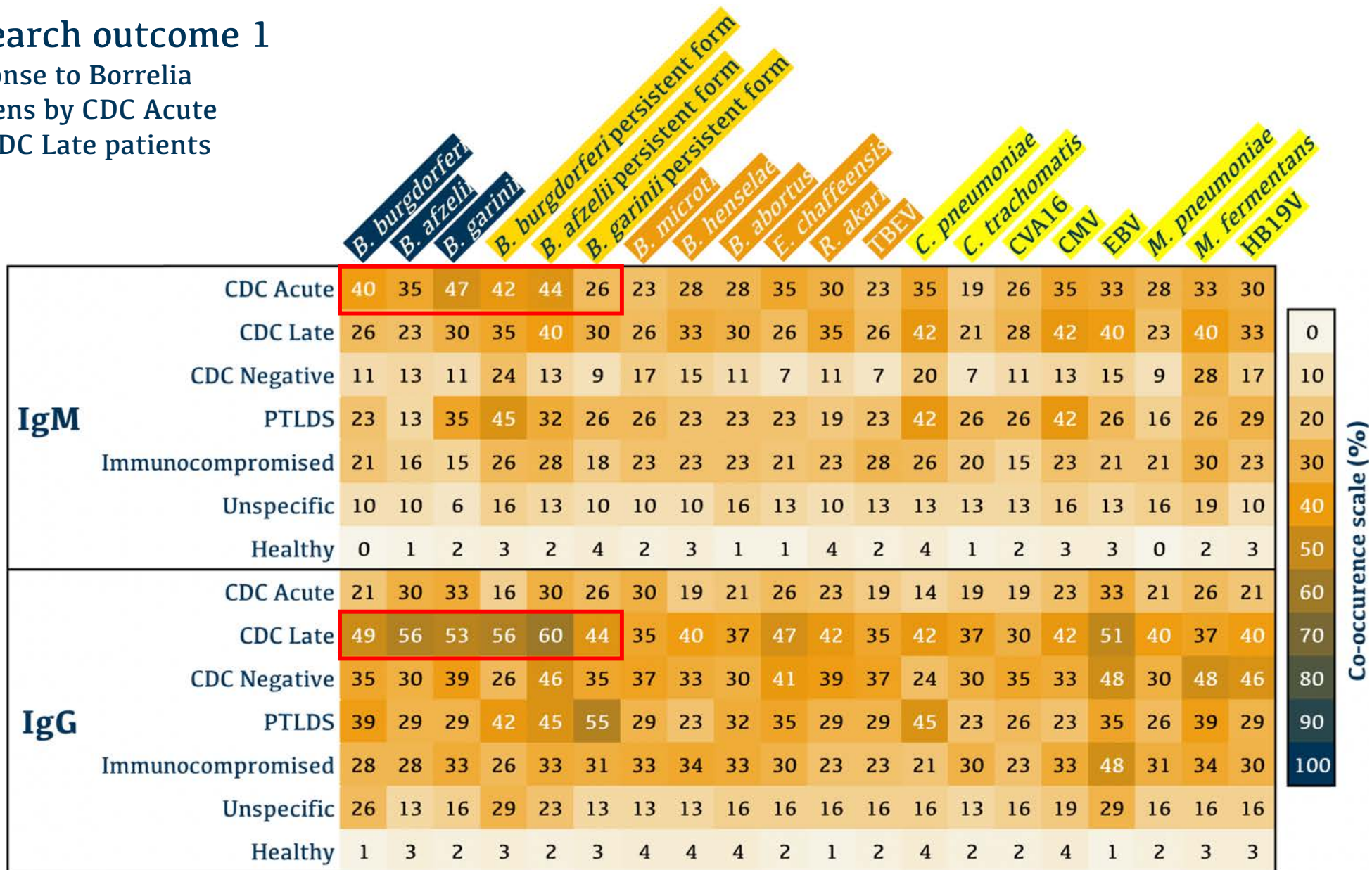
Borrelia persistent forms

over

Borrelia spirochete forms

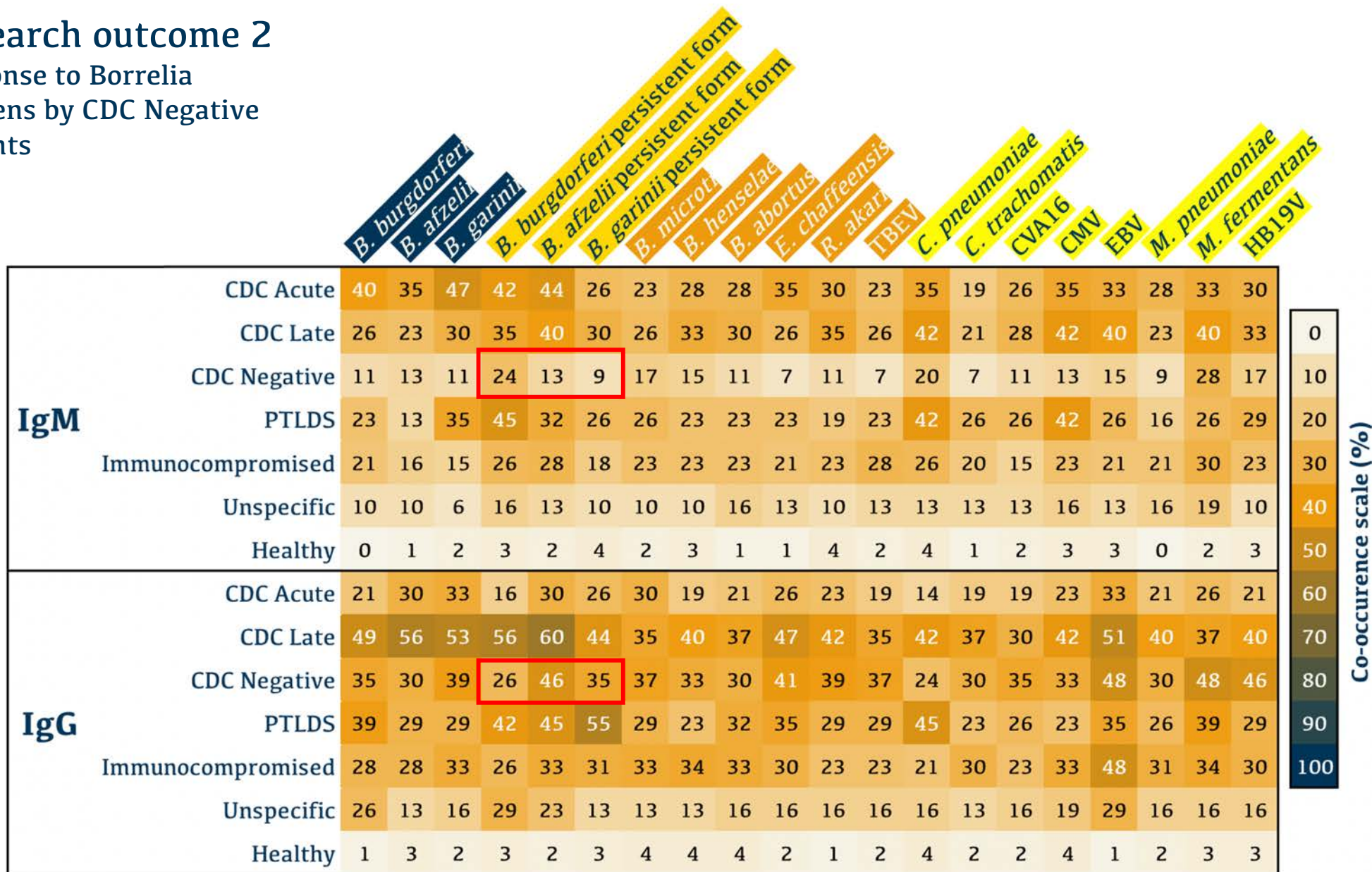
Research outcome 1

Response to Borrelia antigens by CDC Acute and CDC Late patients



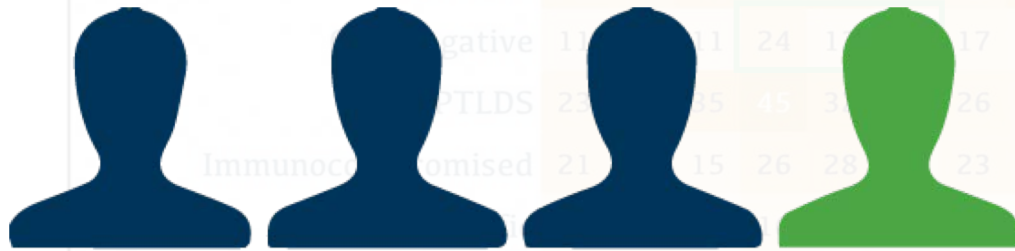
Research outcome 2

Response to Borrelia antigens by CDC Negative patients



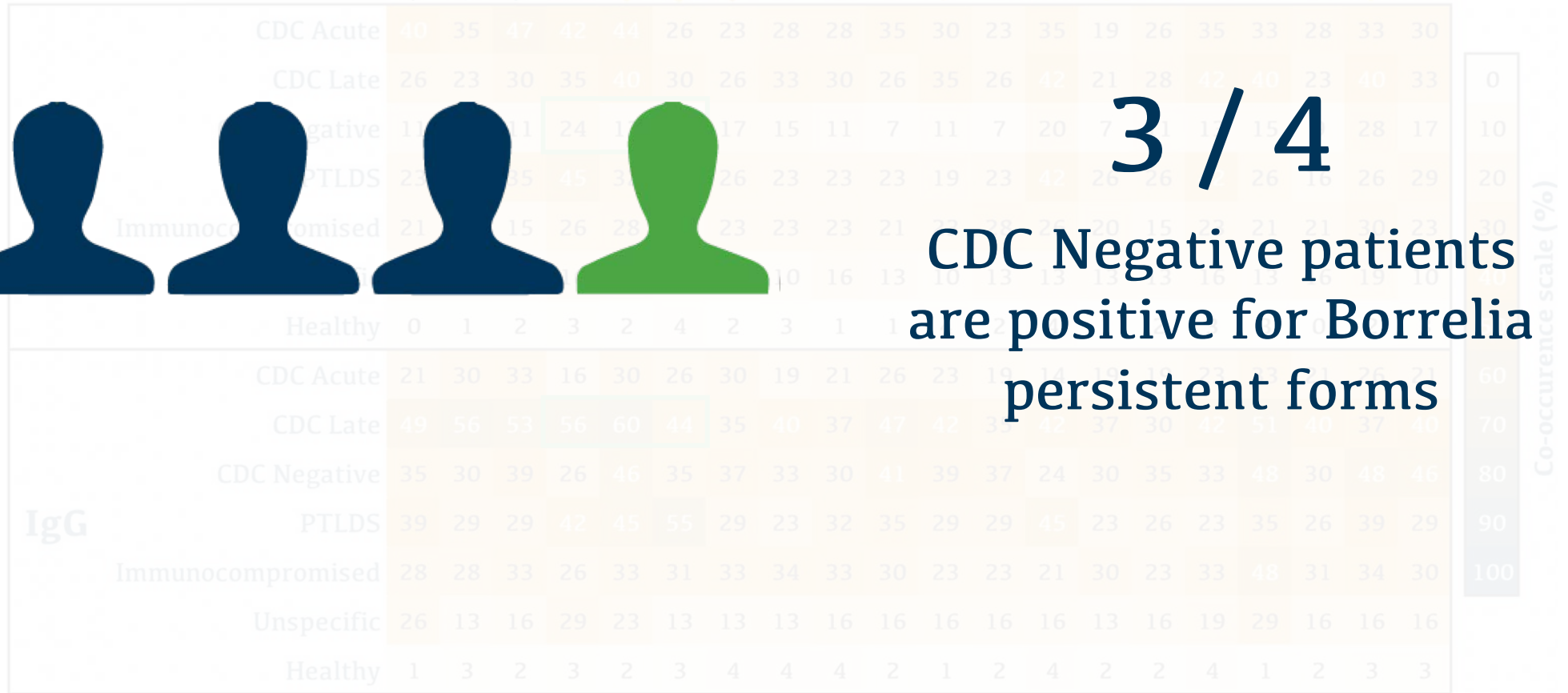
Research outcome 2

Response to Borrelia antigens by CDC Negative patients



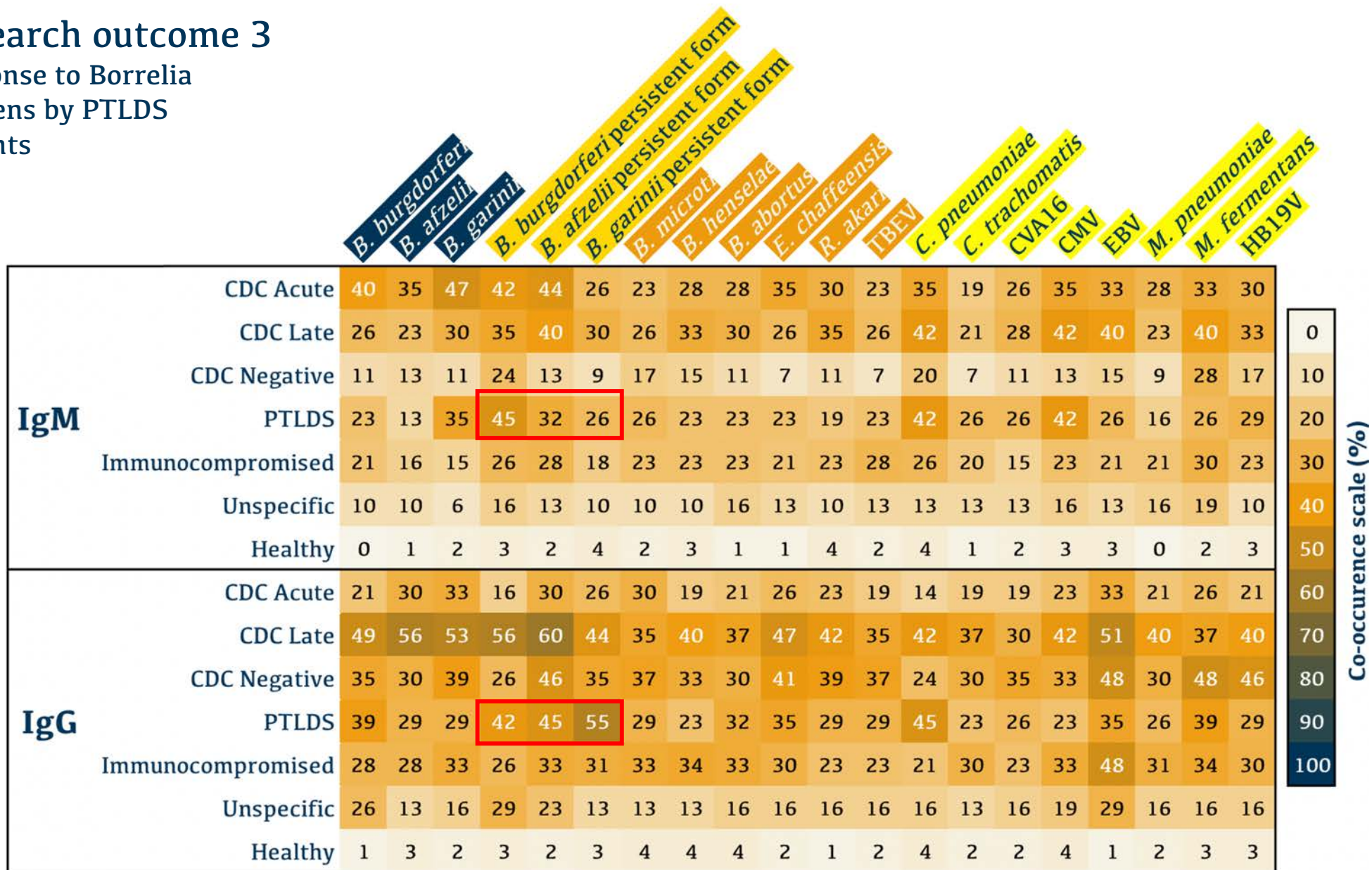
3 / 4

CDC Negative patients are positive for Borrelia persistent forms



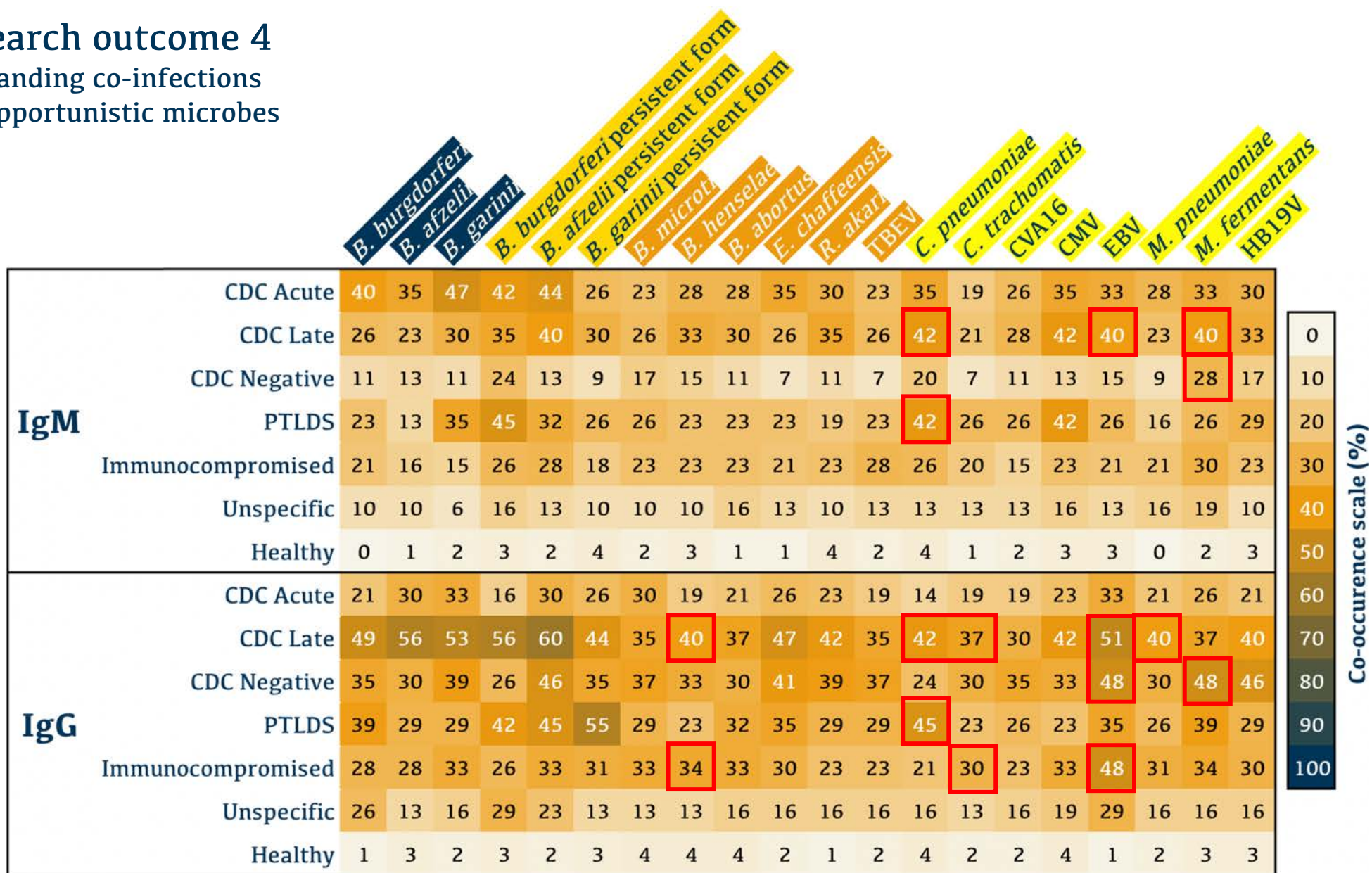
Research outcome 3

Response to Borrelia antigens by PTLDS patients



Research outcome 4

Outstanding co-infections and opportunistic microbes



Differential diagnosis examples

Bartonella henselae

67.5 % Chronic fatigue syndrome¹³

Chlamydia pneumoniae

48.3 % Juvenile idiopathic arthritis¹⁴

Chlamydia trachomatis

6 - 50 % reactive arthritis¹⁵

Epstein-Barr virus

95 % Multiple sclerosis¹⁶

Mycoplasma pneumoniae

59.3 % Chronic fatigue syndrome¹⁷

Mycoplasma fermentans

48 % Chronic fatigue syndrome¹⁷

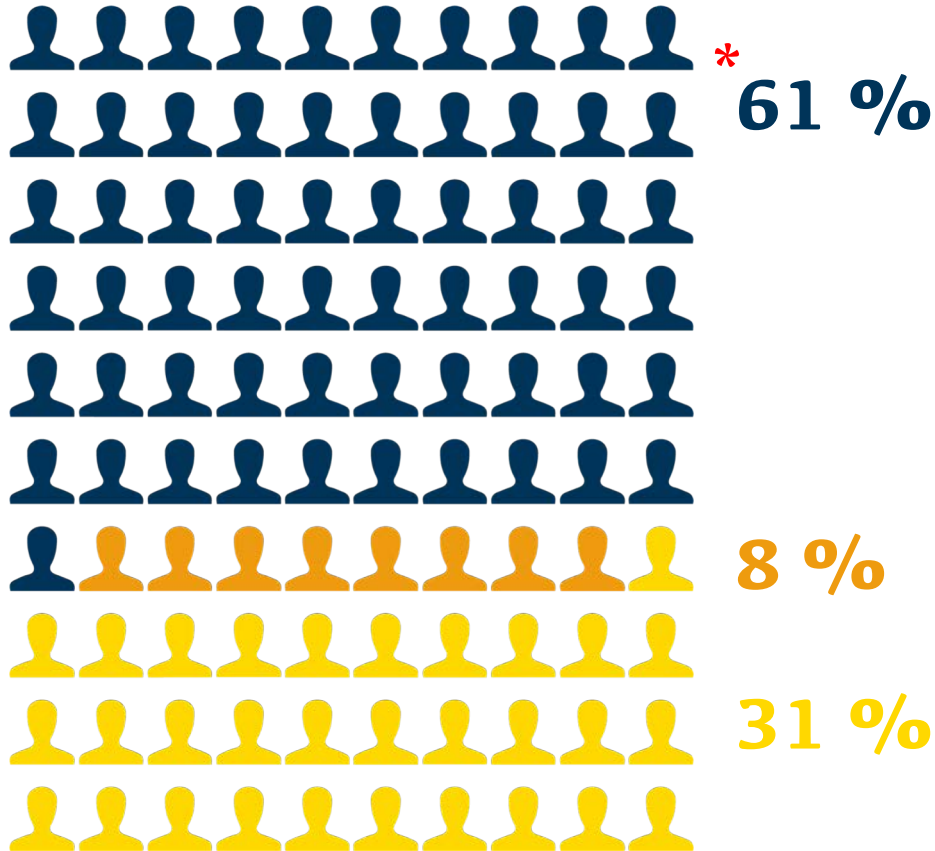
CDC Acute	40	35	47	42	16	26	23	28	28	35	23	35	19	26	35	33	25	25	30
CDC Late	26	23	30	35	16	30	26	28	26	26	42	21	28	42	40	23	23	23	0
CDC Negative	11	13	11	24	13	17	15	11	7	11	7	20	7	11	13	15	9	28	17
IgM																			
PTLDS	23	13	35	45	32	26	26	23	23	19	23	42	26	26	42	26	16	26	29
Immunocompromised	21	16	15	26	28	18	23	23	21	23	28	26	20	15	23	21	21	30	23
Unspecific	10	10	6	16	13	10	10	10	16	13	10	13	13	13	16	13	16	19	10
Healthy	0	1	2	3	2	4	2	3	1	4	2	4	1	2	3	3	0	2	3
CDC Acute	21	30	33	16	16	35	37	33	30	39	19	14	19	19	23	35	26	39	90
CDC Late	49	56	53	56	45	55	28	23	32	35	29	45	23	26	23	35	26	39	29
CDC Negative	35	30	39	26	25	35	37	33	30	39	37	24	30	35	33	48	30	48	46
IgG																			
PTLDS	39	29	29	42	45	55	28	23	32	35	29	45	23	26	23	35	26	39	29
Immunocompromised	28	28	33	26	23	31	33	34	30	23	23	21	30	23	33	31	31	34	30
Unspecific	26	13	16	29	23	15	15	10	10	10	16	16	13	16	19	29	16	10	10
Healthy	1	3	2	3	2	3	4	4	4	2	1	2	4	2	2	4	1	2	3

IgM response to

Borrelia and other TBD microbes

Only Borrelia

Only other TBD microbes

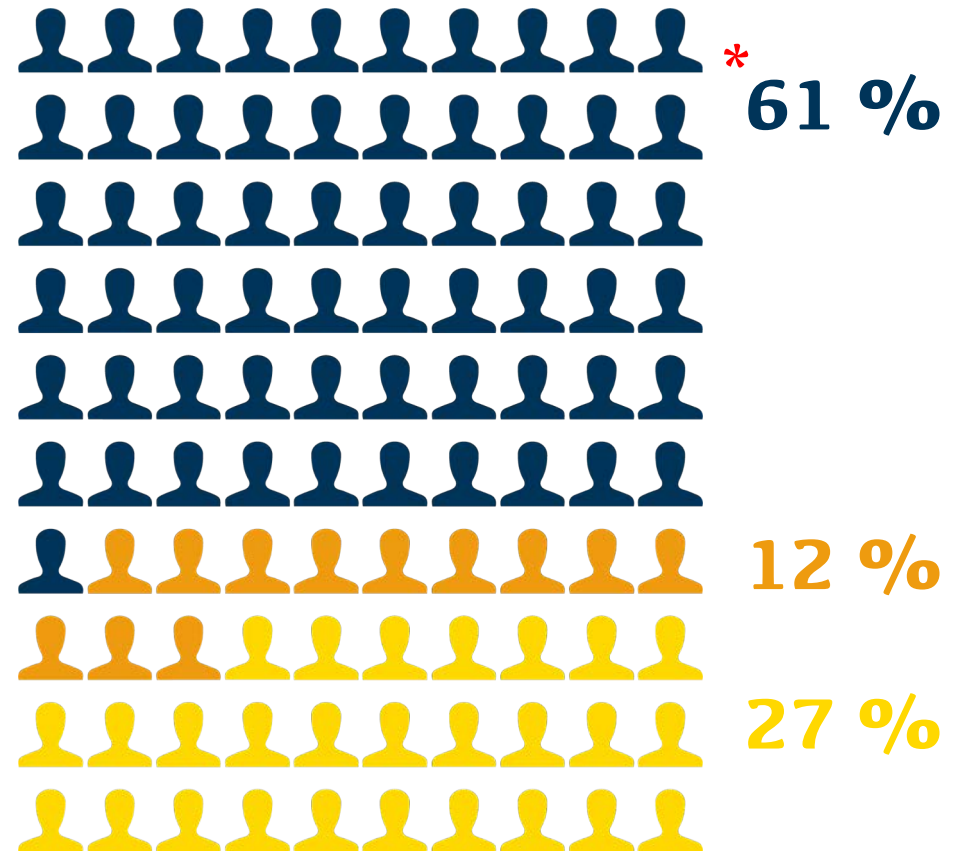


IgG response to

Borrelia and other TBD microbes

Only Borrelia

Only other TBD microbes



IgM response to

Borrelia and other TBD microbes

Only Borrelia

Only other TBD microbes



IgG response to

Borrelia and other TBD microbes

Only Borrelia

Only other TBD microbes



IgM response to

Borrelia and other TBD microbes

Only Borrelia



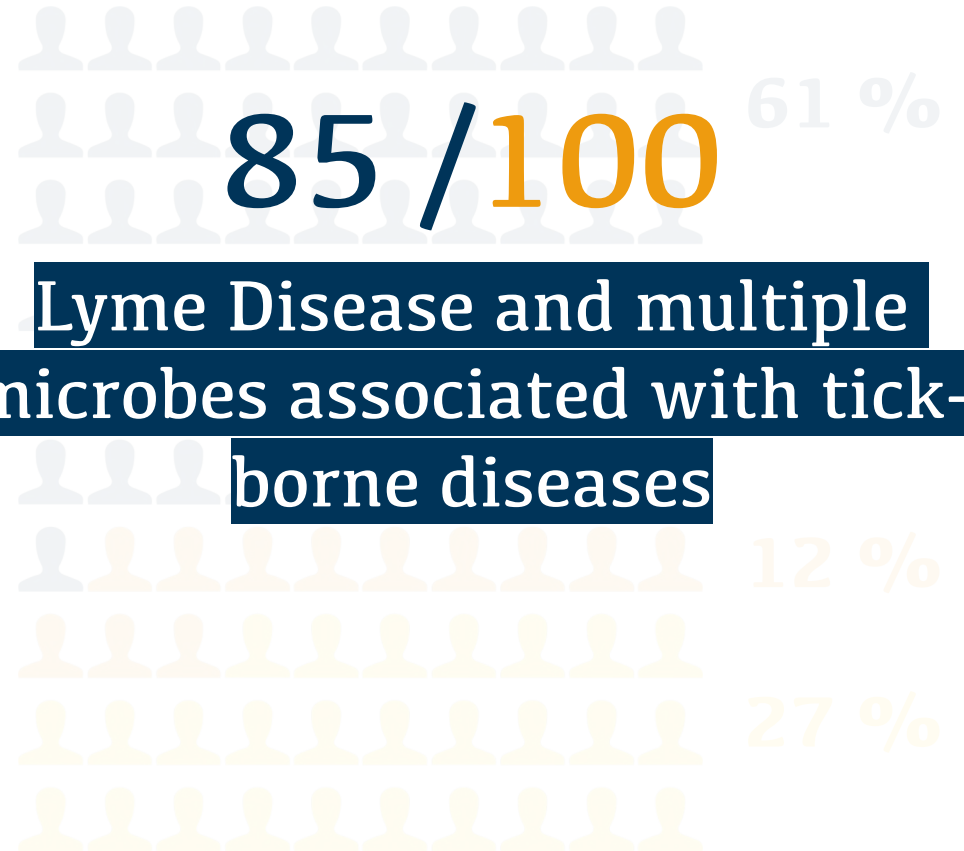
31 %

IgG response to

Borrelia and other TBD microbes

Only Borrelia

Only other TBD microbes



85 / 100

61 %

Lyme Disease and multiple microbes associated with tick-borne diseases

12 %

27 %

CDC and IDSA
guidelines became
the status-quo^{18 - 22}

2006

1982

Correlation between deer
tick and Lyme disease by
Dr. Willy Burgdorfer

2016

Commercially available
tests are only Lyme disease
oriented with no change in
sensitivity^{23, 24}

2018

2050

35 % global population will be⁹
effected by tick-borne diseases

Tick-borne diseases are
exceptionally polymicrobial



**BUSINESS
FINLAND**

Schwartz

Foundation

Non-profit philanthropic foundation

References

1. Nazir, A Muhammad. Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int J Health Sci (Qassim)*. 2017;11(2):72-80.
2. https://www.who.int/gard/publications/chronic_respiratory_diseases.pdf
3. Filkins LM, O'Toole GA (2015). Cystic Fibrosis Lung Infections: Polymicrobial, Complex, and Hard to Treat. *PLoS Pathog* 11(12): e1005258.
4. Buchanan, Paul. **Microbial infection in cystic fibrosis** (<https://www.immunology.org/public-information/bitesized-immunology/pathogens-and-disease/microbial-infection-in-cystic-fibrosis>)
5. World Health Organisation (WHO; <http://www.who.int/features/factfiles/malaria/en/>)
6. World Mosquito program (<http://www.eliminatedengue.com/our-research/dengue-fever>)
7. Ramiro RS, Pollitt LC, Mideo N, Reece SE. Facilitation through altered resource availability in a mixed-species rodent malaria infection. *Ecol Lett*. 2016;19(9):1041-50.
8. Marinho P, Bretas de Oliveira D, Candiani T, Crispim A, Alvarenga P, Castro F, et al. Meningitis Associated with Simultaneous Infection by Multiple Dengue Virus Serotypes in Children, Brazil. *Emerg Infect Dis*. 2017;23(1):115-118.
9. Davidsson, M. The Financial Implications of a Well-Hidden and Ignored Chronic Lyme Disease Pandemic. *Healthcare*. **6**, 16 (2018).
10. Koetsveld, J., Tjisse-Klasen, E., Herremans, T., Hovius, J. W. & Sprong, H. Serological and molecular evidence for spotted fever group Rickettsia and Borrelia burgdorferi sensu lato co-infections in The Netherlands. *Ticks Tick Borne Dis*. **7**, 371–7 (2016).
11. Krause, P. *et al*. Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. *JAMA*. **275**, 1657–60 (1996).
12. Steere, A. *et al*. Prospective study of coinfection in patients with erythema migrans. *Clin Infect Dis*. **36**, 1078–81 (2003).
13. Maggi RG, Mozayeni BR, Pultorak EL, et al. Bartonella spp. bacteremia and rheumatic symptoms in patients from Lyme disease-endemic region. *Emerg Infect Dis*. 2012;18(5):783-91.
14. Altun S, Kasapcopur O, Aslan M, Karaarslan S, Koksall V, Saribas S, Ergin S, Arisoy N, Kocazeybek B. *J. Med. Microbiol*. 53(8):787-790 doi:10.1099/jmm.0.45583-0.
15. Schumacher Jr. Chlamydia trachomatis nucleic acids can be found in the synovium of some asymptomatic subjects. 1999 *Arthritis & Rheumatism*
16. Donatella Donati and Steven Jacobson. **Polymicrobial Diseases** (<https://www.ncbi.nlm.nih.gov/books/NBK2494/>)
17. Nasralla M1, Haier J, Nicolson GL. **Multiple mycoplasmal infections detected in blood of patients with chronic fatigue syndrome and/or fibromyalgia syndrome**. *Eur J Clin Microbiol Infect Dis*. 1999 Dec;18(12):859-65.
18. Centers for Disease Control and Prevention (CDC), Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. *MMWR*. **44**, 590–1 (1995).
19. Halperin, J. J. Lyme Disease: An Evidence-based Approach. 296 (CABI 2011).
20. Aguero-Rosenfeld, M. E., Wang, G., Schwartz, I. & Wormser, G. P. Diagnosis of lyme borreliosis. *Clin Microbiol Rev*. **18**, 484–509 (2005).
21. Nemeth, J. *et al*. Update of the Swiss guidelines on post-treatment Lyme disease syndrome. *Swiss Med Wkly*. **146**, w14353 (2016).
22. Wormser, G. P. *et al*. The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. **43**, 1089–1134 (2006).
23. Connally, N. *et al*. Testing practices and volume of non-Lyme tickborne diseases in the United States. *Ticks Tick Borne Dis*. **7**, 193–198 (2016).
24. Cook, M. & Puri, B. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. *Int J Gen Medicine*. **9**, 427–440 (2016).