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Incidence and antibiotic treatment of erythema migrans (in Norwegian general practice)

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A threefold PhD-project

- *Epidemiology* – Incidence of erythema migrans in Norway
- *Treatment* – RCT comparing three antibiotic cures for erythema migrans in Norwegian general practice
- Health complaints: Measuring *Subjective Health Complaints* (SHC) and general function in EM-patients at day 1 and one year after treatment.

3

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Norwegian guidelines for antibiotic use

Erythema migrans:

- **Phenoxymethylpenicillin**
 - 1,3 g tid p.o. 14 days
- **Doxycycline**
 - 100 mg bid p.o. 14 days
- **Amoxicillin**
 - 500 mg tid p.o. 14 days

UK: «The oral antibiotics doxycycline, amoxicillin or cefuroxime axetil are recommended for 2 weeks (range 10 to 21 days) for erythema migrans»
<https://www.gov.uk/government/publications/ Lyme-disease-diagnosis-and-treatment/ Lyme-disease-diagnosis-and-treatment>

4

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Treatment study

- RCT comparing three antibiotic cures
- 188 EM patients clinically diagnosed in general practice
- Baseline data:
 - Appearance, tick bite?, time lines, age and gender, PCR-positivity i punch biopsies.
- Main outcome: Duration of EM
- Secondary outcomes:
 - Compliance, concomitant symptoms, side effects, antibody production, therapy failure.

5

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Subjective health complaints

- SHC-questionnaire to all EM patients in RCT
- At baseline and 1 year after treatment
- 29 standard symptoms + 3 LB relevant symptoms
- Assessment of general function
- The EM-cohort as a whole + 3 groups

6

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Incidence and antibiotic treatment



Incidence and antibiotic treatment of erythema migrans in Norway 2005–2009

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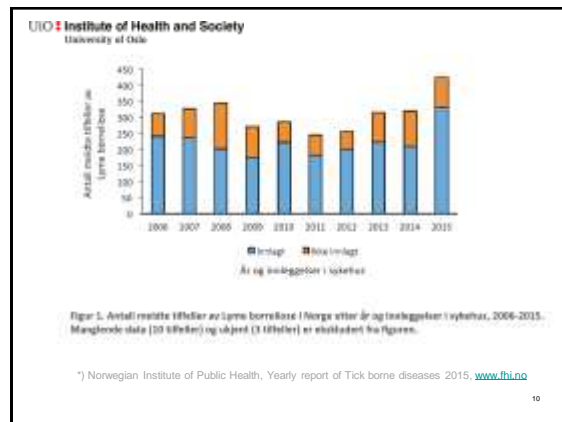
8

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Background

- In Norway, all cases of *second* and *third* stage LB which are *both clinically and microbiologically verified* are notifiable to the National Institute of Public health.
- In the years 2005-2010 there was an average of 307 cases/year (6,5 LB/100.000 inhabitants/year) with a peak of 346 cases (7,3 LB/100.000 inhabitants/year) in 2008.

9



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This slide was a montage of Norwegian newspaper articles (removed because of copyright)

Kvinne GAL av flatt
Ble gal av FLATT-BITT
Ny Farlig Flatt
... etc

If there are only 350 cases /year –
why all the public worry?!

11

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LB incidence

- In 2006, the World Health Organization (WHO) reported that the incidence of LB varied from 0.6/100,000/year in Ireland to 155/100,000/year in Slovenia.

Lindgren E. and Jaenson, T. (2006). Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. WHO Regional Office for Europe. Available from: http://www.euro.who.int/_data/assets/pdf_file/0006/96819/E89522.pdf

12

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Nordic LB incidence 2005-2010

- Norway** 6,5 LB/100.000 inhabitants/year
LB in stage 2 and 3 notifiable from lab/clinician
- Denmark** Approx. 100 NB/year -> 1,8 NB/100.000 inh./year
Only NB is notifiable
- Finland** 25,9 LB/100.000 inh./year
Notifiable from lab. Few EM included.
- Sweden** ?
Not notifiable. A few studies.

13

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UK incidence

«Since the introduction of enhanced surveillance in 1997, over 6,900 cases have been reported. Mean annual incidence rates for laboratory-confirmed cases have risen from 0.38 per 100,000 total population for the period 1997-2000, to 0.64 in 2002, and to **1.64 cases per 100,000 total population in 2010**»

«The data analysed in the following sections are for laboratory-confirmed cases of LB. Reporting levels have improved, but the data remain incomplete because **they do not include cases diagnosed and treated on the basis of clinical features such as erythema migrans**, without laboratory tests. It is estimated that between 1,000 and 2,000 additional cases of LB occur each year in England and Wales»

<https://www.gov.uk/government/publications/lyme-borreliosis-epidemiology/lyme-borreliosis-epidemiology-and-surveillance>

14

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European studies of EM incidence

- Sweden 1995: **69 LB/100.000 inh./year**, 77 % EM ¹⁾
- Southern-Sweden, 2005: **464 EM/100.000 inh./year** ²⁾
- Holland 2010: GP consultations/year for **tick bites and erythema migrans: 495 and 132 per 100.000 inhabitants**, respectively ³⁾

1) Berglund, J., et al., An epidemiologic study of Lyme disease in southern Sweden. N Engl J Med, 1995, 333(20): p. 1319-27.
2) Bennet L et al. Increased incidence of Lyme borreliosis in southern Sweden following mild winters and during warm, humid summers. Eur J Clin Microbiol Infect Dis, 2006 Jul;25(7):426.
3) Høthuis, A., et al., Physicians reported incidence of early and late Lyme borreliosis. Parasit Vectors, 2015, 8: p. 161.

15

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Erythema Migrans

Annular "Bull's eye"
Homogenous
Atypical

Clinical appearance of erythema migrans caused by Borrelia afzelii and Borrelia garinii-effect of the patient's sex. Bennet L, Fraenkel CJ, Garpmo U, Halling A, Ingman M, Ormsten K, Stjernberg L, Berglund J. Wien Klin Wochenschr. 2006 Sep;118(17-18):531-7.

16

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"Incidence and antibiotic treatment of erythema migrans in Norway 2005-2009"

- Incidence of consultations for EM
- Incidence of consultations for TB
- Age and gender distribution
- Antibiotic use
- Rate of antibody testing
- Rate of referral

Incidence and antibiotic treatment of erythema migrans in Norway 2005-2009. Eliassen KE, Berild D, Reiso H, Grude N, Christophersen KS, Finckenhagen C, Lindbak M. Ticks Tick Borne Dis. 2016 17 Jun 30. doi: 10.1016/j.tiddis.2016.06.006. [Epub ahead of print]

17

Figure 11. Hatched area: consultations for EM/100,000 inhabitants / Year. Yellow: incidence of consultations for TB/100,000 inhabitants / Year. Orange: incidence of consultations for TB/100,000 inhabitants / Year.

Prevalence of erythema migrans antibodies in Norway 2005-2009. Eliassen KE, Berild D, Reiso H, Grude N, Christophersen KS, Finckenhagen C, Lindbak M. Ticks Tick Borne Dis. 2016 17 Jun 30. doi: 10.1016/j.tiddis.2016.06.006. [Epub ahead of print]

18

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ICPC-2

- Erythema migrans and tick bites are not diagnoses for themselves.
- A78 «Infectious disease»
- Regular GPs and Out-of-hour services in four counties
- Computer program with 18 tick related terms
- USB-stick with computer program
- Extracted two datasets
- 36.900 + 13.555 journal notes

19

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GP

Out-of-hour services

County	GP	Out-of-hour services
Oslo	11	1
Buskerud	11	1
Telemark	11	1
Westfold	11	1

31.2 GPs (32.3%) and 14 (77.6%) of the out-of-hour services in the four counties delivered data for the study.

20

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Table 4
Incidence of Mycobacterium tuberculosis (MTB) in Norway 2005-2008. The estimated incidence of MTB is derived from the reported incidence of MTB in four Norwegian counties and the incidence of sporadic type infections (STI) nationally and in other countries. The numbers outside brackets are the number of consultations for infectious TB, and the numbers inside brackets are the number of consultations for TB in the study.

Year	STI incidence (number of consultations)	STI incidence (per 100,000 inhabitants/year)	EM incidence (number of consultations)	EM incidence (per 100,000 inhabitants/year)	EM incidence (number of consultations)
2005	311 (211-426)	32 (19.9-52.8)	63	6.5	374
2006	321 (199-544)	33 (20.3-49.2)	24	2.7	347
2007	442 (213-671)	45 (28.0-62.9)	11.6	1.2	342
2008	441 (200-682)	45 (24.4-69.2)	14.7	1.5	376
2009	441 (200-682)	45 (24.4-69.2)	11.6	1.2	342
Mean	431 (199-663)	45 (24.4-69.2)	13.7	1.5	358

EM incidence study counties = EM incidence Norway
LB incidence study counties = LB incidence Norway

National estimate of EM incidence at 148 EM/100,000 inhabitants/year and an estimated national figure of 6,940 EM consultations/year.

21

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- Counting about 7,000 EM consultations per year in Norway, compared to an average of 307 reported LB cases/year in Norway, our findings show that solitary EMs comprised almost 96% of the total LB incidence in Norway.
- In addition 94 TB consultations/100,000 inhabitants/year.
- That is altogether 11.000 consultations/year in Norway.

22

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Age and gender

Fig. 3. Upper and lower respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) by age group and gender in Norway, 2005-2008. Upper and lower respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) by age group and gender in Norway, 2005-2008. Upper and lower respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) by age group and gender in Norway, 2005-2008.

23

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Antibiotic treatment

24

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Fig. 4. Antibiotic prescriptions by age group in Norway, 2005-2008. Upper and lower respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) by age group and gender in Norway, 2005-2008. Upper and lower respiratory tract infections (URTI) and lower respiratory tract infections (LRTI) by age group and gender in Norway, 2005-2008.

25

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Antibody testing

	EM, GPs (n= 4589)		EM, OOHs (n= 1976)		TB, GPs, (n= 2825)		TB, OOHs, n= 1431	
	%	n	%	n	%	n	%	n
Serology	20.4	935	2.4	47	20.5	579	1.9	27

26

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Antibody testing and referral

	EM, GPs (n= 4589)		EM, OOHs (n= 1976)		TB, GPs, (n= 2825)		TB, OOHs, n= 1431	
	%	n	%	n	%	n	%	n
Serology	20.4	935	2.4	47	20.5	579	1.9	27
Referral	1.0	45	0.6	11				

27

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Diagnoses given

Table 2
95% of diagnoses given for respiratory infections (EM and TB) were patients in Norwegian general practice in 2010-2016. The "residual" category includes serious acute bacterial infections in the acute care sector. These figures are not used for comparison in the descriptive analysis of general and total LB (LBA) (LBA=EM+TB) (LBA=EM+TB).

	Resistant, %	Related, %	Cautious, %	Antibiotics, %	Total, n
All EMs	36.3	42.6	1.4	18.4	7,541
All TBs	52.5	2.5	3.1	11.9	4,874
All GPs	15.1	24.0	2.0	58.9	8,822
All OOHs	79.2	45.4	2.0	2.2	5,599
All diagnoses	36.3	27.3	2.0	18.4	12,415

28

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Summary

- Norwegian incidence for EM consultations in general practice: 148/100.000/year
- Great geographical variations
- EM: Higher incidence among women, and among the middle aged.
- TB consultations: 94/100.000/year
- More TB (consultations) in small children

29

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Summary

- Good compliance to antibiotic guidelines
- 2/3 penicillin, 1/4 doxycycline
- 20 % of the TBs got prophylactic antibiotics
- (Same distribution as for EM)
- 15 % got antibody tests (EM and TB)
- EMs comprise 96 % of the total LB count in Norway
- EM and TBs are mostly seen in primary care
- Less than 1 % were referred to secondary care

30

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31

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32

Thank you for your attention!