

Clostridium difficile - diagnostikk og epidemiologi i Norge

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Nasjonalt referanselaboratorium for *Clostridium difficile*

Oslo universitetssykehus

Nasjonal referanselaboratorium for *Clostridium difficile*



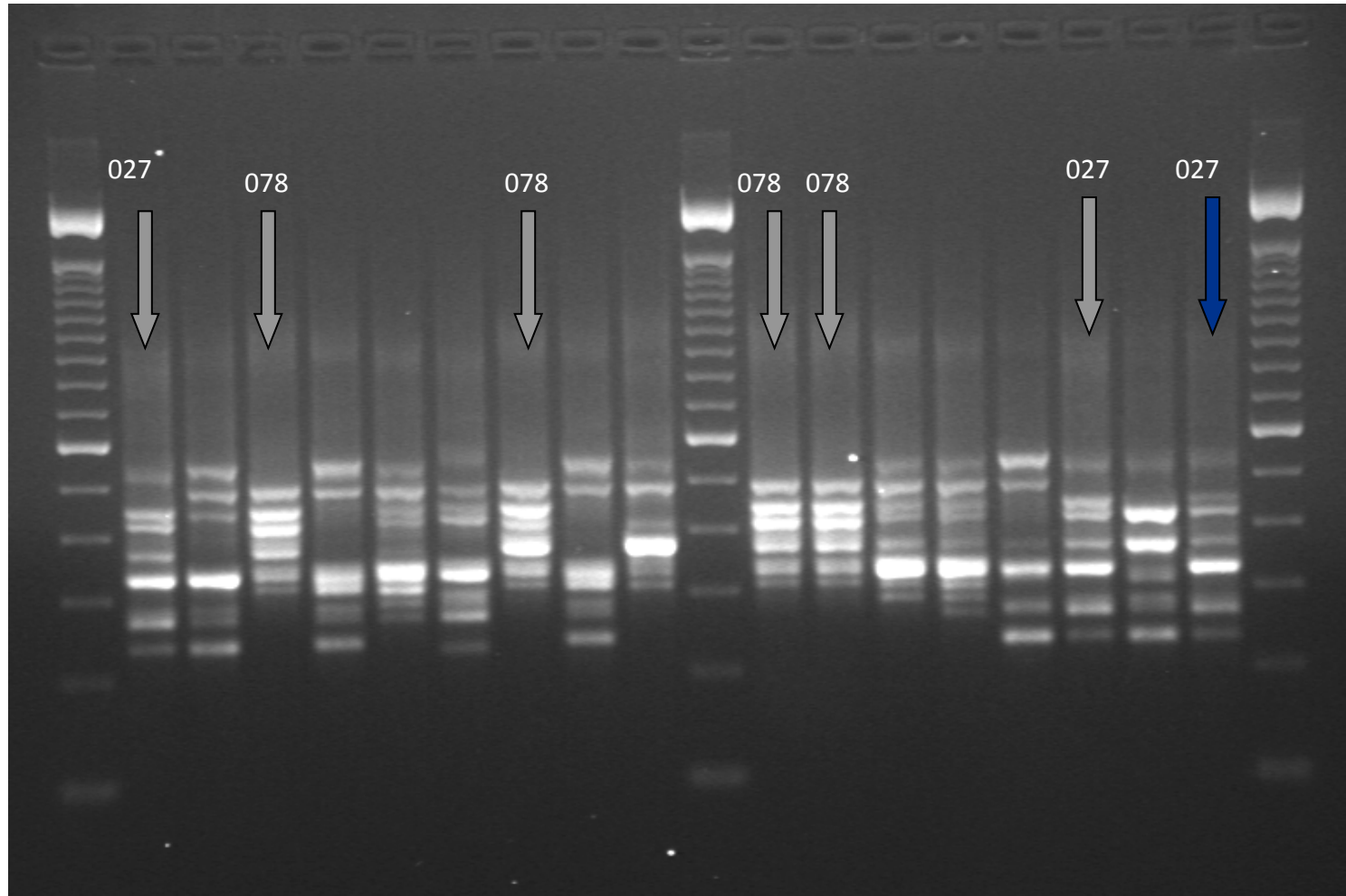
To kasustikker

- Kvinne på sykehjem
- >80 år
- UVI → Mecillinam
- 24T: Divertikulitt → CI + MZ
- Abdominale Abcesser
- Koloskopi : Pseudomembranøs kolitt (PMK)
- *C.difficile* ToxA
- Oral Vancomycin → Utskrevet fra sykehus
- Innleggelse 38d etter
- Akutte abdominale smerter → Toksisk megakolon → PMK
- Kolektomert
- Utskrevet etter 8 dager

To kasustikker

- Kvinne
- >80 år
- Flere innleggelser på sykehus og sykehjem
- Feber og forstoppelse
- CI og MZ
- Mekanisk ileus
- Laparotomi + fjernet deler av ileum
- Etter to uker: diaré
- *C.difficile* ToxA
- MZ
- Forverret almenntilstand - dør av pneumoni 13d etter.

Ribotyping av *C. difficile*



Rapid communications

FIRST CONFIRMED CASES OF C PCR RIBOTYPE 027 IN NORWA

FIGURE

Distribution of *Clostridium difficile* Type 027 by country in Europe* as of June 2008

Euroroundups

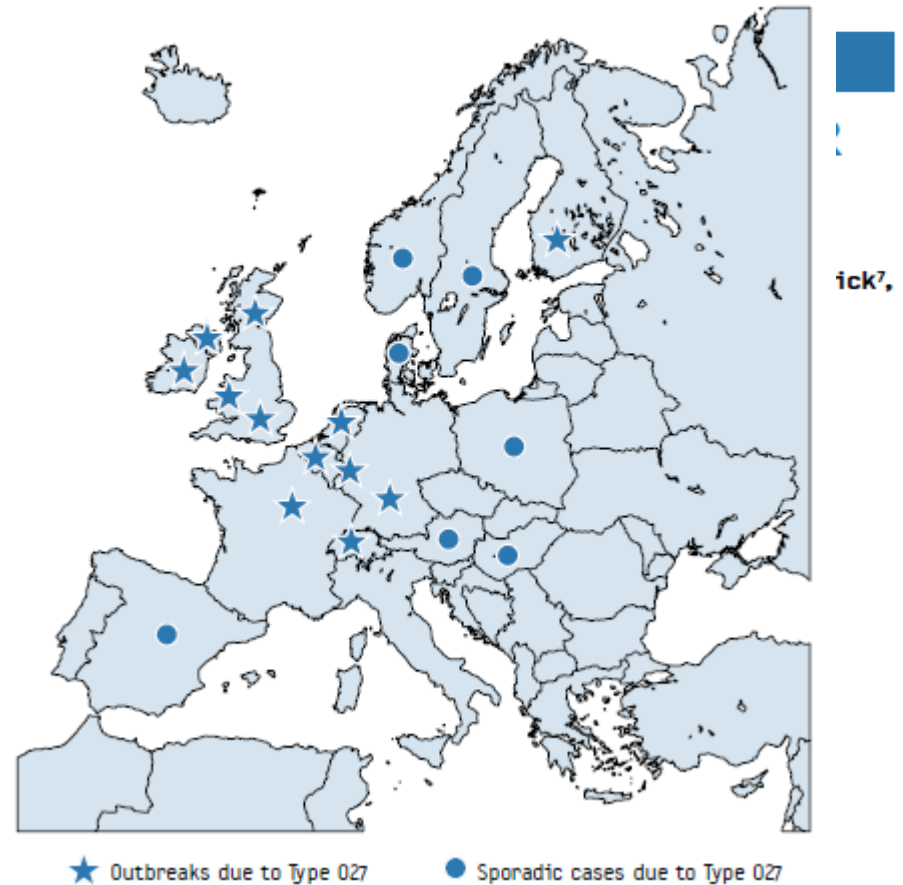
A Ing
1. Def
2. Ins
3. Def
4. Def

UPDATE OF *CLOSTRIDIUM DIFFICILE* RIBOTYPE 027 IN EUROPE, 2007-2008

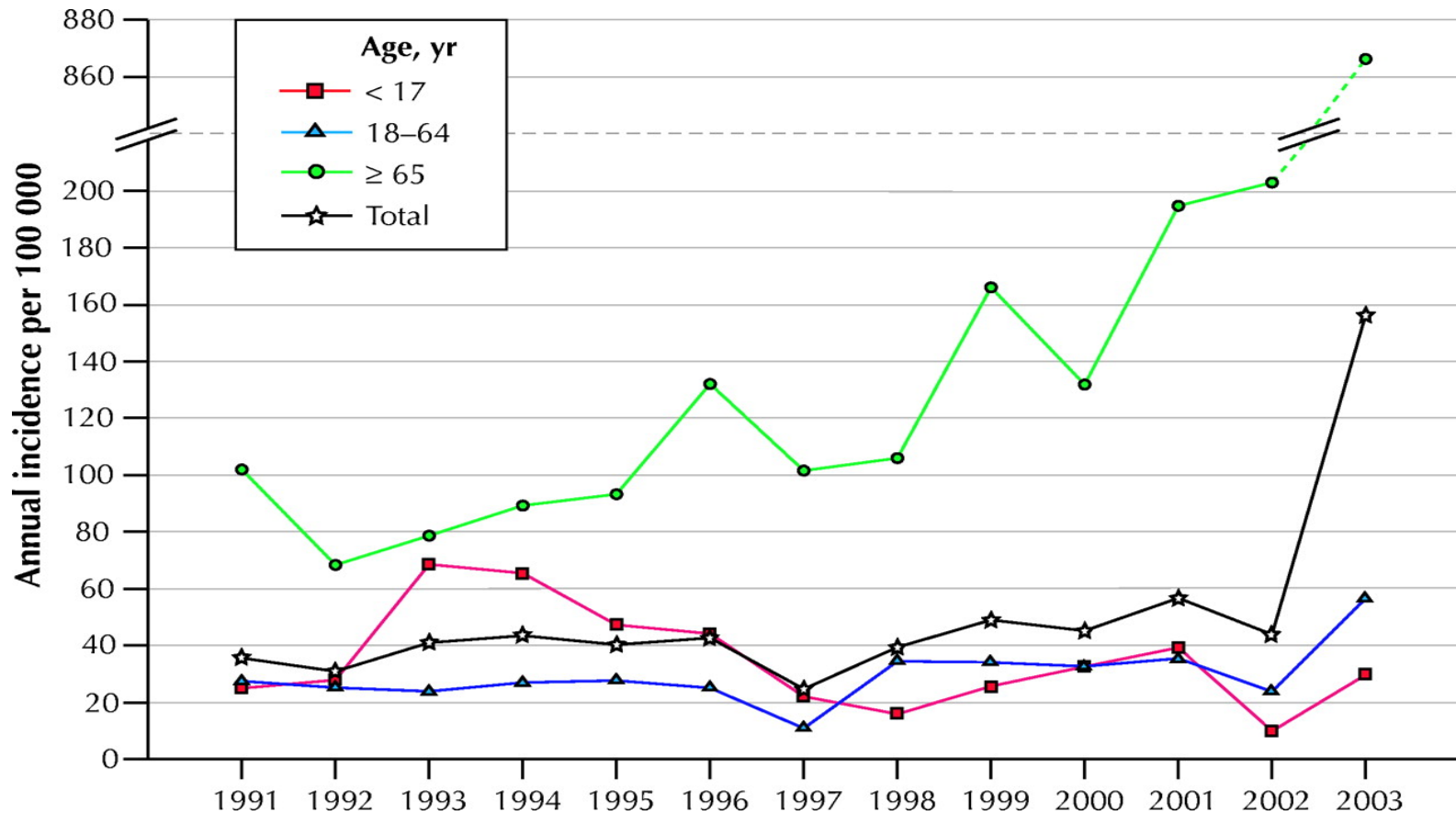
Euro

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Eurosurveillance (2008) vol 13 issue 31



CDI insidens 1991 - 2003



Årlig insidens (pr. 100 000 innbyggere) av CDI i Sherbrooke, Que., 1991-2003. (Pepin et al. CMAJ 2004; 171:466-72.)

Quebec, Canada.

- Utbrudd av CDI fra sent 2002 til 2005.
 - 35.6 tilfeller pr. 100 000 innb. i 1991 til 156.3 tilfeller pr. 100 000 innb. i 2004.
 - Økning i komplikasjoner fra 7.1% (1991) til 18.2% (2003)
 - Økning i mortalitet fra 4.5% (1991) til 22% (2004).

(Pepin et al. CMAJ.2004;171:466-472, Pepin et al. CMAJ.2005;173:1037-1042).

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An Epidemic, Toxin Gene–Variant Strain of *Clostridium difficile*

L. Clifford McDonald, M.D., George E. Killgore, Dr.P.H., Angela Thompson, M.M.Sc.,
Robert C. Owens, Jr., Pharm.D., Sophia V. Kazakova, M.D., M.P.H., Ph.D., Susan P. Sambol, M.T.,
Stuart Johnson, M.D., and Dale N. Gerding, M.D.



CDI i UK

HOME > NEWS / SHOWBIZ > UK NEWS > *C.diff hospital chiefs could be prosecuted*

UK NEWS

C.DIFF HOSPITAL CHIEFS COULD BE PROSECUTED



Friday August 8, 2008

By Paul Gilbride

Health officials may be prosecuted for criminal negligence over conditions in a hospital where 18 people died during Scotland's worst C.Difficile outbreak.

Fifty-five people were infected during the outbreak, which some staff members dismissed as a "wee bug".

Health Secretary Nicola Sturgeon

Health Secretary Nicola Sturgeon yesterday revealed an independent report

into the Vale of Leven Hospital outbreak has been handed to the procurator fiscal.

The report was ordered by her after a public outcry over the extent of the outbreak in the first six months of the year.

“ I understand them calling for a public inquiry. That's why I'm passing the report to the Lord Advocate, who has asked the procurator fiscal to consider if further action should be taken ”

It was scathing of the hospital management and Greater Glasgow and Clyde Health Board.

The report said that they had allowed wards at the hospital to become shabby, staff morale to plummet and hygiene procedures to deteriorate.

It said the hospital had suffered the consequences of 10 years under threat of closure and there was a lack of "focus and leadership".

DAILY EXPRESS
THE WORLD'S GREATEST NEWSPAPER

UK NEWS

POLICE LAUNCH PROBE INTO 18 C.DIFF DEATHS



Vale of Leven hospital

Friday November 28, 2008

By Kerry Gill

A major police incident room has been set up to investigate the Clostridium difficile outbreak linked to 18 deaths at the Vale of Leven Hospital.

A dedicated team of 16 detectives and uniformed police will work from the incident room in Dumbarton Police Station.

The probe will also be conducted alongside a six-strong Health and Safety Executive team.

Health Secretary Nicola Sturgeon confirmed that the investigators hoped to submit their reports to the procurator fiscal by March.

Since the C.diff deaths, victims' relatives have been campaigning for a public inquiry.

But Ms Sturgeon said an immediate public inquiry could risk prejudicing future criminal proceedings.

Last night, however, Michelle Stewart, secretary of the families' C.diff Justice Group, said: "We are feeling quite angry that Nicola Sturgeon has released this to the press after writing to us to ask for a meeting to update us.

“ We are feeling quite angry that Nicola Sturgeon has released this to the press after writing to us to ask for a meeting to update us ”

Michelle Stewart, secretary of

"We are seeing her next week, but it looks as though we can read all about it now.

"We don't see how she can be talking about the police and Health and Safety Executive inquiries ending in March when they have hardly started yet.

"We also find it quite strange that all this is coming from the Health Secretary, who is ultimately responsible for what happened at the Vale of Leven, and not the Lord Advocate.

"If it is all going through the Health Secretary how do we know we will get an independent inquiry?"

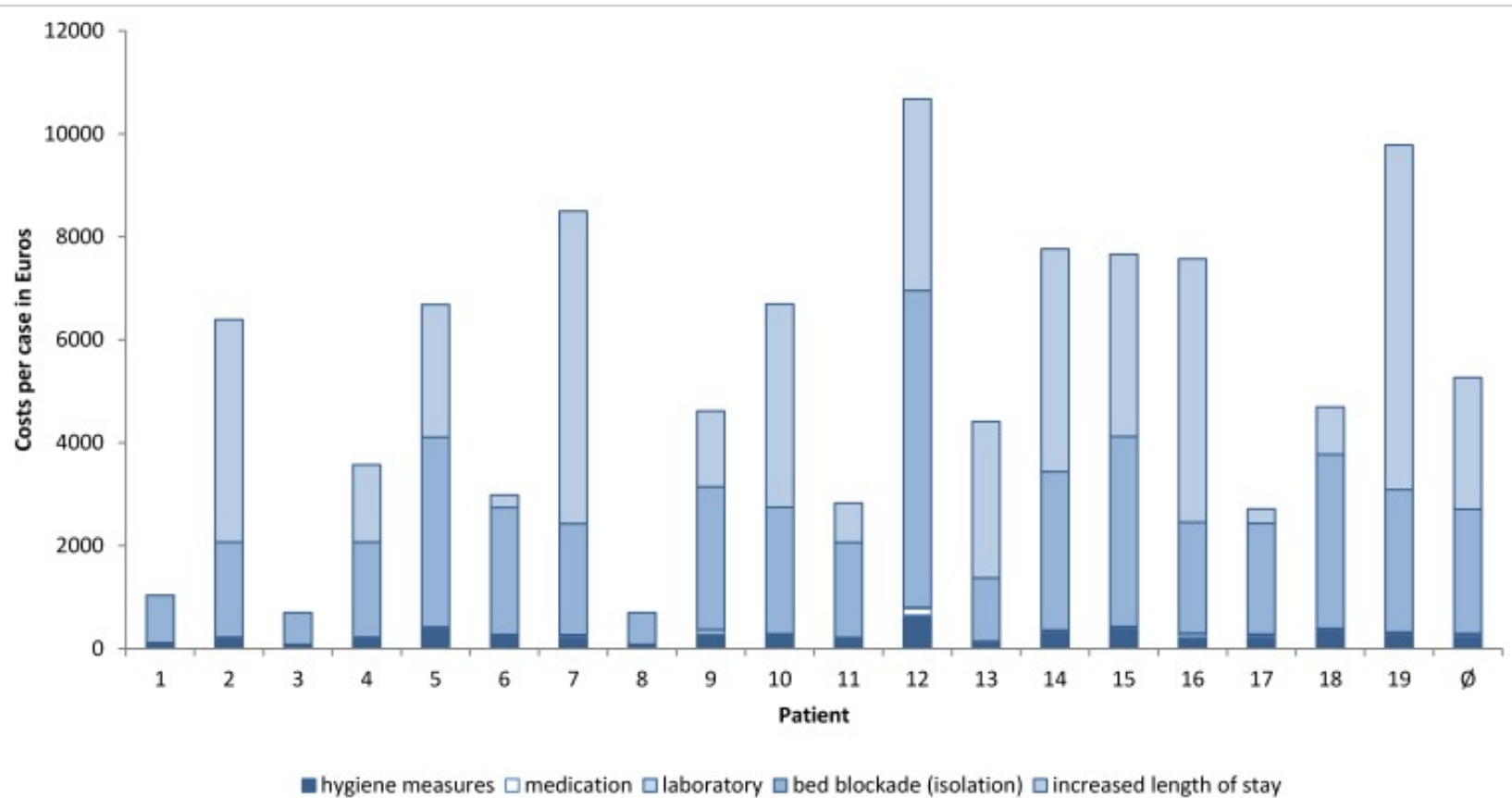
Kostnader knyttet til CDI i sykehus

Patient	Length of stay (mean length of stay ²)	Days in isolation	Expenses due to					Total expenses
			hygiene measures (personnel and material)	bed blockage during isolation	medication	laboratory	increased length in stay	
1	8 (9.1)	3	€ 96.24	€ 923.12	€ 1.96	€ 18.30	€ 0.00	€ 1,039.62
2	29 (14.1)	6	€ 193.97	€ 1,846.25	€ 7.35	€ 18.30	€ 4,325.25	€ 6,391.12
3	14 (15.8)	2	€ 63.66	€ 615.42	€ 0.49	€ 21.40	€ 0.00	€ 700.97
4	14 (9.1)	6	€ 193.97	€ 1,846.25	€ 7.35	€ 18.30	€ 1,507.77	€ 3,573.64
5	15 (6.1)	12	€ 389.43	€ 3,692.50	€ 16.17	€ 11.90	€ 2,574.85	€ 6,684.85
6	17 (16.2)	8	€ 259.12	€ 2,461.66	€ 6.86	€ 11.90	€ 246.17	€ 2,985.71
7	35 (5.2)	7	€ 226.55	€ 2,153.96	€ 26.10	€ 18.30	€ 6,074.47	€ 8,499.37
8	5 (8.4)	2	€ 63.66	€ 615.42	€ 1.47	€ 18.30	€ 0.00	€ 698.85
9	21 (16.2)	9	€ 291.70	€ 2,769.37	€ 68.83	€ 11.90	€ 1,477.00	€ 4,618.80
10	36 (16.8)	8	€ 259.12	€ 2,461.66	€ 6.86	€ 21.40	€ 3,943.02	€ 6,692.07
11	23 (20.5)	6	€ 193.97	€ 1,846.25	€ 2.45	€ 18.30	€ 769.27	€ 2,830.24
12	25 (12.9)	20	€ 650.05	€ 6,154.16	€ 132.33	€ 18.30	€ 3,723.27	€ 10,678.11
13	26 (5.3)	4	€ 128.81	€ 1,230.83	€ 4.41	€ 11.90	€ 3,038.69	€ 4,414.65
14	29 (3.9)	10	€ 324.28	€ 3,077.08	€ 13.23	€ 21.40	€ 4,326.71	€ 7,762.70
15	23 (11.5)	12	€ 389.43	€ 3,692.50	€ 21.83	€ 18.30	€ 3,538.64	€ 7,660.70
16	42 (20.9)	7	€ 226.55	€ 2,153.96	€ 55.21	€ 18.30	€ 5,118.76	€ 7,572.77
17	7 (6.1)	7	€ 226.55	€ 2,153.96	€ 35.28	€ 18.30	€ 276.94	€ 2,711.02
18	14 (11)	11	€ 356.86	€ 3,384.79	€ 14.70	€ 18.30	€ 923.12	€ 4,697.77
19	60 (17.4)	9	€ 291.70	€ 2,769.37	€ 11.76	€ 18.30	€ 6,692.25	€ 9,783.39
total	443	149	€ 4,825.63	€ 45,848.48	€ 434.64	€ 331.40	€ 48,556.17	€ 99,996.32
per case	23.316	7.842	€ 253.98	€ 2,413.08	€ 22.88	€ 17.44	€ 2,555.59	€ 5,262.96
per day¹			€ 32.39	€ 307.71	€ 3.34		€ 109.61	€ 225.73
			4.83%	45.85%	0.43%	0.33%	48.56%	100.00%

¹ The data on average costs of hygiene management and bed blockage per day are based on days of isolation (7.842 days/case on average). The data on average pharmaceutical costs per day are based on the actual amount of days of antibiotics administration (6.842 days/case on average). The data on average costs due to an increase in length of stay and the total costs per day are based on the average total length of stay (23.316 days/case).

² The data on mean length of stay are based on the G-DRG remuneration catalogue, 2010 version.

Kostnader knyttet til CDI i sykehus



Hübner et al. 2015 GMS Hyg. Infect. Control

Clostridium difficile

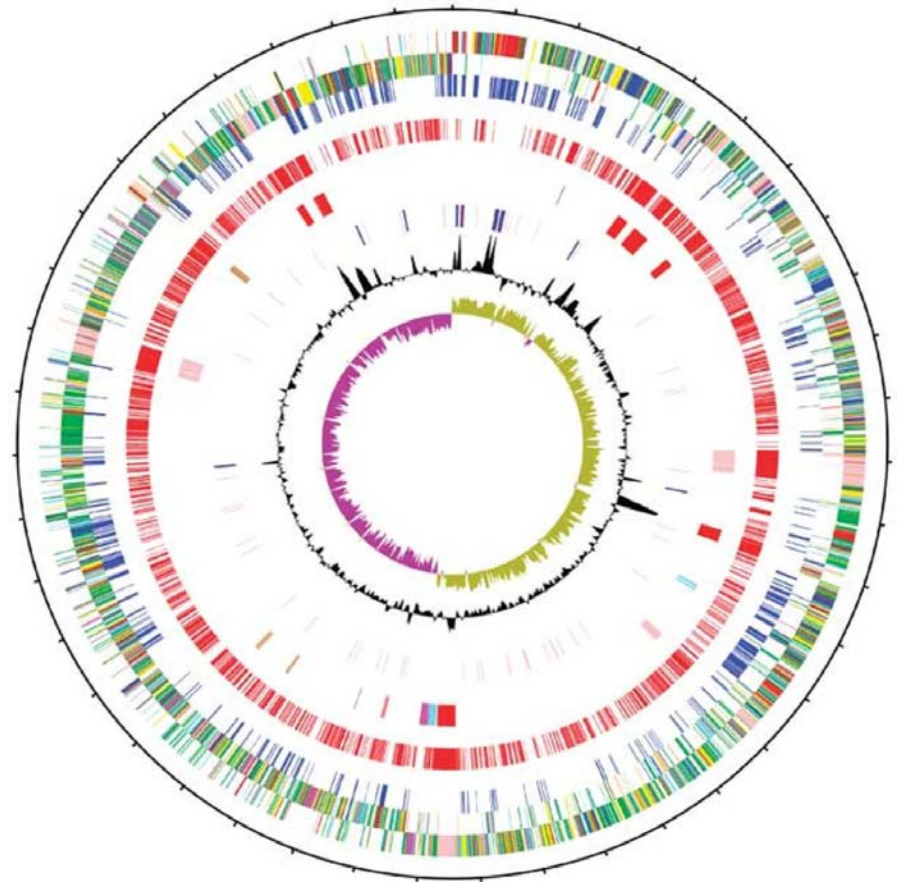
- Isolert for første gang i 1935 av Hall & O'Toole. (*Am.J.Dis.Child.*1935;49:390-402)
- Naturlig habitat; jord (+ dyr)
- Gram positiv, sporedannende stavbakterie
- Bevegelig
- Anaerob metabolisme
- Kan ikke redusere sulfat til sulfid
- Temperaturløstoleranse: Mesofil
- 10 Referansegenom
- Funn er meldepliktig til MSIS

Fullsekvenserte og annoterte *C.difficile*

- *C.difficile* stamme 630 (RT12, Sveits 1982)
- *C.difficile* stamme CD37 (RT009, USA 1980)
- *C.difficile* stamme M68 (RT017, Irland 2006)
- *C.difficile* stamme CF5 (RT017, Belgia 1995)
- *C.difficile* stamme M120 (RT078, UK 2007)
- *C.difficile* stamme G46 (RT027, UK 2006)
- *C.difficile* stamme R20291 (RT027, UK 2006)
- *C.difficile* stamme 196 (RT027, Frankrike 1985)
- *C.difficile* stamme 2007855 (RT027, USA 2007)
- *C.difficile* stamme BI1 (RT027, USA 1988)

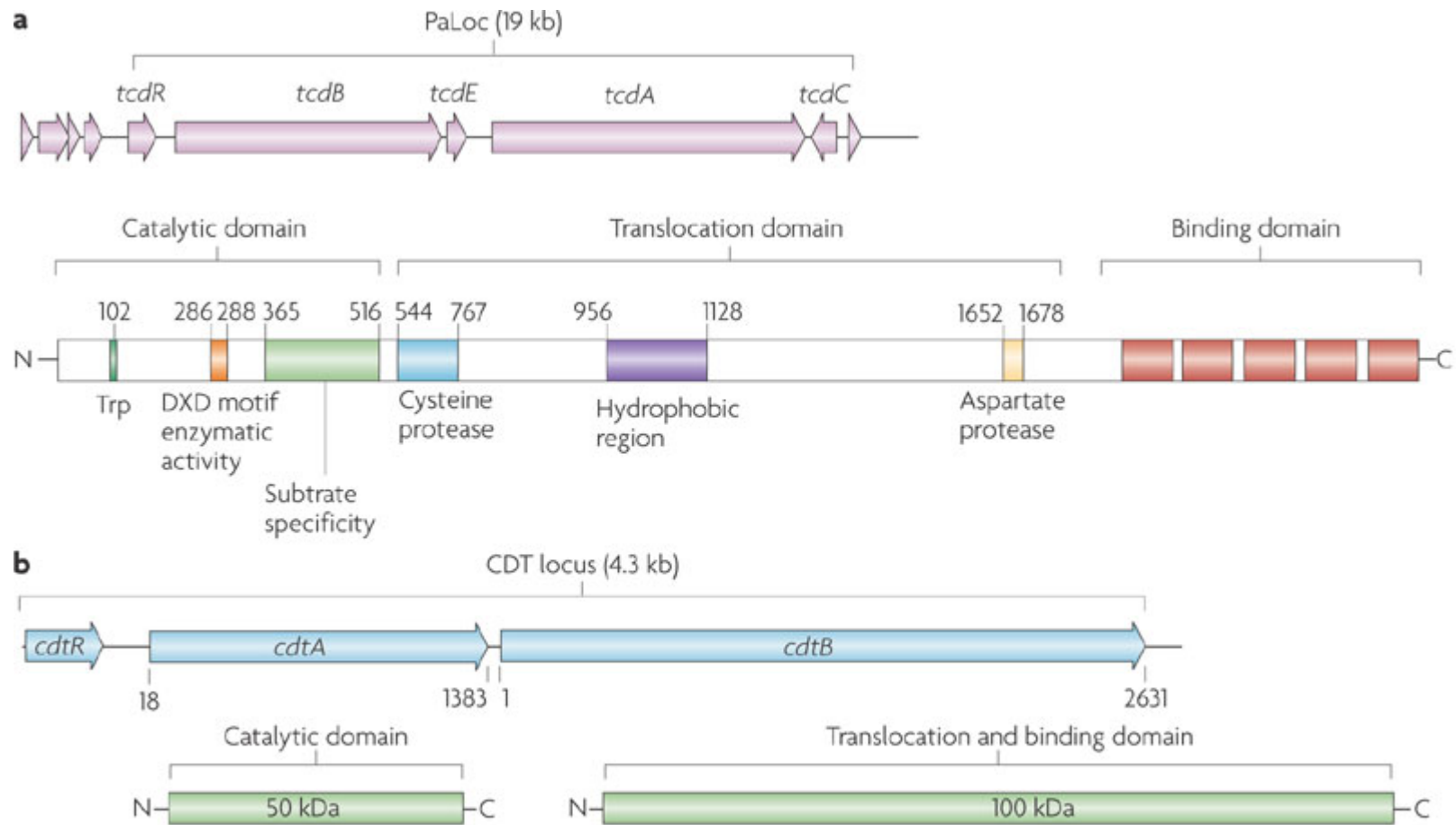
Clostridium difficile genomet

- Høy andel mobile genetiske elementer (11%)
- CDS gjenspeiler livet i det gastrointestinale system + overlevelse i suboptimale forhold
- Kan overleve lenge i vertsorganismen
- Stort genom (4,3Mb)
- Liten grad av konservert genom



Daniel R. Knight et al. *Clin. Microbiol. Rev.* 2015;28:721-741

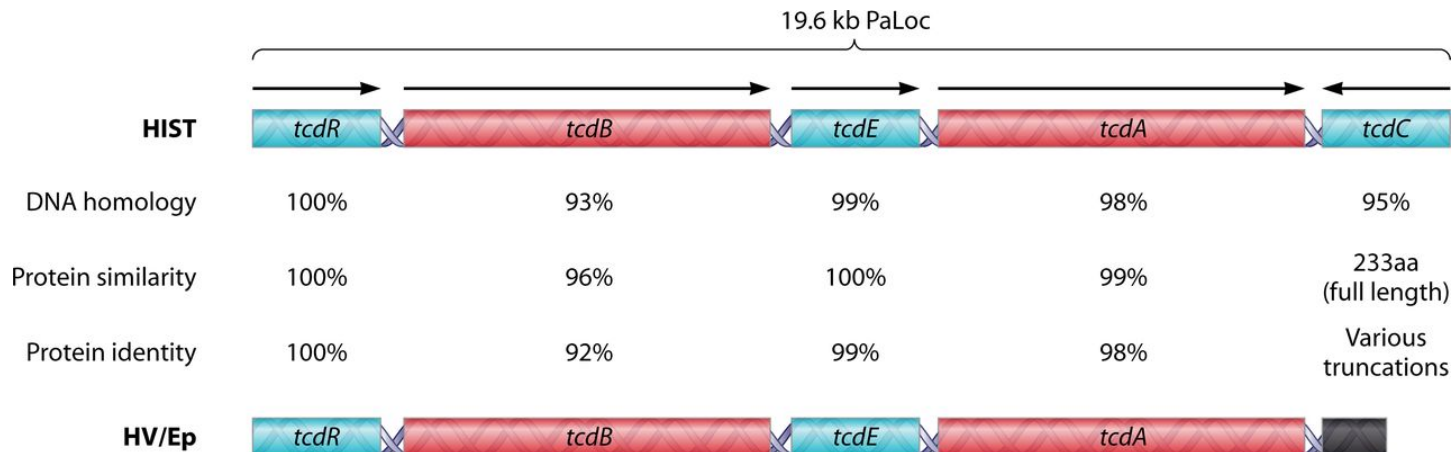
Toksin loci i *Clostridium difficile*-genomet



Nature Reviews | Microbiology

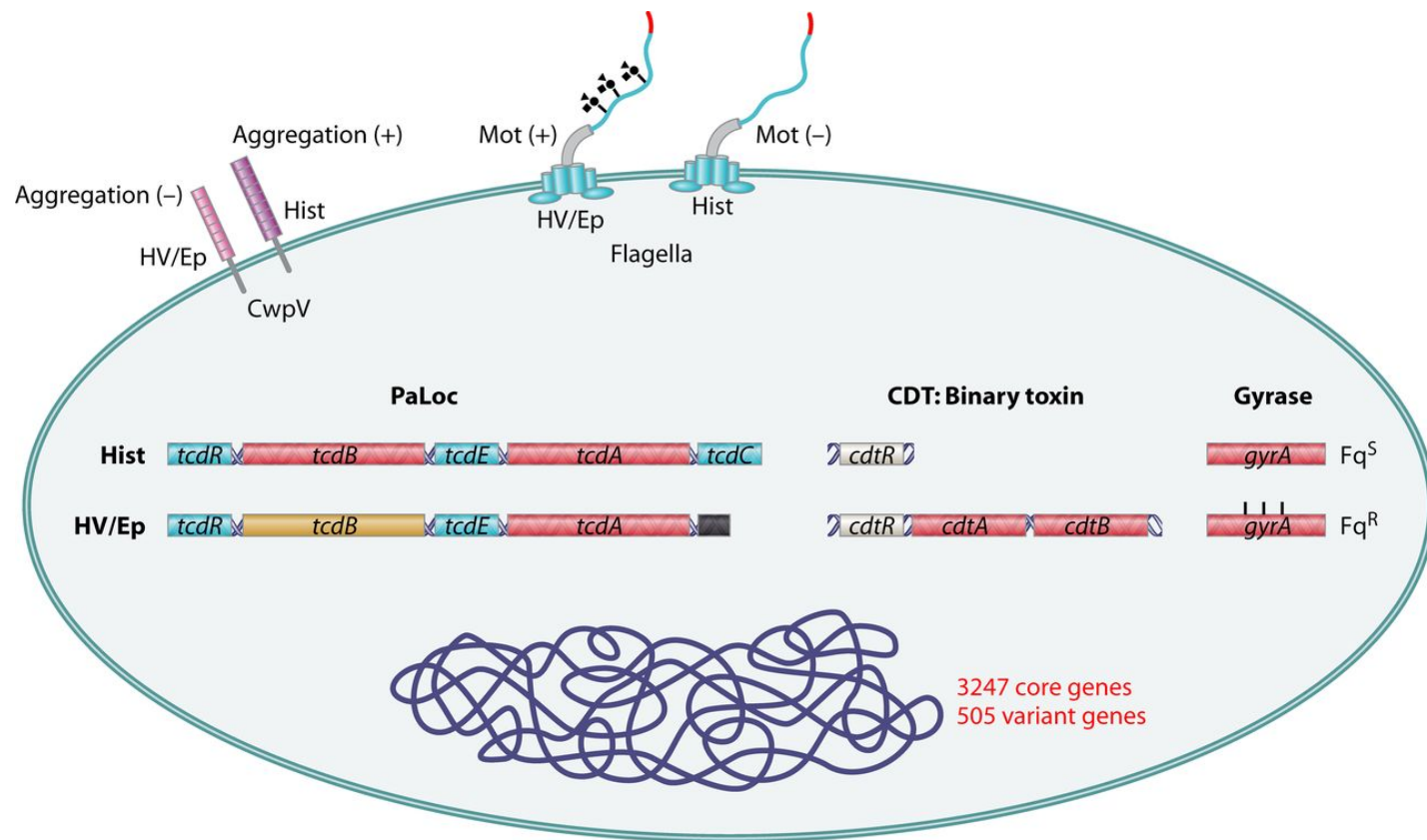
Rupnik et al. 2009 .Nature Reviews Microbiology 7, 526-536

Sammenligning av hypervirulente/historiske stammer



Hunt J J , and Ballard J D Microbiol. Mol. Biol. Rev.
2013;77:567-581

Sammenligning av hypervirulente/historiske stammer

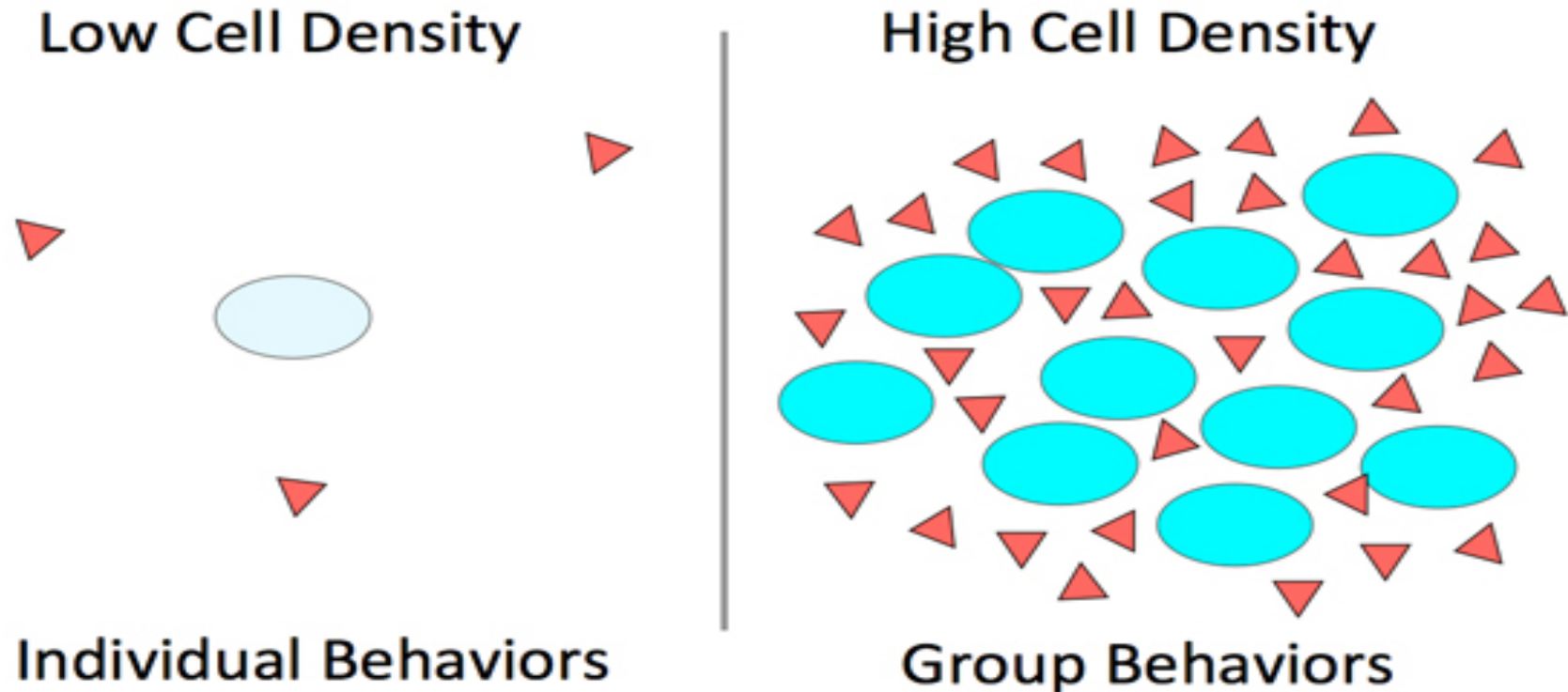


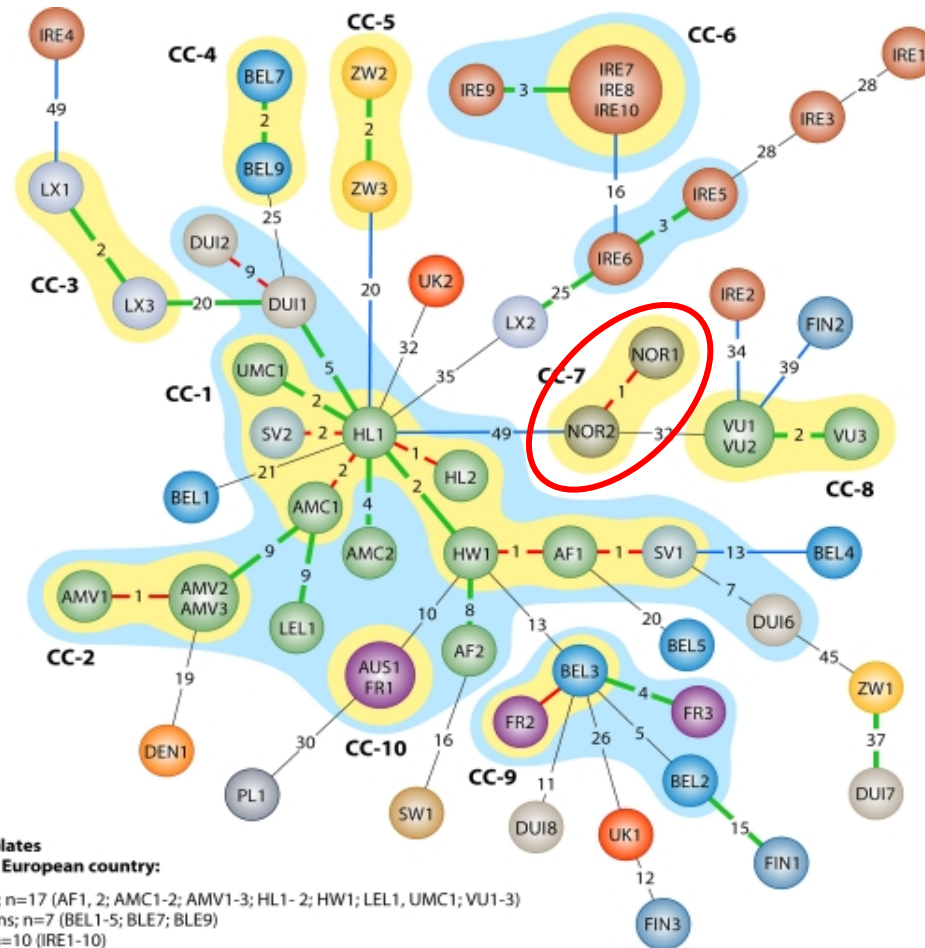
Hunt J J , and Ballard J D Microbiol. Mol. Biol. Rev. 2013;77:567-581

Hypervirulente *Clostridium difficile*

- Binært toksin
- Antibiotikaresistens
- Variasjoner i *tcdB*
- Variasjoner i *tcdC*
- Produserer mer p-cresol
- Variasjon i sporulering
- Variasjon av *agr*-locus







Bacterial Quorum Sensing



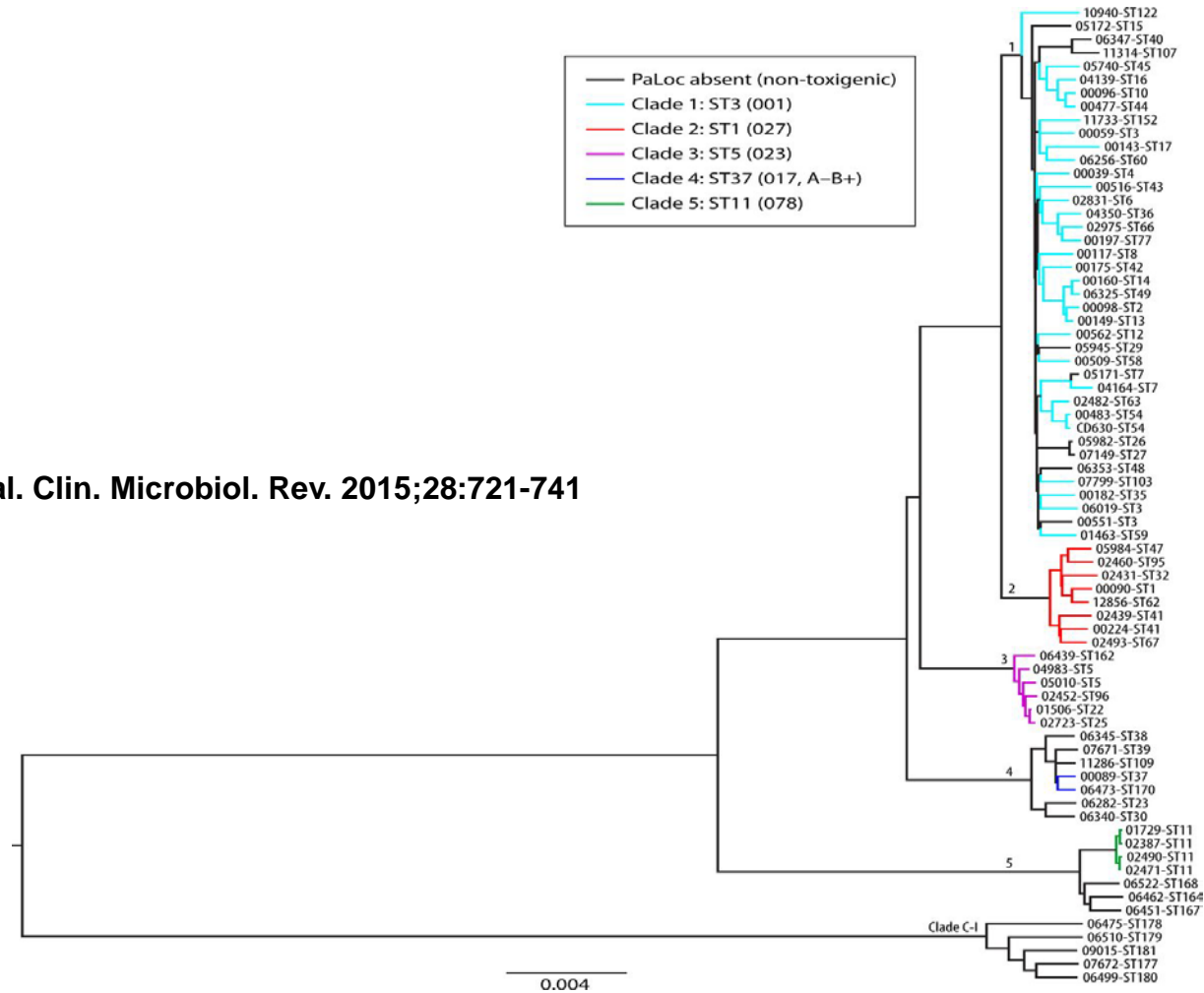


**The N=59 isolates
Classified by European country:**

Dutch Strains; n=17 (AF1, 2; AMC1-2; AMV1-3; HL1- 2; HW1; LEL1, UMC1; VU1-3)
 Belgium Strains; n=7 (BEL1-5; BLE7; BLE9)
 Irish Strains; n=10 (IRE1-10)
 UK Strains; n=2 (UK1-2)
 French Strains; n=3 (FR1-3)
 German Strains; n=5 (DUI1; DUI2; DUI6-8)
 Swiss Strains n=3 (ZW1-3)
 Norwegian Strains n=2 (NOR1-2)
 Swedish Strains n=1 (SWE1)
 Finnish Strains n=3 (FIN1-3)
 Luxembourg Strains n=3 (LX1-3)
 Polish Strains n=1 (PL1)
 Danish Strains n= 1 (DEN1)
 Austrian Strains n=1 (AUS1)

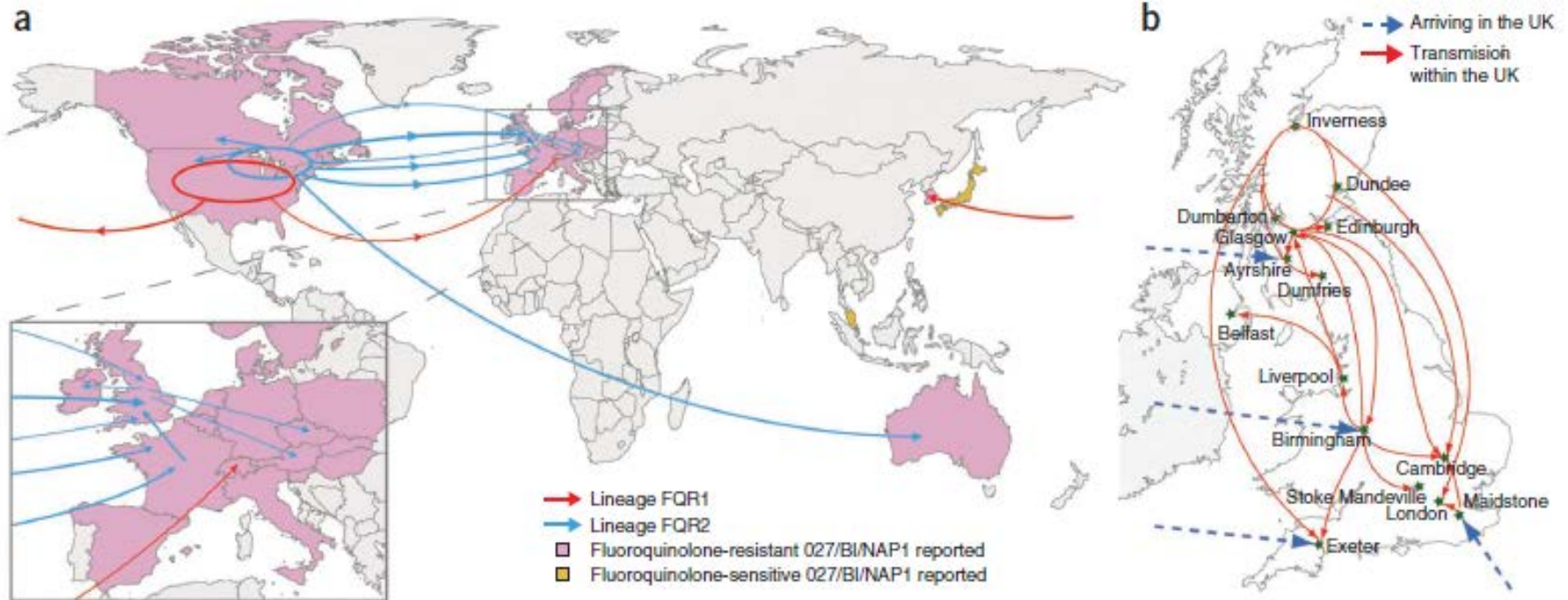
 Clonal complex
 Genetically related clusters
 Single Locus Variant
 Double Locus Variant
 Triple Locus Variant
 Quadruple Locus Variant

Populasjonsstruktur *C.difficile*



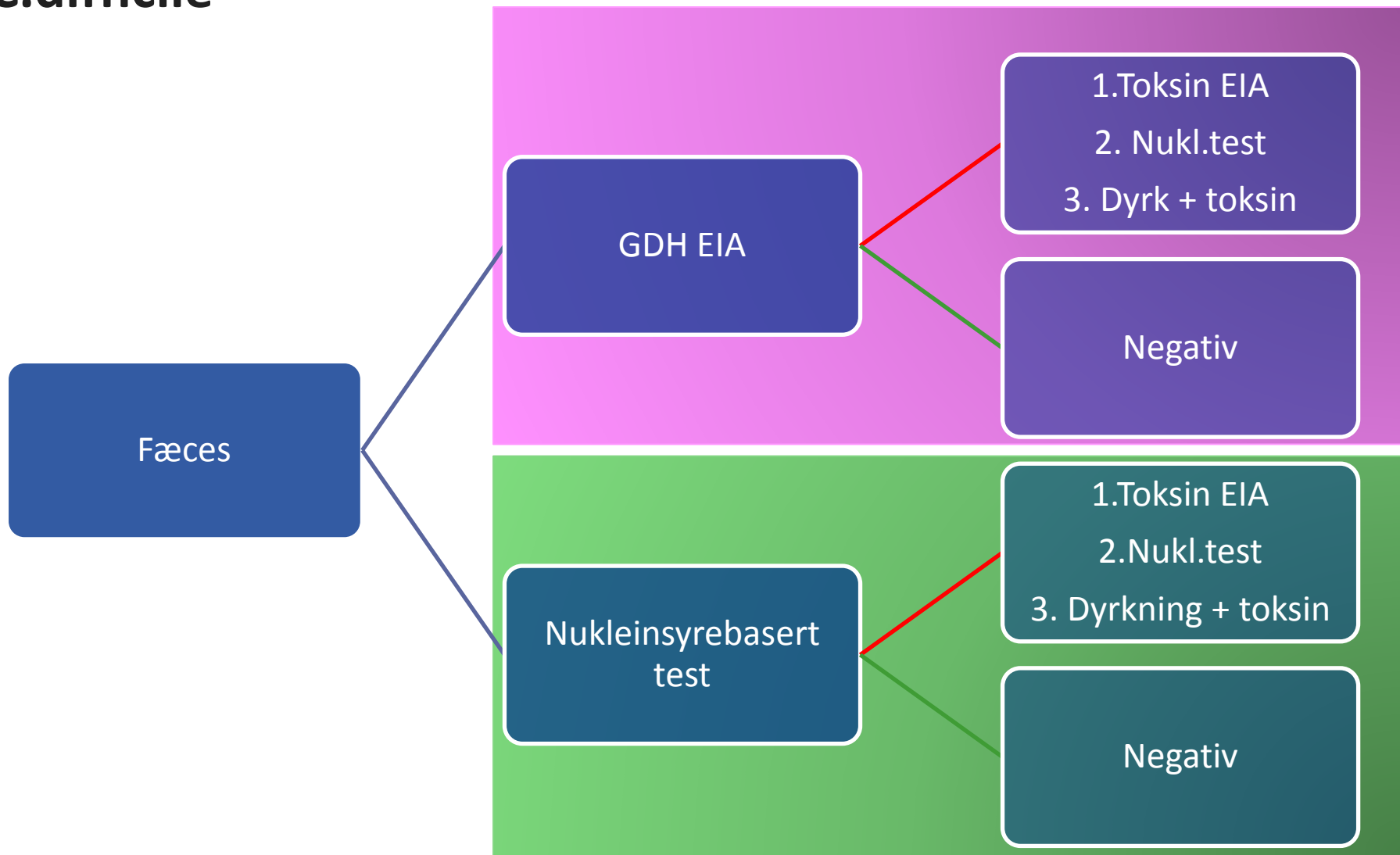
Daniel R. Knight et al. Clin. Microbiol. Rev. 2015;28:721-741

Opprinnelsen til CDRT027



He, M. et al. Nature Genetics 2013. 45, 109–113

Diagnostikk: Testalgoritmer for påvisning av toksigen C.difficile



Videre karakterisering av *C.difficile* (Ref.Lab)

Dyrkning av pos.
fæcesprøver

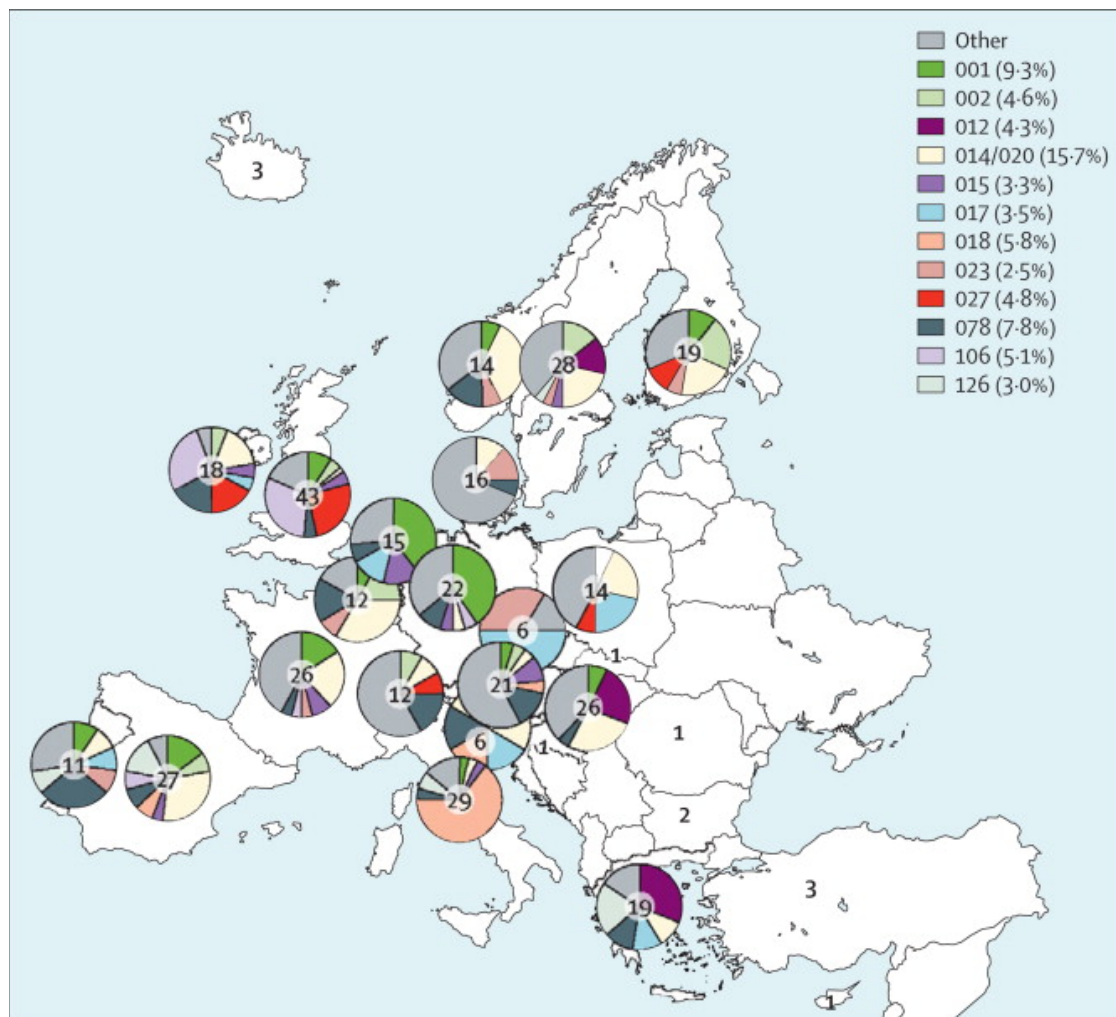
Identifikasjon

- MALDI TOF MS
- *gluD*-PCR
- Deteksjon av PaLoc /cdtLoc elementer
- Resistenstesting

Typing

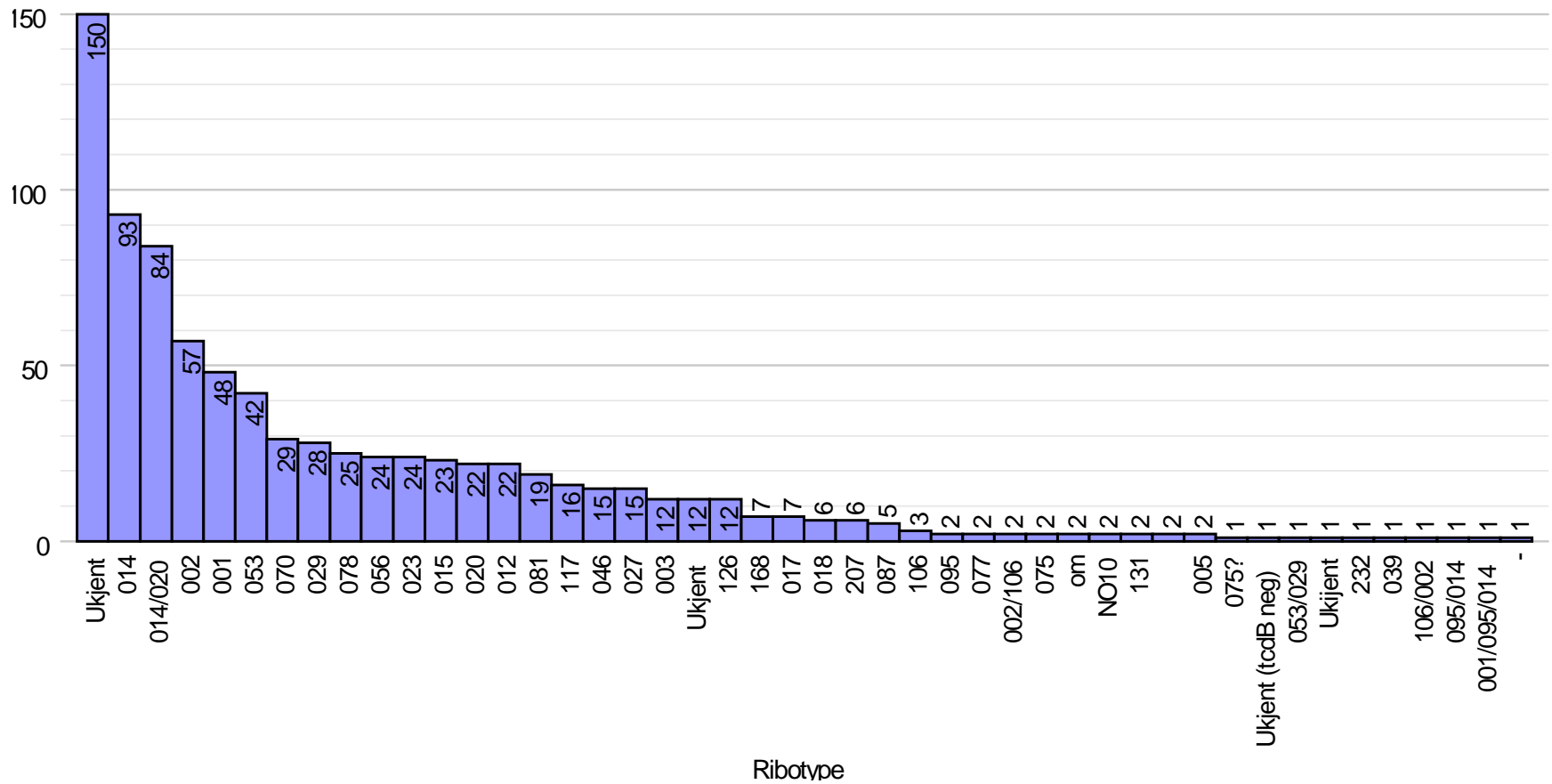
- PCR Ribotyping
- MLVA
- Fremtiden: Sekvensering (WGS)

Ribotypefordeling i Europa

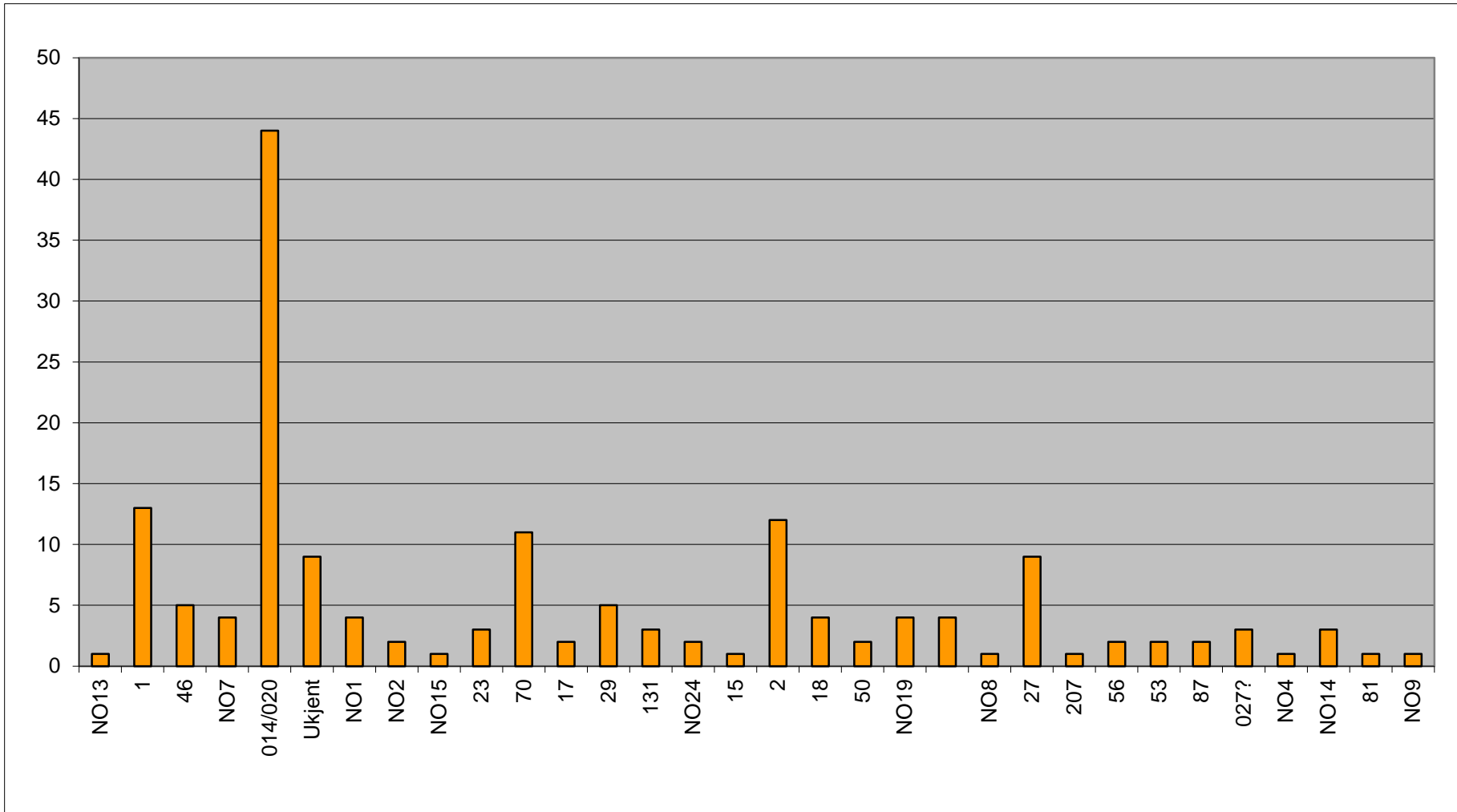


Bauer et al. 2010. Lancet 377; 63-73

Ribotyperfordeling 2010-2012 (n=834)



Oversikt ribotyper ved OUS 2013



Kilder – *C.difficile*



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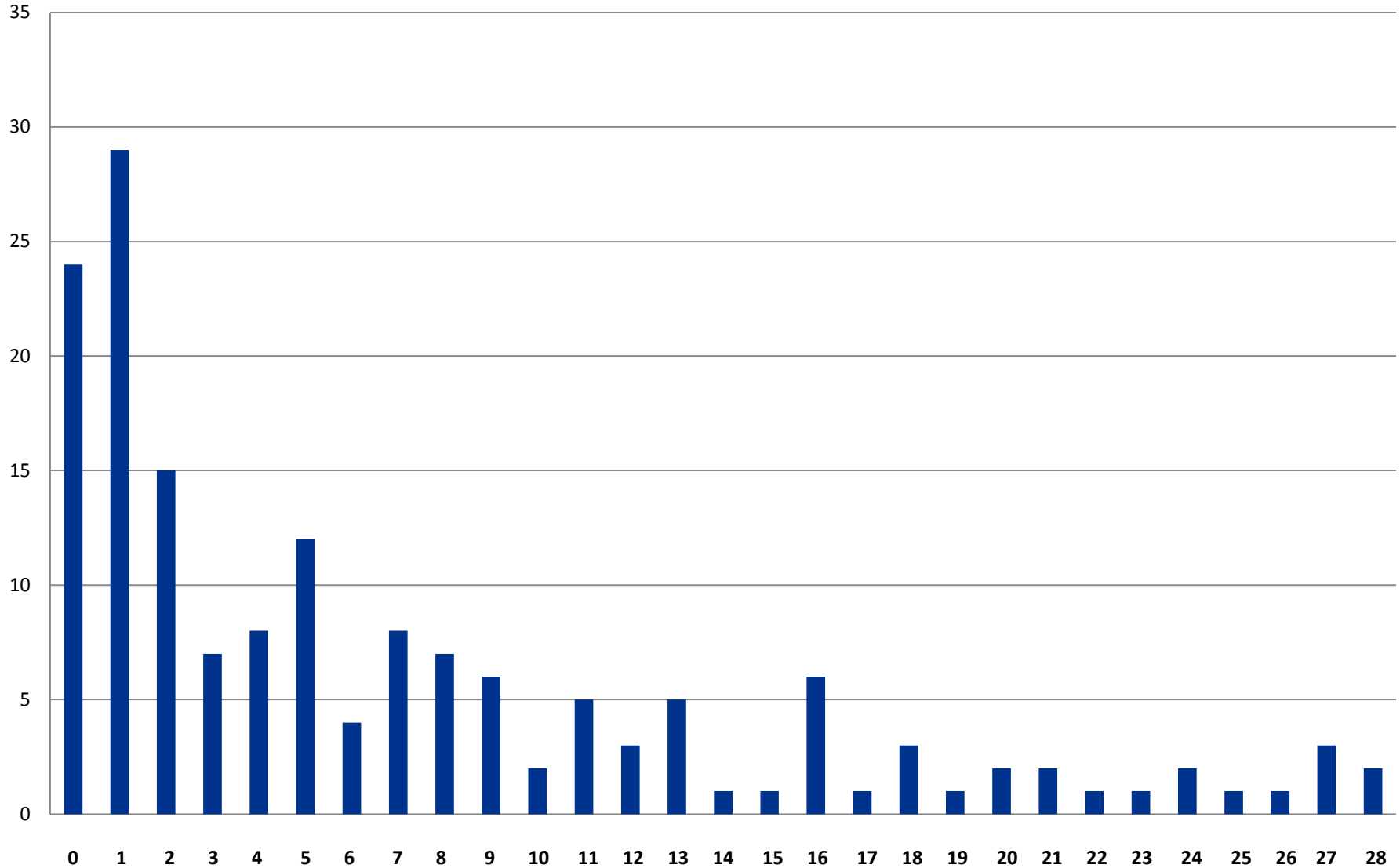
Diverse Sources of *C. difficile* Infection Identified on Whole-Genome Sequencing

David W. Eyre, B.M., B.Ch., Madeleine L. Cule, Ph.D., Daniel J. Wilson, D.Phil., David Griffiths, B.Sc.,
Alison Vaughan, B.Sc., Lily O'Connor, B.Sc., Camilla L.C. Ip, Ph.D., Tanya Golubchik, Ph.D., Elizabeth M. Batty, Ph.D.,
John M. Finney, B.Sc., David H. Wyllie, Ph.D., Xavier Didelot, D.Phil., Paolo Piazza, Ph.D., Rory Bowden, Ph.D.,
Kate E. Dingle, Ph.D., Rosalind M. Harding, Ph.D., Derrick W. Crook, M.B., B.Ch., Mark H. Wilcox, M.D.,
Tim E.A. Peto, D.Phil., and A. Sarah Walker, Ph.D.

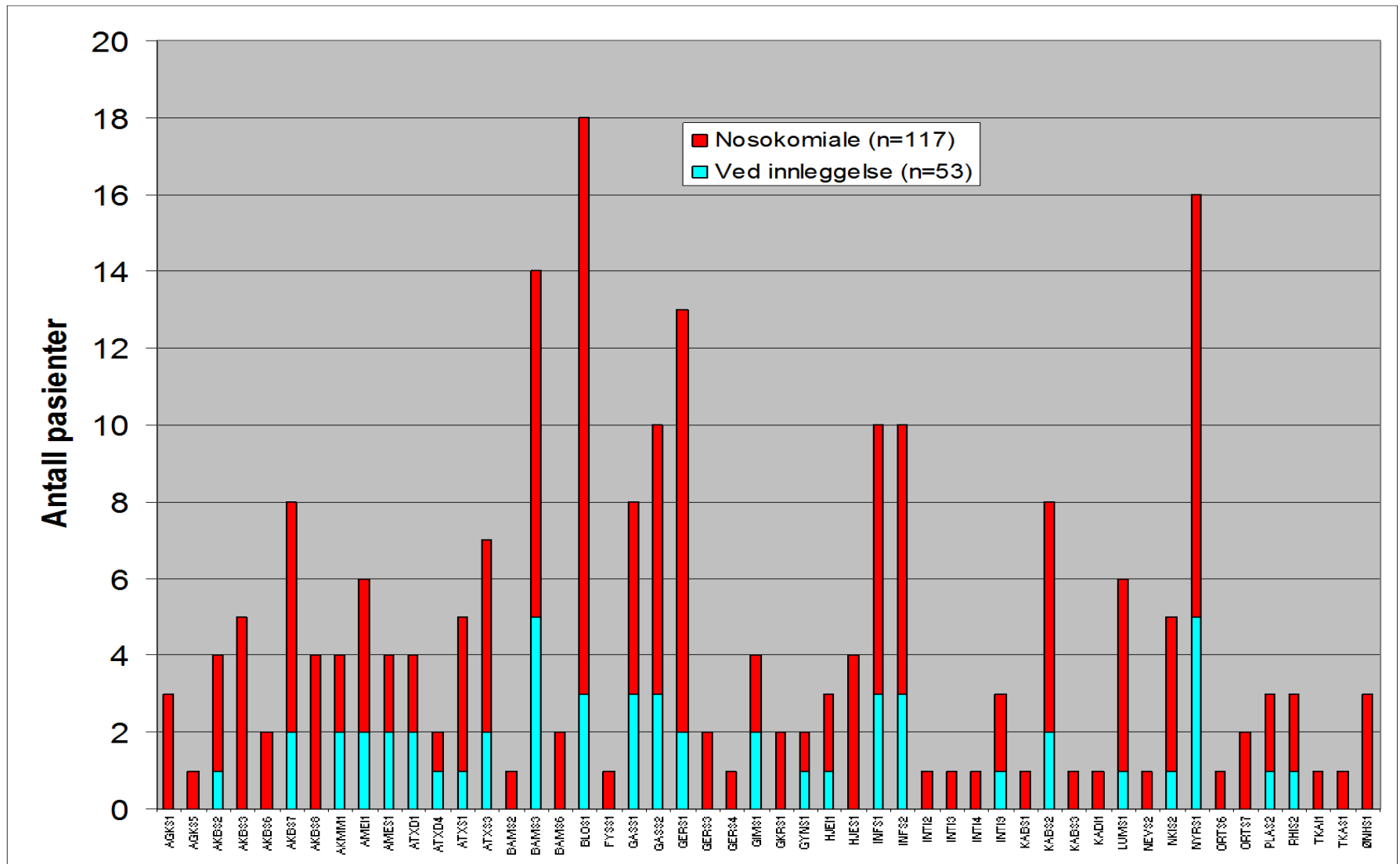
Kilder – *C.difficile*

- Konklusjon:
 - Av 957 stammer var 45% genetisk forskjellige fra hverandre
 - Av 957 stammer var 35% lik en annen stamme
 - 38% av disse hadde hatt nærkontakt med en annen pasient
 - 36% hadde ikke hatt noen kontakt med andre pasienter verken på sykehus eller ute i samfunnet ellers.

Første positive prøve etter innleggelse i OUS (d)



Clostridium difficile ved OUS i 2014



Oppsummert

- C.difficile er en formidabel patogen
- Adaptert til et økosystem i stadig forandring
- Er en økonomisk byrde for sykehus
- Det finnes flere hypervirulente stammer
- Vi finner disse også i Norge
- Nasjonal referanselaboratorium for C. difficile er etablert
- Flere kilder til CDI enn tidligere antatt
- Mye er fremdeles ukjent

