

The significance of asymptomatic colonization of *Clostridium difficile*

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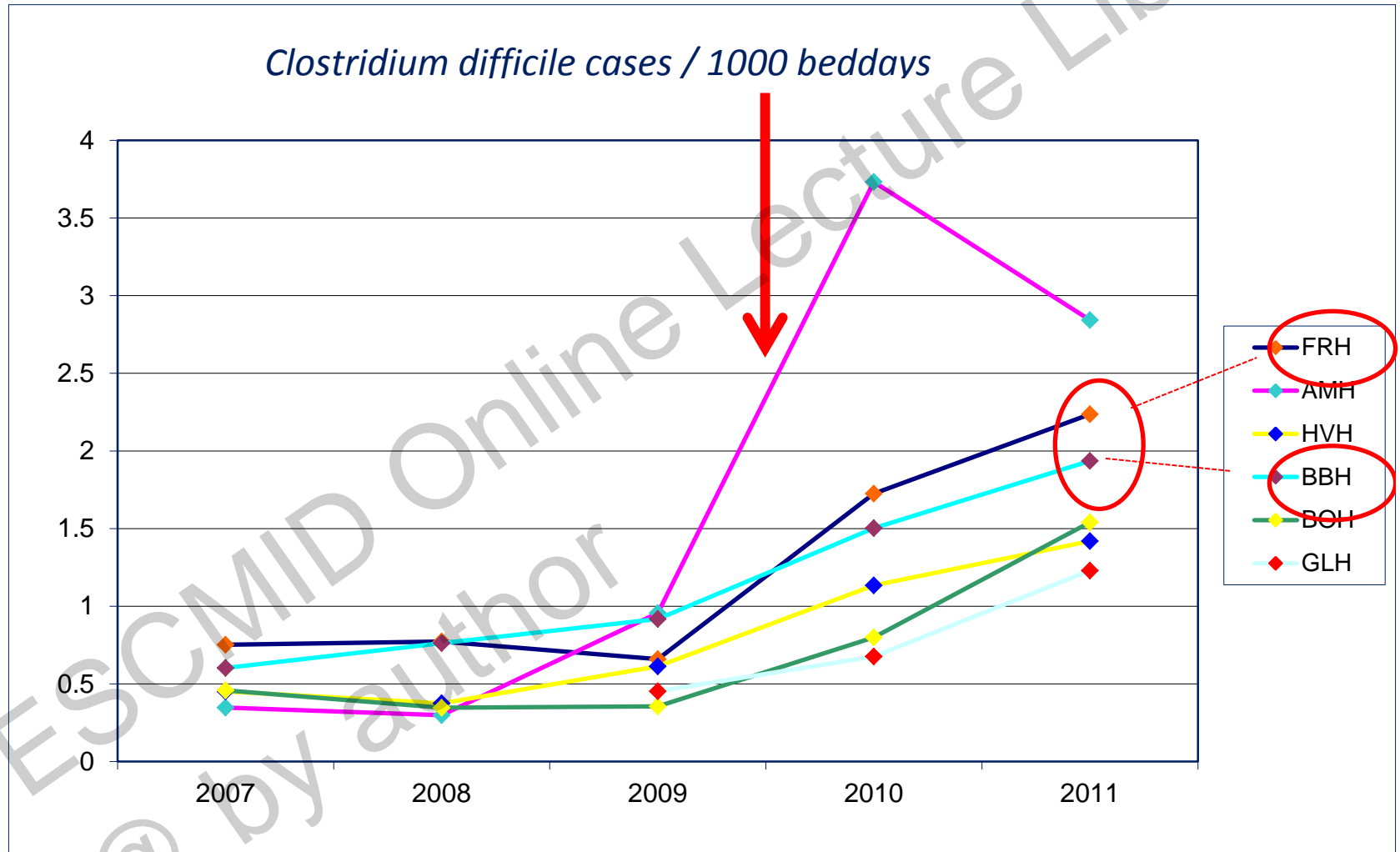
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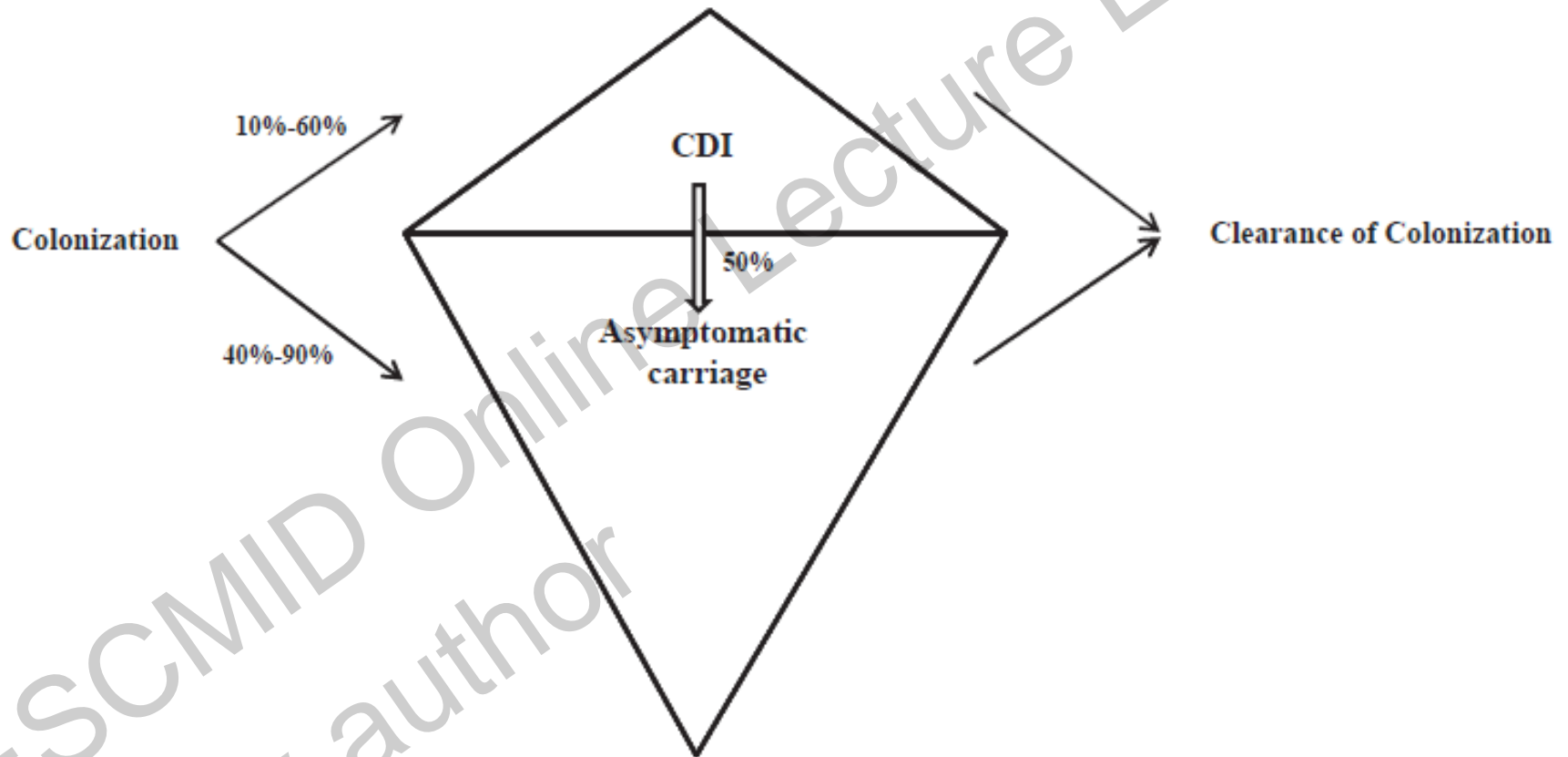
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Copenhagen history



Theory



Donskey CJ, et al. Infect Dis Clin N Am 2015; 29: 13-28.

Due to the increased incidence of CDI (*Clostridium difficile* Infection)

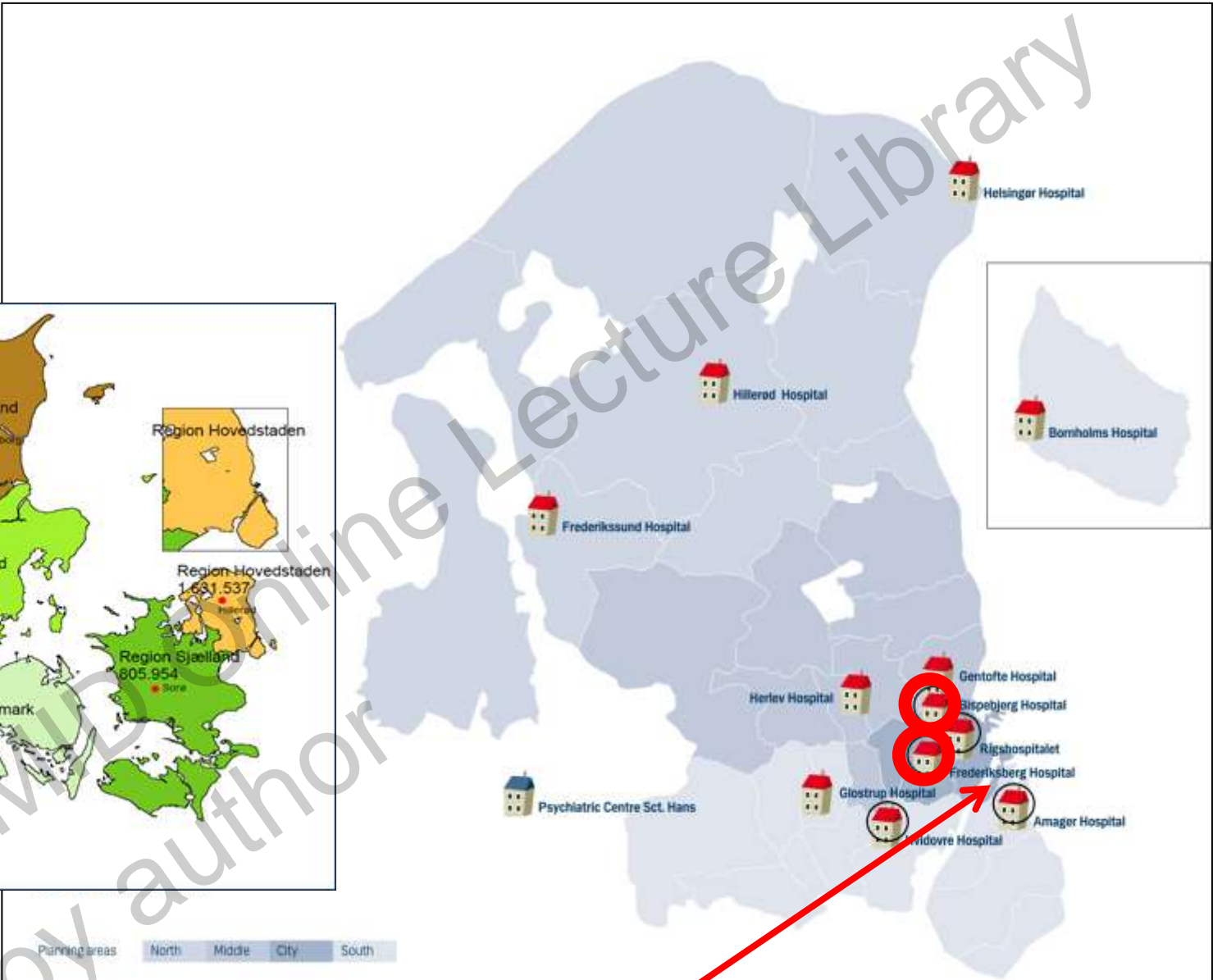
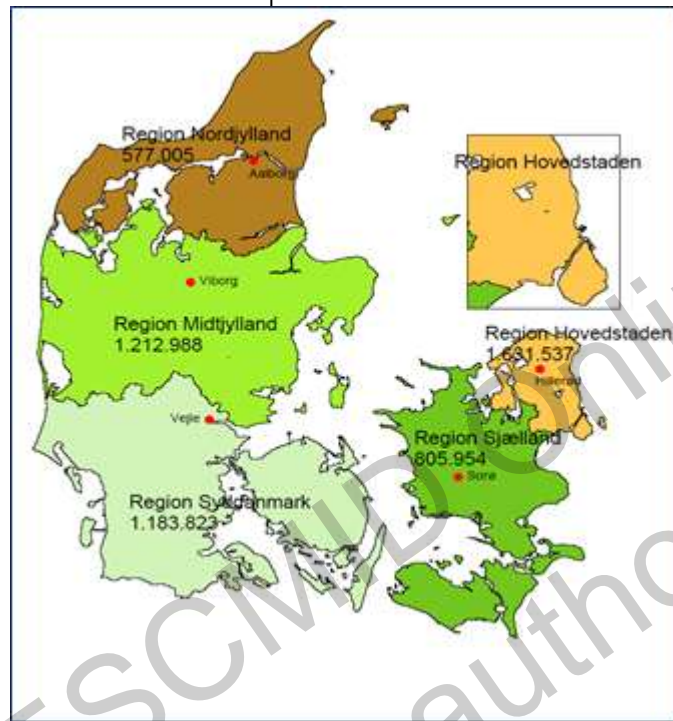
The questions were:

- Do we have asymptomatic carriers of *C. difficile* ?
- Do asymptomatic carriers of *C. difficile* contribute to nosocomial CDI's in the hospitals ?
- Do carriers experience CDI more frequently than non-carriers of *C. difficile* ?

((PCR-positive without diarrhea = colonized with *C. difficile* = **carrier**))

Setting

- Two university hospitals in Copenhagen
 - Public hospitals, tax financed
 - Catchment area with 416.000 inhabitants
- Eight medical wards participated in the study
 - 188 beds, mostly 2-4 bedded rooms
 - Approximately 1250 patients per month
- All information was collected on patients co-morbidities, medications, admission, laboratory data (also CDI), death within 1 year, +/-nursing-home status, etc., - through different data-sources



You are here

Study design

- **Prospective study** (management, ethical and data-protection agency approved)
- 4 months with inclusion of all patients
- October 1, 2012, to January 31, 2013, and further two weeks of follow up in hospitals, and one months for CDI
- All patients were rectal swabbed within 48h after admission
- All patients already admitted in the medical wards October 1, and not discharged on the day, were swabbed at study start

Methods

- fecalSwabs, Copan[®] (rectal or feces swab, demanding visible feces on the tip)
- In-house realtime multiplex PCR for *tcdA*, *tcdB*, *tcdC* (also detecting the $\Delta 117$ deletion), and *cdtA*, [Hoegh M, et al. Eur J Clin Microbiol Infect Dis. 2012; 31:1073-1079]
- PCR-positive samples were cultured, and *C. difficile* isolates were typed using MLST
- Patients were followed during their admission, every day at 8 AM, by ward, room-number, bed-number

Hospital
Department

Room-bed

Example of registration

Date

Danish personal unique identification number

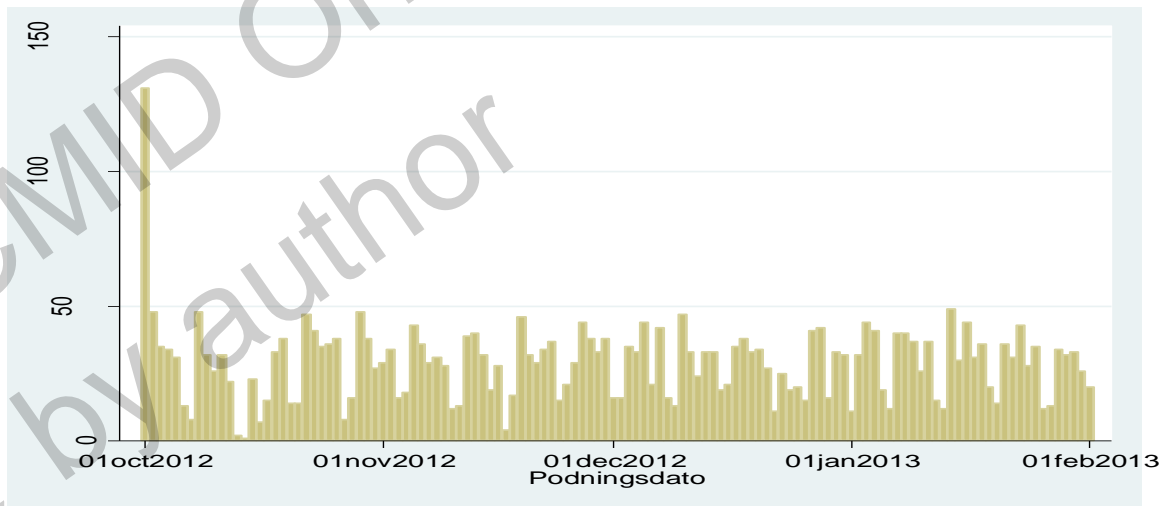
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FRH, M2								
Stue 1-1	170619-0224	170619-0224	170619-0224	170619-0224	170619-0224	170619-0224	170619-0224	170619-0224
Stue 1-2								
Stue 2-1	190829-0212	190829-0212	090219-0392	090219-0392	090219-0392	030830-1958	030830-1958	030830-1958
Stue 2-2	190830-0188	190830-0188	190830-0188	190830-0188	190830-0188	190830-0188	021123-1416	021123-1416
Stue 2-3	210626-1744	210626-1744	210626-1744	210626-1744	210626-1744	210626-1744	210626-1744	210626-1744
Stue 2-4								
Stue 3-1		140426-1858	140426-1858	140426-1858	010150-xxxx	060919-0116	060919-0116	
Stue 3-2	110323-0558	110323-0558	110323-0558	110323-0558	060919-0116	140426-1858	140426-1858	
Stue 4-1					131217-0252	131217-0252	131217-0252	131217-0252
Stue 4-2	210626-0438	210626-0438	210626-0438	210626-0438	210626-0438	210626-0438	210626-0438	210626-0438
Stue 5-1	170432-1836	170432-1836	170432-1836	170432-1836	170432-1836	170432-1836	170432-1836	170432-1836
Stue 5-2	271125-1580	271125-1580	271125-1580	271125-1580	271125-1580	101222-0932	101222-0932	101222-0932
Stue 5-3	270225-0326	270225-0326	270225-0326	270225-0326	270225-0326	270225-0326	270225-0326	270225-0326
Stue 5-4								
Stue 6.X								
Stue 6-1	010934-1363	010934-1363	010934-1363	010934-1363	010934-1363	010934-1363	010934-1363	
Stue 6-2	140115-0125	140115-0125	140115-0125	080631-0107	080631-0107	080631-0107	080631-0107	080631-0107
Stue 6-3	150933-0227	150933-0227	150933-0227	160412-2011	160412-2011	170544-1363	170544-1363	170544-1363
Stue 7-1			220841-2224	220841-2224	220841-2224	200327-1954	200327-1954	

Patient flow

4508 patient admissions

3605 cases included

903 cases not included



Reasons for not being included

(903 cases ~ 20.0%)

	Number (%)
Denial	243 (26.9)
Unstable patients , referred to ICU	29 (3.2)
Language barriers	15 (1.7)
Mental illness	6 (0.7)
Dying or estimated terminally ill	8 (0.9)
Discharged	593 (65.7)
Unknown	9 (1.0)

Patient flow

4508 patient admissions

3605 cases included

903 cases not included

104 admitted at start of study *

3 with CDI at start: 2.9%

12 carriers (12/101): 11.9%

3501 admitted and included

37 admitted with CDI: 1.1%

213 carriers (213/3463) 6.1%

$p=0.201$

$p=0.023$

*not discharged on the day of start, October 1.

Patients

4508 admissions, 3826 patients

- 407 were admitted twice, 119 were admitted three or more times
- 80% of all patient admission were included

	CDI at admission	Asymptomatic carriers	Not carrier	Not included
N	37	213	3251	903
Age, mean, [range]	82 [24-97]	81 [23-100]	74 [17-105]	64 [16-104]
Male %	41	41	43	45
Hospitalized within 1 year	80.3%	86.5%	57.4%	52.5%
Charlson 0	30%	19%	36%	48%
1-2	32%	41%	39%	35%
≥3	38%	40%	25%	17%
Length of stay (mean days)	13.6	10.4	8.5	5.4

Analyses

Analytic units "cases of admission"

- Follow up period for CDI (in and outside hospitals) was one month
- Only carriers, and not the patients admitted with CDI were included as a risk for other patients, because CDI patients were in strict isolation from admission

Carriers potential contribution to nosocomial CDI

Who got CDI within one month

Already admitted October 1:

Among 12 carriers, 3 experienced CDI: **25.0%**

Among 89 non-carriers, 4 experienced CDI: **4.5%**

Admittance in the 4 months study period:

Among 213 carriers, 20 experienced CDI: **9.4%**

Among 3251 non-carriers, 76 experienced CDI: **2.3%**

Carriers: (23/225)

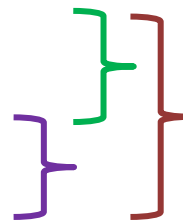
10.2%

Non-carriers: (80/3340)

2.4%

Not included: (11/903)

1.2%



p < 0.001

p < 0.001

p < 0.042

Odds ratio of CDI between groups

	OR	95 % confidence interval
Carriers	1	reference
Non-carriers	0.22	0.130-35
Not included	0.11	0.05-0.23

PCR and cultivation of rectal swabs

225 samples from asymptomatic carriers were PCR positive:

Culture yield: 169 *C. difficile* isolates (75%)

154 samples from patients with CDI were PCR positive:

Culture yield: 137 *C. difficile* isolates (89%)

$p < 0.001$

MLST typing

All Carriers CD

MLST	Antal
ST001	23
ST002	14
ST003	1
ST004	1
ST005	2
ST006	5
ST007	2
ST008	14
ST009	4
ST010	1
ST011	13
ST013	1
ST014	3
ST015	1
ST016	1
ST017	3
ST028	2
ST031	1
ST034	3
ST035	3
ST036	2
ST042	1
ST043	1
ST044	6
ST046	1
ST048	1
ST049	1
ST050	2
ST053	1
ST054	4
ST055	2
ST058	4
ST059	1
ST077	1
ST102	1
ST103	23
ST124	1
ST139	3
ST205	1
ST-U1	2
0	68
	225

CDI isolates from carriers

Bærere		
MLST	Antal	
ST001	2	
ST002	2	
ST005	1	
ST008	4	
ST011	2	
ST016	1	
ST058	0	
ST103	3	
ST139	1	
ST-U3	0	
ST-U4	0	
0	1	
Total	17	

CDI isolates from patients admitted with CDI

Ikke bærere		
MLST	Antal	
ST001	56	
ST002	1	
ST004	1	
ST005	1	
ST006	3	
ST008	1	
ST009	3	
ST011	3	
ST013	1	
ST044	1	
ST049	1	
ST054	1	
ST149	1	
0	17	
Total	91	

Carriage and CDI

In all cases of nosocomial CDI in patients being carrier at admittance, were isolates of *C. difficile* could be typed, we found the same type

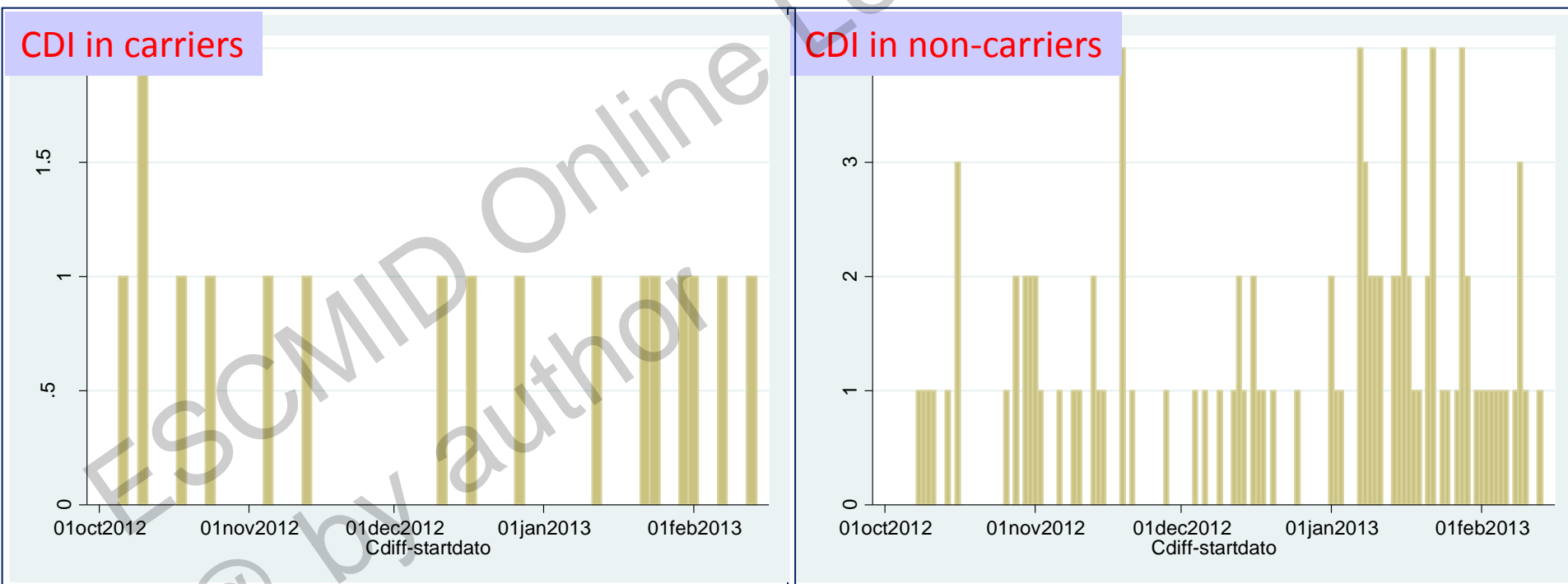
- Being carriers did not protect against CDI -

C. difficile types and CDI

	Total	ST 1/027	Non-ST 1/027	Not cultured / not typed
Asymptomatic carriers	225	23 (10.2%)	134 (59.6%)	68 (30.2%)
CDI in asymptomatic carriers	23	2 (8.7%)	14 (60.9%)	7 (30.4)
CDI patients	91	56 (61.5%)	18 (19.8%)	17 (18.7)

CDI cases occurred sporadic

No difference in carriage, CDI, or spread of *C. difficile* were found between the two hospitals



Example: a non carrier in a wards with other patients, carriers and non-carriers, every day

Infection pressure

afd	dato	bærer_w	obs_af~o	obs_af~r	obs_af~1	obs_af~s	s~s_alle	s~s_unds	s~t_alle	s~t_unds
BBH, Afd L23	18oct2012	0	12	.	.	12	0	0	.0651809	.0685536
BBH, Afd L23	19oct2012	0	11	.	.	11	0	0	.0651809	.0685536
BBH, Afd L23	20oct2012	0	11	.	.	10	0	0	.0651809	.0685536
BBH, Afd L23	21oct2012	0	16	1	0	13	.0625	.0769231	.0651809	.0685536
BBH, Afd L23	22oct2012	0	17	1	0	14	.0588235	.0714286	.0651809	.0685536
BBH, Afd L23	23oct2012	0	17	1	0	13	.0588235	.0769231	.0651809	.0685536
BBH, Afd L23	24oct2012	0	17	1	0	15	.0588235	.0666667	.0651809	.0685536
BBH, Afd L23	25oct2012	0	19	2	1	19	.1052632	.1052632	.0651809	.0685536
BBH, Afd L23	26oct2012	0	17	1	0	17	.0588235	.0588235	.0651809	.0685536
BBH, Afd L23	27oct2012	0	15	1	0	15	.0666667	.0666667	.0651809	.0685536
BBH, Afd L23	28oct2012	0	19	2	1	19	.1052632	.1052632	.0651809	.0685536
BBH, Afd L23	29oct2012	0	20	2	1	20	.1	.1	.0651809	.0685536
BBH, Afd L23	30oct2012	0	19	1	0	19	.0526316	.0526316	.0651809	.0685536
BBH, Afd L23	31oct2012	0	18	1	0	18	.0555556	.0555556	.0651809	.0685536
BBH, Afd L23	01nov2012	0	20	1	0	20	.05	.05	.0651809	.0685536
BBH, Afd L23	02nov2012	0	15	1	0	15	.0666667	.0666667	.0651809	.0685536
BBH, Afd L23	03nov2012	0	15	2	1	15	.1333333	.1333333	.0651809	.0685536
BBH, Afd L23	04nov2012	0	20	2	1	19	.1	.1052632	.0651809	.0685536
BBH, Afd L23	05nov2012	0	19	2	1	18	.1052632	.1111111	.0651809	.0685536

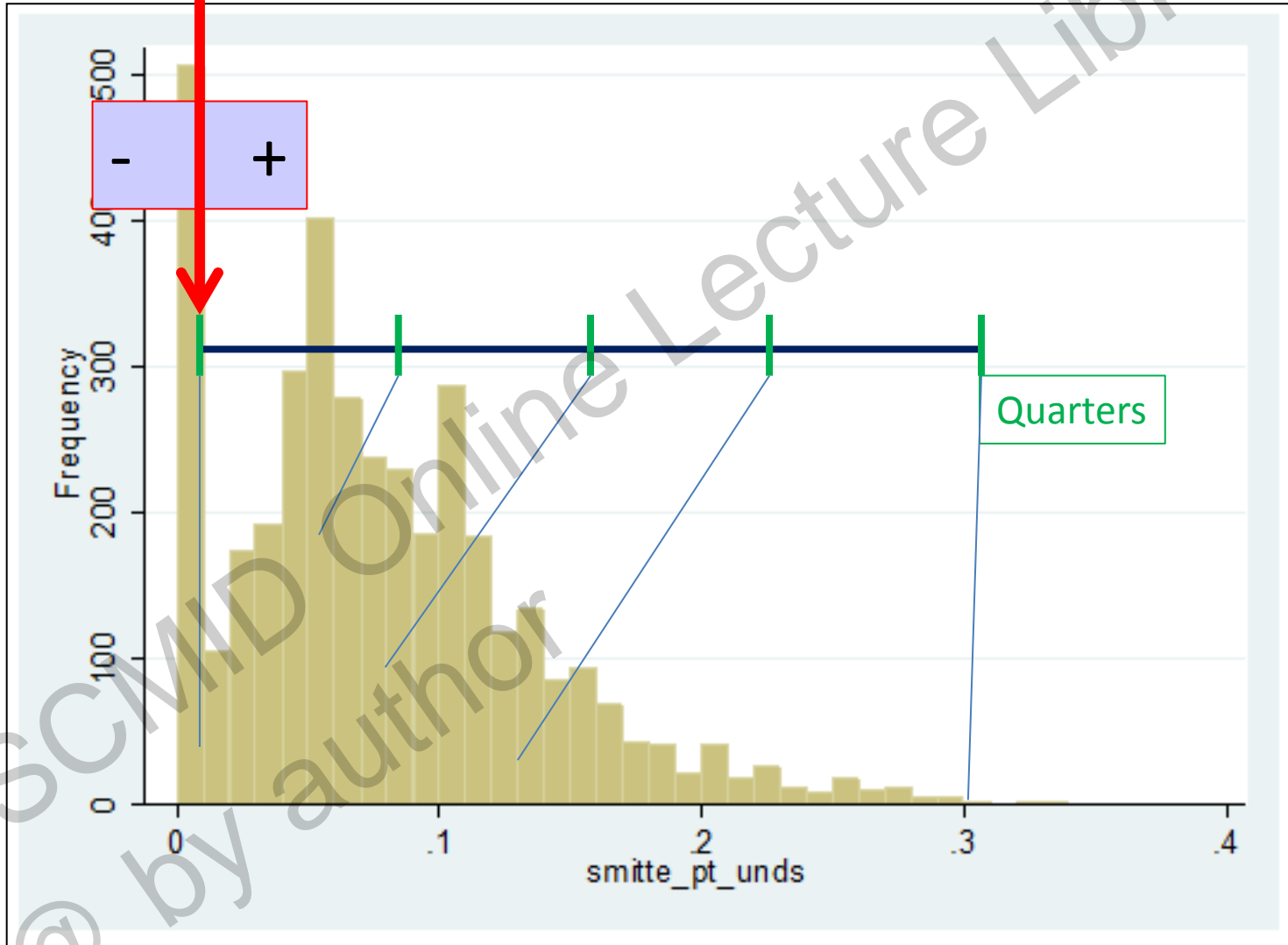
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+-----+
| bærer_w obs_af~o obs_af~r obs_af~1 obs_af~s |
s~t_alle s~t_unds |
+-----+
| 0 20 1 0 18 .05 .0555556 .0937434 .1076846 |
| 0 20 1 0 18 .05 .0555556 .0763315 .0837232 |
| 0 20 1 0 18 .05 .0555556 .0470324 .0582846 |
| 0 20 1 0 18 .05 .0555556 .0369048 .0449039 |
| 0 20 1 0 18 .05 .0555556 .0898498 .095468 |
| 0 20 1 0 18 .05 .0555556 .0688753 .0755533 |
| 0 20 1 0 18 .05 .0555556 .069122 .0764724 |
| 0 20 1 0 18 .05 .0555556 .0531877 .0576023 |
| 0 20 1 0 18 .05 .0555556 .0779801 .090552 |
| 0 20 1 0 18 .05 .0555556 .0885957 .103574 |
| 0 20 1 0 18 .05 .0555556 .0477743 .0615706 |
| 0 20 1 0 18 .05 .0555556 .0934266 .1036039 |
| 0 20 1 0 18 .05 .0555556 .0731361 .0805344 |
| 0 20 1 0 18 .05 .0555556 .1120262 .1249442 |
| 0 20 1 0 18 .05 .0555556 .0531877 .0576023 |
| 0 20 1 0 18 .05 .0555556 .0790977 .0871345 |
| 0 20 1 0 18 .05 .0555556 .0804646 .0885695 |
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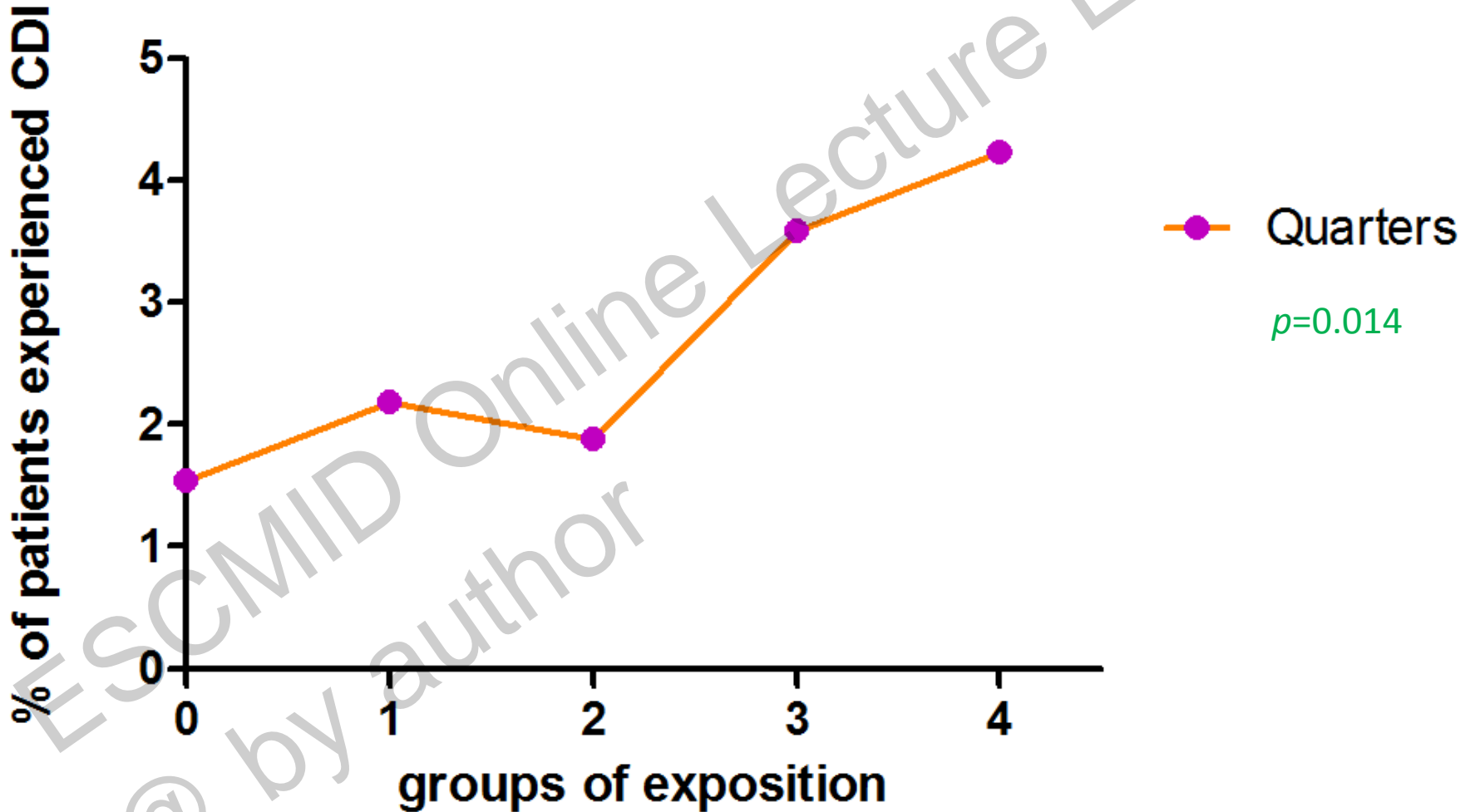
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Carriers and non carriers in the wards every day

Exposure to carriers



CDI according to infection pressure



Do asymptomatic carriers of *C. difficile* contribute to nosocomial CDI's in the hospitals ?

- / +:

CDI in patients in wards with carrier present : 2.96%

CDI in patients in wards without carrier present: 1.54%

$p=0.076$, OR 2.095 (c.i.: 0.9678-4.5340)

No exposure and graduated (in quarters)
exposure: $p=0.014$

Conclusions

- Yes, we have asymptomatic carriers, and we produce even more asymptomatic carriers during hospitalization
- Asymptomatic carriers experience CDI significantly more often, and from their own carrier isolate
- Carriers seldom carry CD ST1/027
- CD ST1/027 is far the most frequent nosocomial CD

Carriers potential contribution to nosocomial CDI ?

- We observed an increased risk for CDI in patients admitted to wards at the same time as asymptomatic carriers of *C. difficile*, - the higher exposure, the higher risk for CDI

Who else participated?

Fellows in the wards

Swabs (~50%)

Steering committee for IC regarding *C. difficile*

Thomas Blix Fellow, MD

Swabs, data, writer

Marie Stangerup IC nurses

Swabs

Jette Houлинд IC nurses

Swabs

Jakob Seidelin Senior hospital physicians

Project plans

Anne Lester Senior hospital physicians

Project plans

Christian Homan, Senior hospital physicians

Project plans

Kim Oren Gradel Epidemiologist Vet PhD

Analyses

Kristian Schønning MD DrMsci

C. difficile-PCR, typing

Explanation ?

Table 2
Skin and environmental contamination in patients with CDI versus asymptomatic carriers

Ref. #	Subjects	No. Positive/No. Sampled (%)			
		Patients with CDI		Asymptomatic Carriers	
		Skin	Environment	Skin	Environment
2	Medical ward	—	44 of 90 (49)	—	11 of 38 (29)
18	LTCF residents	14 of 18 (78)	14 of 18 (78)	21 of 35 (61)	20 of 35 (61)
14	Acute care	5 of 6 (83)	4 of 6 (67)	2 of 18 (11)	2 of 18 (11)
56	Oncology unit	—	19 of 97 (20)	—	5 of 74 (7)
54	LTCF residents	—	—	11 of 25 (44)	10 of 25 (40)
8	Acute care patients and LTCF residents ^a	—	—	15 of 26 (58)	13 of 26 (50)
55	Outpatients ^a	1 of 1 (100)	1 of 1 (100)	13 of 43 (30)	11 of 43 (26)

^a All asymptomatic carriers were patients with prior CDI.

Donskey CJ, et al. Infect Dis Clin N Am 2015; 29: 13-28.

Similar findings?

Asymptomatic Carriers (n = 40)		CDI Protocol A (n = 74)		CDI Protocol B (n = 49)	
Strain ^a	No.	Strain ^a	No.	Strain ^a	No.
014/020 ^{*,***}	14 (35%)	027	23 (31%)	027	8 (16%)
012 ^{*,**}	10 (25%)	106/174	9 (12%)	WU42	8 (16%)
053 [*]	4 (10%)	014/020	7 (9%)	014/020	6 (12%)
077	3 (8%)	002	7 (9%)	001	4 (8%)
027 ^{*,***}	1 (3%)	005	4 (5%)	106/174	3 (6%)

Prevalence and Risk Factors for Asymptomatic *Clostridium difficile* Carriage

Table 4.

Five Most Common Toxigenic *Clostridium difficile* Strains From Asymptomatic Carriers, Protocol A, and Protocol B

^a **Strain name is the polymerase chain reaction ribotype. If the strain did not match to a ribotype, the Washington University (WU) strain number is provided. If unable to discriminate between different ribotypes, both ribotypes the strain matched to are provided.**

- ^{*} $P \leq .005$, asymptomatic carriers compared with protocol A.
- ^{**} $P < .001$, asymptomatic carriers compared with protocol B.
- ^{***} $P \leq .03$, asymptomatic carriers compared with protocol B.

Clin Infect Dis 2014 Jul 15;59(2):216-22. doi: 10.1093/cid/ciu258. Epub 2014 Apr 21.

Prevalence and risk factors for asymptomatic *Clostridium difficile* carriage.

Alasmari F¹, Seiler SM², Hink T², Burnham CA³, Dubberke ER².

Similar findings ?

Ref. #	2	3	4	5	6	15
Setting	Medical Ward, n (%)	Medical-Surgical Ward, n (%)	3 ICUs/2 Medical-Surgical Wards, n (%)	2 Medical Wards, n (%)	6 Hospitals, n (%)	Medical Wards, n (%)
<i>C difficile</i> positive on admission	29 of 428 (7)	65 of 634 (10) ^a	55 of 496 (11) ^b	37 of 271 (14)	—	16 of 168 (10) ^c
Asymptomatic carriage	17 of 29 (59)	61 of 65 (94)	44 of 55 (80) ^d	19 of 37 (51) ^e	184 of 4143 (4)	16 of 168 (10)
CDI	12 of 29 (41)	4 of 65 (6)	11 of 55 (20)	18 of 37 (49)	^f	Excluded
<i>C difficile</i> acquired during hospital stay	83 of 399 (21)	54 of 569 (10)	34 of 234 (15) ^g	47 of 253 (19)	240 of 3959 (6)	12 of 152 (8)
Asymptomatic carriage	52 of 83 (63)	51 of 54 (94)	25 of 34 (74)	19 of 47 (40)	123 of 240 (51)	8 of 12 (75)
CDI	31 of 83 (37)	3 of 54 (6)	9 of 34 (26)	28 of 47 (60)	117 of 240 (49)	4 of 12 (25)
Persistence of carriage	68 of 83 (82) colonized on discharge ^h	—	44 of 71 (62) colonized on follow-up cultures	—	—	—

Abbreviation: ICU, intensive care unit.

^a Includes toxigenic and nontoxigenic strains.

^b Includes 406 subjects with initial culture within 72 hours of admission and 90 with initial culture greater than 72 hours after admission.

^c Only toxigenic strains included based on real-time polymerase chain reaction and culture.

^d Twenty-four of 44 (55%) toxigenic.

^e Cytotoxin activity was detected in stools of 15 of 19 (79%) asymptomatic carriers and 3 of 4 with negative cytotoxin activity carried nontoxigenic strains.

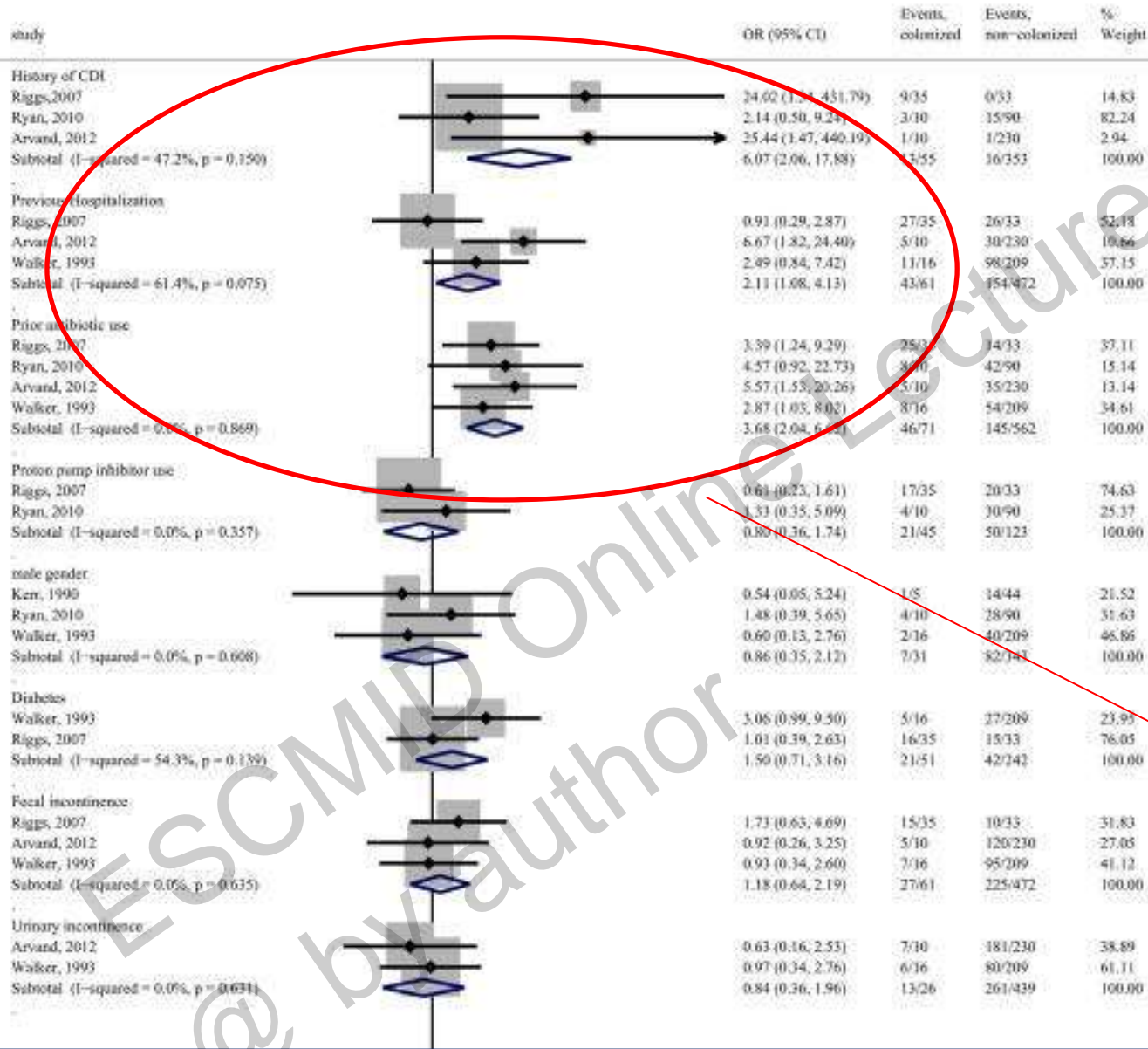
^f Seventy-five patients either developed CDI within 3 days of admission (n = 60) or were asymptotically colonized on admission and subsequently developed CDI (n = 15).

^g Nineteen of 34 (56%) toxigenic with 10 remaining asymptomatic and 9 developing CDI.

^h Includes both asymptomatic carriers and patients with CDI.

Donskey CJ, et al. Infect Dis Clin N Am 2015; 29: 13-28.

Risk factors for colonization, patient-level exposure



PLoS One. 2015 Feb 23;10(2):e0117195. doi: 10.1371/journal.pone.0117195. eCollection 2015.

Asymptomatic carriers of toxigenic *C. difficile* in long-term care facilities: a meta-analysis of prevalence and risk factors.

Ziakas PD¹, Zacharioudakis IM¹, Zervou FN¹, Grigoras C¹, Pliakos EE¹, Mylonakis E¹.

History of CDI
Previous hospitalization
Prior antibiotics
???



There is nothing as the pure nature !

Cool pool party !

Borrowed from **WulffMorgenthaler**