The Changing Face of *Clostridium difficile* infection

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CDI 027 Netherlands severity, outcome

2008

Characteristic	No. of patients with available information: All	Strain type: Ribotype 027, toxinotype III	Strain type: Other	OR (95% CI): Univariate analysis	OR (95% CI): Multivariate analysis
Severity of diarrhea[a]					
All	215	49	166	…	…
Mild	181	38 (77.6)	143 (86.1)	…	…
Severe	34	11 (22.4)	23 (13.9)	1.80 (0.81–4.02)	1.99 (0.83–4.73)[b]
Clinical course[c]					
All	211	48	163	…	…
Not complicated	192	42 (87.5)	150 (92.0)	…	…
Complicated	19	6 (12.5)	13 (8.0)	1.65 (0.59–4.60)	…
Death due to CDAD	5	3 (6.3)	2 (1.2)	5.37 (0.87–33.1)	3.30 (0.41–26.4)
Recurrence					
All	863	218	645	…	…
Yes	141	45 (20.6)	96 (14.9)	1.49 (1.00–2.20)	1.44 (0.94–2.20)
1 recurrence	…	32 (14.7)	74 (11.5)	1.32 (0.85–2.08)	1.27 (0.79–2.06)
>1 recurrence	…	13 (6.0)	22 (3.4)	1.80 (0.89–3.63)	1.80 (0.84–3.85)
No	722	173 (79.4)	549 (85.1)	…	…

[a] Severe diarrhea was defined as bloody diarrhea or diarrhea with hypovolemia, fever, and leukocytosis; with hypoalbuminemia; or with pseudomembraneous colitis.
[b] When adjusted for hospital, the OR was 3.97 (95% CI, 1.05–15.0).
[c] A complicated course was defined as admission to an intensive care unit, surgical intervention, or death associated with CDAD.

Goorhuis A, *et al. Clin Infect Dis* 2007; 45:695–703.

CDI 027 case-control study

summary outcome

- Excess treatment (metronidazole) failures (29 vs 3%; P=0.03)
- More likely to have increase in creatinine (20 vs 3%; P=0.055)
- High mortality

30 (25 vs 14%) day mortality

60 (29 vs 31%) day mortality

90 (34 vs 37%) day mortality

Ellames D, Wilcox M, Fawley W, *et al.* ICAAC 2007. Abstract K-605.

C. difficile ribotypes

England, Apr-Sept 2008

Region	Ribotype prevalence (%)				No. of samples received (ribotyped)
	001	027	106	other 'common' ribotype	
East	2	60	7	CD 014/020 (9%)	158 (137)
E & W Mid	<3	53	8	CD 015 (7%)	405 (356)
London	3	54	0	CD 026 (11%)	149 (132)
North East	19	18	24	CD 002 (22%)	280
North West	11	31	34	CD 002 (4%)	280 (271)
South East	3	34	21	CD 015 (5%)	302 (273)
South West	2	24	23	CD 014/020 (10%)	147 (126)
Yorks & Hu	11	41	9	CD 002 (5%)	431 (399)
CDRNE	**8**	**39**	**16**	**N/A**	**2152 (1972)**

Enhanced Fingerprinting to discriminate within CD ribotypes

- 91 *C. diffiicle* 027 isolates from 9 hospitals in England
- Pulsed field gel electrophoresis discriminated 5 pulsovars
- MLVA detected 23 types
- Identified 2 new & 2 enlarged CDI case clusters

Fawley WN *et al. J Clin Microbiol* 2008;46:954-60

Enhanced fingerprinting of *Clostridium difficile*

Health Protection Agency

Clostridium difficile Ribotyping Network for England (CDRNE)

Introduction

Multilocus variable repeat analysis (MLVA) can be used to characterise and improve the understanding of the transmission of epidemic *C. difficile* strains within healthcare institutions. Importantly, the method can provide a high level of discrimination among epidemic *C. difficile* ribotypes, including 001, 027 and 106; these accounted for approximately 70% of more than 2000 *C. difficile* isolates ribotyped by CDRNE in 2007-08.[1] For example, MLVA can distinguish more than 20 sub-types of *C. difficile* ribotype 027.[2] MLVA is far superior to most other fingerprinting methods, including pulsed field gel electrophoresis, for analyzing closely related *C. difficile* strains.[4]

The Enhanced Fingerprinting Service

The Health Protection Agency funded the development of CDRNE in England from April 2007. The HPA is now introducing a service development to enable enhanced fingerprinting of *C. difficile* (MVLA) to be carried out. There is no charge for this service for NHS hospitals in England. Access to the service will have to be strictly controlled, in the first instance by Regional Microbiologists, given its high cost and need to balance availability with the scale of CDI challenge. MLVA is available via the Leeds laboratory (based at Leeds General Infirmary), which acts as the reference laboratory for the CDRNE service.

Criteria Used to Determine Access to the Service

- **A hospital/trust with a high rate of CDI as identified with the local SHA; *or***
- **A hospital/trusts that is failing to meet its *C. difficile* target trajectory despite implementation and audit of control measures; *or***
- **A declared outbreak of CDI as agreed with the local Health Protection Unit.**

In addition:

- **Ribotyping carried out by CDRNE must have confirmed the presence of a dominant *C. difficile* ribotype;**
- **A plan should be in place of how results of *C. difficile* enhanced fingerprinting will contribute to the control of CDI;**
- **Infection Control Teams/Consultant Microbiologists will first need to agree with the Regional Microbiologist that use of the *C. difficile* enhanced fingerprinting service is merited; *and***
- **Numbers of samples/isolates to be examined will be agreed with the Leeds laboratory on a case-by-case basis, taking account of the scale of CDI challenge.**

References

1. Health Protection Agency. Surveillance of Healthcare Associated Infections Report 2008: Clostridium difficile. Pages 26-28. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1216193833496.
2. Fawley WN, Freeman J, Smith C, Hammond C, van den Berg RJ, Kuijper EJ, Wilcox MH. Use of highly discriminatory fingerprinting to analyze clusters of *Clostridium difficile* infection cases due to epidemic ribotype 027 strains. *J Clin Microbiol* 2008;46:954-60.
3. Killgore G, Thompson A, Johnson S, et al. Comparison of seven techniques for typing international epidemic strains of *Clostridium difficile*. *J Clin Microbiol* 2008;46:431-7.

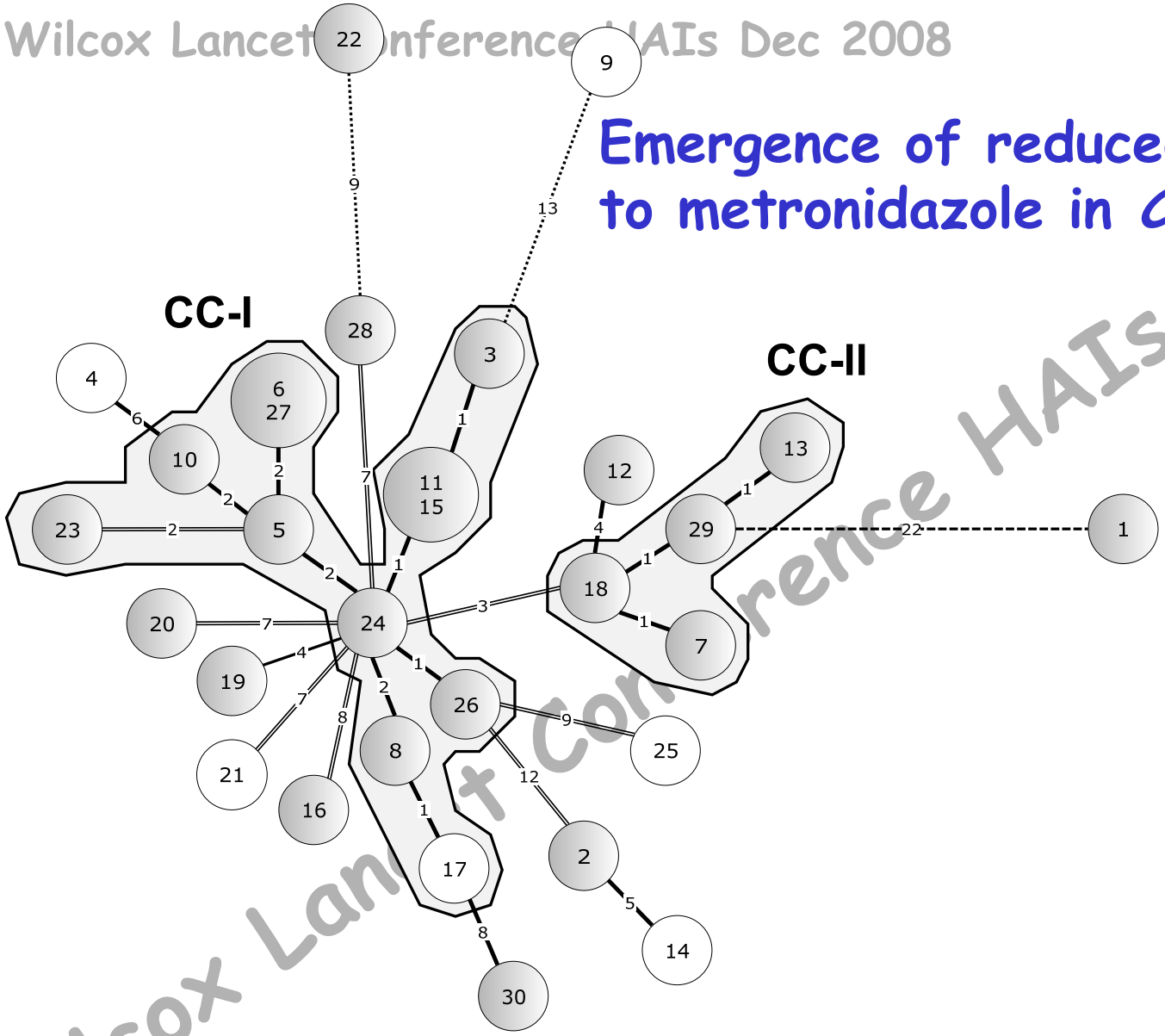
Professor M H Wilcox
HPA Regional Microbiology Network Lead on *C. difficile*
September 2008

Emergence of *C. difficile* 078

- In Netherlands prevalence of CDI due to ribotype 078 increased from 3 to 13% between 2005-08
- CD 078 vs 027 patients were
  - younger (67.4 vs. 73.5 years)
  - more frequently had community-associated disease (17.5% vs. 6.7%; odds ratio, 2.98; 95% CI 2.11-8.02)
- CD 078 isolates had genes for both major toxins, binary toxin, a 39 bp deletion in toxin regulator gene (tcdC), and a point mutation at position 184, resulting in a stop codon
- MLVA showed that CD 078 isolates from humans and pigs were highly genetically related

Goorhuis A, *et al. Clin Infect Dis* 2008;47:1162-70

Emergence of reduced susceptibility to metronidazole in *C. difficile*.



White circles indicate metronidazole-susceptible isolates; grey circles indicate *C. difficile* with reduced susceptibility to metronidazole. Two circles may contain more than 1 isolate: these are 100% homologous at all 7 VNTR loci.

The numbers between the circles represent the summed tandem repeat differences (STRDs) between MLVA types.

CC-1 and CC-2 represent clonal complexes with a STRD ≤ 2.

Single locus variant
Double locus variant
Triple locus variant
Pentuple locus variant

Baines SD, O'Connor R, Freeman J, Fawley WN, Harmanus C, Mastrantonio P, Kuijper EJ, Wilcox MH. *J Antimicrob Chemother* 2008;62:1046-52.

Laboratory diagnosis of CDI

What do we want to know?

Is *C. difficile* is present?

culture
antigen (GDH) detection

Is *C. difficile* toxin is present?

cytotoxin assay
enzyme-immunoassay
membrane assays

Is *C. difficile* present with the capacity to produce toxin?

cytotoxigenic culture
detection of toxin (B) gene

Accuracy of CD toxin detection kits

- Although NPVs are relatively high (typically >95%), crucially, as the prevalence of CDI decreases then the PPV reduces markedly.

- This has implications for the validity of testing especially as testing increases and/or in low prevalence settings.

- Benchmarking data for 5 teaching and 13 non-teaching UK NHS institutions

- Median number of requests for CD testing increased

  from 3613 in 2005/06

  to 5020 in 2007/08

  (a 39% increase)

Planche T, *et al. Lancet Infect Dis* 2008;8:777-84.
Wilcox MH. Personal communication 2008.
National Pathology Benchmarking Review. University of Keele 2008.

Community CDI

- Exposure to antibiotics in previous 4 weeks, particularly multiple agents ($P < 0.001$), aminopenicillins ($P < 0.05$) and oral cephalosporins ($P < 0.05$), was significantly more frequent among cases than controls
- Hospitalization in the preceding 6 months was significantly associated with CDI (45% *vs* 23%; P=0.022)
- However, almost half the cases had not received antibiotic therapy in the month before CDI
- Approx one-third neither had exposure to antibiotics nor recent hospitalization
- Connecticut 2006 - 32% of patients had no recent exposure to antimicrobials

Wilcox *et al. J Antimicrob Chemother* 2008; 62: 388-96.
MMWR Morb Mortal Wkly Rep. 2008 Apr 4;57(13):340-3.

Antibiotics and risk of CDi

Need to minimise all antibiotic use - polypharmacy and duration

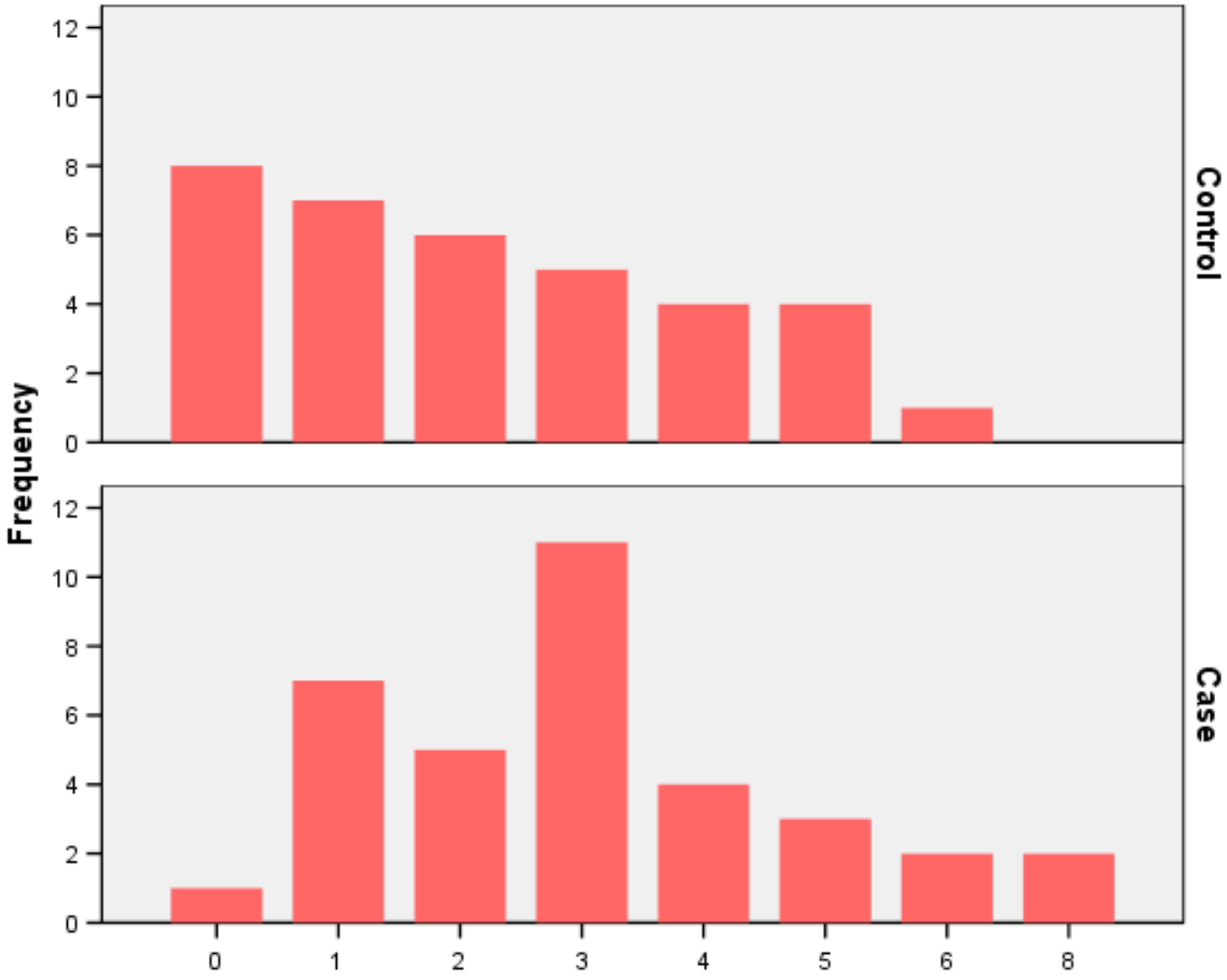
High risk	Medium risk	Low risk
cephalosporins	ampicillin/amoxy	aminoglycosides
clindamycin	co-trimoxazole	metronidazole
	macrolides	anti-pseudomonal penicillins ± beta-lactamase inhibitor
	tetracyclines	rifampicin
	fluoroquinolones	vancomycin

Evidence to support the restriction of these as control measure for CDI

CDI may still occur !

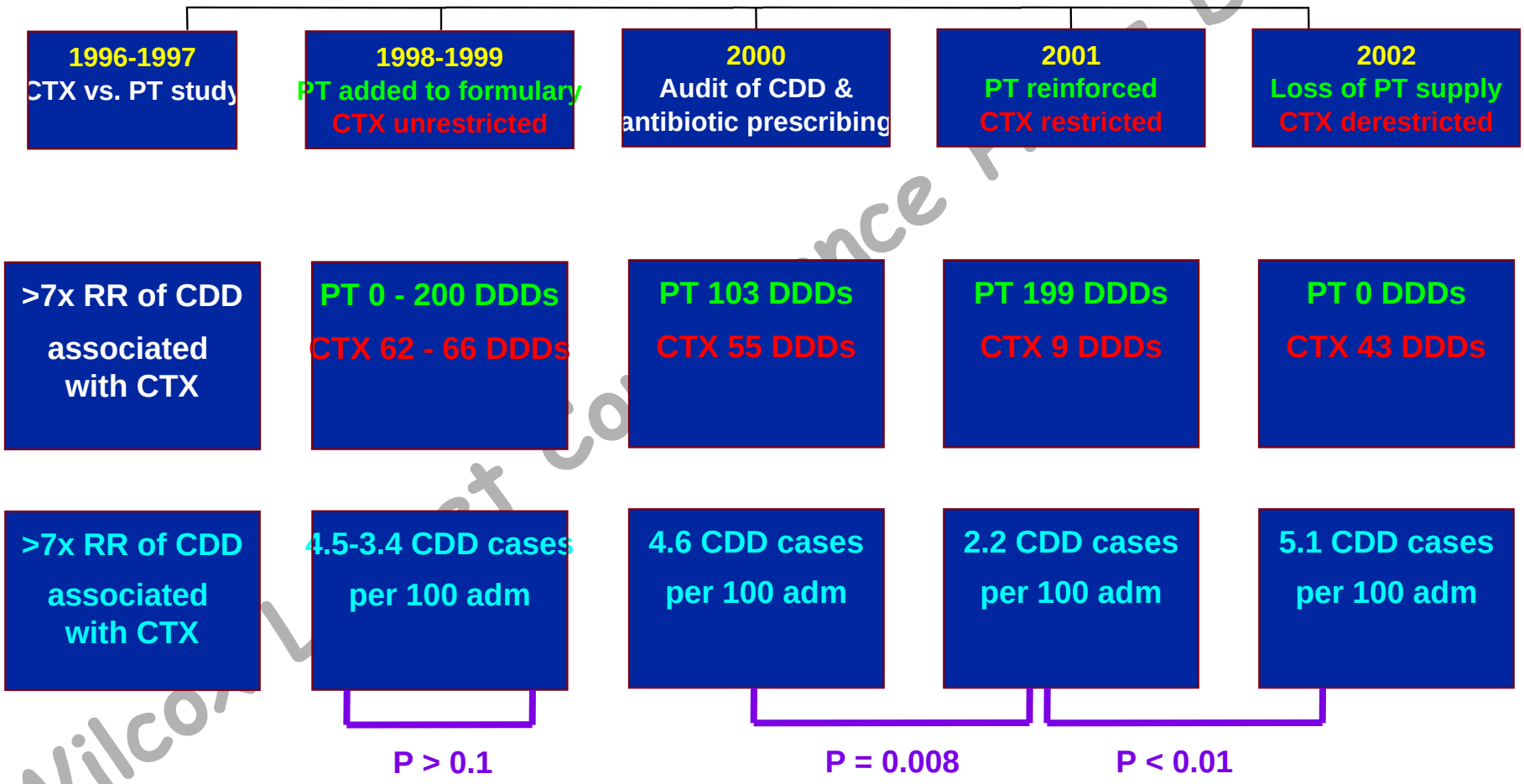
Number of antibiotics received by 027 cases and controls in 30 days prior to CDi diagnosis

2008



5 year summary of CDD rates & antibiotic prescribing

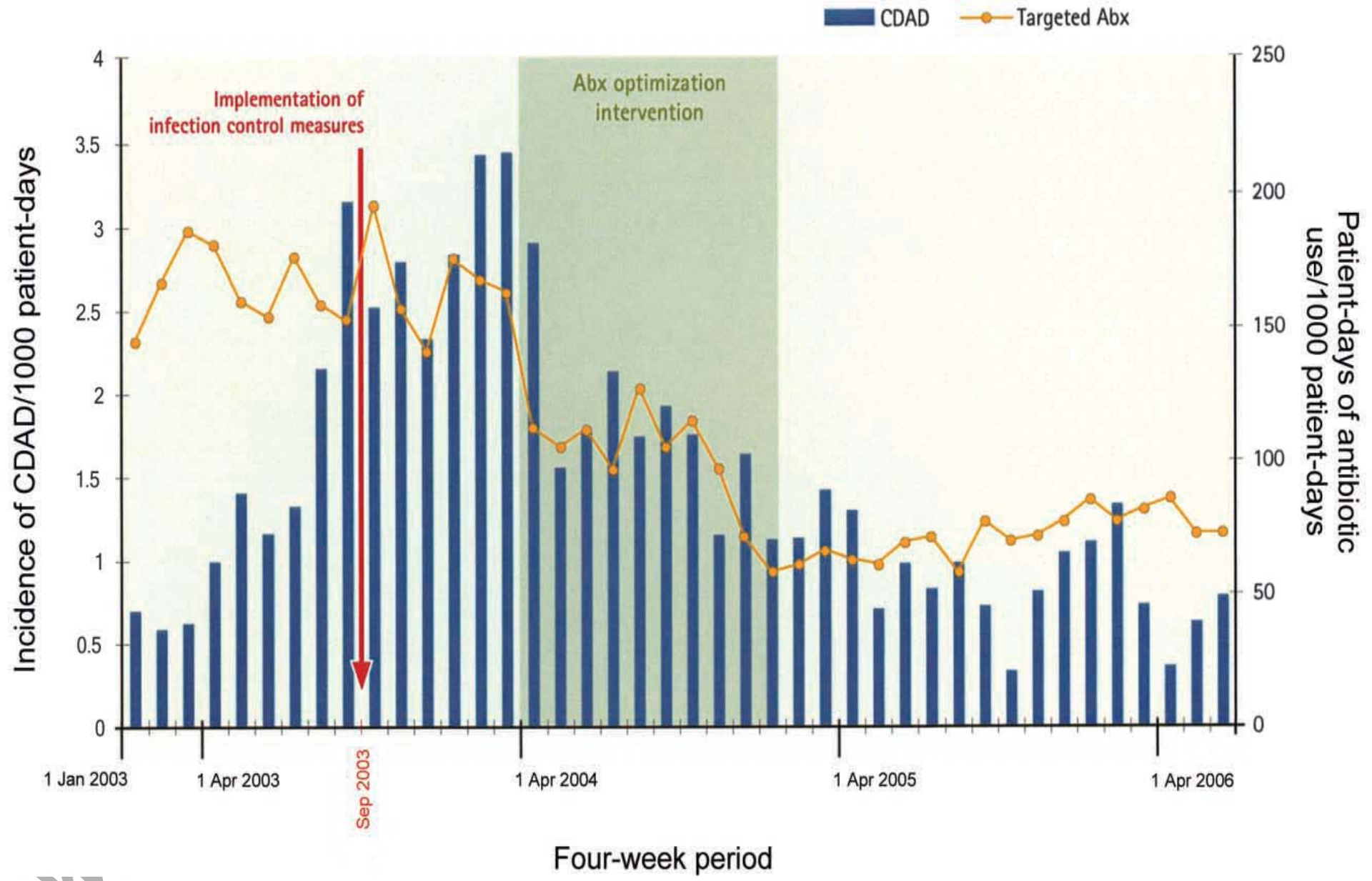
Leeds General Infirmary



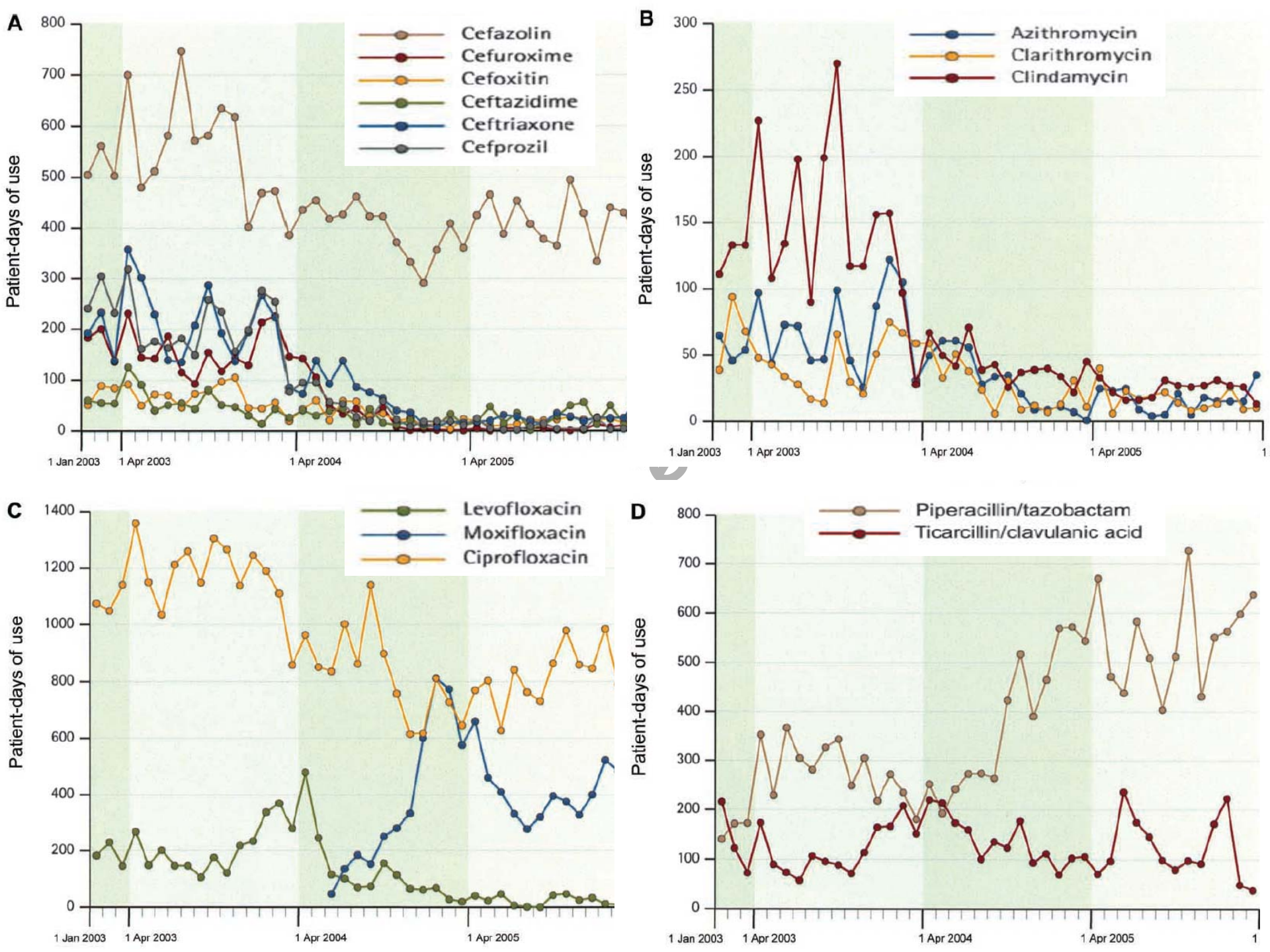
Wilcox MH et al. *J Antimicrob Chemother* 2004

Settle CD et al. *Aliment Pharmacol Ther* 1998;12:1217-23

Wilcox Lancet Conference HAIs Dec 2008



Valiquette L, *et al. Clin Infect Dis* 2007;45:S112-21.


A
Patient-days of use
800
700
600
500
400
300
200
100
0
Cefazolin
Cefuroxime
Cefoxitin
Ceftazidime
Ceftriaxone
Cefprozil
1 Jan 2003
1 Apr 2003
1 Apr 2004
1 Apr 2005
B
Patient-days of use
300
250
200
150
100
50
0
Azithromycin
Clarithromycin
Clindamycin
1 Jan 2003
1 Apr 2003
1 Apr 2004
1 Apr 2005
C
Patient-days of use
1400
1200
1000
800
600
400
200
0
Levofloxacin
Moxifloxacin
Ciprofloxacin
1 Jan 2003
1 Apr 2003
1 Apr 2004
1 Apr 2005
D
Patient-days of use
800
700
600
500
400
300
200
100
0
Piperacillin/tazobactam
Ticarcillin/clavulanic acid
1 Jan 2003
1 Apr 2003
1 Apr 2004
1 Apr 2005

Use of specific antibiotics 2003-2006

Antibiotic	2003–2004[a]	2004–2005	2005–2006	Change between 2003–2004 and 2005–2006, %
Cephalosporins				
First-generation	47.0	35.9	37.1	−21
Second-generation	32.8	8.0	2.4	−93
Third-generation	19.4	6.7	4.1	−79
Clindamycin	10.6	3.3	1.8	−87
Macrolides	8.6	3.3	1.9	−78
Ciprofloxacin	87.5	63.6	62.4	−29
Respiratory fluoroquinolones[b]	15.6	33.5	28.0	+79
Piperacillin/tazobactam	19.6	29.4	42.0	+114

NOTE. Data are patient-days of use per 1000 patient-days of hospitalization, unless otherwise indicated.

[a] Includes 3 additional fiscal periods (January–March 2003), for a total of 16 periods.

[b] Moxifloxacin was introduced in June 2004.

Valiquette L, *et al. Clin Infect Dis* 2007;45:S112-21.

Current CDI treatment issues

- Poor treatment response in severe CDI
- Vancomycin is superior to metro in severe CDI
- Microbiological response superior for vanc vs metro
- Reduced susceptibility is emerging in metronidazole
- Increasing dependence on vancomycin
- Recurrence rate

Lahue BJ, Davidson DM. Metronidazole and vancomycin outcomes for CDAD in a US hospital database. ECCMID Munich, 2007. Abstract O331.

Zar *et al.* A comparison of vancomycin and metronidazole for the treatment of CDAD, stratified by disease severity. *Clin Infect Dis* 2007; 45: 302-7.

Bouza E, *et al.* Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in patients with Clostridium difficile-associated diarrhoea. 18th ECCMID 2008. Abstract O464).

Louie T, *et al.* Results of a Phase III Trial Comparing Tolevamer, Vancomycin and Metronidazole in Patients with *Clostridium difficile*-Associated Diarrhea. *ICAAC* 2007; LB abstract 3826.

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- Nassir WN, Sethi AK, Nerandzic MM, Bobulsky GS, Jump RL, donskey CJ. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. *Clin Infect Dis* 2008;47:56-62.

- Kuijper EJ, Wilcox MH. Decreased effectiveness of metronidazole for the treatment of *Clostridium difficile* infection? *Clin Infect Dis* 2008;47:63-5).

Frequency of markers of 'severe' CDI

- 108 CD toxin positive cases (10% CD 027)
- 49% of patients had severe CDI based on criteria (day -3 to +3 relative to sample received)
  - leukocytosis (LEU) ≥15 x109/L (21%)
  - serum creatinine (CRE) ≥1.5 x increase above baseline(10%)
  - core body temperature (T) ≥38.5°C (6%)
  - evidence of colitis (<1%)

A. Dale, W. Fawley, S. Baines, M. Wilcox. ICAAC 2008

Frequency of markers of 'severe' CDI

- No correlation between diarrhoea frequency & CDI severity
- LEU & increased CRE usually occurred before lab diagnosis
  - highest mean LEU (23.2 x109/L) and serum CRE (158 mmol/L) occurred on days -2 and -3, respectively
- Vanc treatment given to 29% of this cohort

A. Dale, W. Fawley, S. Baines, M. Wilcox. ICAAC 2008

N. American Phase 3 CDI Study of OPT-80 vs Vancomycin

Per Protocol (microbiologically evaluable)	OPT-80 (200mg bid)	Vancocin® capsules (125mg qid)	p-value	95% Confidence Interval
Clinical Cure	92.1% (244/265 patients)	89.8% (254/283 patients)	NA	(-2.6,)*
Recurrence	13.3% (28/211)	24.0% (53/221)	0.004	(-17.9, -3.3)
Global Cure	77.7% (206/265)	67.1% (190/283)	0.006	(3.1, 17.9)
Modified Intent-to-Treat (mITT)	OPT-80 (200mg bid)	Vancocin® capsules (125mg qid)	p-value	95% Confidence Interval
Clinical Cure	88.2% (253/287 patients)	85.8% (265/309 patients)	NA	(-3.1,)*
Recurrence	15.4% (39/253)	25.3% (67/265)	0.005	(-16.6, -2.9)
Global Cure	74.6% (214/287)	64.1% (198/309)	0.006	(3.1, 17.7)

* one-sided 97.5% CI
NA= Not Applicable (trial met non-inferiority endpoint)

http://www.optimerpharma.com/news.asp?news_story=69&page_num=
11.10.2008 SAN DIEGO, CA

New issues pertinent to transmission control

- Effectiveness of cleaning at spore removal
  - Physical methods, chlorine, hydrogen peroxide, steam
- Viral gastroenteritis
- Cohorting (CDI wards) vs side rooms
- Asymptomatic carriage as risk factor for environmental contamination or transmission
- Incontinence devices
- Airborne dispersal

Current (CDI) cleaning controversies
Microfibre cleaning

- Dry cleaning
- Water based cleaning
- Reprocessing, efficacy, lifespan
- Damage to fibres
- User dependability, 8-fold method
- Not all products equal efficacy

Moore & Griffith. *J Hosp Infect* 2006;64:379-85.
Wren *et al. J Hosp Infect* 2008;70:265-71.

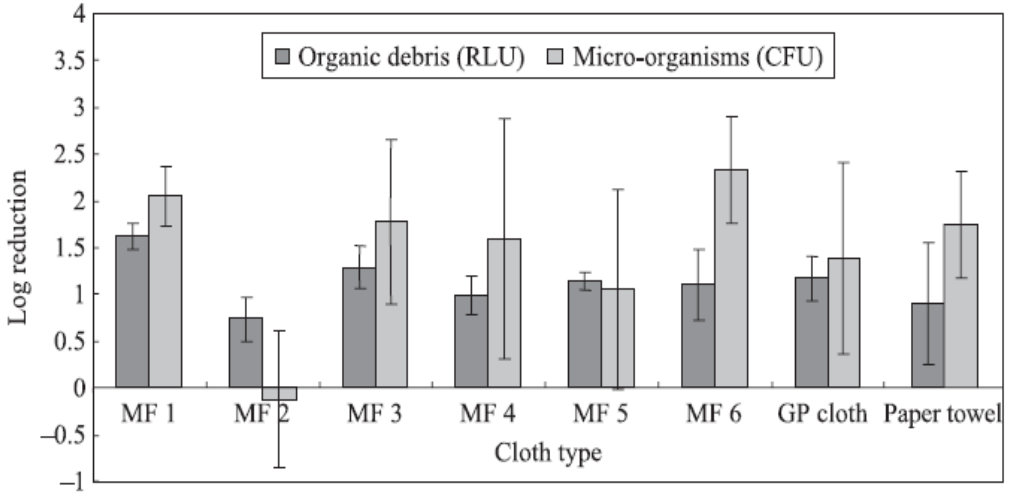


Figure 1 Reduction [mean ($N = 5$) $\pm$ 2 standard errors] in the level of organic debris and associated micro-organisms when a dry surface was wiped using a wet cloth. MF, microfibre cloth; GP, general purpose; RLU, relative light units; CFU, colony-forming units.

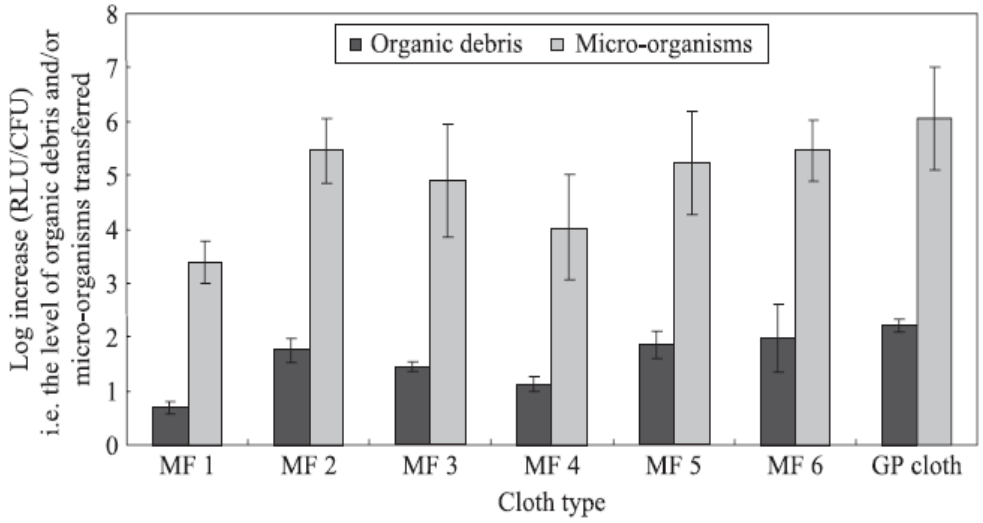


Figure 2 Increase [mean ($N = 5$) $\pm$ 2 standard errors] in the level of organic debris and associated micro-organisms when a clean dry surface was wiped using a contaminated damp cloth. MF, microfibre cloth; GP, general purpose; RLU, relative light units; CFU, colony-forming units.

Effect of viral gastroenteritis on incidence of CDi

0.036 CD toxin +ve cases per ward day

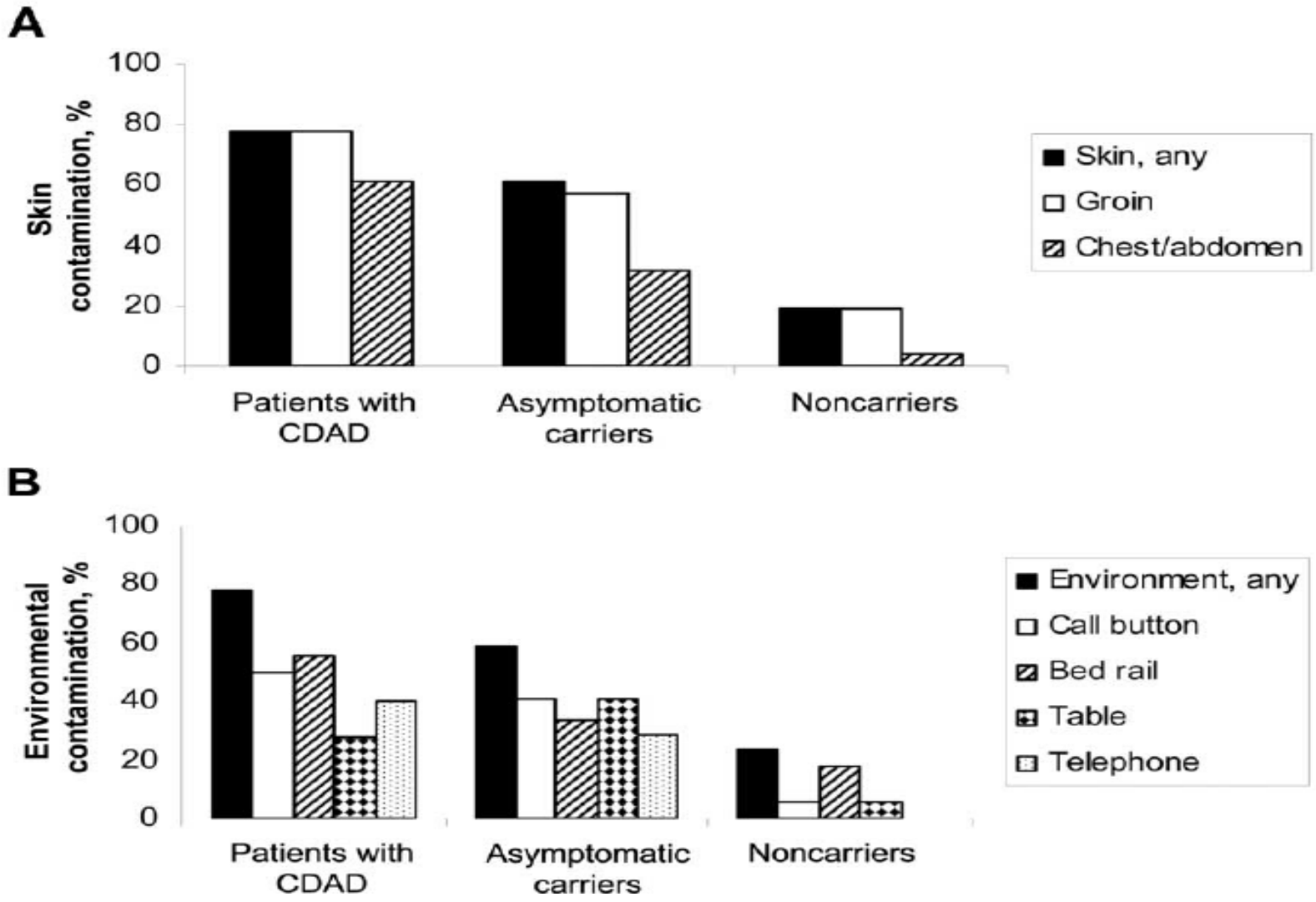
2.75x increase in faecal sample testing (P=0.001)

0.076 CD toxin +ve per day that ward has confirmed cases of viral gastroenteritis

(P=0.02)

Wilcox MH, Fawley WN. *J Hosp Infect* 2007.

CD carriage & contamination



Riggs et al. *Clin Infect Dis* 2008;45:992-8.

BMJ

RESEARCH

Results 7/57 (12%) of the probiotic group developed diarrhoea associated with antibiotic use compared with 19/56 (34%) in the placebo group (P=0.007). Logistic regression to control for other factors gave an odds ratio

'This has the potential to decrease morbidity, healthcare costs, and mortality if used routinely in patients aged over 50.'

(3 to 15). No one in the probiotic group and 9/53 (17%) in the placebo group had diarrhoea caused by *C difficile* (P=0.001). The absolute risk reduction was 17% (7% to 27%), and the number needed to treat was 6 (4 to 14).

antibiotics. Exclusions included diarrhoea on admission, bowel pathology that could result in diarrhoea, antibiotic use in the previous four weeks, severe illness,

and various species of lactobacilli and bifidobacteria.

Diarrhoea associated with antibiotic use and caused by *Clostridium difficile* is a complication of treatment

Potential confounding issues

Actimel study BMJ 2007

- Use of milk based control
- Diagnostic method for CDI cases (PPV 51%)
- Only 7% of screened patients were enrolled (135/1760); 113 followed for evidence of diarrhoea
- Atypical patients: median lengths of hospital stay = 1 & 8.5 d, before and after randomisation. Leeds study: mean length of stay before onset of infective AAD = 29 d.
- Definition of high risk antibiotics
- Few patients exposed to polypharmacy
- 25% of study patients had perioperative prophylaxis
- No data on risk of exposure to CD
- These results CANNOT be extrapolated to routine practice

Wilcox MH, Sandoe JA. *eBMJ* 13 July 2007. http://www.bmj.com/cgi/eletters/335/7610/80

CDI key control measures

- Early warning system to identify changes in local epidemiology
- Reduce risk of transmission
- Isolation/cohorting of patients with diarrhoea
- Environmental cleaning, chlorine
- Hand hygiene soap & water
- Examine/optimise/reduce overall antibiotic use
- Limit high risk agents in high risk patients
- Feedback CDI and antibiotic data on a regular basis