Surveillance and control of *C. difficile* infection (CDI) in UK

Professor Mark Wilcox

Leeds Teaching Hospitals, University of Leeds,

Health Protection Agency

CDI key control measures

- An early warning system to identify changes in local epidemiology: this needs accurate diagnosis
- Increased emphasis on investigation of cases (RCAs) and especially clusters (ribotyping, MLVA)
- Reduce risk of transmission by rapid isolation or cohorting of suspected cases
- Introduction of CDI treatment pathways
- Environmental cleaning using chlorine containing disinfectants
- Hand (and skin) hygiene with soap & water
- Optimised/reduce overall antibiotic use, including restricting high risk agents in high risk patients

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Unless you can see what's going on,
how can you control it ?

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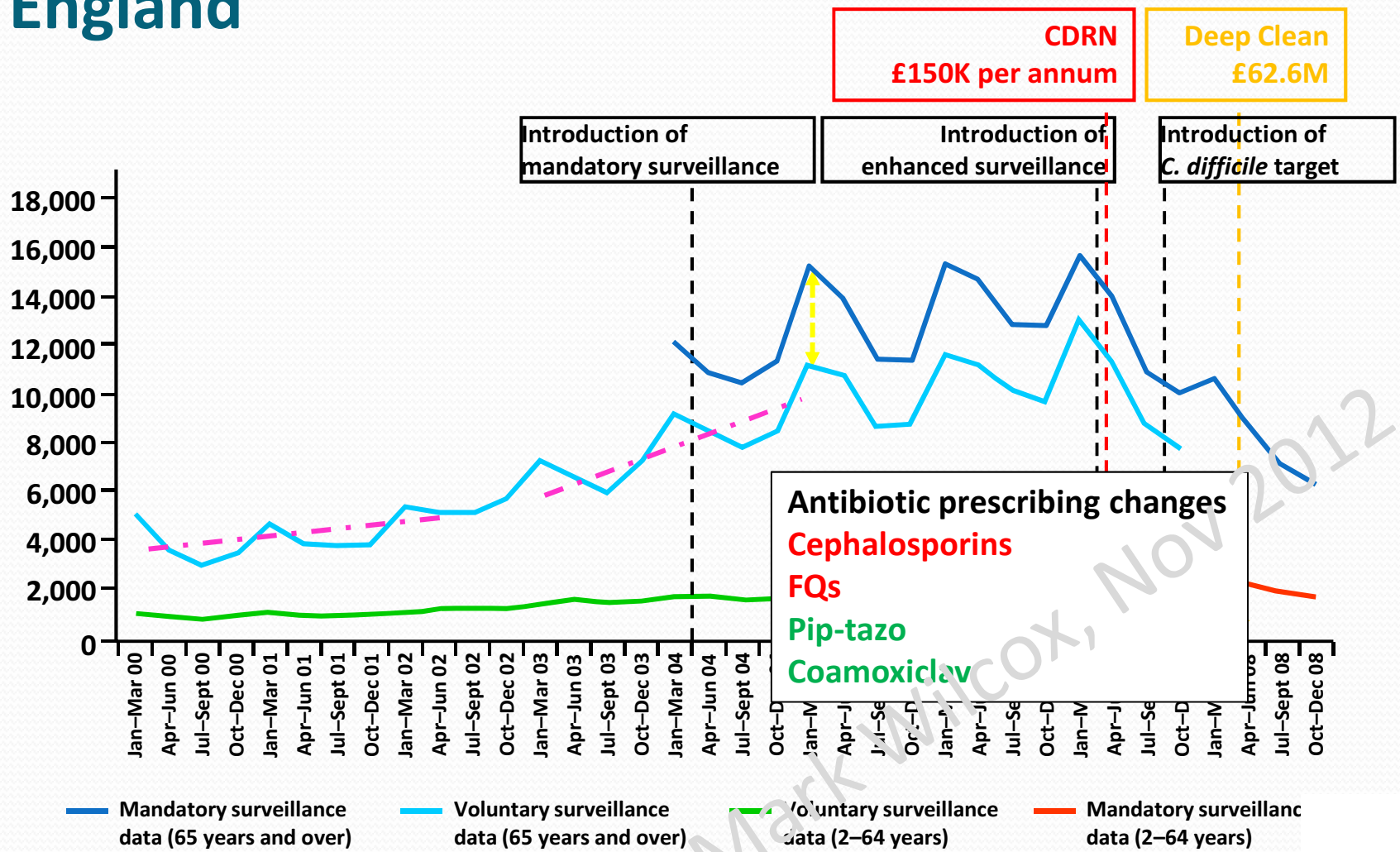
C. difficile Reports and Key Interventions, England



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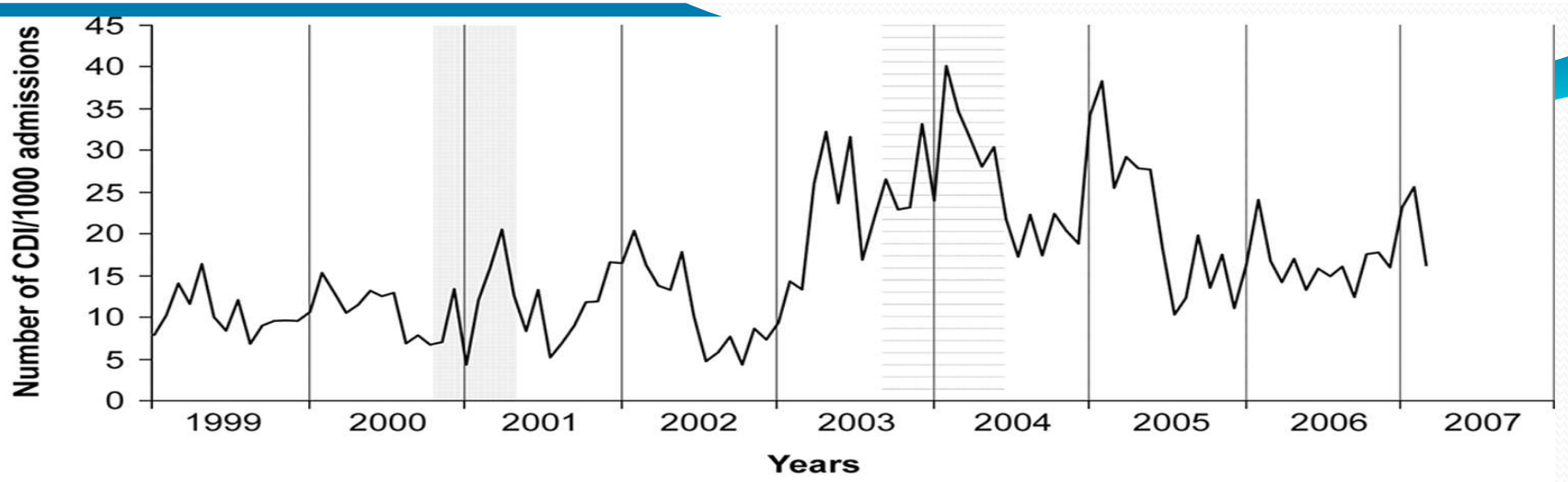
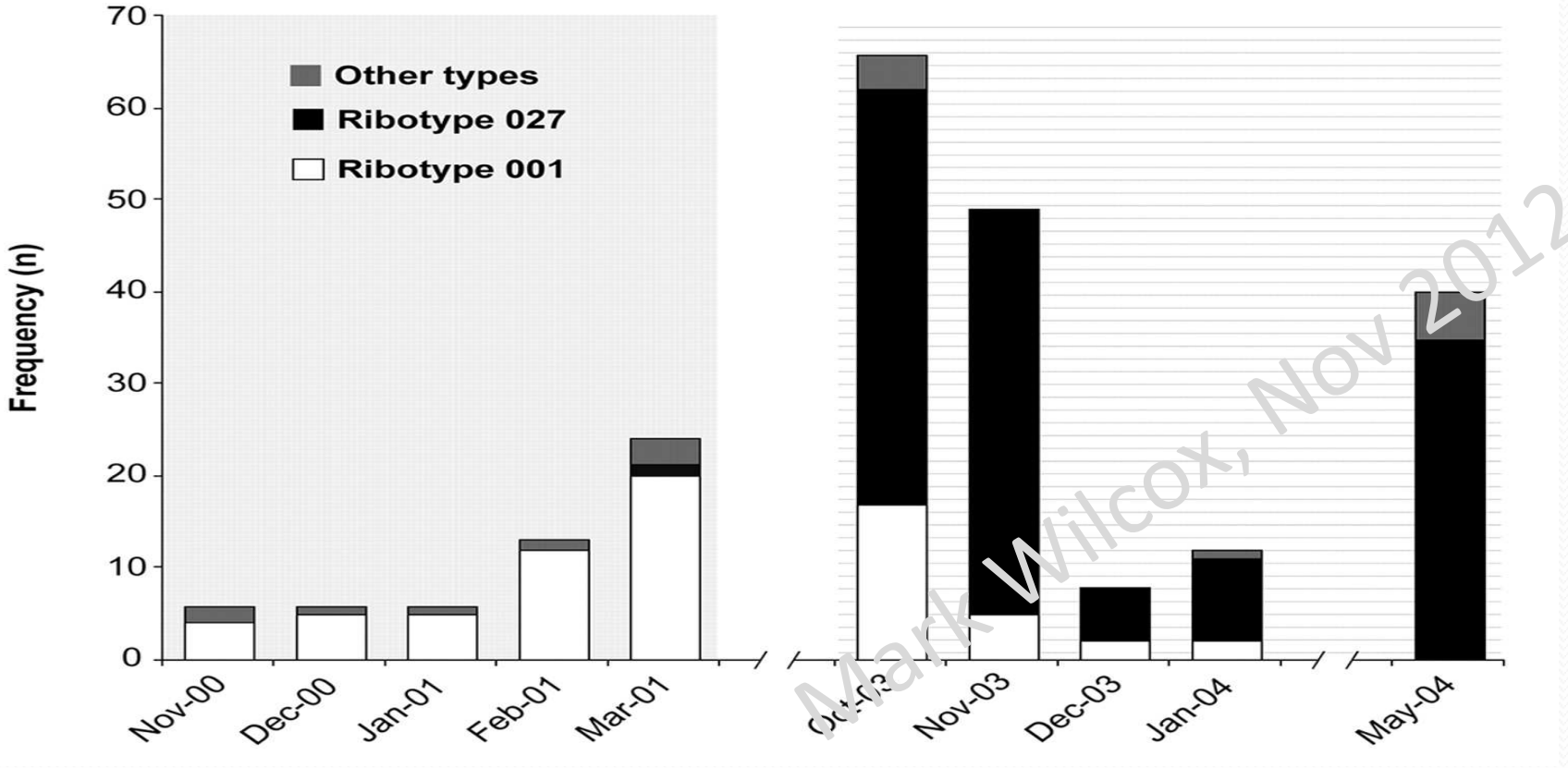
National Audit Office. *Reducing Healthcare Associated Infections in Hospitals in England.* London, England: National Audit Office; 2009.
Copyright © National Audit Office. Table data from the Health Protection Agency.





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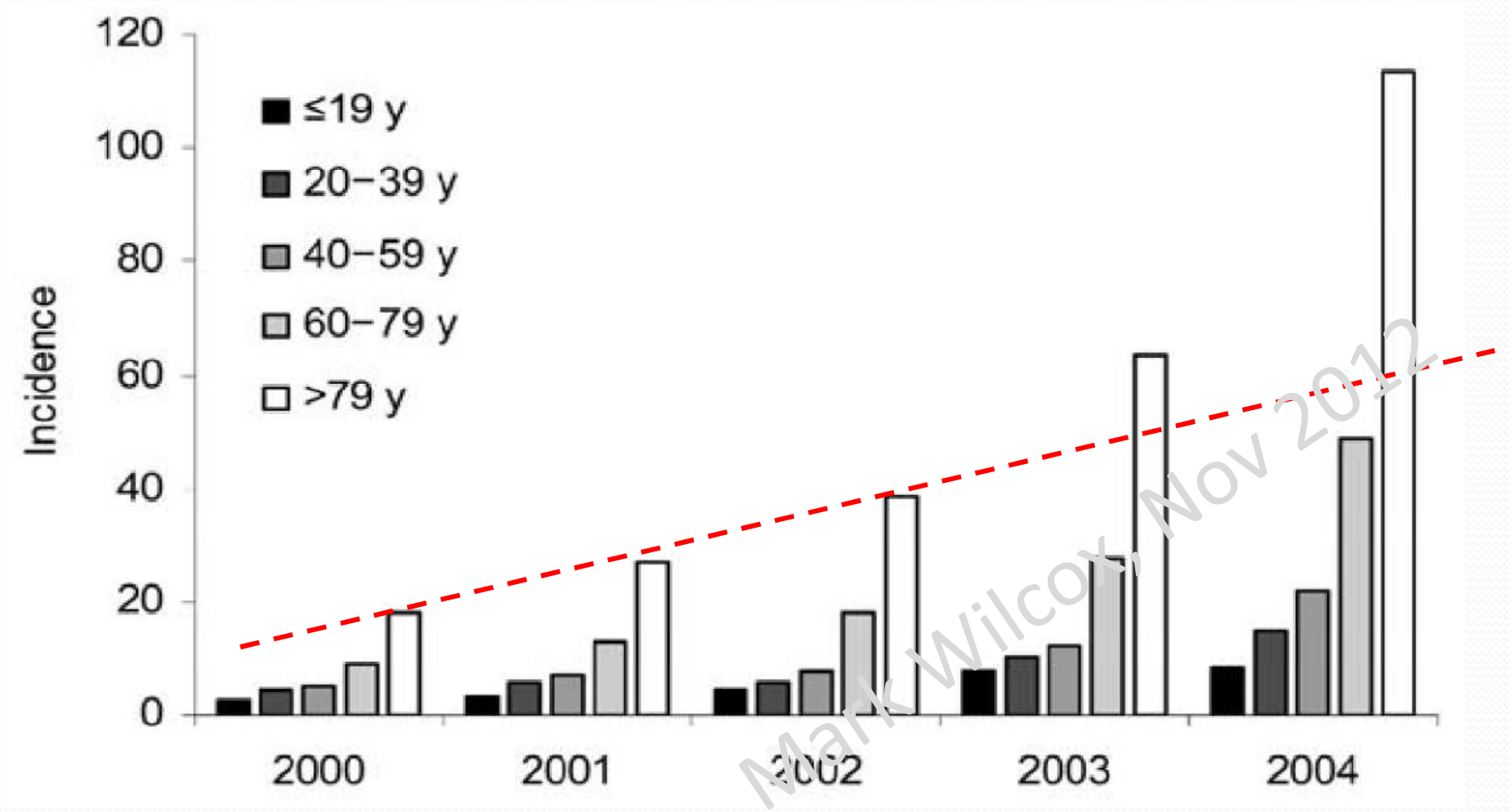
Labbé *et al. Antimicrob Agents Chemother* 2008;52:3180-7.

Incidence of CDAD per 100,000 inpatients (discharge diagnoses) in Germany 2000-2004



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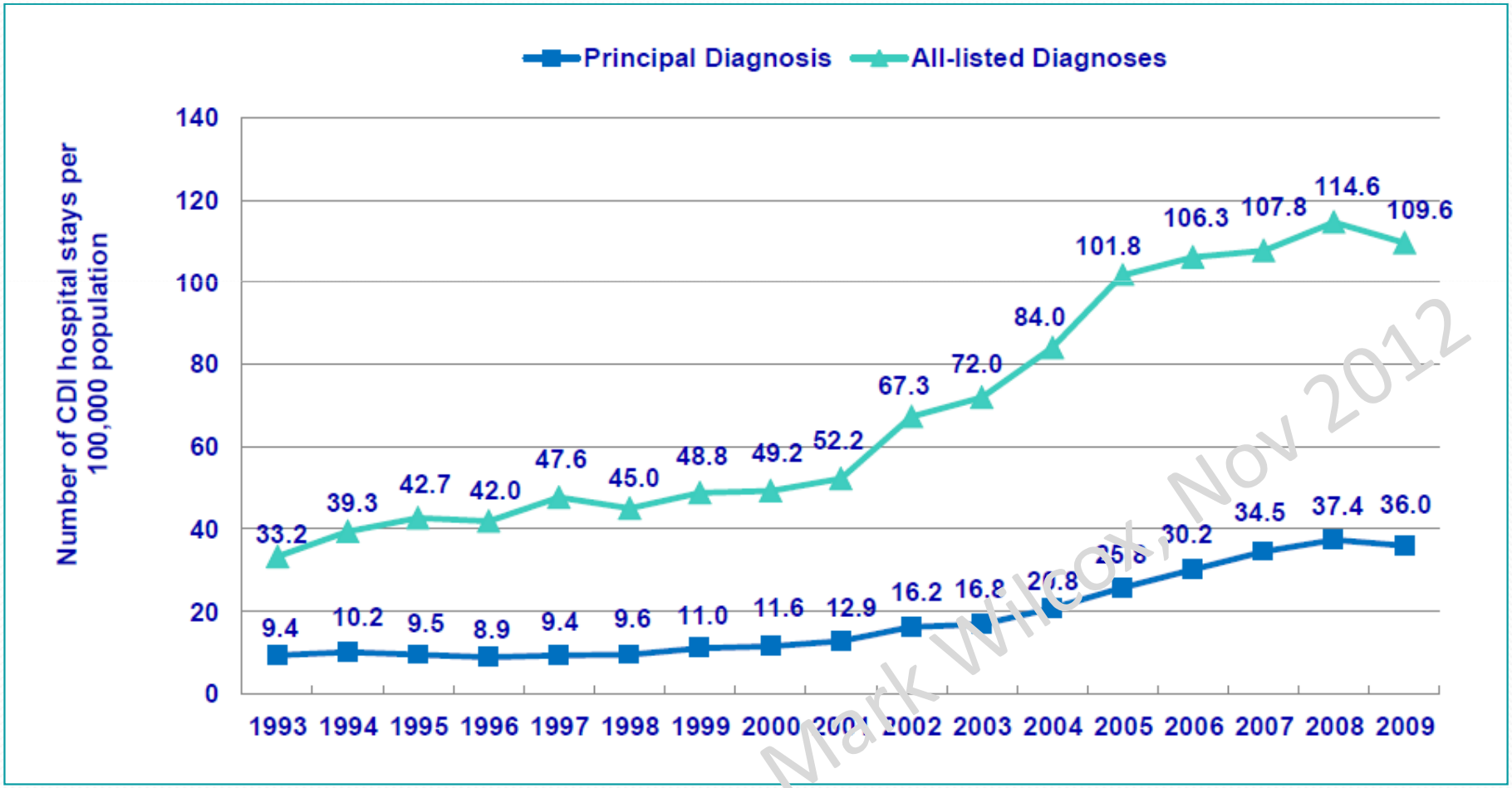
Vonberg RP, *et al*. http://www.cdc.gov/ncidod/eid/13/1/179.htm

Trends in hospital stays associated with CDI

per 100,000 population, USA, 1993–2009



Lucado, J. (Social & Scientific Systems), Gould, C. (CDC), and Elixhauser, A. *HCUP Statistical Brief #124. January 2012. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf*

C. difficile surveillance, England

- All NHS hospitals required to report each CD laboratory positive each month
  - Location, demographics;
  - Risk factor data optional;
  - Root Cause Analysis of cases;
  - Mandatory reduction in CDI rates;
  - DH Improvement Teams; HPA experts
- *C. difficile* Ribotyping Network for England & N.I. (CDRN)
- All *C. difficile* related deaths are recorded

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Key points (i)

- Early warning sytems are vital to identify changes in CDI incidence
- Mandatory reporting of laboratory *C. difficile* positives (and MRSA bacteraemias) has been in place for all NHS hospitals in England since 2004 (and 2001)
- Mandatory reporting is associated with a clear increase in the detection of cases compared voluntary surveillance data
- Targets/objectives were subsequently introduced at both national and institutional levels. More recently these have been 'enhanced' using financial penalties

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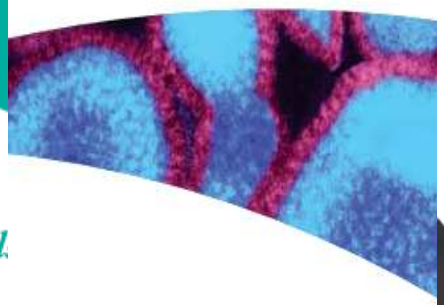
DH Department of Health

National Standards, Local Action

Health and Social Care Sta
and Planning Framework

2005/06–2007/08

DH Department of Health



Winning Ways

Working together to reduce Healthc
Associated Infection in England

Report from the Chief Medical Officer

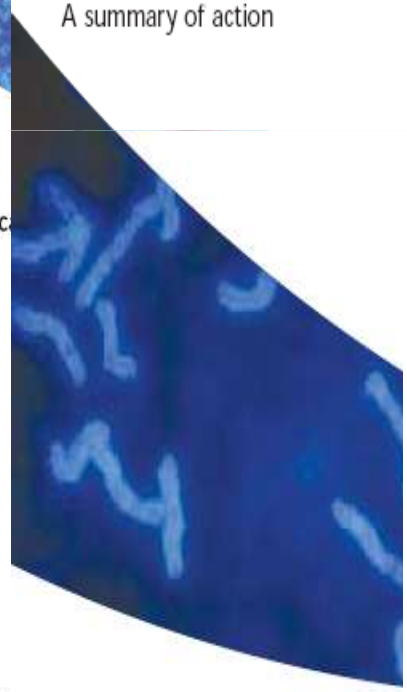
DH Department of Health

NHS

Towards cleaner hospitals
lower rates of infection

A summary of action

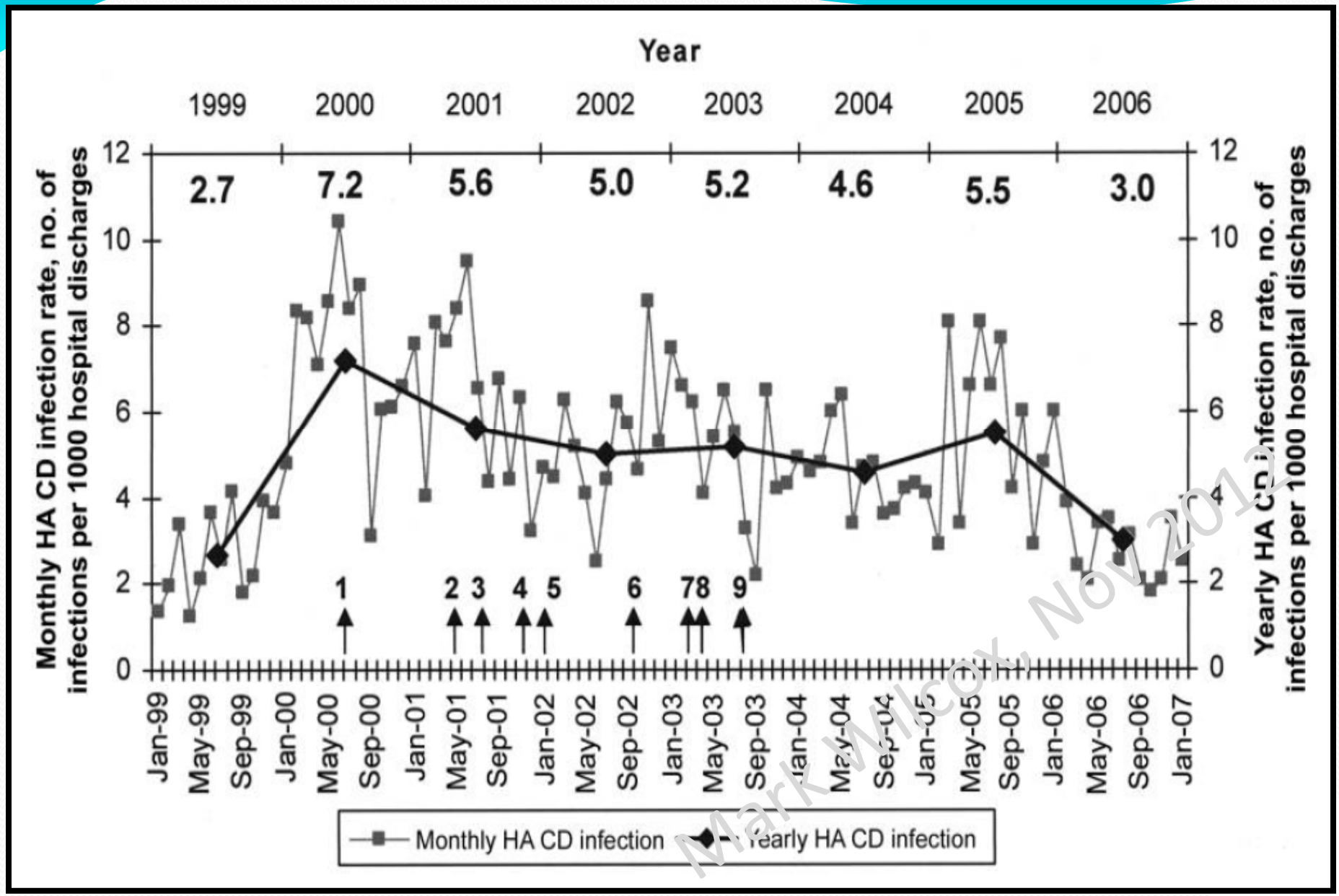
A Matron's Charter:
An Action Plan
for Cleaner Hospitals



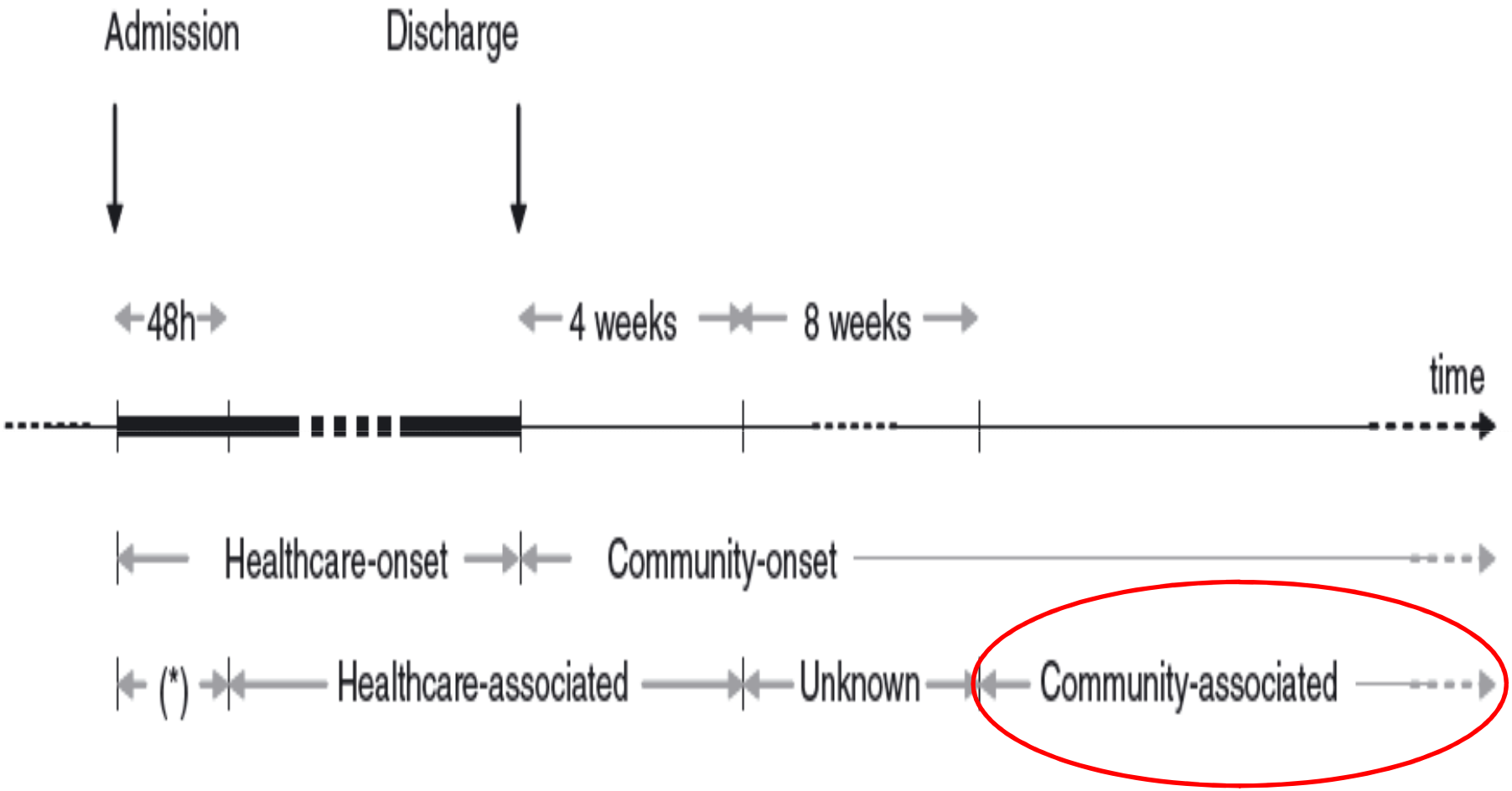








Muto C, *et al*. *Clin Infect Dis* 2007;45:1266-73.



(*) : - may be community- or healthcare-associated, depending on case's history.

- if healthcare-associated, may have been acquired in the same facility or imported from another.

© 2006 Copyright by the European Society of Clinical Microbiology and Infectious Diseases, *CMI*, **12 (Suppl. 6)**, 2–18

CDI in the community

- **A large proportion of community CDI cases do not have a recent history of antibiotic use or hospital admission**

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

- Some 'community' cases are clearly potentially related to healthcare
  clearer data
- Poorly understood causes
  community focussed surveillance and studies
- How many cases are missed in the community (10?:1)?
  increased submission/testing
- Relevance to care/nursing homes
  community focussed surveillance and studies
- Are community cases managed optimally?
  better communication to GPs

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Key points (ii)

- Very large decreases in the incidences of MRSA bacteraemias (>70%) and *C. difficile* (>70%) occurred following the introduction of mandatory surveillance and target/objective setting
- Have not proven which were the key interventions responsible for these marked reductions in HCAI
- Comparing what introductions occurred when in different institutions may help to determine the key interventions
- We know very little about community CDI

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CDI key control measures

- An early warning system to identify changes in local epidemiology: this needs accurate diagnosis
- Increased emphasis on investigation of cases (RCAs) and especially clusters (ribotyping, MLVA)
- Reduce risk of transmission by rapid isolation or cohorting of suspected cases
- Introduction of CDI treatment pathways
- Environmental cleaning using chlorine containing disinfectants
- Hand (and skin) hygiene with soap & water
- Optimised/reduce overall antibiotic use, including restricting high risk agents in high risk patients

Which samples are sent for testing ?

Some... which ones... all

Which tests are used ?

Good... bad... ugly

Which positives are reported ?

Some... which ones... all

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Algorithm for Management of Patient with Unexplained Diarrhoea

Suspected Clostridium difficile infection (CDI)

If a patient has diarrhoea (Bristol Stool Chart types 5-7) that is not clearly attributable to an underlying condition (e.g. inflammatory colitis, overflow) or therapy (e.g. laxatives, enteral feeding) then it is necessary to determine if this is due to CDI. If in doubt please seek advice.

This pathway relates to the diagnosis of CDI. Patients should be considered for treatment of CDI *before* test results are available, particularly if symptoms / signs indicate severe infection. Patients with suspected infectious diarrhoea should be isolated to prevent the transmission of *C. difficile*, norovirus or other transmissible pathogens.

Ideally isolate patient in a single room - if unable to do this within 2 hours escalate the problem.

Collect stool specimen & send to Microbiology
In order for the specimen to be processed for *C. difficile* the sample must take on the shape of the container and ideally be at least ¼ filled (to indicate the patient has diarrhoea).

Diarrhoeal samples should be tested for *C. difficile* from:

- hospital patients aged >2 years, and
- community patients aged ≥65 years, and
- community patients aged <65 years whenever clinically indicated.

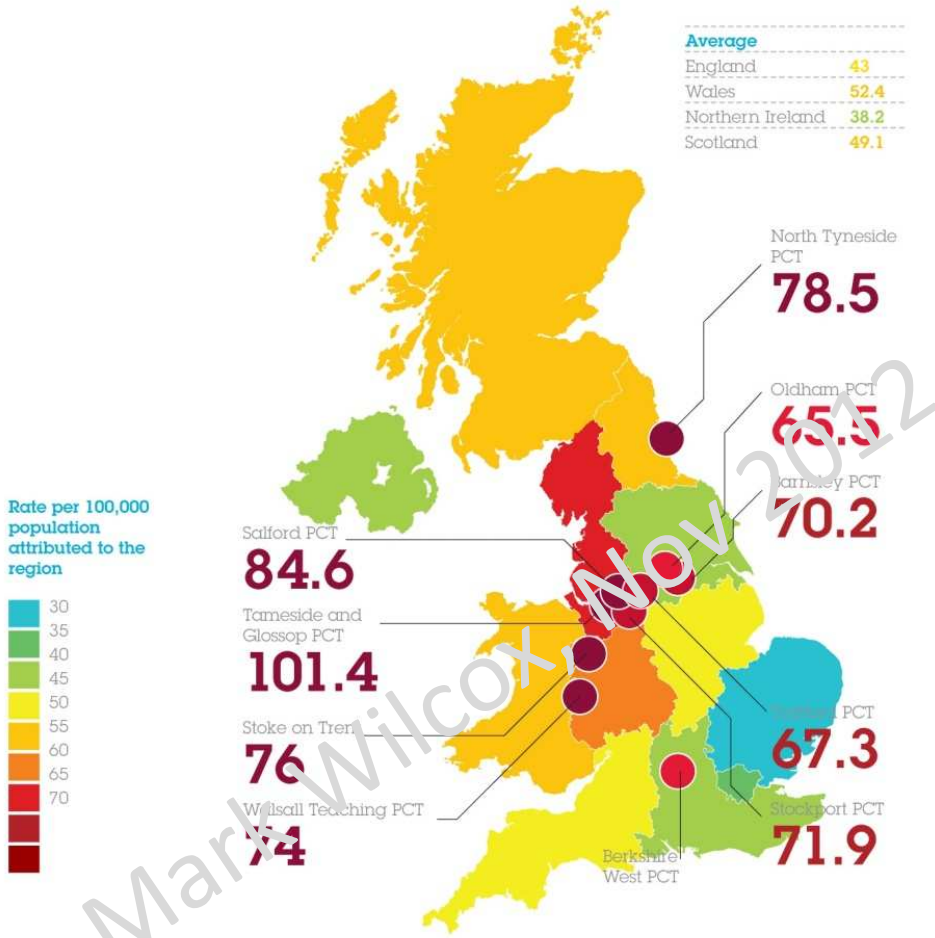
Correlation between frequency of CDI testing and measured CDI incidence

(ECDIS Study, Nov 2008.) Bauer MP et al. Lancet 2011;377:63–73.

Variation in CDI rates - real or fiction?

CDI rates vary widely between hospitals

- may reflect the gap between the best and worst performers
- **and/or** the accuracy of diagnosis and reporting



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CDI laboratory diagnosis

Target	Testing method
C. difficile toxin	Cell cytotoxicity assay*
	Immunoassays (EIA & membrane)
C. difficile	Culture
	Antigen (GDH) detection
Toxigenic *C. difficile*	Cytotoxigenic culture*
	PCR

***Reference test methods detect different targets and are NOT directly comparable**

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Results of *C. difficile* testing according to reference methods

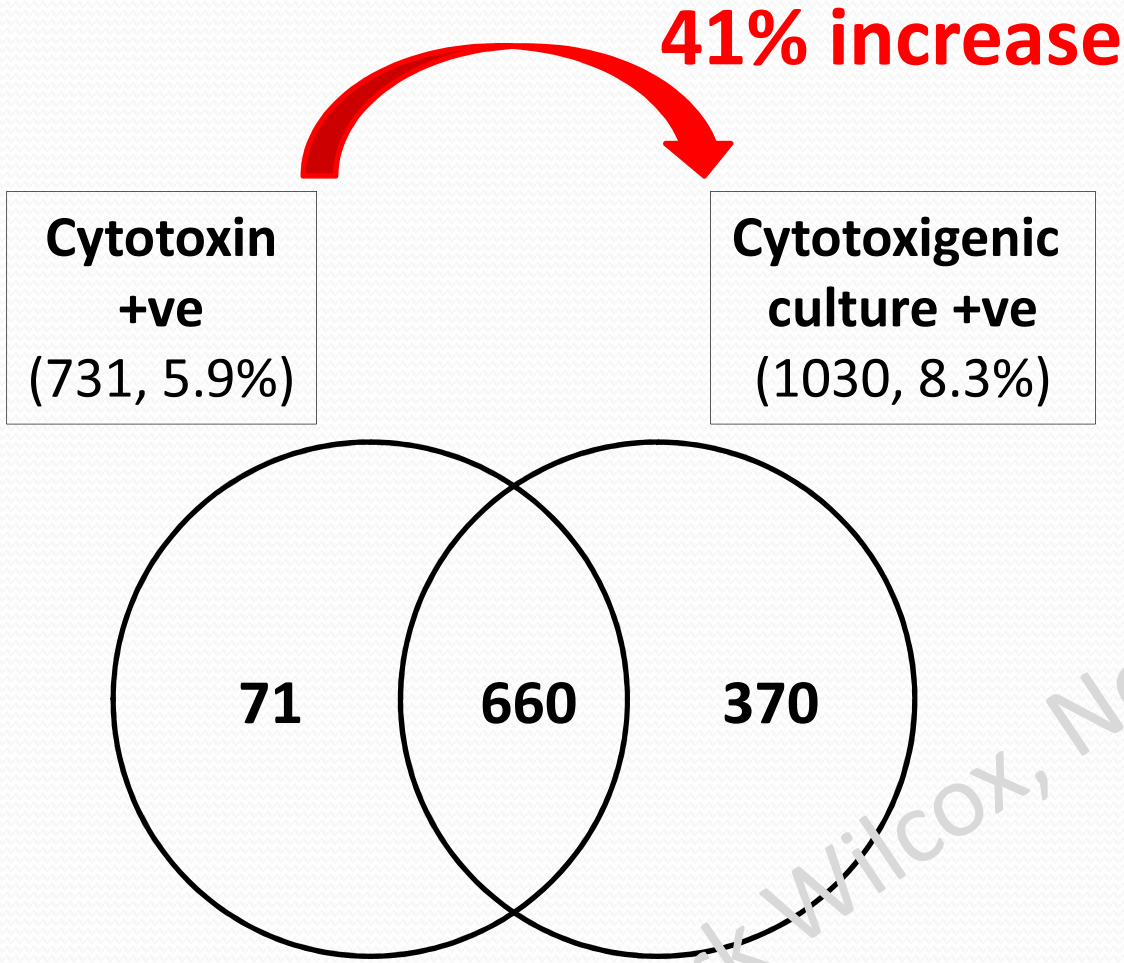

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Planche TD et al. Clinical validation of *C. difficile* infection diagnostics: importance of toxin detection. 52nd ICAAC, 2012. Abstract D-160.

The more you test, the more you find

“We introduced PCR testing and our CDI rate went up.”

“No, it didn’t. The CDI rate stayed the same; you just issued more positive results.”

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GDH EIA (or NAAT) positive, toxin EIA (or cytoxin) positive:
CDI is likely to be present
→ **for mandatory reporting to HPA**

or

GDH EIA (or NAAT) positive, toxin EIA negative:
C. difficile could be present i.e. potential *C. difficile* excretor
→ **not for mandatory reporting**
(but may have transmission potential and be suitable for local reporting)

or

GDH EIA (or NAAT) negative, toxin EIA negative:
C. difficile or CDI is very unlikely to be present
→ **not for mandatory reporting**
but may have transmission potential (other pathogens)

Refer to the following local policies:

- Remember the **SIGHT** list
- *Clostridium difficile* Policy
- *Clostridium difficile* Treatment Guideline
- Source Isolation Policy
- Source Isolation Cleaning Policy

Consider other causes of diarrhoea
Consider continuation of single room isolation and other measures to reduce risk of CDI

Consider other causes of diarrhoea; if not infective may consider ending single room isolation

Algorithm for Management of a Patient with Unexplained Diarrhoea

Suspected Clostridium difficile infection (CDI)

If a patient has diarrhoea (Bristol Stool Chart types 5-7) that is not clearly attributable to an underlying condition (e.g. inflammatory colitis, overflow) or therapy (e.g. laxatives, enteral feeding) then it is necessary to determine if this is due to CDI. If in doubt please seek advice.

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Diarrhoeal samples should be tested for *C. difficile* from:
- hospital patients aged ≥2 years, and,
- community patients, aged ≥65 years, and
- community patients aged <65 years wherever clinically indicated.

GDH EIA (or NAAT) positive, toxin EIA or cytotoxin positive:
CDI is likely to be present,
- *for mandatory reporting to HPA;**

OR

GDH EIA (or NAAT) positive, toxin EIA negative:
C. difficile could be present i.e. potential *C. difficile* excretor,
- *not for mandatory reporting (but may have transmission potential and be suitable for local reporting);*

OR

GDH EIA (or NAAT) negative, toxin EIA negative: *C. difficile* or CDI is very unlikely to be present,
- *not for mandatory reporting but may have transmission potential (other pathogens)*

→ **Refer to the following local policies:**
- Remember the SIGHT list (see bottom of page)
- *Clostridium difficile* Infection Policy
- *Clostridium difficile* Treatment Guideline
- Source Isolation Policy
- Source Isolation Cleaning Policy
- Inform patient, relative/carer of test result

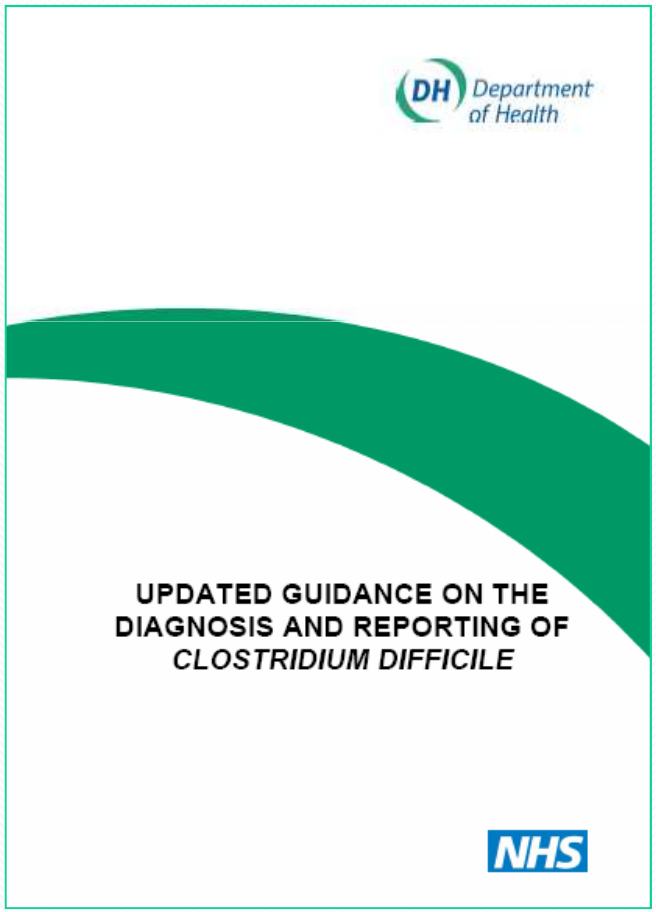
→ Consider other causes of diarrhoea.
Consider continuation of single room isolation and other measures to reduce risk of CDI.

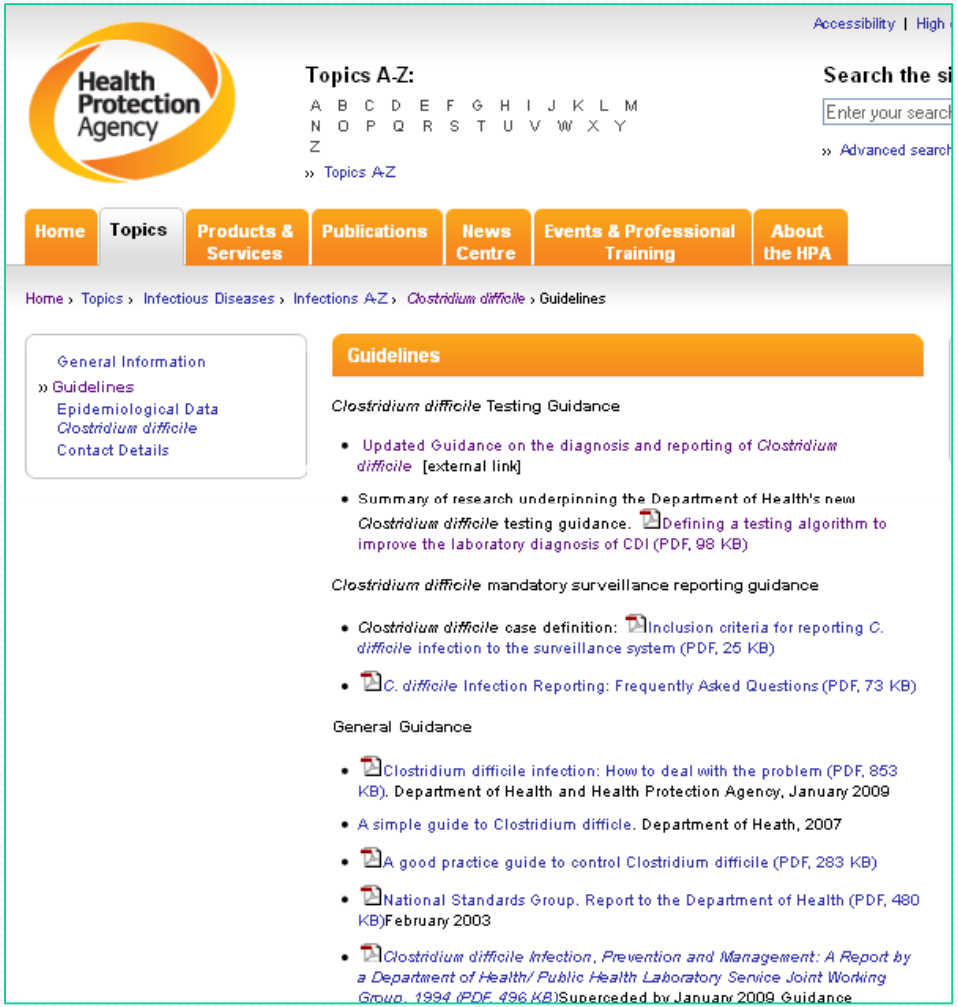
→ Consider other causes of diarrhoea; if not infective may consider ending single room isolation.

* Please note other indications for mandatory reporting of CDI at:
http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1179746915068
NB: A cytotoxin assay may be considered as an alternative to a sensitive toxin EIA, but it yields slower results and this will need to be taken into account when making management decisions on infection control.

S	Suspect that a case may be infective when there is no clear alternative cause for diarrhoea
I	Isolate the patient within 2 hours
G	Gloves and aprons must be used for all contacts with the patient and their environment
H	Hand washing with soap and water should be carried out before and after each contact with the patient and the patient's environment
T	Test the stool for *C. difficile* by sending a specimen immediately

http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/ClostridiumDifficile/Guidelines/





http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_133016.pdf

Wilcox, Planche, Crook, Shetty, Davies, Coen, et al. 2012.

Key points (iii)

- Laboratory testing
  - The more you test, the more you find
  - The two CD testing reference methods do not have the same clinical implications
  - Toxin (CTA) positive samples are associated with increased mortality. This is not true if only toxigenic strains (CC) are present
  - Results support CDI being defined by a positive toxin test
  - Use of a high sensitivity screening test (GDH or toxin gene PCR) can rapidly identify who may have CDI, but a second (toxin) test is needed to provide specificity

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CDI key control measures

- An early warning system to identify changes in local epidemiology: this needs accurate diagnosis
- Increased emphasis on investigation of cases (RCAs) and especially clusters (ribotyping, MLVA)
- Reduce risk of transmission by rapid isolation or cohorting of suspected cases
- Introduction of CDI treatment pathways
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Clinical Infectious Diseases Advance Access published August 3, 2012

MAJOR ARTICLE

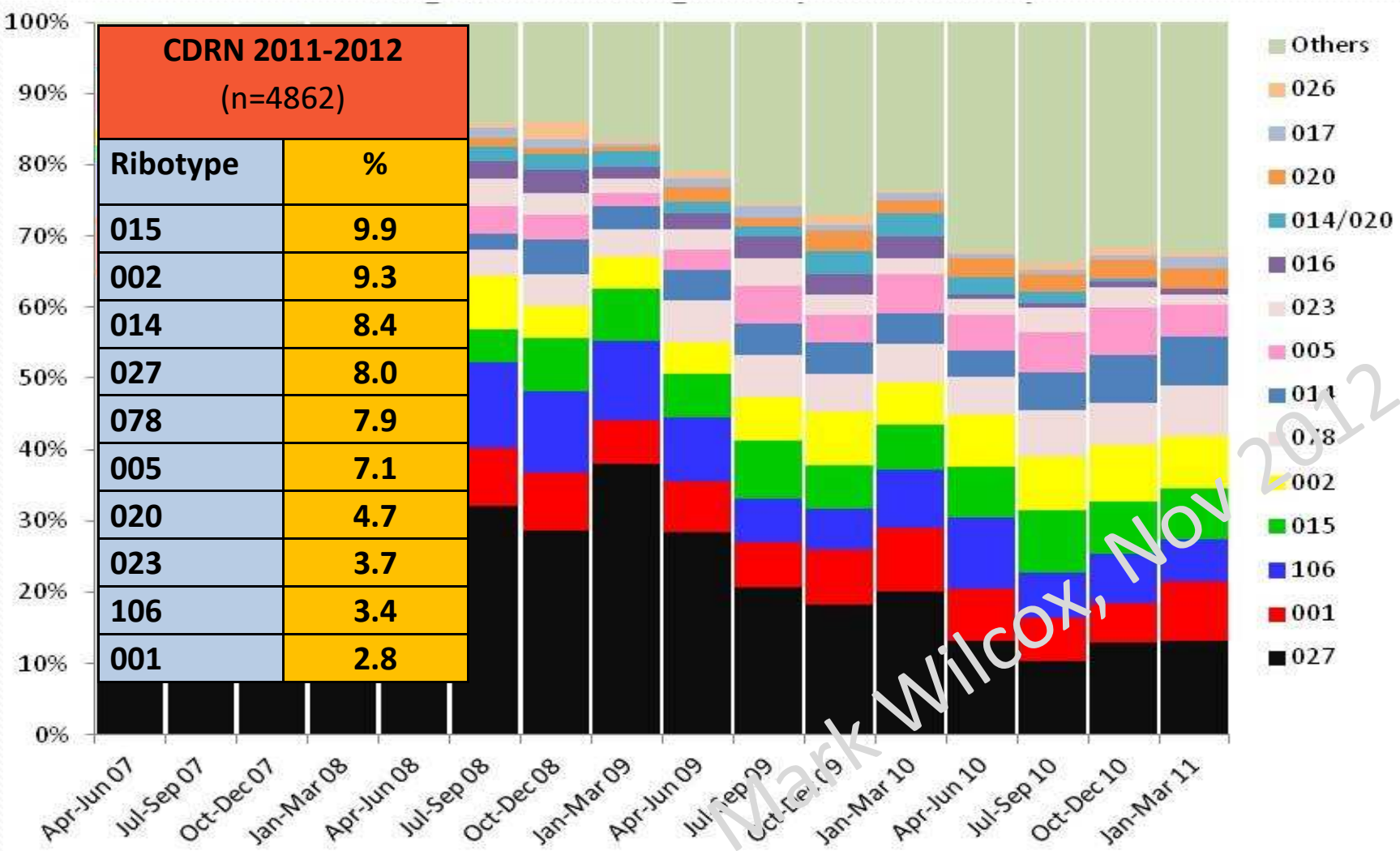
Changing Epidemiology of *Clostridium difficile* Infection Following the Introduction of a National Ribotyping-Based Surveillance Scheme in England

M. H. Wilcox,[1] N. Shetty,[2] W. N. Fawley,[1] M. Shemko,[2] P. Coen,[2] A. Birtles,[3] M. Cairns,[4] M. D. Curran,[5] K. J. Dodgson,[3] S. M. Green,[6] K. J. Hardy,[7] P. M. Hawkey,[7] J. G. Magee,[8] A. D. Sails,[8] and M. W. D. Wren[2]

[1]Department of Microbiology, Leeds Teaching Hospitals Trust and University of Leeds; [2]Health Protection Agency Collaborating Centre at Department of Clinical Microbiology, University College London Hospitals NHS Foundation Trust; [3]North West Regional Health Protection Agency Laboratory, Manchester; [4]Public Health Laboratory London, Health Protection Agency, Division of Infection, The Royal London Hospital; [5]Health Protection Agency Public Health Laboratory, Addenbrooke's Hospital, Cambridge; [6]Health Protection Agency South East, Southampton Laboratory, Southampton General Hospital; [7]Public Health Laboratory, Heart of England NHS Foundation Trust, Birmingham; and [8]Health Protection Agency Public Health Laboratory Newcastle, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom

Changing Distribution of Most Common *C. difficile* Ribotypes in England

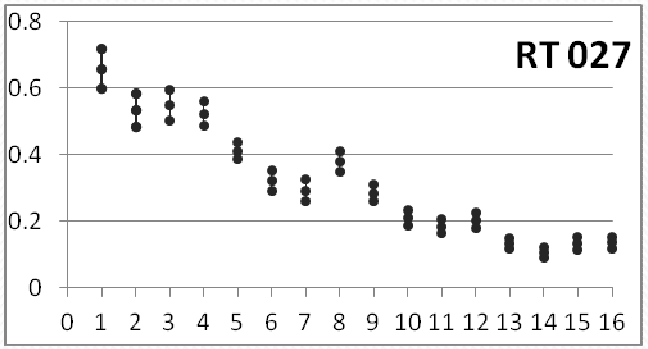
Apr 2007–Mar 2011

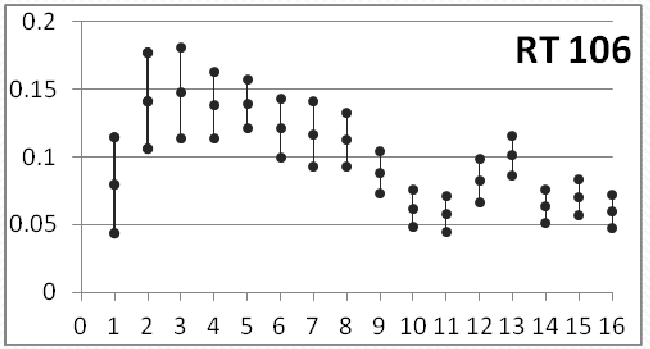


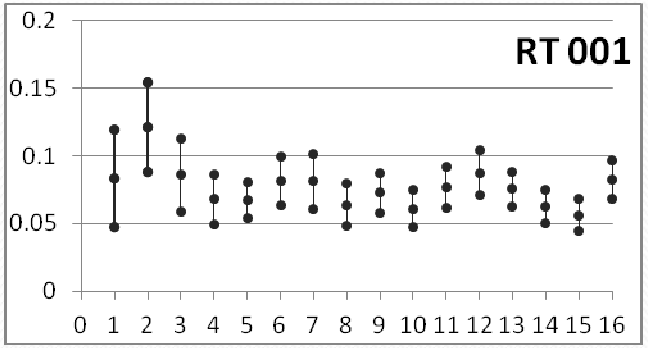
Trends in the quarterly rates (proportions) of most frequently identified *C. difficile* ribotypes in England

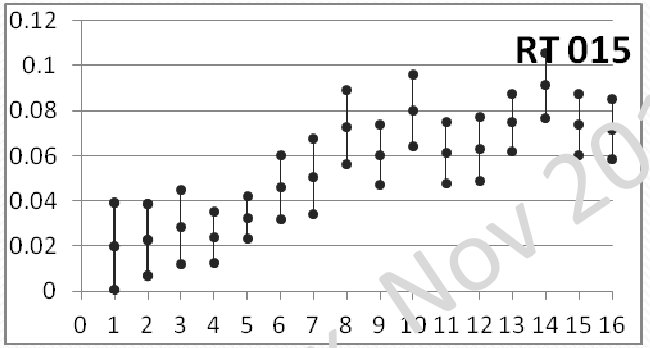
(April 2007 – March 2011)

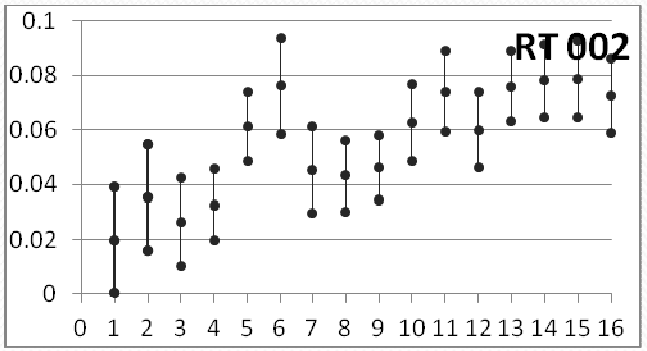
Rate (proportion of total during period)

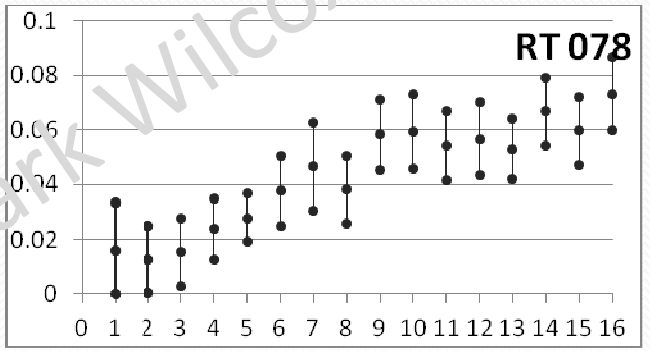












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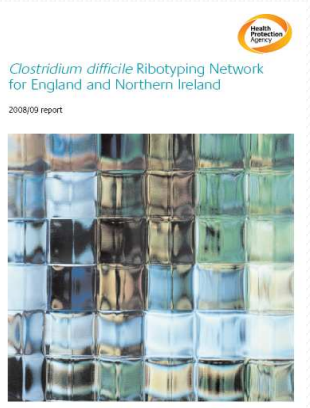
CDI outcome - CDRN database

- 30-day all-cause mortality was 20.3% in those who responded to this question (n = ~2000)



Variable	2008–10		2008–9		2009–10	
	OR	P-value	OR	P-value	OR	P-value
Age > 60 vs ≤60 years	2.78	<0.001	2.53	0.018	3.06	0.001
Fluoroq. (taken vs not)	1.57	0.051	1.08	0.853	1.91	0.024
Had surgery vs not	17.6	<0.001	87.9	<0.001	0.746	0.606
Yorkshire & H. vs other	0.513	0.023	0.198	0.005	0.792	0.512
Severe CDI	4.89	<0.001	5.41	<0.001	6.06	<0.001
027 vs other ribotypes	1.99	<0.001	1.91	0.004	1.85	<0.001

OR = odds ratio

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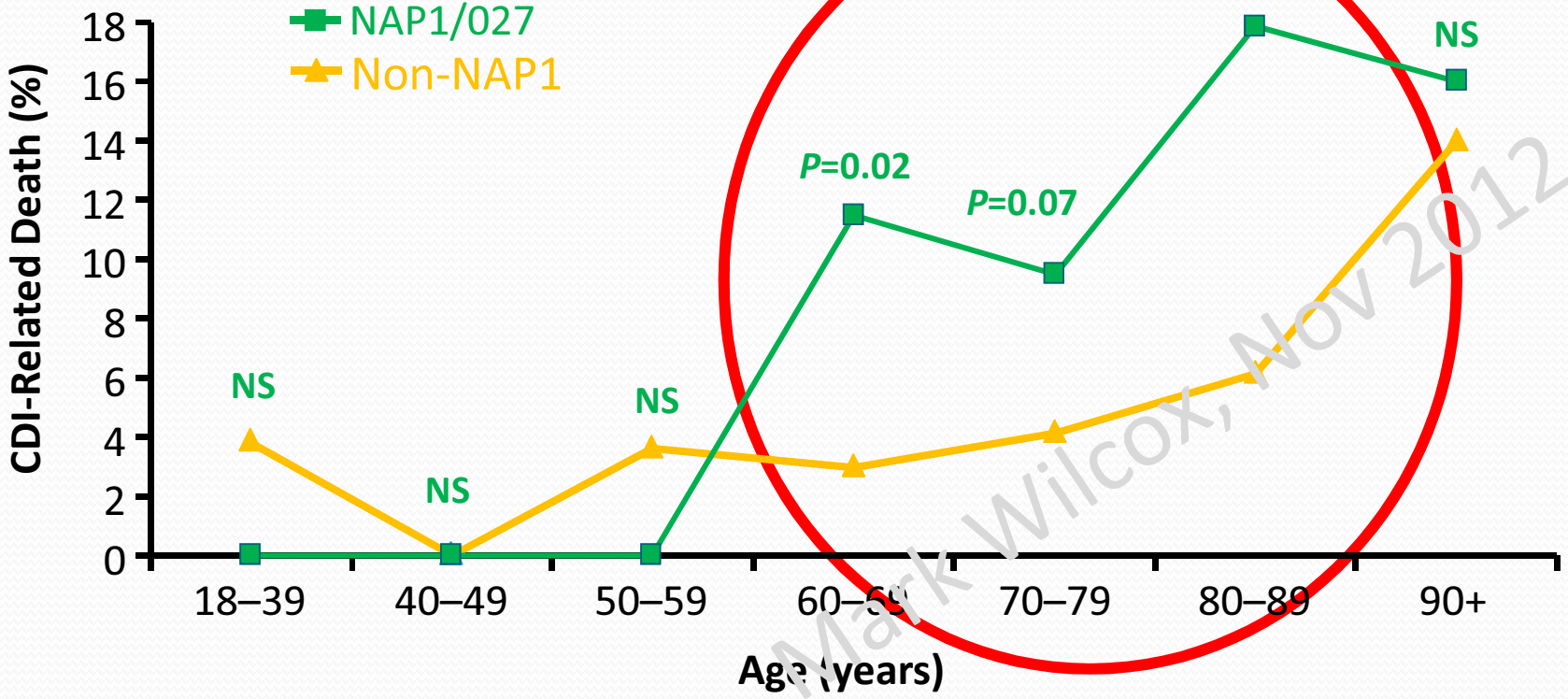
http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1258560554236

Strain ribotype & risk of CDI-related death

n=1008 CDI cases

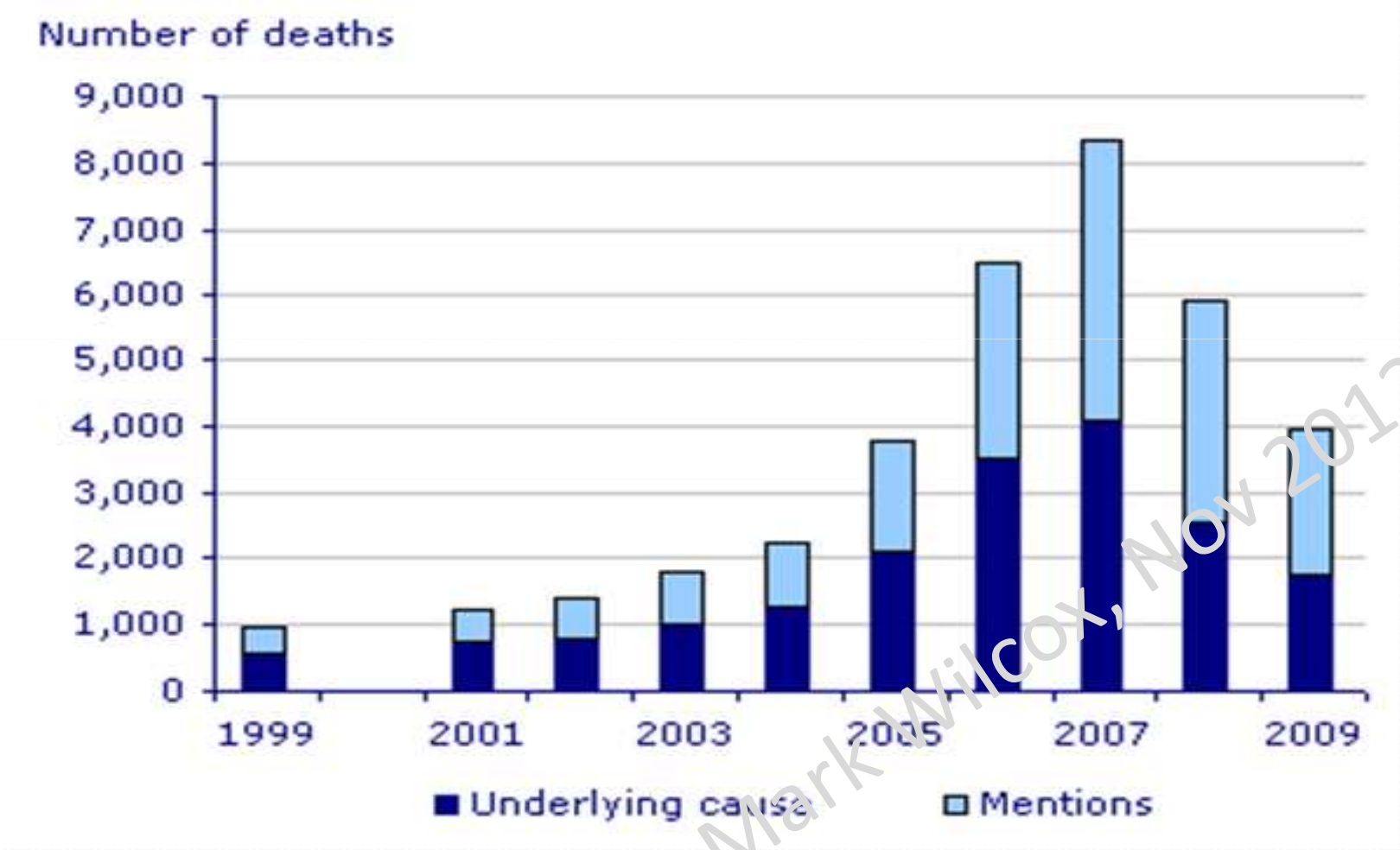
CD 027 infection associated with 2.5–3.5-fold increased death rate



Mark Wilcox, Nov 2012

Miller M et al. *Clin Infect Dis.* 2010;50:194.

Numbers of death certificates mentioning *C. difficile* England & Wales, 1999-09



Mark Wilcox, Nov 2012

Office for National Statistics on deaths involving *Clostridium difficile* in England & Wales.
http://www.statistics.gov.uk/cci/nugget.asp?id=1735

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2011, p. 4333–4337 Vol. 49, No. 12
0095-1137/11/$12.00 doi:10.1128/JCM.05873-11
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An Enhanced DNA Fingerprinting Servi To Investigate Potential *Clostridium difficile* Infection Case Clusters Sharing the Same PCR Ribotype[▽]

Warren N. Fawley[1] and Mark H. Wilcox[1,2]* on behalf of the *Clostridium difficile* Ribotyping Network for England and Northern Ireland

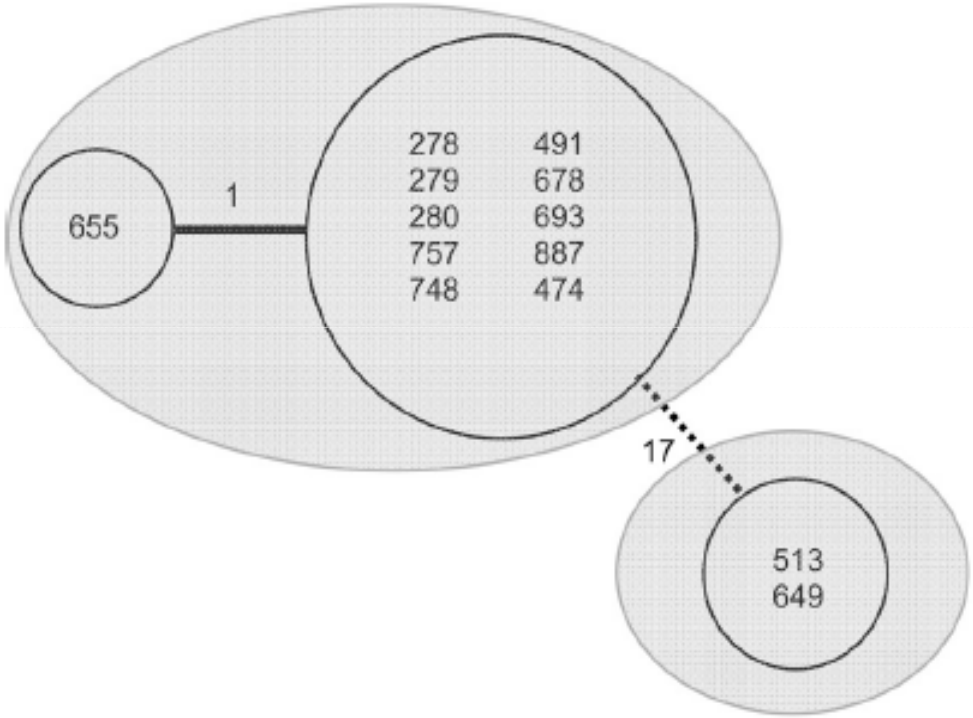
Department of Microbiology, The General Infirmary, Old Medical School, Leeds LS1 3EX, United Kingdom,[1] and Leeds Institute of Molecular Medicine, University of Leeds, Leeds LS2 9JT, United Kingdom[2]

MLVA fingerprinting to investigate ribotype clusters

- 53 clusters, 2-41 patients, 286 isolates, 27 institutions
- 19% comprised unrelated isolates
- 34% comprised a mixture of related & distinct
- CD 027 significantly more likely to be associated with transmission
- **Value of highly discriminatory fingerprinting to confirm or refute CDI transmission**

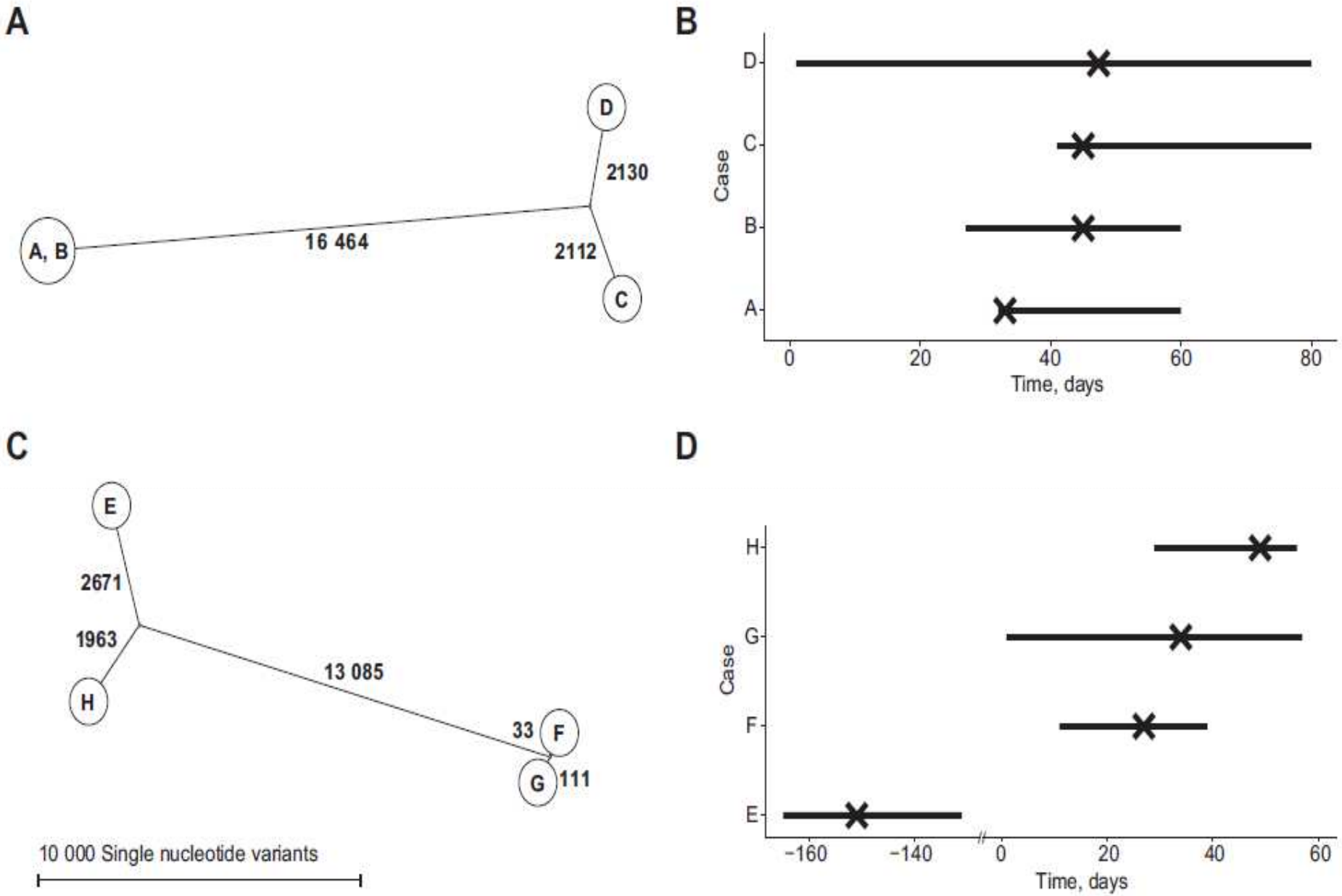
Mark Wilcox, Nov 2012

Fawley WN, Wilcox MH. *J Clin Microbiol* 2011;49:4333-7.



Isolate	Patient location at time sample submitted (Hosp, Ward)	Date of cytotoxin-positive faecal specimen
280	1, B	July 09
278	1, C	August 09
279	1, A	August 09
513	1, E	October 09
649	1, B	November 09
757	1, F	November 09
748	1, A	November 09
474	1, G	January 10
491	2, H	January 10
678	2, H	January 10
655	2, H	February 10
693	2, J	February 10
887	2, J	February 10

Fawley WN, Wilcox MH. *J Clin Microbiol* 2011;49:4333-7.



Eyre DW, Golubchik T, Gordon NC, et al. A pilot study of rapid benchtop sequencing of *S. aureus* and *C. difficile* for outbreak detection and surveillance. BMJ Open 2012; 2 (3).

Key points (v)

- Investigation of clusters / transmission
  - Some *C. difficile* types are clearly associated with worse outcome
  - Need for access to CD typing / more discriminatory methods to investigate suspected clusters and routes of transmission
  - We focus current efforts on linking known CDI cases
  - What about unknown 'cases/donors/excretors' ?
  - Potential of whole genome sequencing

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CDI key control measures

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Extent of *C. difficile* environmental contamination

Date	Sample	Ribotype	MLVA type
17/02/2009	**Air (12.50)**	106	24-14-23-2-6-4-2
	Bed	106	24-14-22-2-6-4-2
	Table	106	24-14-22-2-6-4-2
	Sink	106	24-14-22-2-6-4-2
	Bin	106	24-14-22-2-6-4-2
	Commode	106	24-14-22-2-6-4-2
	Floor	106	24-14-22-2-6-4-2
18/02/2009	Bed	106	24-14-22-2-6-4-2
	Table	106	24-14-22-2-6-4-2
	Commode	106	24-14-22-2-6-4-2
	Air (11.40)	106	24-14-22-2-6-4-2
	Air (12.40)	106	24-14-22-2-6-4-2
25/02/2009	**Air (11.10)**	106	24-14-22-2-6-4-2
	Air (15.45)	106	24-14-22-2-6-4-2
	Bed	106	24-14-22-2-6-4-2
	bin	106	24-14-22-2-6-4-2
	walking frame	106	24-14-22-2-6-4-2
	stool	106	24-14-22-2-6-4-2

Best , Fawley, Parnell, Wilcox. *Clin Infect Dis* 2010.

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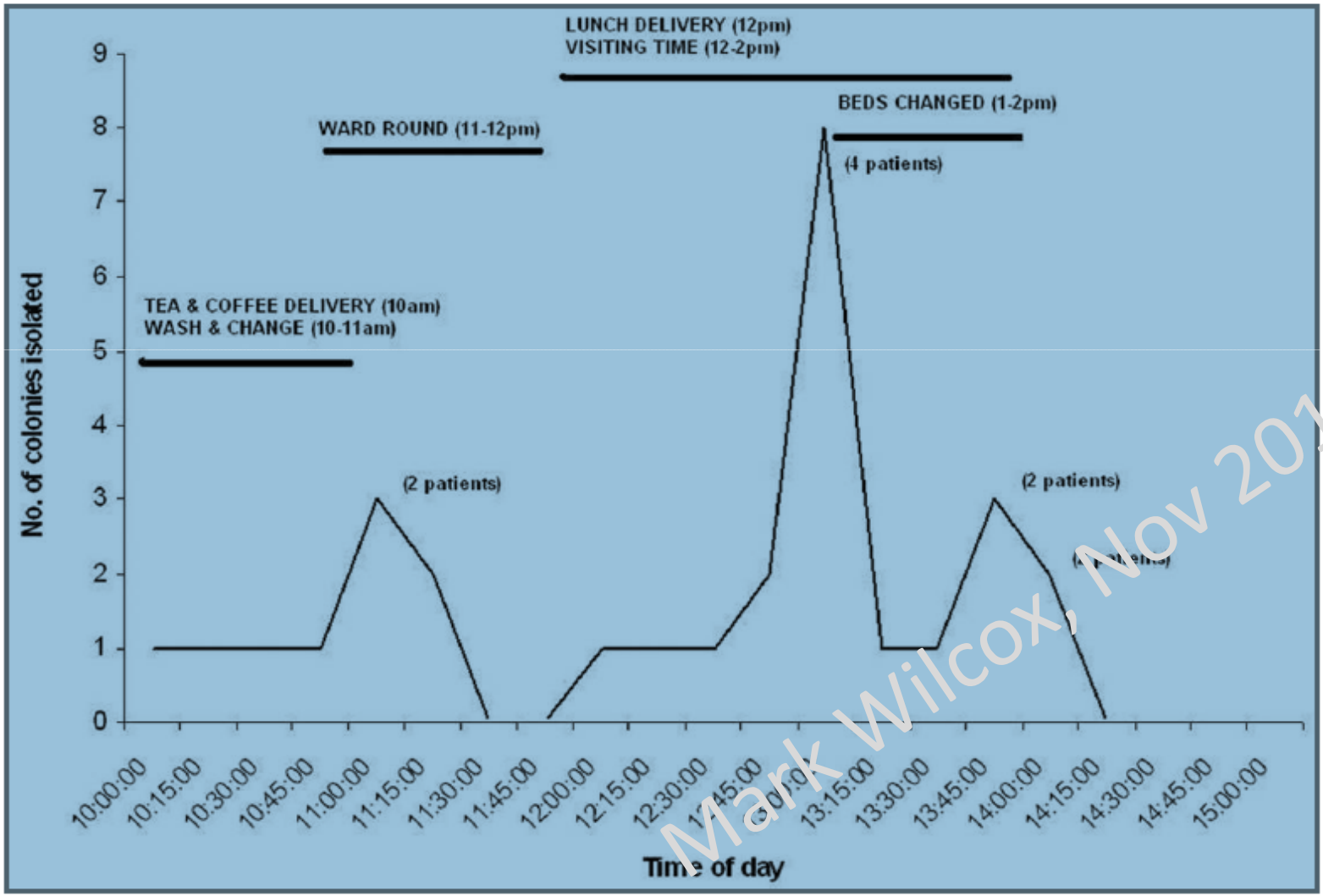
Airborne *C. difficile* total number of *C. difficile* colonies recovered throughout the day (10 patients tested for 2 days)



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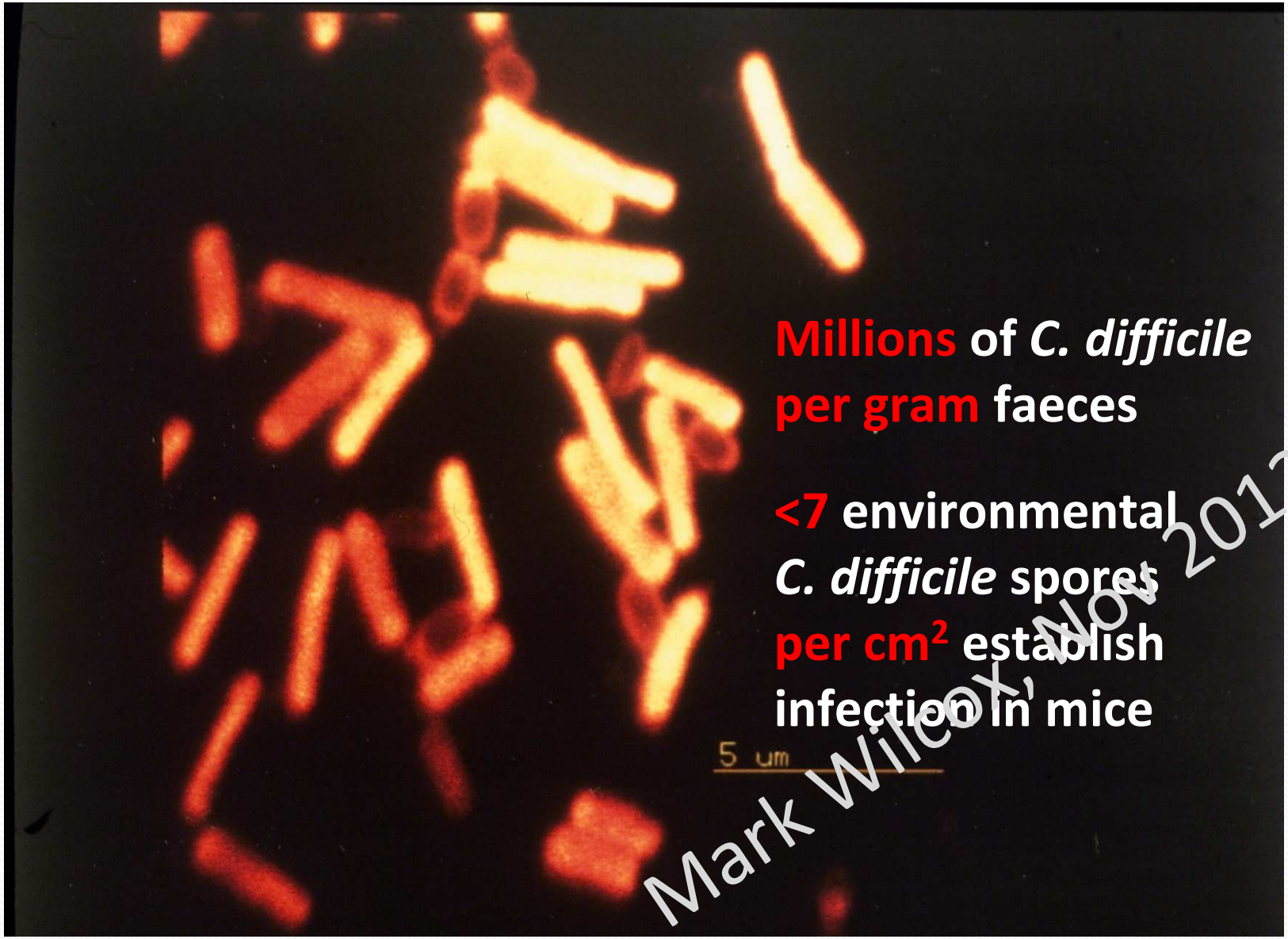
Best , Fawley, Parnell, Wilcox. *Clin Infect Dis* 2010.



Lawley TD, *et al*. *J Bacteriol* 2009;191:5377-86.

Comparison of recovery of *C. difficile* from the air with the toilet seat open and closed

Sample Time	*C. difficile* detected in air samples 0-90 mins after each flush mean CFU *C. difficile*					
	Control tests (water only added)	Toilet lid closed		Toilet lid open		
		10cm above	Seat height	25cm above	10cm above	Seat height
0-30 mins	0	4	3	7	6	35
30-60 mins	0	1	7	4	0	3
60-90 mins	0	0	0	1	0	0

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Best EL, Sandoe JA, Wilcox MH. *J Hosp Infect* 2012;80:1-5.

Droplets ejected from toilets following a single flush

Location	Toilet style	Usage	No. of droplets*
Microbiology	A	staff	8
Microbiology	A	staff	13
Hospital ward	A	staff	12
Hospital ward	A	patient	7
Hospital ward	A	patient	14
Hospital ward	A	patient	16
Hospital ward	A	patient	26
Hospital ward	B	patient	55
Hospital ward	B	Patient	43
Hospital ward	B	patient	61
Hospital ward	B	patient	46
Hospital ward	B	patient	29

A standard wash down design; **B** rimless pan with a raised seat

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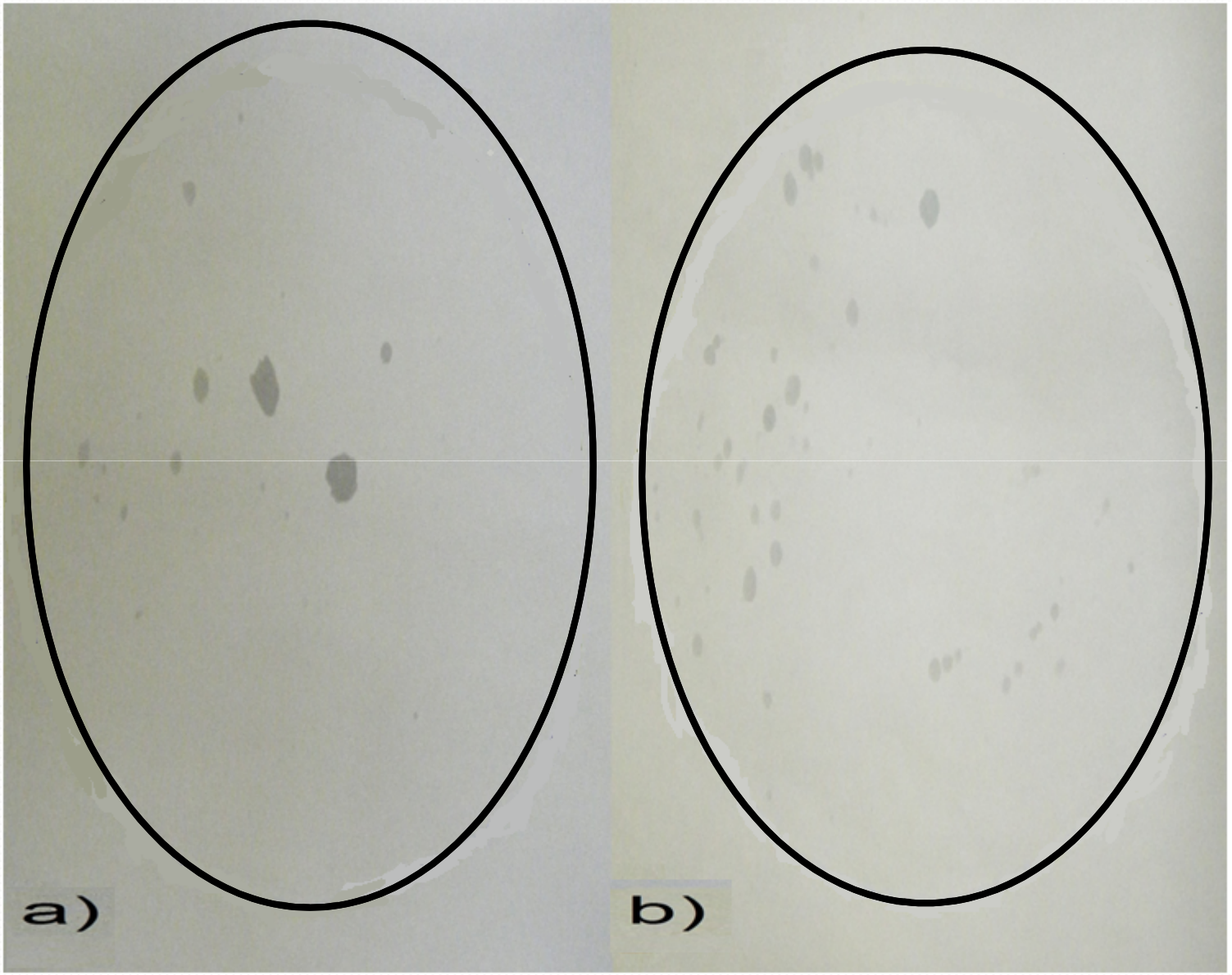

Best EL, Sandoe JA, Wilcox MH. *J Hosp Infect* 2012;80:1-5.

Key points (v)

- Airborne spread of *C. difficile*
  - Aerosolisation of CD occurs commonly (but sporadically) particularly in symptomatic CDI patients
  - This may help to explain the widespread dissemination of CD in the hospital environment
  - This will compromise the effectiveness of environmental cleaning/decontamination
  - Importance of **early single room isolation to limit CD dissemination** (especially to control epidemic strains)
  - Lidless toilets appear to contribute to the risk of *C. difficile* environmental contamination

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Environmental intervention CDI studies

- Kaatz *et al*. *Am J Epidemiol* 1988;127:1289-93
- Mayfield *et al*. *Clin Infect Dis* 2000;331:995-1000.
- Wilcox *et al*. *J Hosp Infect* 2004;54:109-14.
- Other studies

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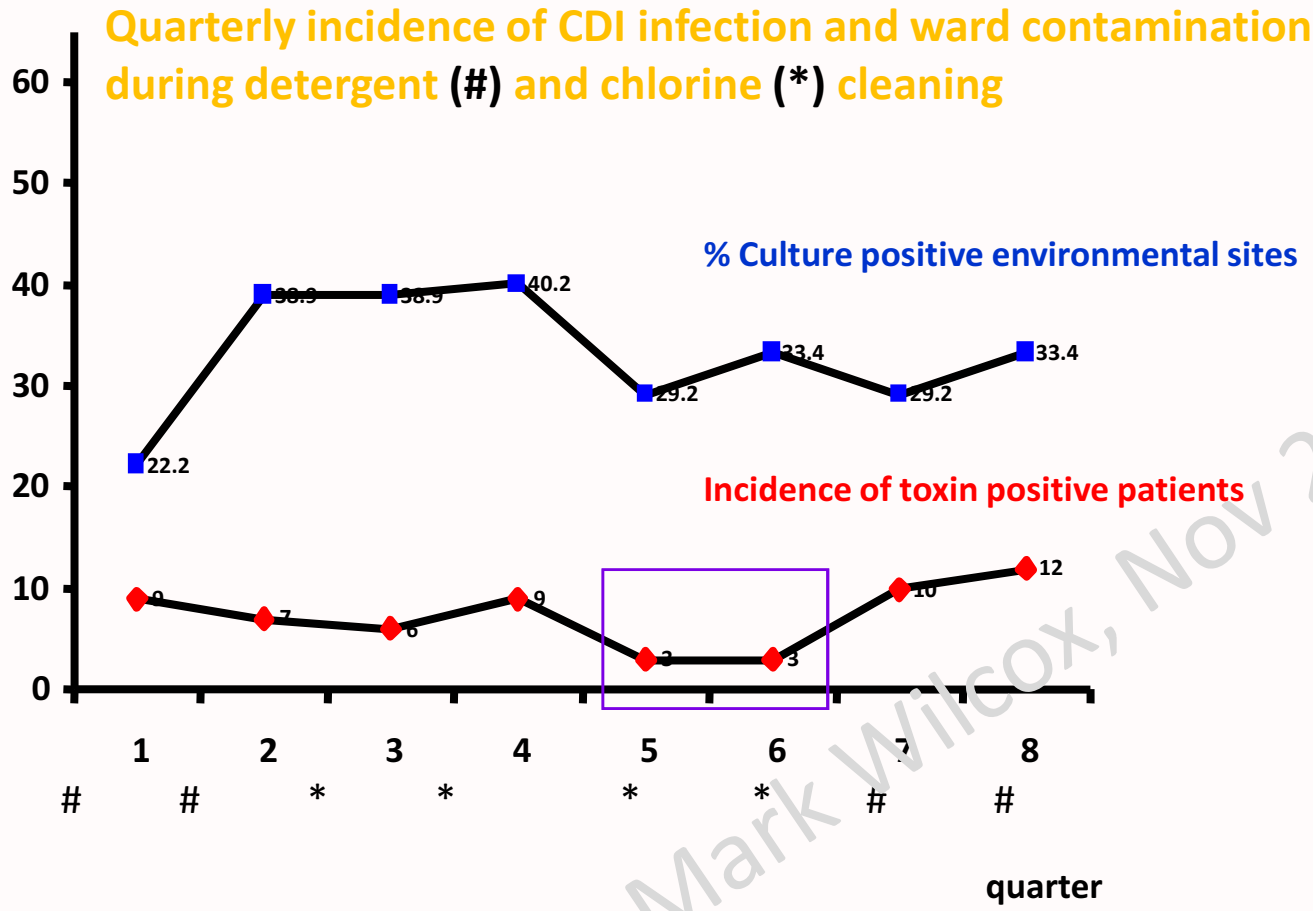
Evidence for role of chlorine-based cleaning (1000 ppm) to control CDI



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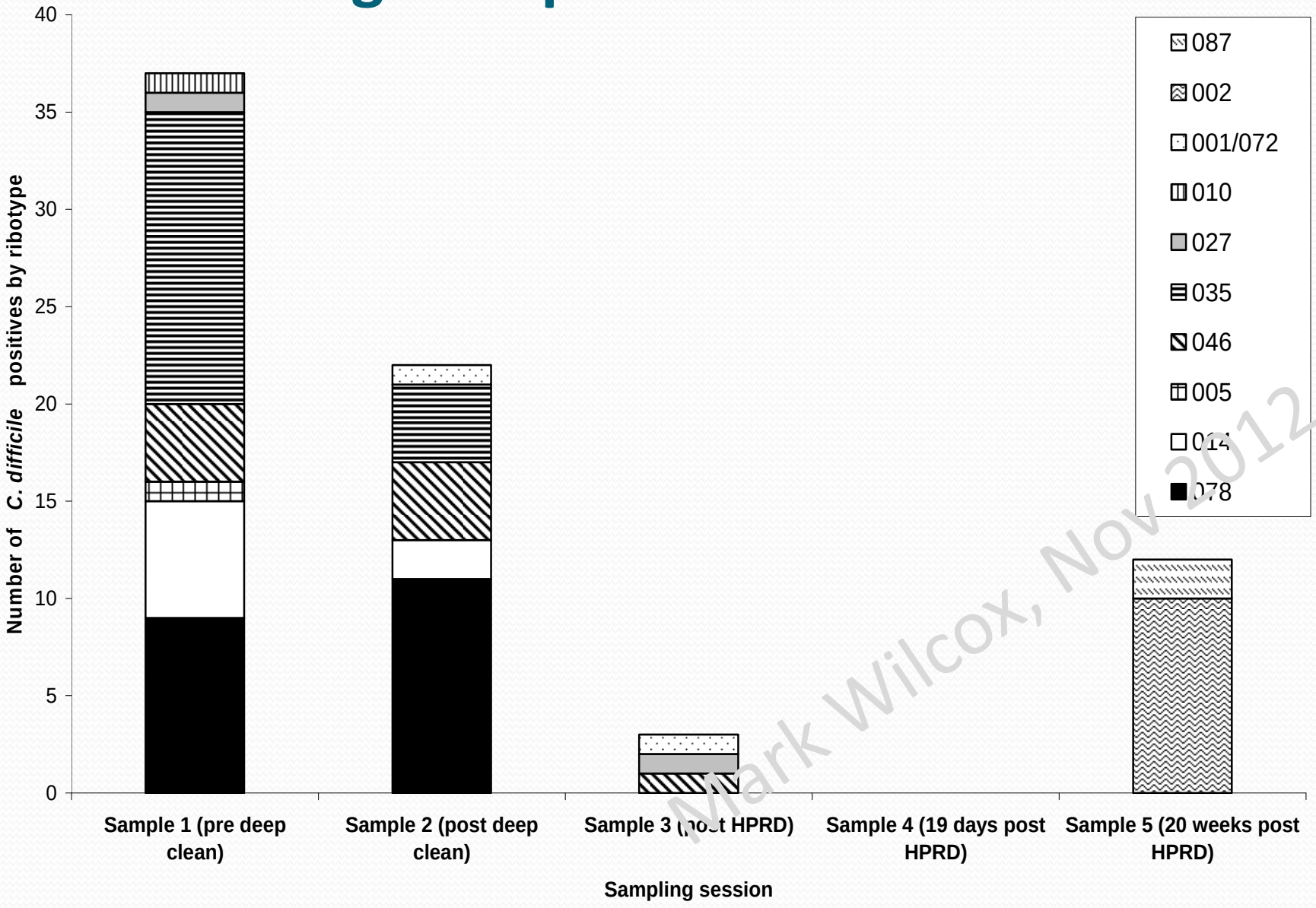
Fawley, Wilcox *et al. J Hosp Infect* 2003; 54: 109-14.

Cleaning vs vapour decontamination



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Antibiotics and risk of CDi

Need to minimise all antibiotic use - polypharmacy and duration

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

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

CDI may still occur !

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Antibiotic polypharmacy in CDI cases

CDRN referrals in four consecutive years

Year	N (%) reporting antibiotic exposure	Proportion (%) receiving >1 antibiotic	Proportion (%) receiving ≥3 antibiotics
2007-08	954 (44)	66	30
2008-09	1874 (79)	61	25
2009-10	3209 (56)	63	17
2010-11	4937 (70)	59	7

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http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/LaboratoriesAndReferenceFacilities/ClostridiumDifficileRibotypingNetworkService/

Common antibiotics reported in CDI cases

CDRN referrals in four consecutive years

	Proportion (%) reporting use of:			
Year (n)	**Cephalosporins**	**Co-amoxiclav**	**Fluoroquins**	**Piperacillin-tazobactam**
2007-08 (954)	**38**	**33**	**27**	**?**
2008-09 (1874)	**31**	**33**	**13**	**24**
2009-10 (3209)	**16**	**30**	**7**	**24**
2010-11 (4937)	**8**	**18**	**4**	**21**

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Note: antibiotic receipt should not be taken to imply CDI causality

http://www.hpa.org.uk/ProductsServices/MicrobiologyPathology/LaboratoriesAndReferenceFacilities/ClostridiumDifficileRibotypingNetworkService/

CDI (antibiotic) risk factor studies

- Most are flawed
- Inappropriate controls
- Failure to control for key confounders
- Antibiotic duration
- Antibiotic polypharmacy
- Exposure to *C. difficile*
- Multiple interventions

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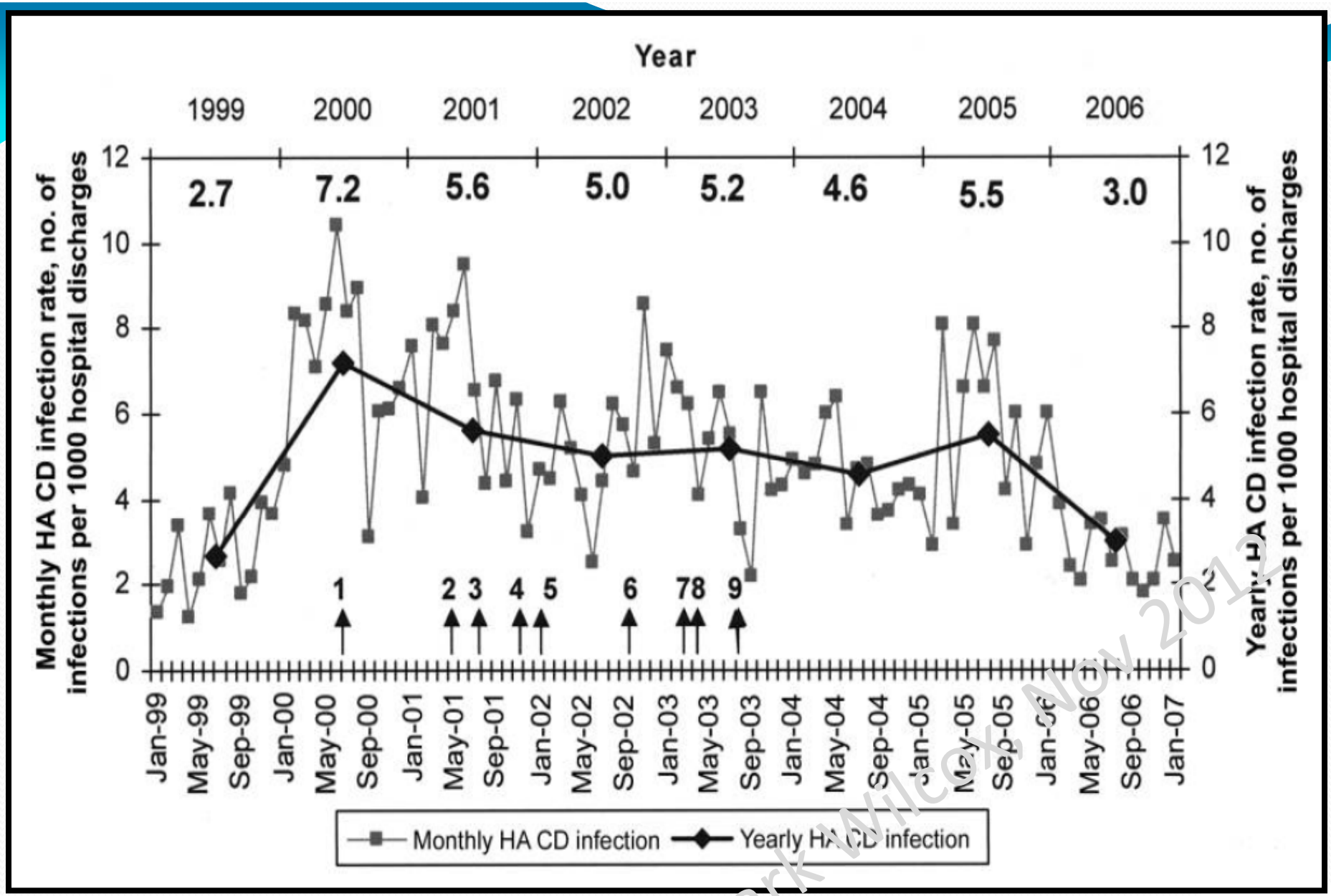

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Muto C, *et al*. *Clin Infect Dis* 2007;45:1266-73.

Bundle of interventions to control CDI

- ‘In 2005, a formulary switch from levofloxacin to moxifloxacin plus ciprofloxacin resulted in increased overall flouroquinolone use, yet CDI rates further decreased in 2006’

- ‘Therefore, blaming antimicrobial agents alone may be too simplistic’

- ‘However, reducing the use of antimicrobials agents may contribute to sustained low rates of infection’

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Muto C, *et al*. *Clin Infect Dis* 2007;45:1266-73.

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