Clostridium difficile infection: the Australian experience

Tom Riley

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History

- Tedesco et al. (1974) describe clindamycin colitis

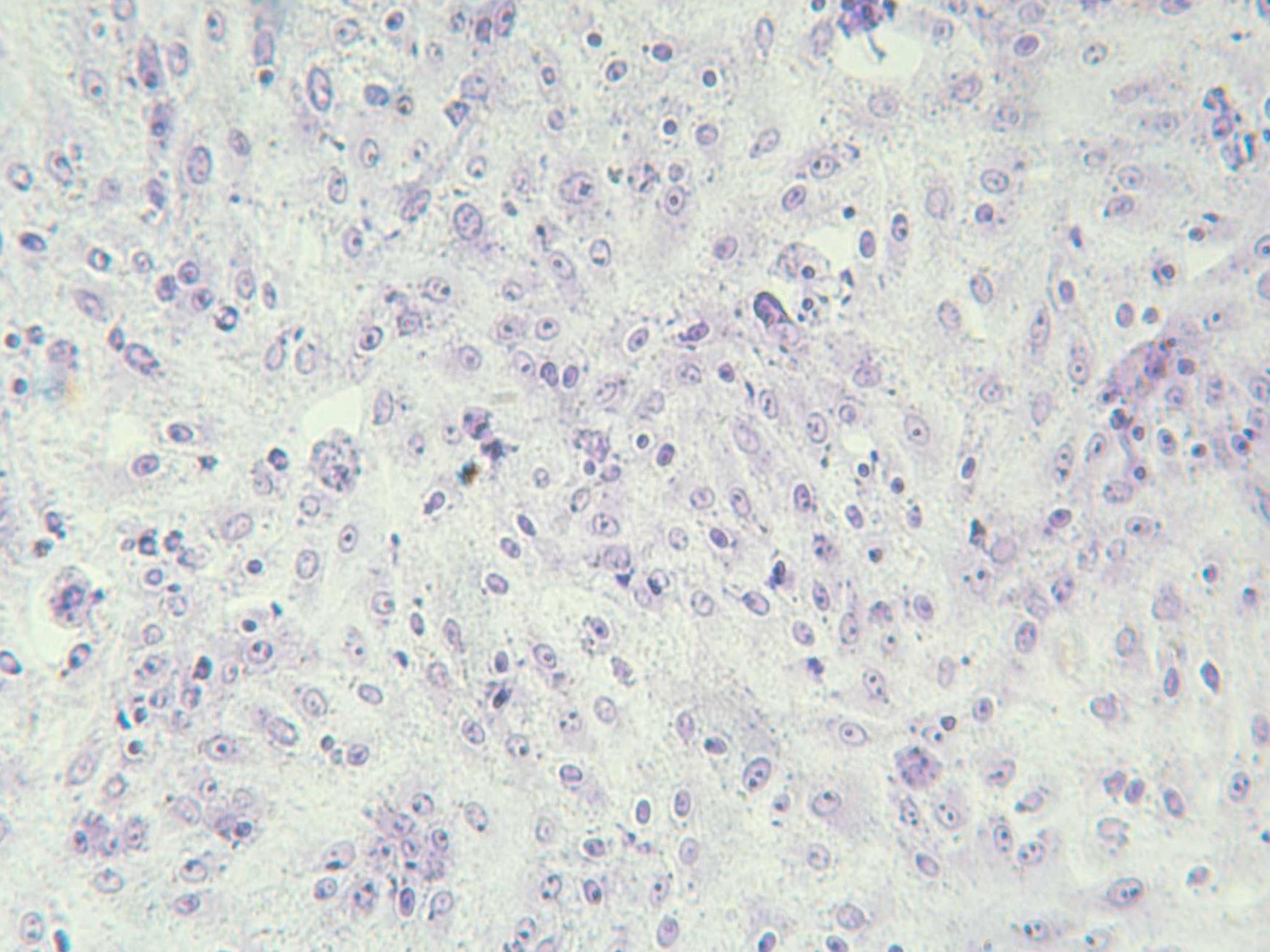
"serious colitis" following administration of clindamycin is in the range of one in 50,000 to one in 100,000. This information is in striking contrast with a prospective study[7] of 200 patients in hospitals who were given clindamycin for various reasons. In that study, diarrhea (21 percent) and pseudomembranous colitis (10 percent) were frequently found. Since all symptoms disappeared on

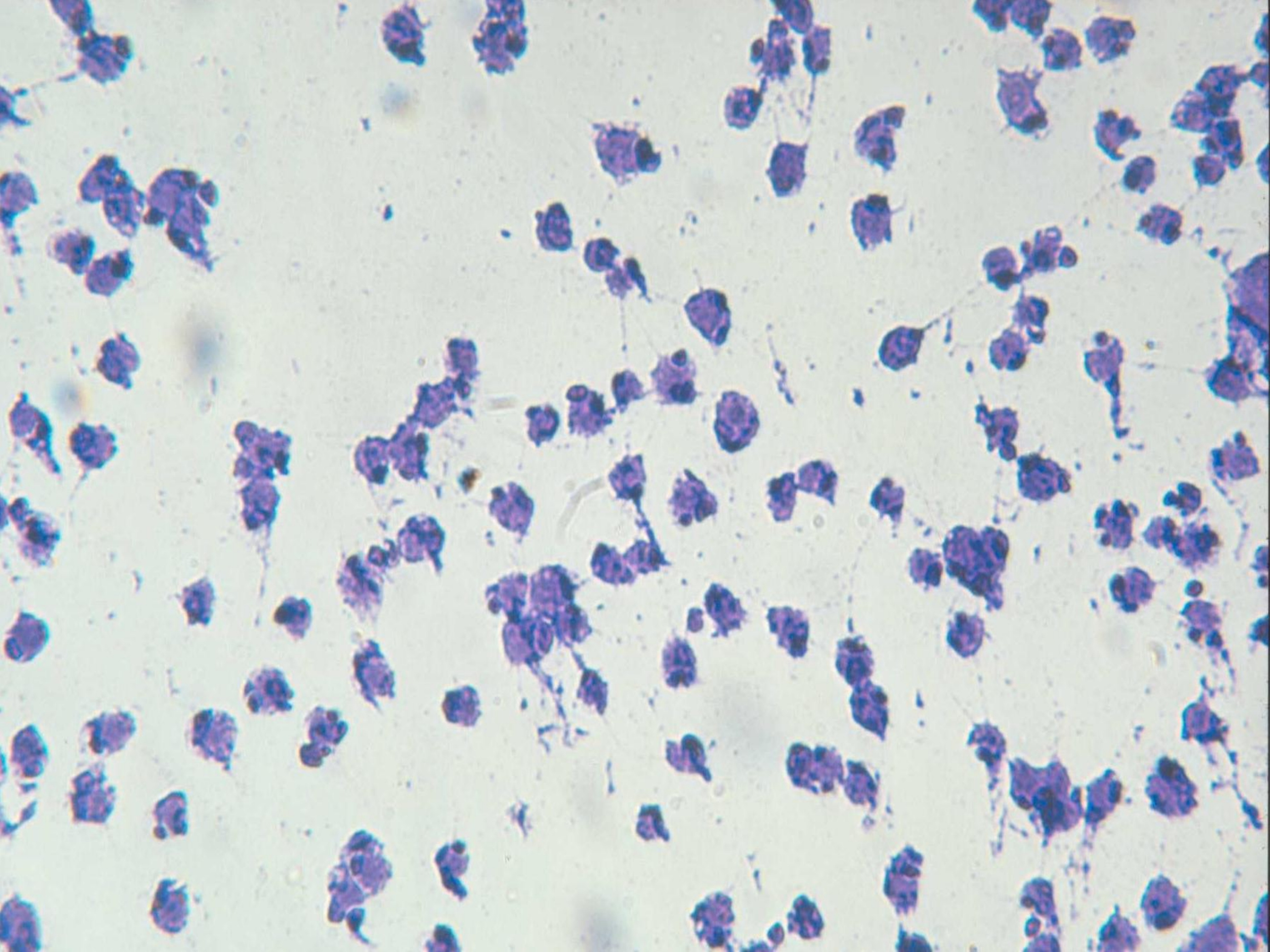
YALE JOURNAL OF BIOLOGY AND MEDICINE **3**, 166–181 (1974)

The Association of Viral Activation with Penicillin Toxicity in Guinea Pigs and Hamsters[1]

ROBERT H. GREEN[2]

Departments of Pathology and Internal Medicine, Yale University School of Medicine, and the West Haven Veterans Administration Hospital, New Haven, Connecticut 06510





CLOSTRIDIUM DIFFICILE: ISOLATION AND CHARACTERISTICS

S. HAFIZ* AND THE LATE C. L. OAKLEY

Department of Microbiology, Medical School, University of Leeds, LS2 9NL

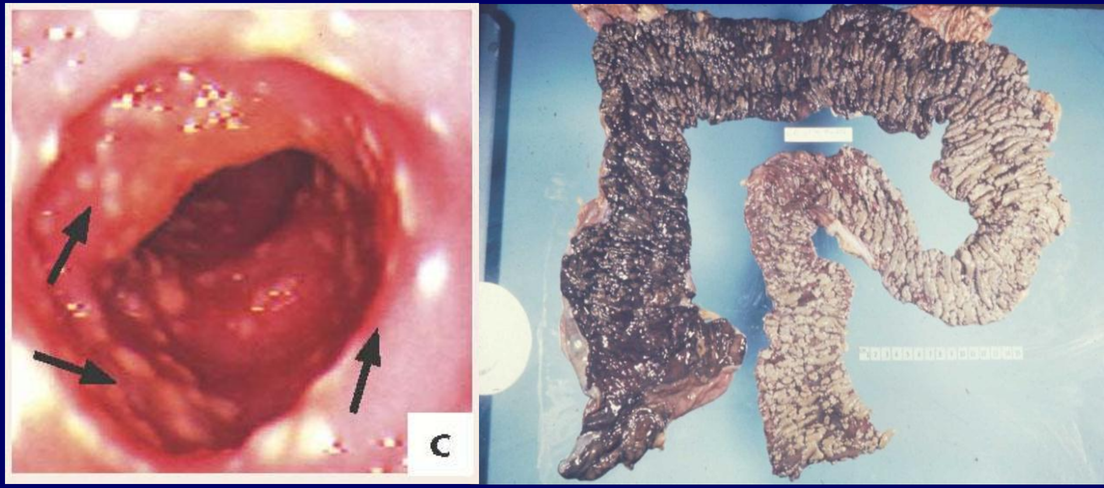
J. MED. MICROBIOL.—VOL. 9 (1976)

ARCTIC OCEAN
Greenland
Svalbard (Nor.)
United States
Norway
United Kingdom
Ireland
Portugal
Spain
France
Morocco
Algeria
Egypt
Saudi Arabia
U.A.E.
Oman
Yemen
Djibouti
Eritrea
Sudan
Ethiopia
Somalia
Mauritania
Mali
Niger
Chad
Senegal
Sierra Leone
Cote d' Ivoire
Ghana
Togo
Nigeria
C.A.R.
Gabon
Dem. Rep. of Congo
Rep. of the Congo
Uganda
Kenya
Tanzania
Angola
Zambia
Malawi
Madagascar
Namibia
Zimbabwe
Botswana
Mozambique
Swaziland
Lesotho
South Africa
PACIFIC
ATLANTIC
OCEAN
INDIAN
OCEAN
Kyrgyzstan
Tajikistan
China
Afg.
Pakistan
Nepal
Bhutan
India
Bangl.
Burma
Laos
Thailand
Cambodia
Sri Lanka
Malaysia
Brazil
Peru
Chile

Historical background

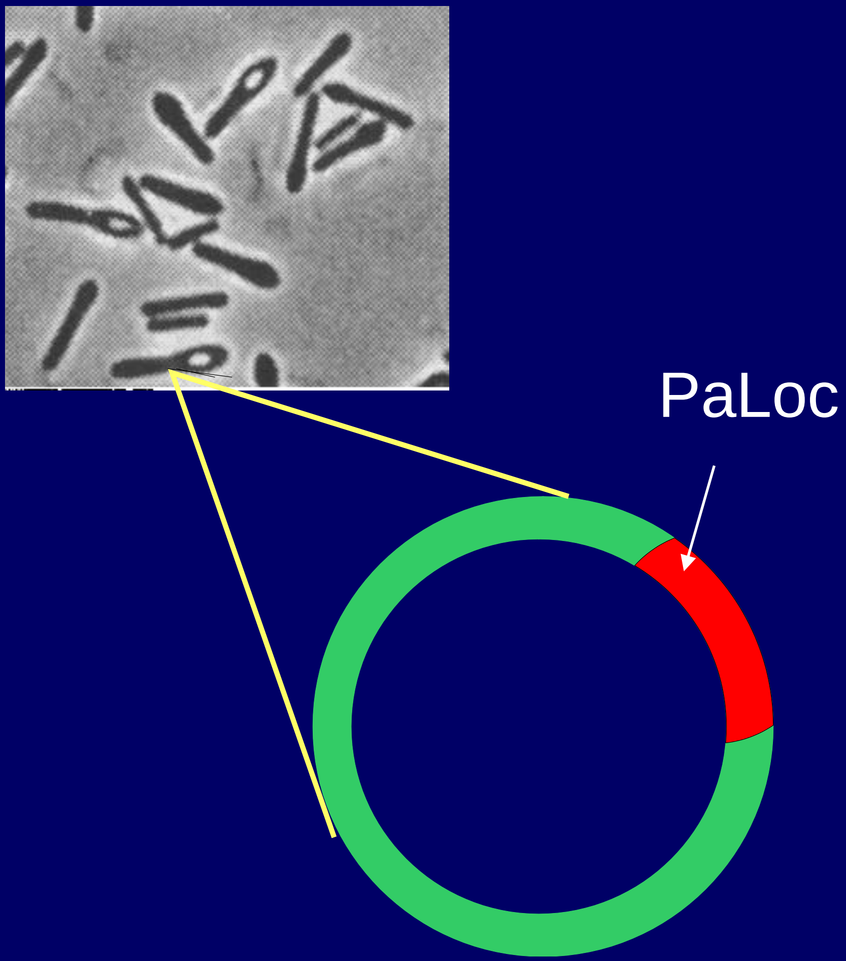
- *Clostridium difficile* – an anaerobic Gram +ve bacillus
- specific anti-anaerobe drugs developed in 70s, e.g. clindamycin
- clindamycin-associated diarrhoea became a real problem in some hospitals in the USA
- outbreaks of pseudomembranous colitis
- cause elucidated in 1978

- Largely ignored until 2000s
- Bit of diarrhoea in the elderly
- Not too many people died!



C. difficile infection

- Most common cause of infectious diarrhoea in hospital patients
- 2 major virulence factors:
  - toxin A (an enterotoxin)
  - toxin B (a cytotoxin)
- 3rd "binary" toxin



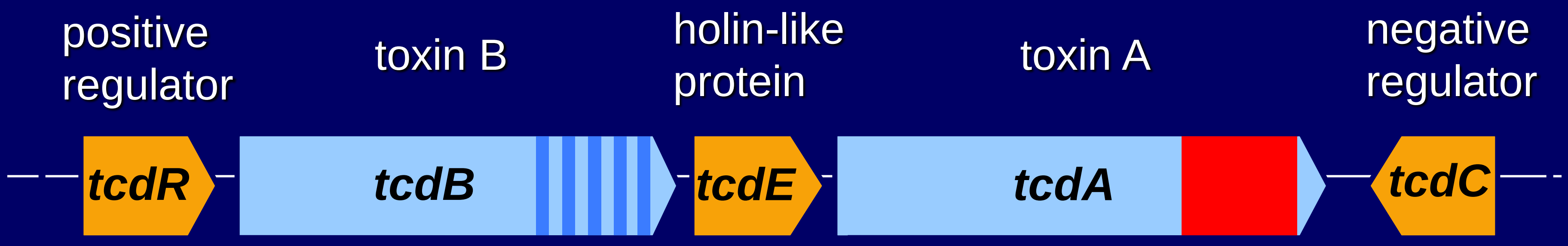
Bartlett, JG, *Clin Infect Dis* 1994,18:S265-72

Toxin A & toxin B

- Large structurally and functionally related proteins
- Genes are contained on a 19.6-kB Pathogenicity Locus (PaLoc) which is absent in non-toxigenic strains
- Majority of pathogenic strains produce both toxins which affect actin cytoskeleton
- Polymorphisms in the PaLoc can affect toxin production - toxin A-negative, toxin B-positive strains

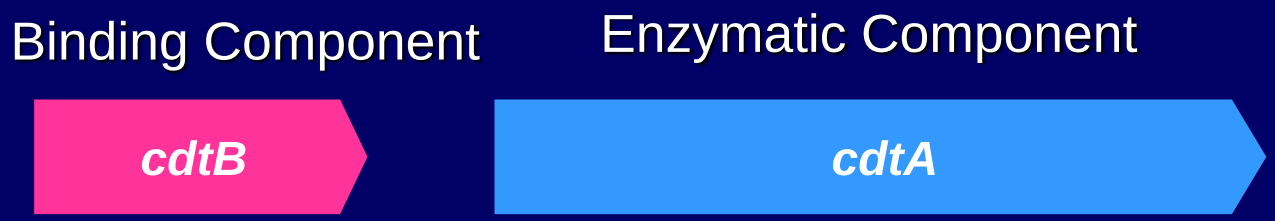
Toxin phenotypes

- $A^{+}B^{+}$
- $A^{-}B^{+}$
- $A^{-}B^{-}$



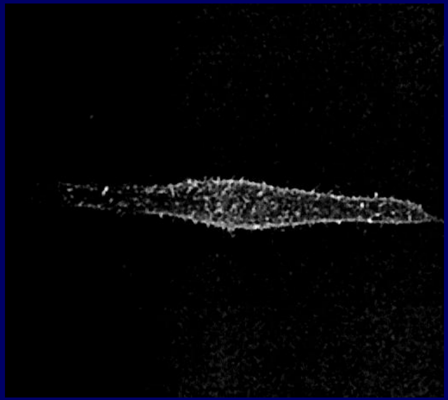
Binary toxin

- Additional toxin produce by 2-5% of isolates
- Consists of two component proteins, the genes for which are contained within the CDT locus on the chromosome
- Actin-specific ADP-ribosyltransferase
- Unknown significance in disease, but associated with increased severity of diarrhoea



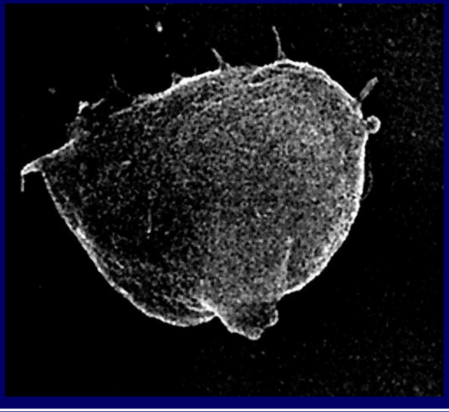
Cytopathic effects

Infect Immun 2001; 69:5487-93



Cellular Morphology

- Cell-rounding
- Detachment from extracellular matrix

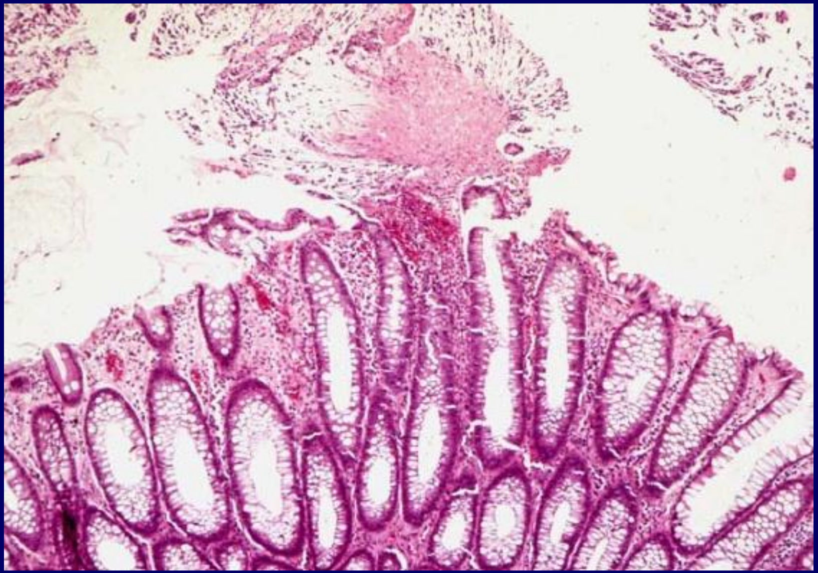


Cellular Processes

- Activation of caspases → apoptosis
- Decrease in integrity of tight-cell junctions
- Inflammatory response
  - Release of cytokines & chemokines
  - Production of reactive oxygen intermediates

Histological effects

- Massive inflammatory response
- Recruitment of polymorphonuclear neutrophils to area
- Increase in epithelial permeability

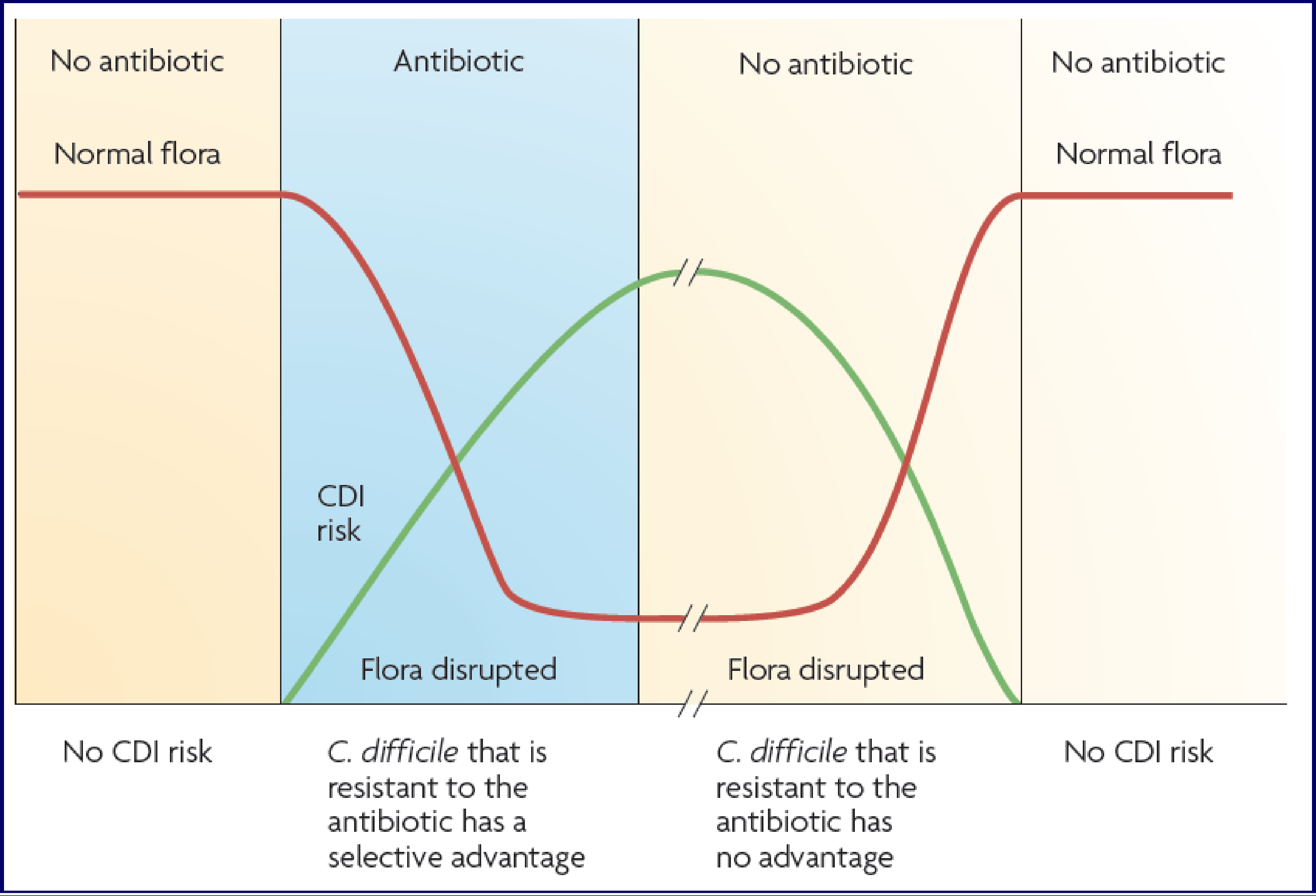


Kelly *et al*. N Engl J Med 1994;330:257-262.

Risk factors for getting *C.difficile* ?

- Exposure to the organism – how much?
- Exposure to antibiotics – clindamycin, then cephalosporins, now fluoroquinolones
- Maybe others now?

Effect of antibiotics on normal flora



Rupnik *et al*. Nat Rev Microbiol 2009;7:526-36

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*–Associated Diarrhea with High Morbidity and Mortality

Vivian G. Loo, M.D., Louise Poirier, M.D., Mark A. Miller, M.D., Matthew Oughton, M.D., Michael D. Libman, M.D., Sophie Michaud, M.D., M.P.H., Anne-Marie Bourgault, M.D., Tuyen Nguyen, M.D., Charles Frenette, M.D., Mirabelle Kelly, M.D., Anne Vibien, M.D., Paul Brassard, M.D., Susan Fenn, M.L.T., Ken Dewar, Ph.D., Thomas J. Hudson, M.D., Ruth Horn, M.D., Pierre René, M.D., Yury Monczak, Ph.D., and André Dascal, M.D.

Investigation

Investigation into outbreaks of *Clostridium difficile* at Stoke Mandeville Hospital, Buckinghamshire Hospitals NHS Trust

July 2006

Healthcare Commission

http://www.healthcarecommission.org.uk/_db/_documents/Stoke_Mandeville.pdf

Superbug kills war hero who survived three years as a PoW

By **Luke Salkeld**

Fearless officer: Major Sam Weller, left, who was decorated for his bravery, is pictured with his brother Tony in 1947

THE family of a distinguished war veteran have criticised the hospital where he was infected by a killer bug.

Major Sam Weller – who survived three years as a prisoner of war – died after catching Clostridium Difficile following an operation on his hip. Yesterday, his relatives said he had been let down by the country he fought for.

Major Weller, 88, had surgery at Gloucestershire Royal Hospital but he developed an infection and was given a course of antibiotics.

Weeks later he died and an inquest was told the medicine had left him more vulnerable to catching the superbug.

Yesterday, his family criticised the hospital treatment he received and standards of

2,247

ALMOST 56,000 vulnerable and elderly patients have been infected with C. Diff in the past year.

Between January and March alone, 15,592 caught the bug – an astonishing 22 per cent rise on the previous three months.

C.Diff, which is spread by dirty hands and bedding, is a bigger killer than MRSA. It claimed 2,247 lives in 2005 – a 69 per cent rise on the previous year.

It exists naturally in the stomachs of many healthy adults, where it is kept under control by 'friendly' bacteria.

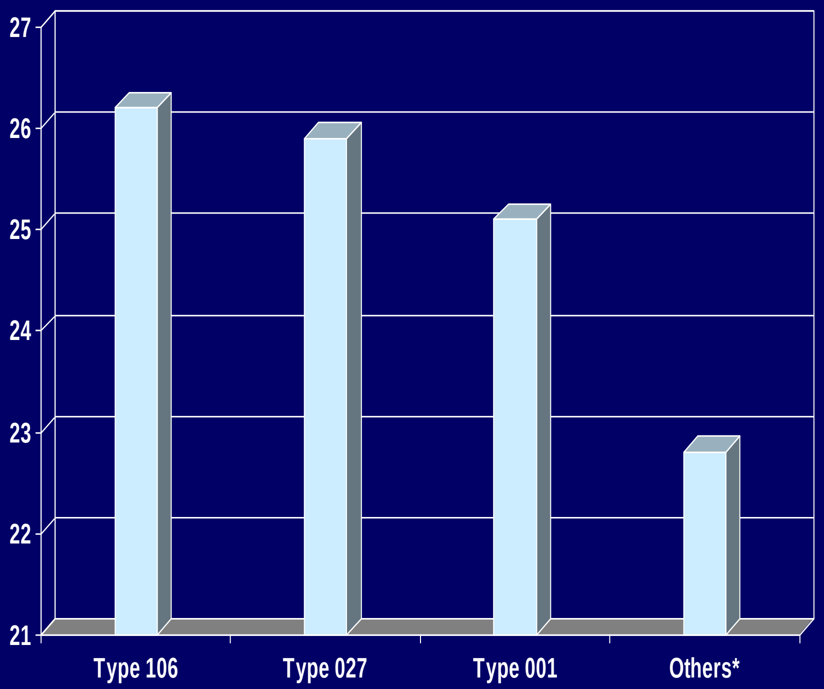
Problems start if the balance of bacteria is disturbed, perhaps as a result of taking antibiotics for another infection.

Once the 'friendly' bacteria are killed off, the C. Diff is able to multiply and produce the toxins which cause diarrhoea and, in the worst cases, a fatal infection of the abdomen.

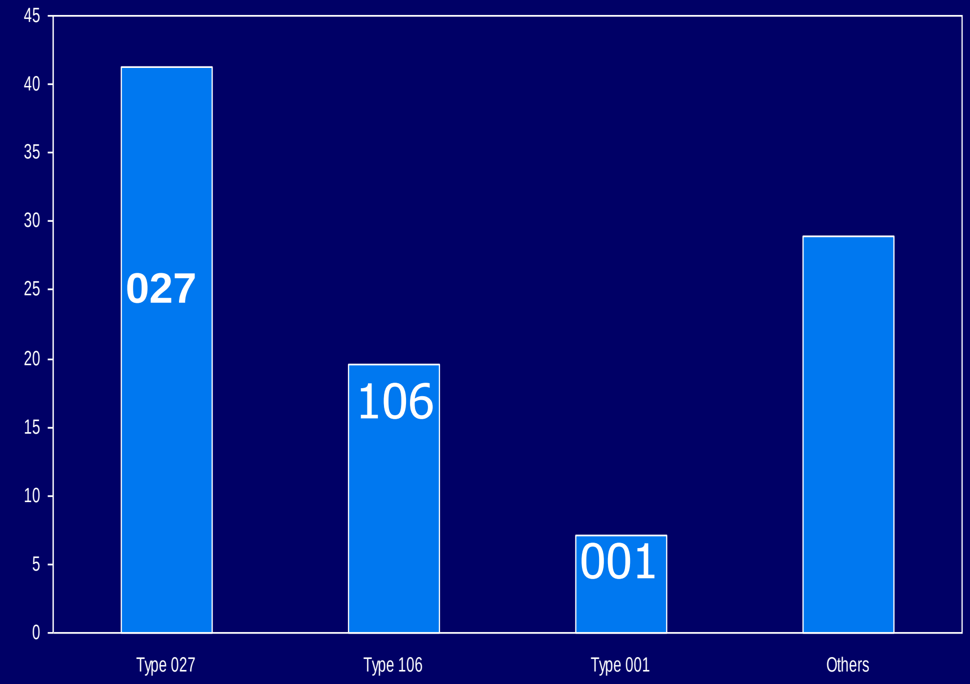
C. difficile PCR ribotype 027

- More severe disease
- Produces more toxins A and B
- Produces binary toxin
- Fluoroquinolone resistant
- Epidemic spread across North America and UK/Europe from early 2000s
- Numbers dropping in UK/Europe
- Still major issue in USA
- Three clusters in Australia since 2009

England distribution of PCR ribotypes 2005/6 to 2007/8 as percentages



2005-6 (n=881)



2007-8* (n=677)

* Brazier et al. *Eurosurveillance* Vol.13;4. October 2008

Table 1. Reported rates of health care–associated *Clostridium difficile* infection (CDI), by province or region, among adults hospitalized in Canadian Nosocomial Infection Surveillance Program hospitals (n = 1430).

Hospital location	No. of cases of CDI	No. of hospital admissions	No. of cases per 1000 hospital admissions	No. of patient-days	No. of cases per 100,000 patient-days
British Columbia	128	42,197	3.0	279,911	46
Alberta	153	75,728	2.0	372,966	41
Saskatchewan and Manitoba	67	25,214	2.7	184,153	36
Ontario	666	112,658	5.9	824,658	81
Quebec	282	21,964	12.8	217,507	130
Atlantic Canada	134	30,270	4.4	333,137	40
Total	1430	308,031	4.6	2,212,332	65

Study done 04/05.

Similar overall rate as earlier study but attributable mortality increased about 4 fold.

Gravel *et al. Clin Infect Dis* 2009; 48: 568-76.

Rates in England 2008-11

Comparison of the Burdens of Hospital-Onset, Healthcare Facility–Associated *Clostridium difficile* Infection and of Healthcare-Associated Infection due to Methicillin-Resistant *Staphylococcus aureus* in Community Hospitals

Becky A. Miller, MD;[1] Luke F. Chen, MD, MPH;[1]
Daniel J. Sexton, MD;[1] Deverick J. Anderson, MD, MPH[1]

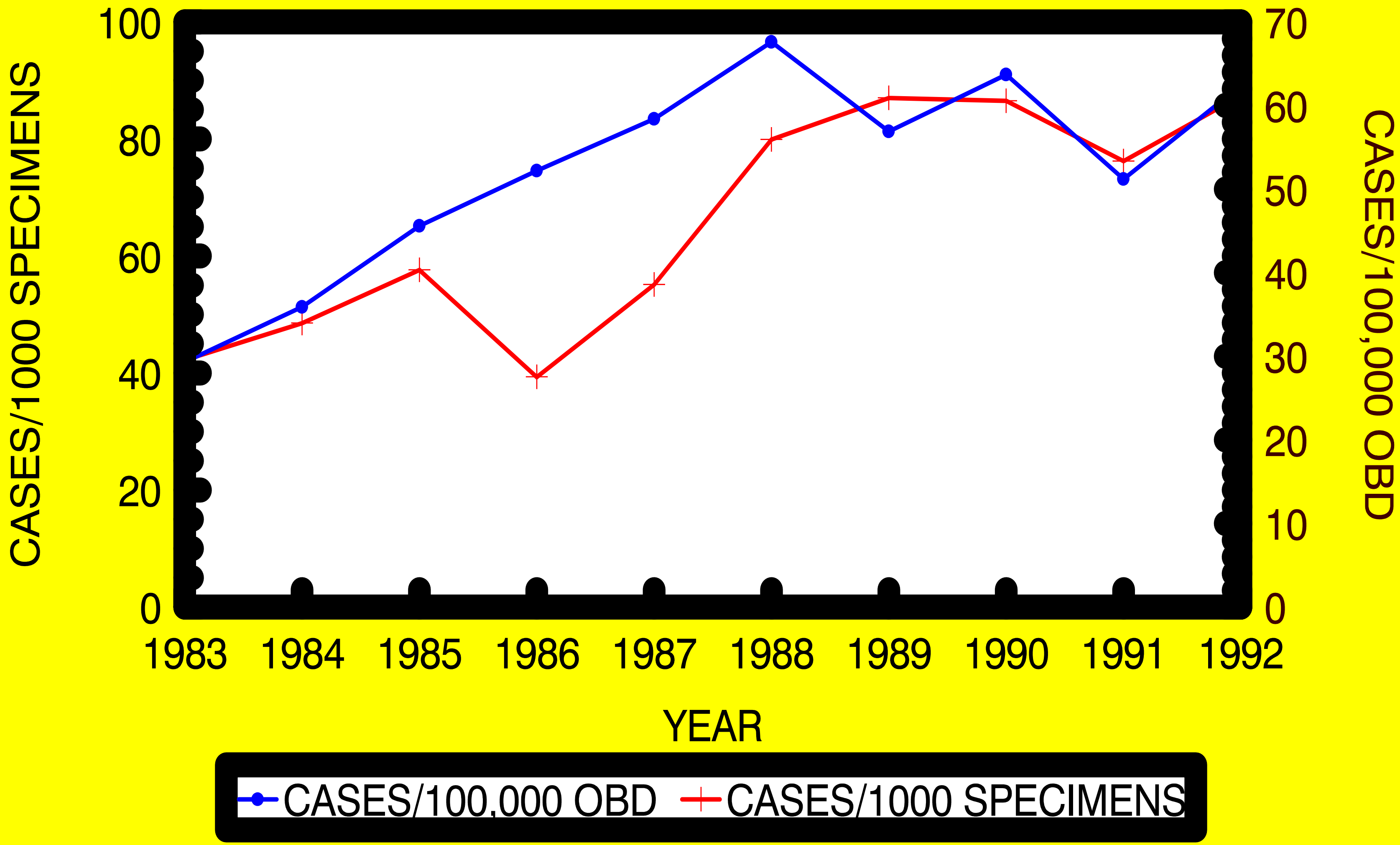
We sought to determine the burden of nosocomial *Clostridium difficile* infection in comparison to other healthcare-associated infections (HAIs) in community hospitals participating in an infection control network. Our data suggest that *C. difficile* has replaced MRSA as the most common etiology of HAI in community hospitals in the southeastern United States.

Infect Control Hosp Epidemiol 2011;32(4):387-390

CDI in Australia

- Not a notifiable infection
- But mandatory reporting by hospitals since 2010
- Reporting of "hospital identified" cases of CDI

Fig.2 Incidence of *Clostridium difficile*-associated diarrhoea at SCGH, 1983-92



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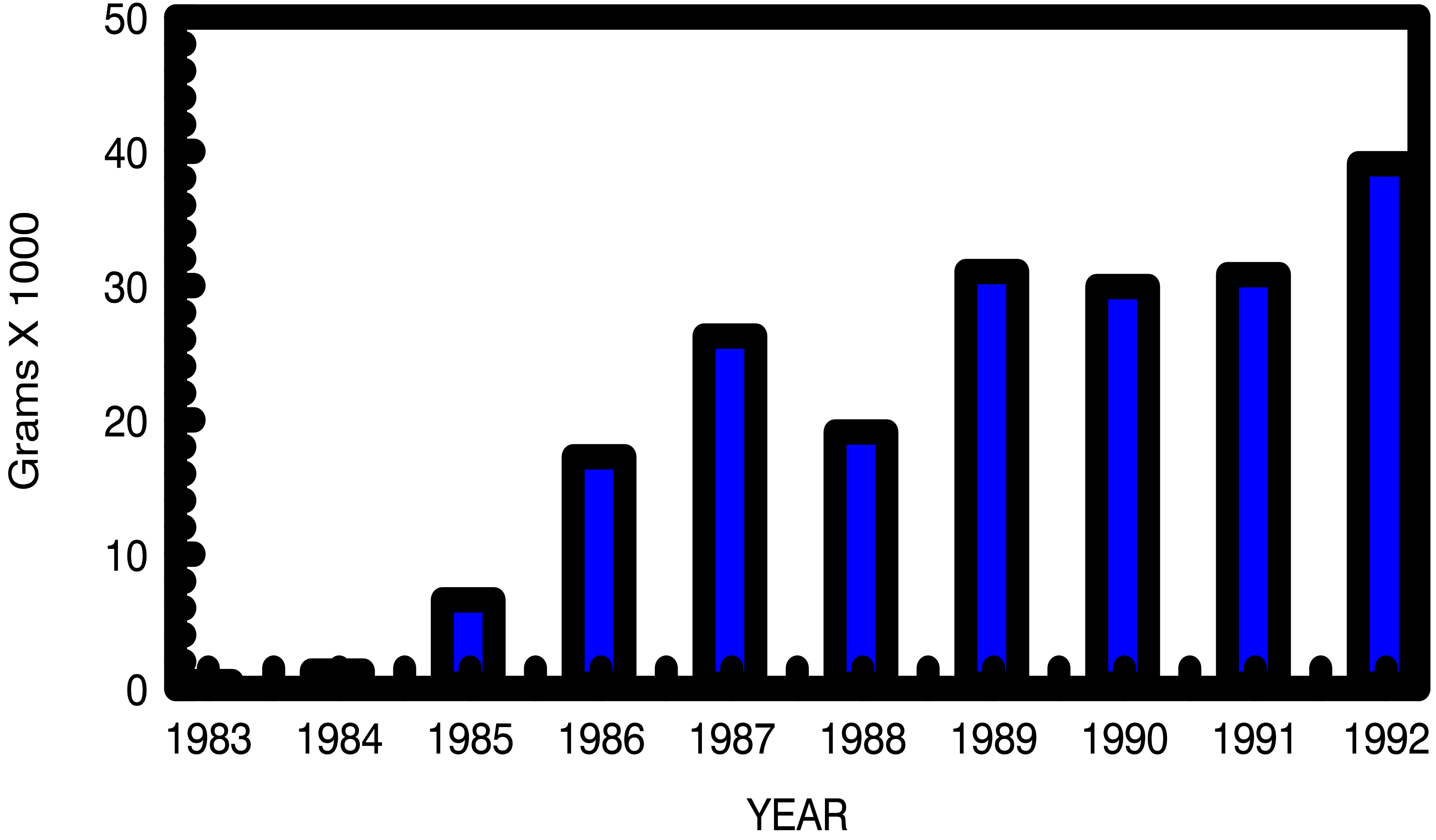
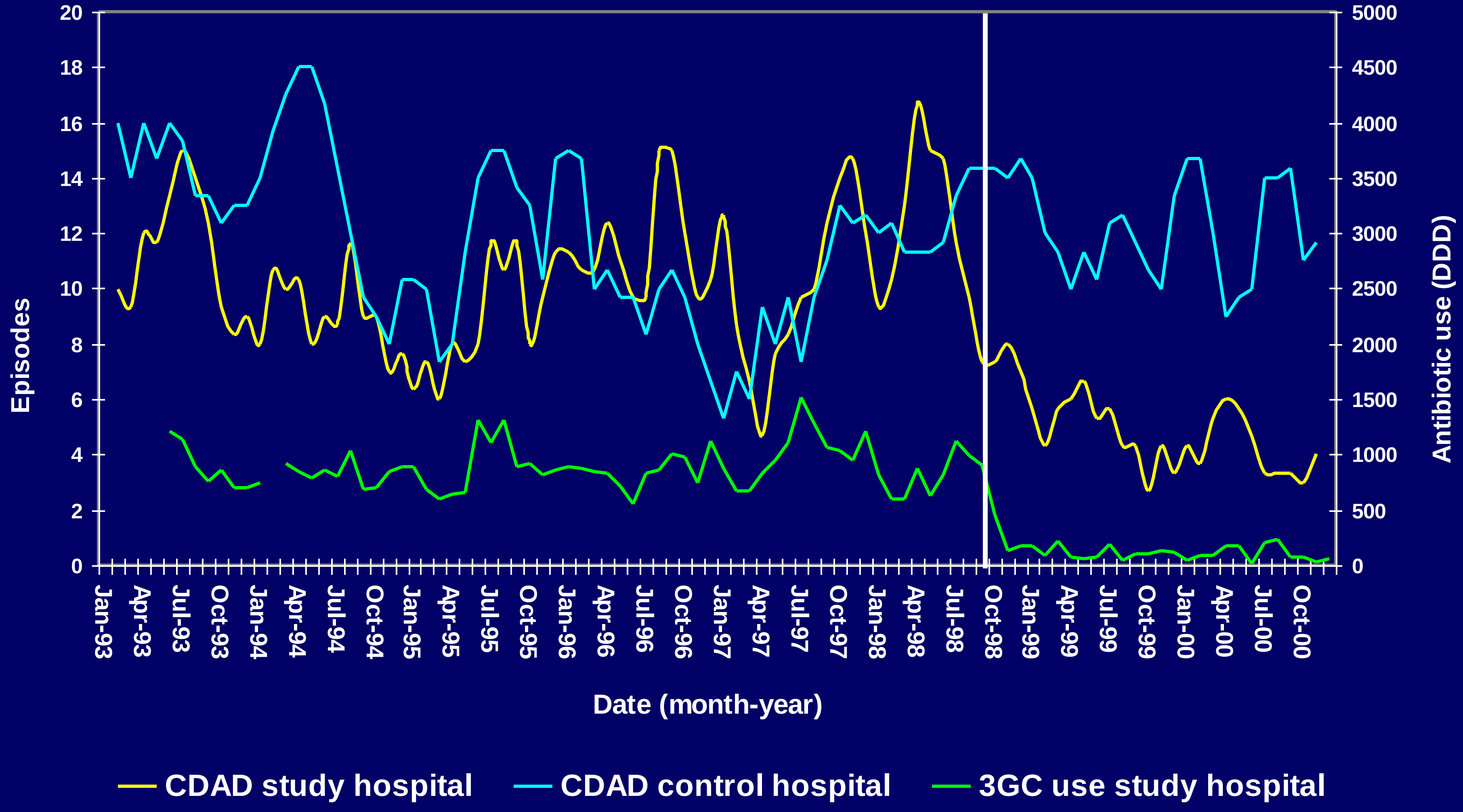
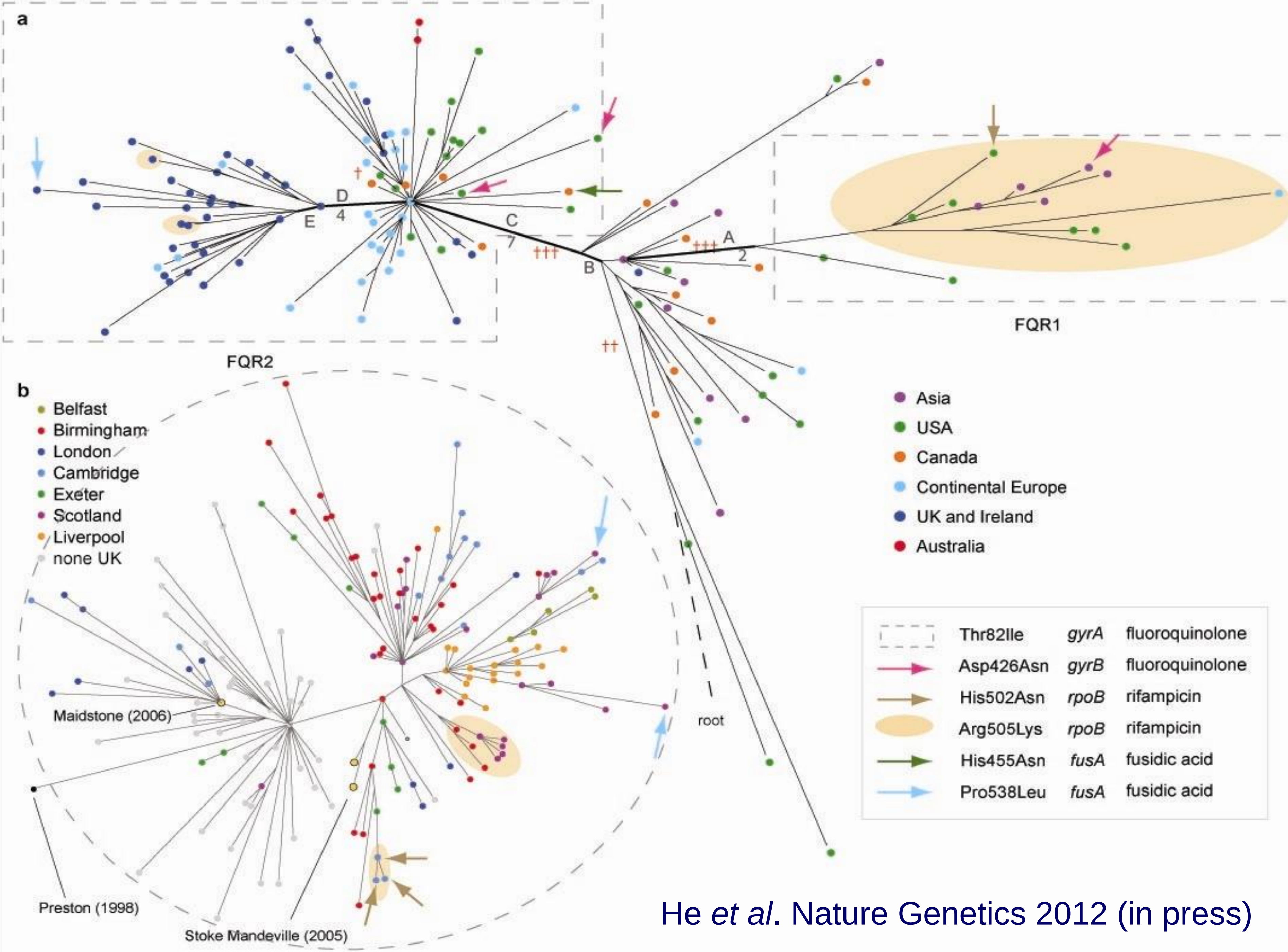
Riley, T.V., O'Neill, G.L., Bowman, R.A. and Golledge, C. L. 1994. *Clostridium difficile*-associated diarrhoea: epidemiological data from Western Australia. *Epidemiol. Infect.* 113: 13-20.

Cephalosporin use SCGH, 1983-92



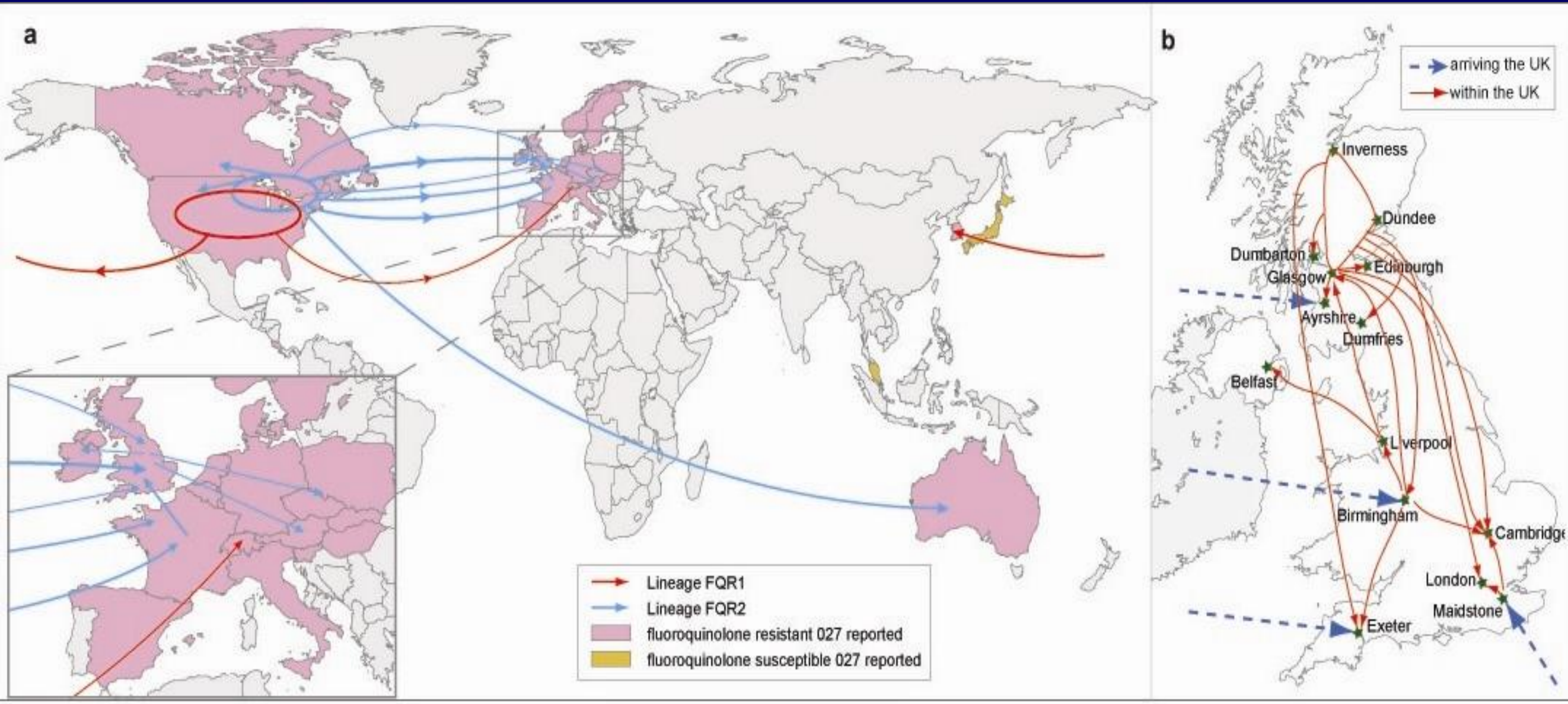
C.difficile: monthly episodes 1993-2000

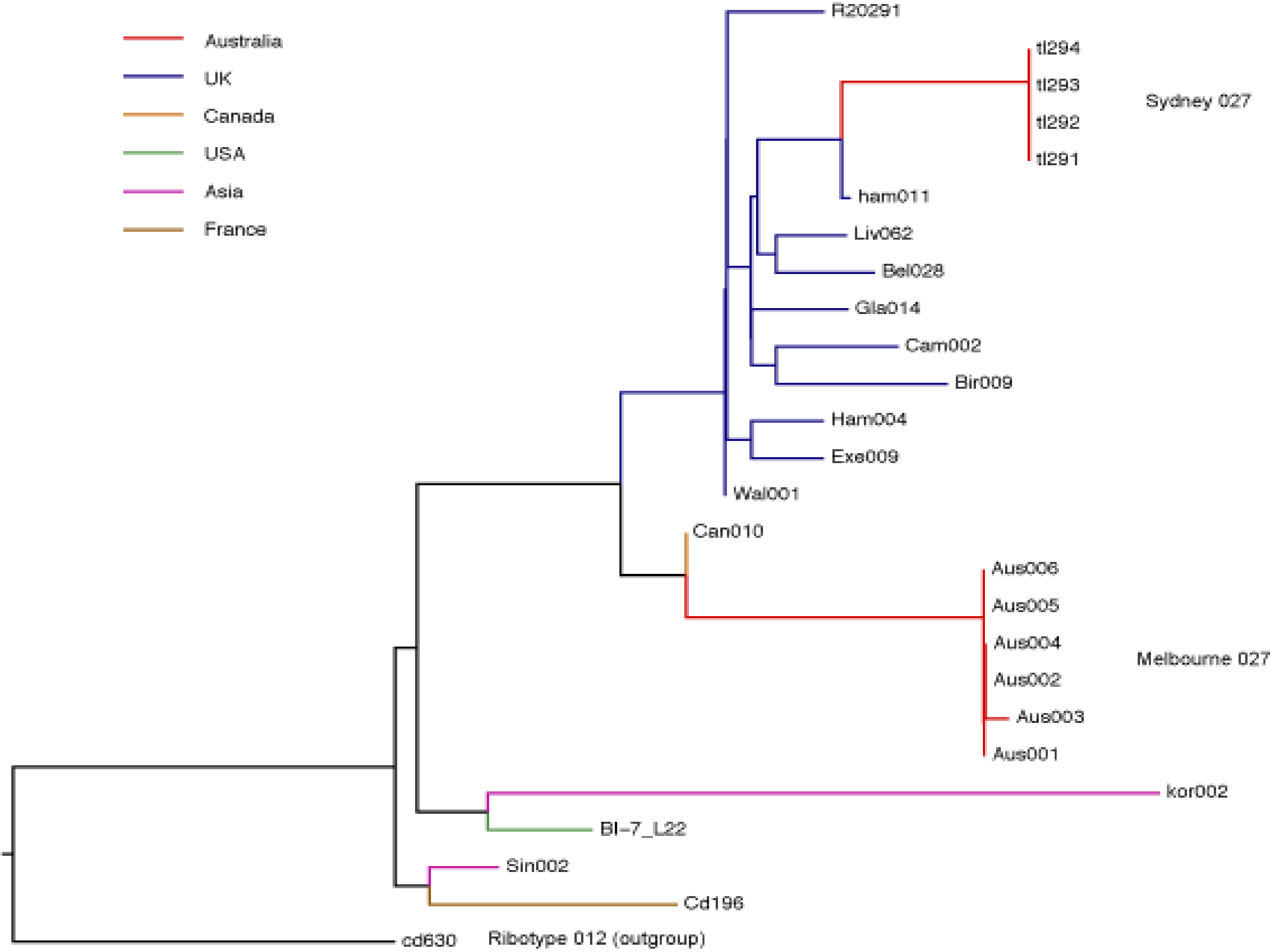




He *et al*. Nature Genetics 2012 (in press)

He *et al*. Nature Genetics 2012 (in press)

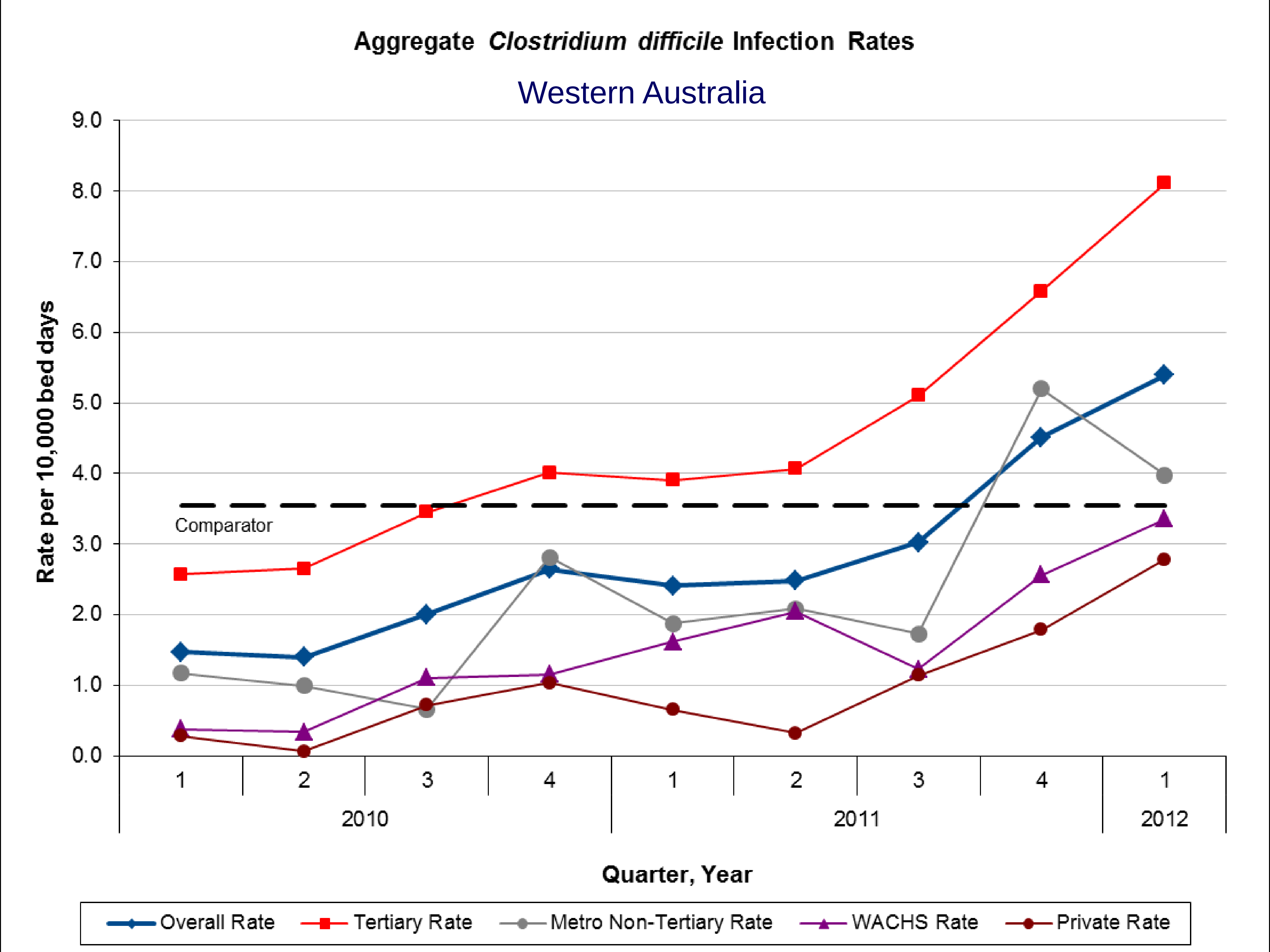




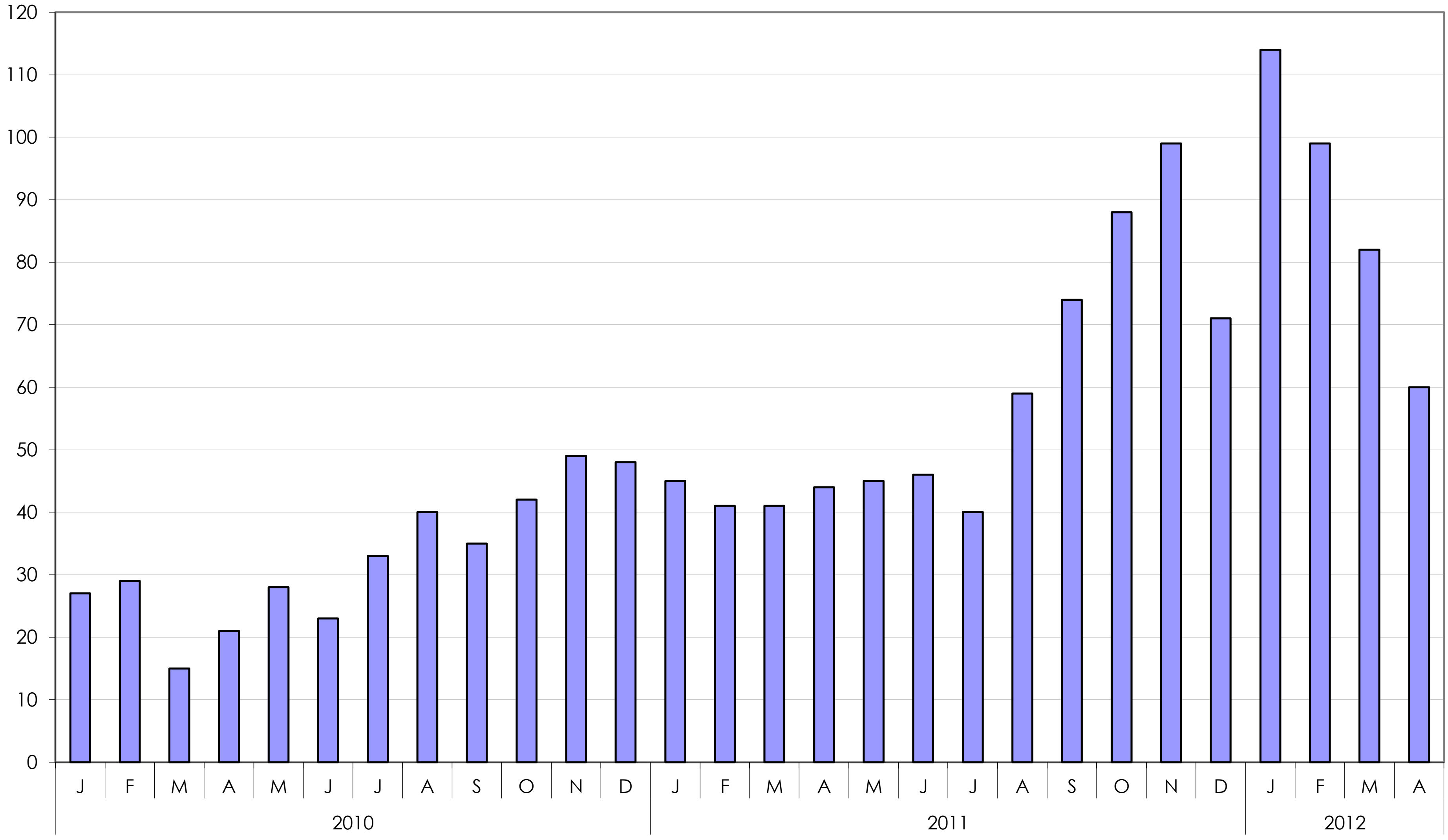
Australia
UK
Canada
USA
Asia
France
R20291
tl294
tl293
tl292
tl291
Sydney 027
ham011
Liv062
Bel028
Gls014
Cam002
Bir009
Ham004
Exe009
Wal001
Can010
Aus006
Aus005
Aus004
Aus002
Aus003
Aus001
Melbourne 027
kor002
BI-7_L22
Sin002
Cd196
cd630
Ribotype 012 (outgroup)

Ribotype	State/Territory* No. (%)					Australia
	NSW	Qld	WA	SA	Tas/ACT	No. (%)
014/020	39 (25)	13 (17)	15 (26)	6 (26)	5 (25)	78 (24)
002	24 (16)	6 (8)	5 (9)	2 (9)	-	37 (11)
112	5 (3)	5 (7)	11 (19)	-	-	21 (6)
010	6 (4)	-	-	-	-	6 (2)
027	3 (2)	-	-	-	-	3 (1)
001	-	1 (1)	2 (3)	-	-	3 (1)
012	-	1 (1)	2 (3)	-	-	3 (1)
078	2 (1)	-	-	-	-	2 (<1)
005	-	-	1 (2)	-	-	1 (<1)
026	1 (<1)	-	-	-	-	1 (<1)
Other	74 (48)	50 (66)	22 (40)	14 (61)	15 (75)	175 (53)
UTR#				1 (4)		1 (<1)
Totals	154 (47)	76 (23)	58 (18)	23 (7)	20 (6)	330

ACSQH snap-shot October-November 2010


Aggregate Clostridium difficile Infection Rates
Western Australia
Rate per 10,000 bed days
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Comparator
1
2
3
4
1
2
3
4
1
2010
2011
2012
Quarter, Year
Overall Rate
Tertiary Rate
Metro Non-Tertiary Rate
WACHS Rate
Private Rate

CDI CASES 2010 - 2012



Reasons for increase

- Changes in test numbers
  - Some evidence of this
  - Greater awareness
- Changes in testing methods
  - Yes – when and what impact?
- If a real increase then why?
  - Healthcare associated vs community-associated
  - Changes in risk factors??????

The Epidemiology of Community-Acquired *Clostridium difficile* Infection: A Population-Based Study

Sahil Khanna, MBBS[1], Darrell S. Pardi, MD, MS, FACG[1], Scott L. Aronson, MD[1,2], Patricia P. Kammer, CCRP[1], Robert Orenstein, DO[3], Jennifer L. St Sauver, PhD[4], W. Scott Harmsen, MS[5] and Alan R. Zinsmeister, PhD[5]

Study highlights

What is current knowledge?

- *Clostridium difficile infection* is increasing worldwide with hospitalization and antibiotic exposure as the most common risk factors.
- The epidemiology and characteristics of community-acquired *Clostridium difficile* infection are not well defined.

What is new here?

- A major proportion of *Clostridium difficile* infection patients is community-acquired.
- These patients are younger, often lack traditional risk factors, and have less severe disease than patients with hospital-acquired infection.

Am J Gastroenterol. 2012 January ; 107(1): 89–95. doi:10.1038/ajg.2011.398.

Community acquired CDI

- This is not new!
- Very much under-diagnosed for years
- *C. difficile* is ubiquitous
- Many sources in the community
- All animals get colonised at birth incl. humans
- But – generally requires exposure to an infectious dose <u>AND</u> prior gut insult
- Risk factors need further investigation

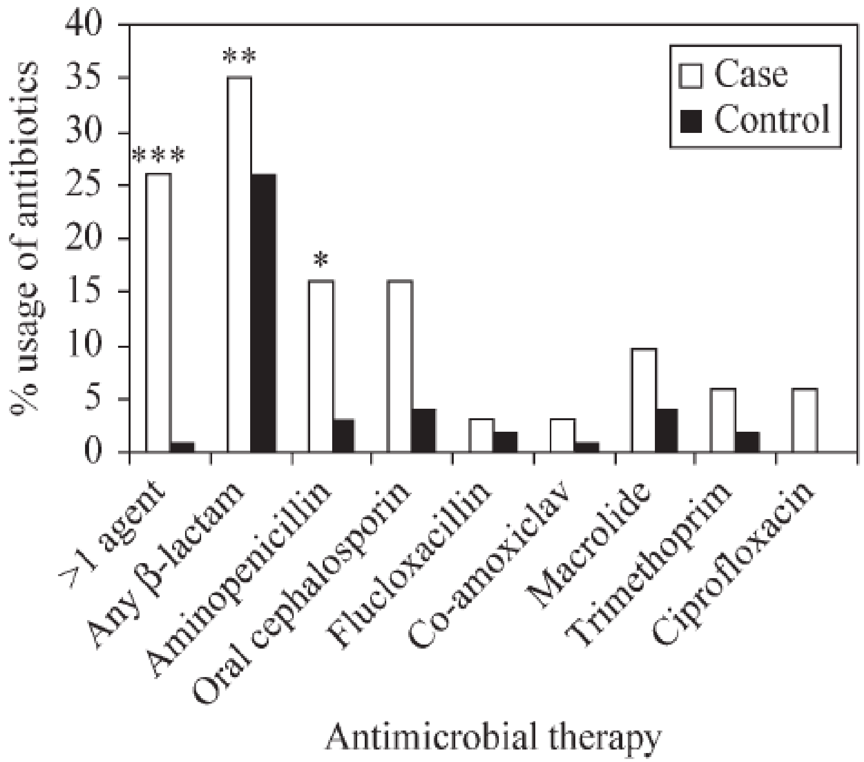
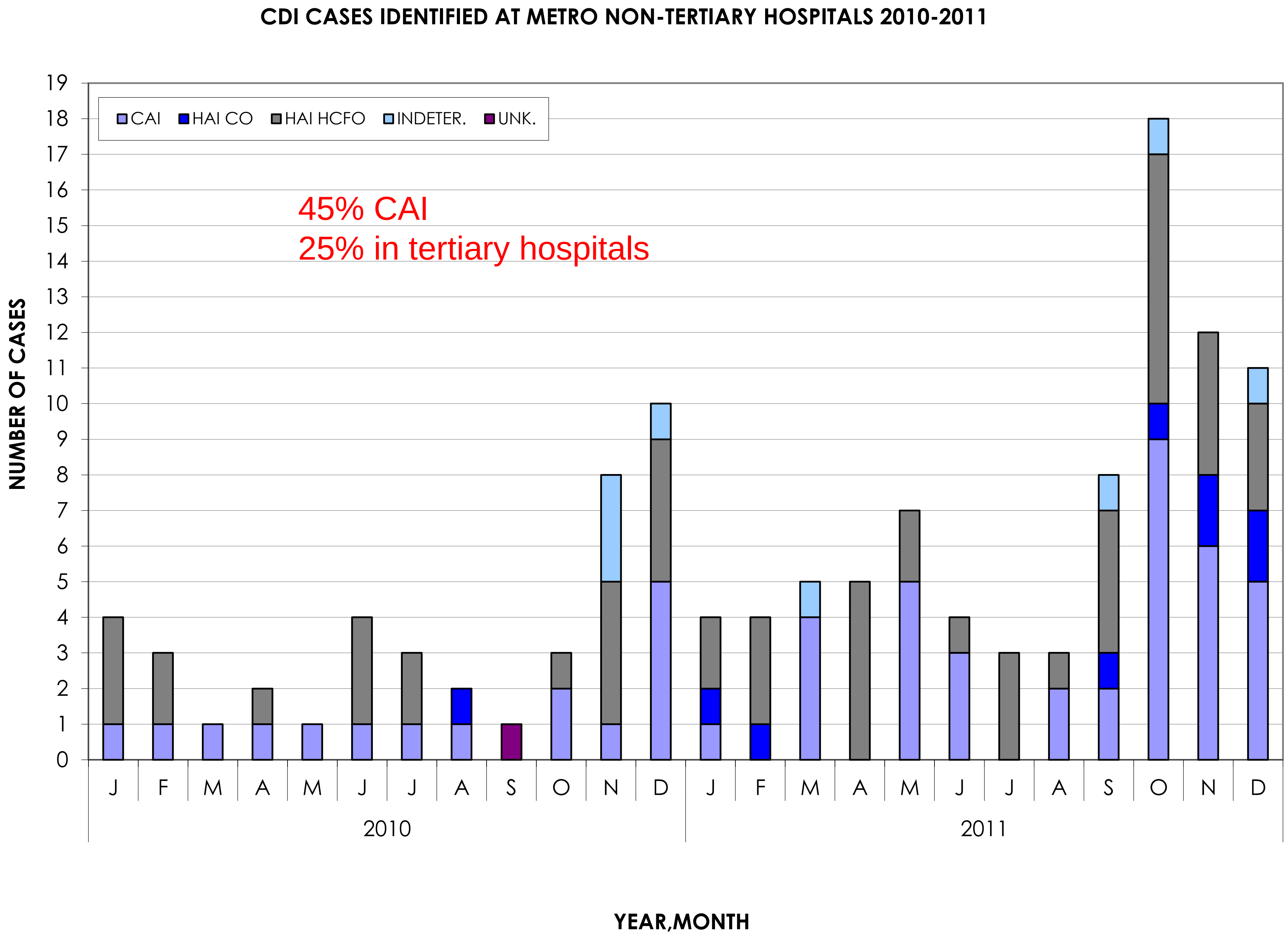


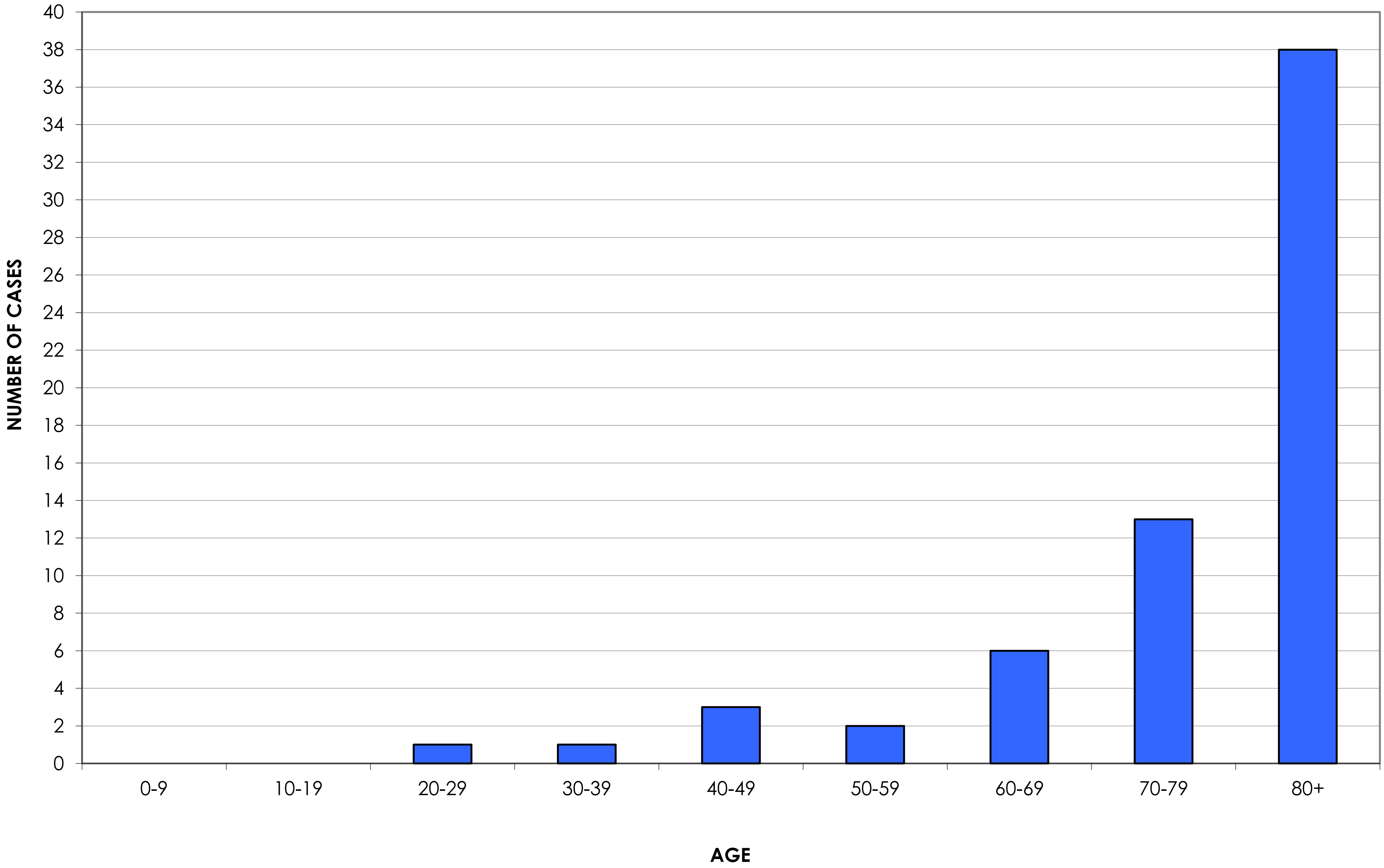
Figure 1. Comparative antibiotic usage in randomly selected community-associated CDI cases and controls. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

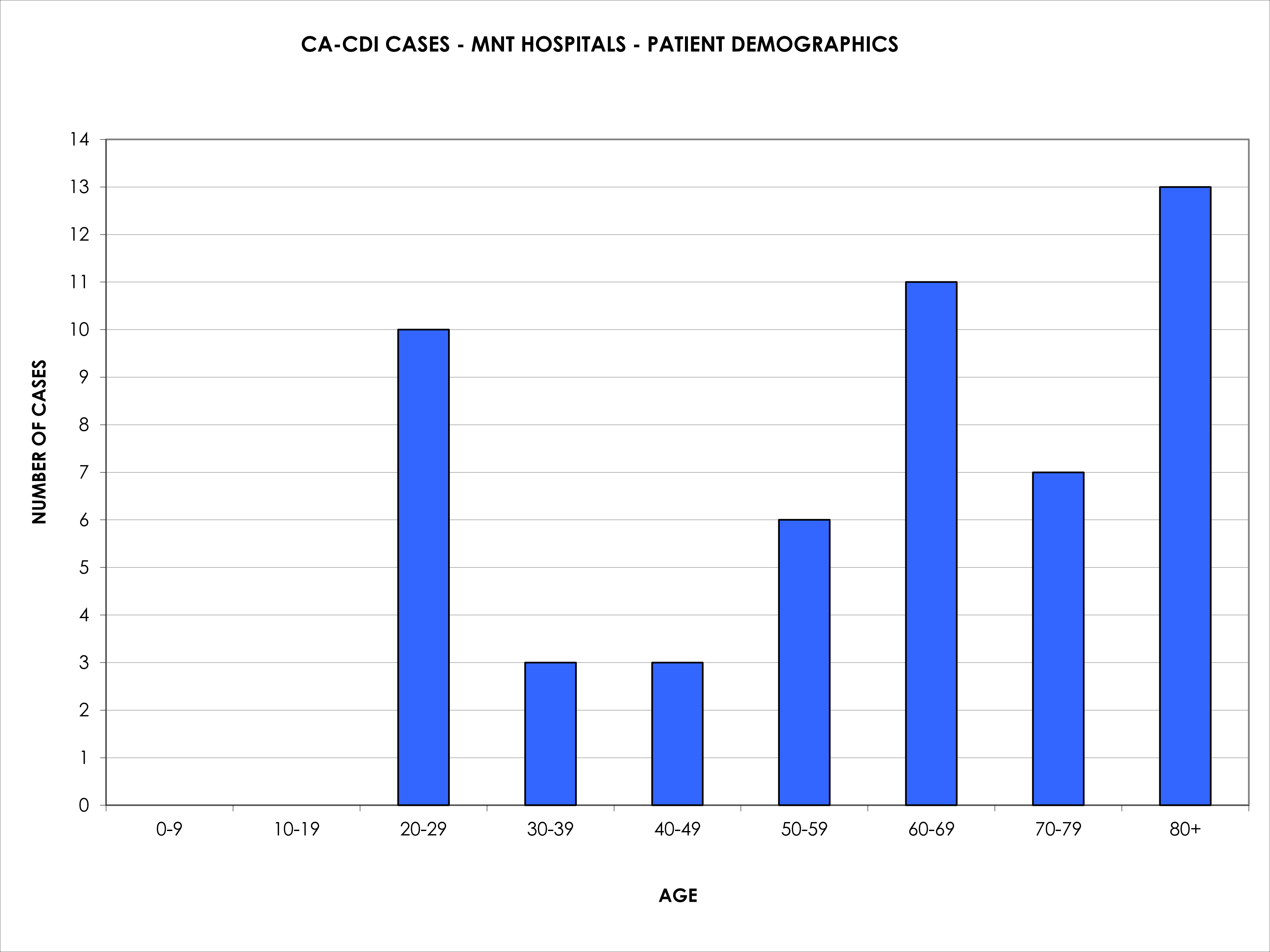
Contact with infants <2 years old significantly associated with CDI

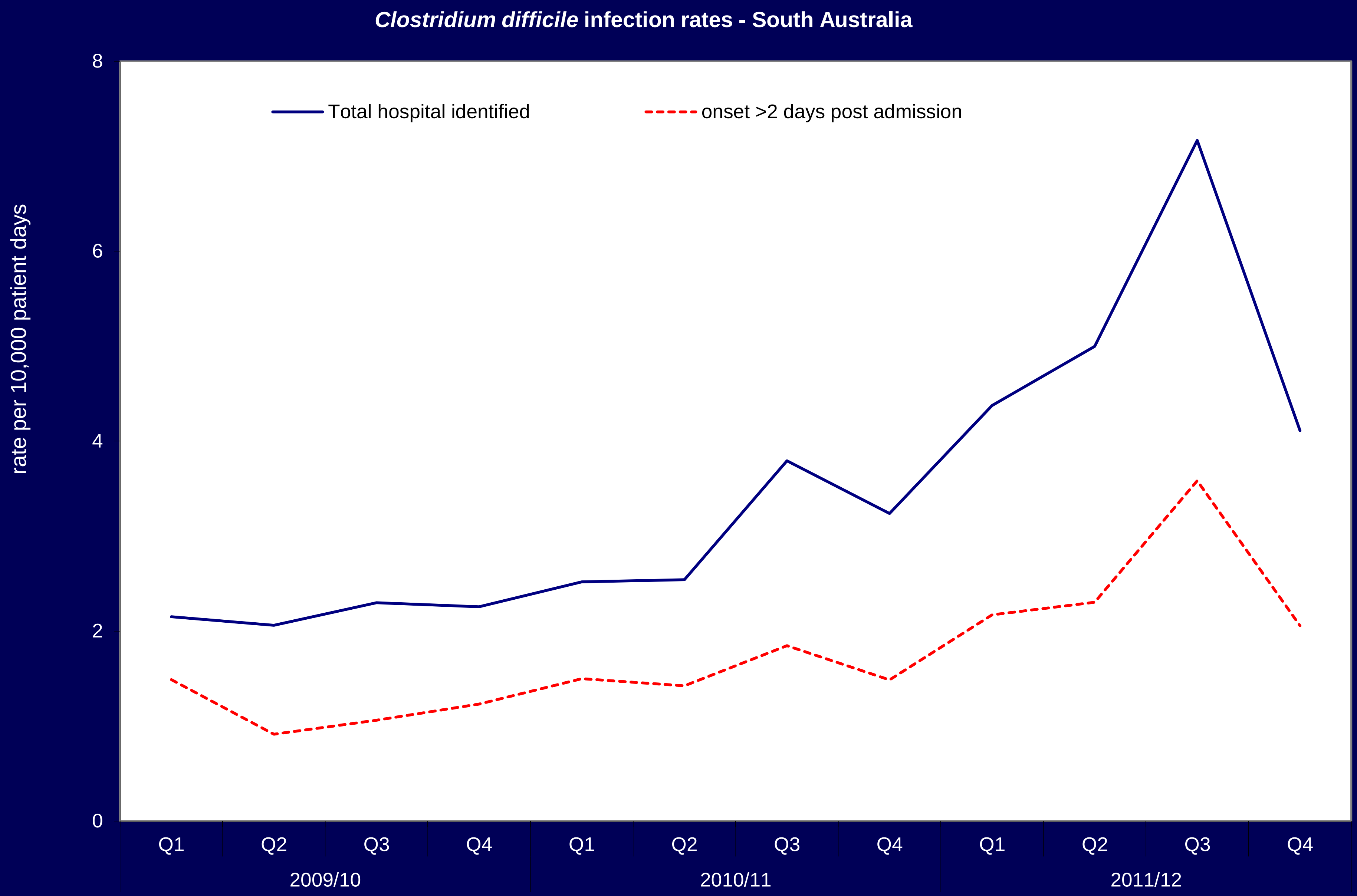
Wilcox *et al. J Antimicrob Chemother* 2008; 62: 388-396.


CDI CASES IDENTIFIED AT METRO NON-TERTIARY HOSPITALS 2010-2011
CAI
HAI CO
HAI HCFO
INDETER.
UNK.
45% CAI
25% in tertiary hospitals
NUMBER OF CASES
YEAR,MONTH
2010
2011
J F M A M J J A S O N D
J F M A M J J A S O N D

HA-CDI - MNT HOSPITALS - PATIENT DEMOGRAPHICS



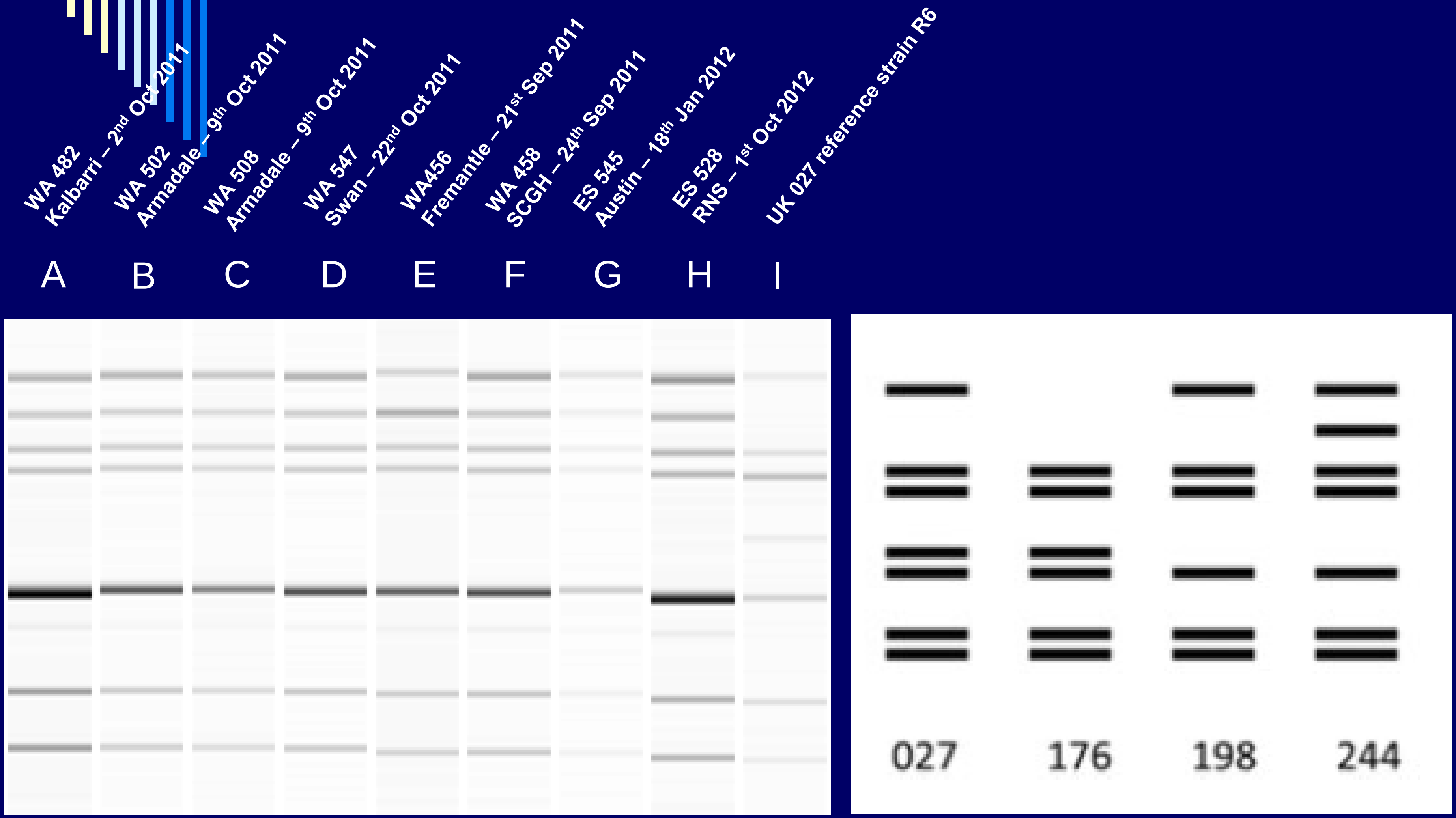

CA-CDI CASES - MNT HOSPITALS - PATIENT DEMOGRAPHICS
NUMBER OF CASES
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0-9
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80+
AGE



Clostridium difficile infection rates - South Australia
rate per 10,000 patient days
Total hospital identified
onset >2 days post admission
0
2
4
6
8
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
Q1
Q2
Q3
Q4
2009/10
2010/11
2011/12

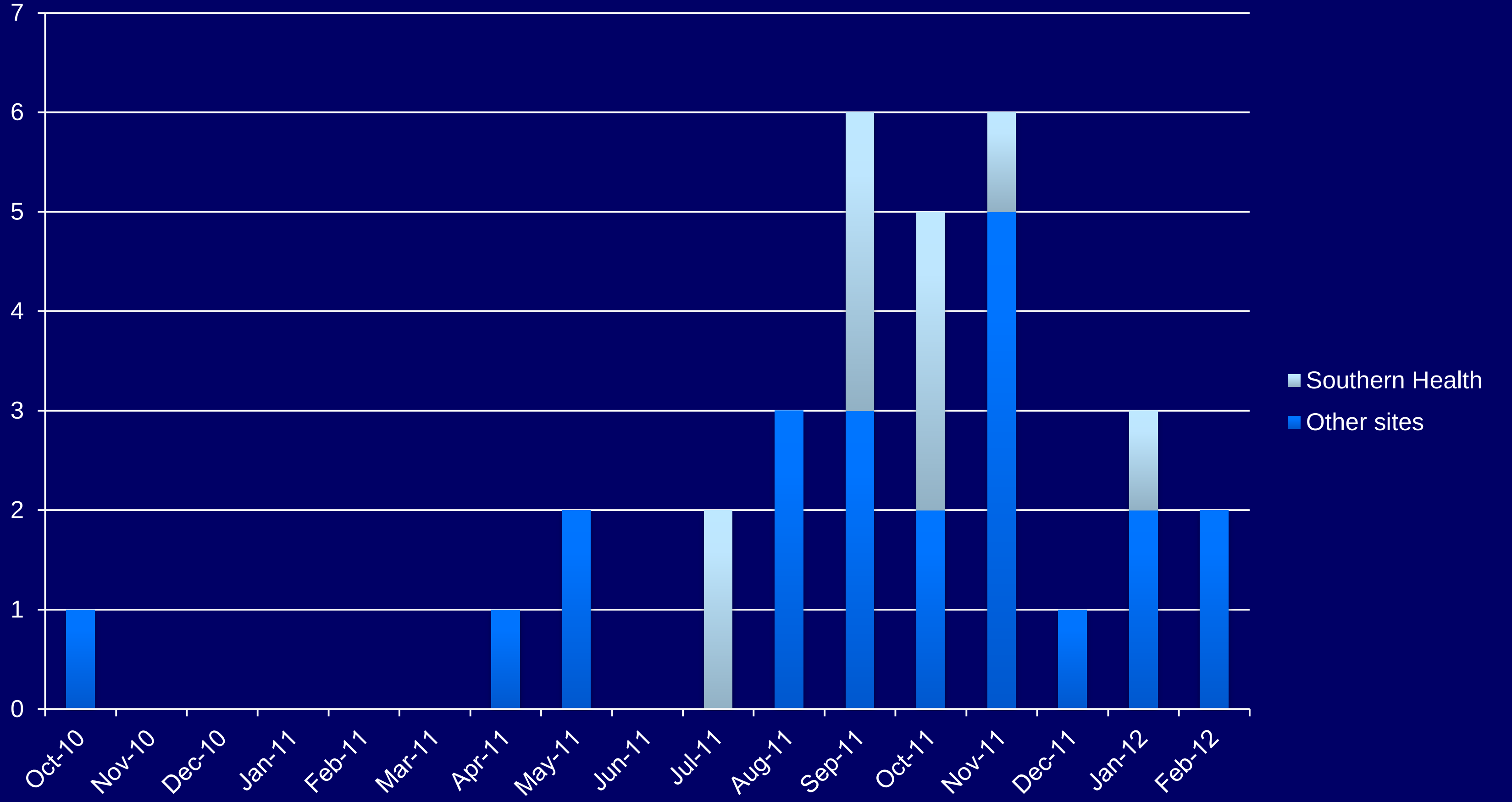
C. difficile PCR ribotype 244

- More severe disease – attributable mortality 30% (Dr Rhonda Stuart)
- Currently community acquired
- Produces more toxins A and B
- Produces binary toxin
- Fluoroquinolone susceptible
- Putative 027 with GeneXpert
- Sept-Oct 2010 ACSQHC snapshot – one isolate
- Now 3rd most common ribotype in Australia ~5%



Valiente *et al*. J Med Microbiol 2012

“MDU – 064” - Victoria

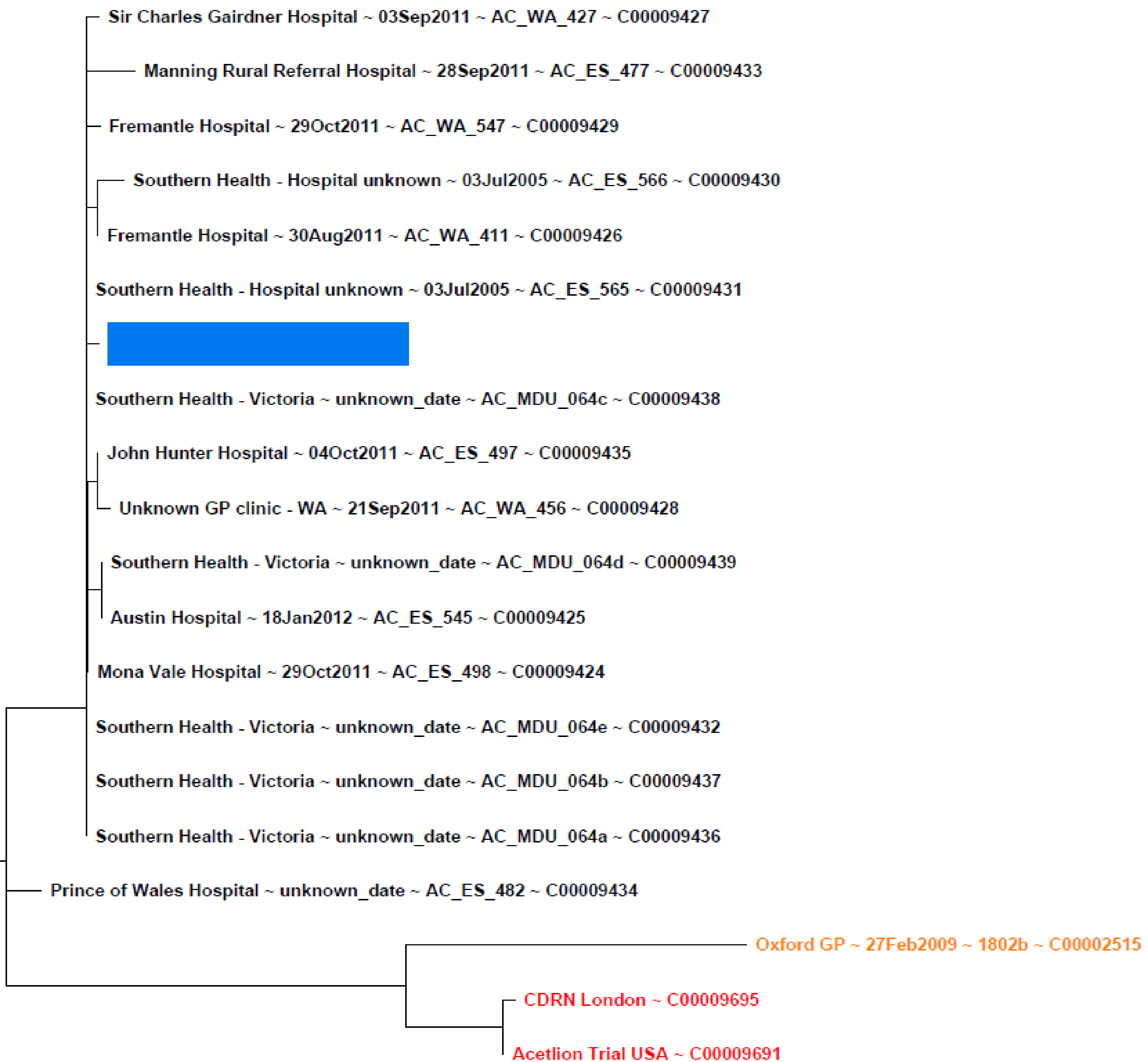


Case control study – Dr Rhonda Stuart

- 10 cases – July - December 2011
  - Mean age 74 years (range 38 – 92)
  - 80% > 65 years
  - Comorbidities
    - Diabetes 30%
    - Malignancy 20%
    - IHD 50%
    - No comorbidities 10%
  - Onset
    - Community onset = 80%
    - Community acquired = 40%
- 20 Controls
  - Matched to site and time (within 4 weeks) of isolate

	MDU - 064	Non- 064	P	OR (95% CI)
Disease Severity				
Creat > 200 or > 50% baseline	6/10 (60)	1/20 (5)	0.002	28 (2 – 306)
Albumin < 25	8/10 (80)	3/17 (18)	0.003	18 (2 – 136)
Fever > 38	3/10 (30)	5/20 (25)	NS	
WCC > 15	4/10 (40)	4/20 (20)	NS	
A [illegible]	[illegible]	[illegible]	[illegible]	[illegible]
I [illegible]	[illegible]	[illegible]	[illegible]	[illegible]
C [illegible]				
[illegible]	[illegible]	[illegible]	[illegible]	
Severe disease (Zar)	8/10 (80)	7/20 (35)	0.006	7 (1 – 84)
Treatment				
Vancomycin	8/10 (80)	2/20 (10)	< 0.001	36 (3 – 495)
Outcome				
Response	7/10 (70)	18/20 (90)	NS	
Death within 30 days	4/10 (40)	0/20 (0)	0.007	
Attributable mortality	3/10 (30)	0/13 (0)	0.029	

	MDU-064	Non-MDU 064	P	OR
Total June – Dec 11	10	246		
In Hospital Deaths	2	2	0.008	30 (4 – 244)


Sir Charles Gairdner Hospital ~ 03Sep2011 ~ AC_WA_427 ~ C00009427
Manning Rural Referral Hospital ~ 28Sep2011 ~ AC_ES_477 ~ C00009433
Fremantle Hospital ~ 29Oct2011 ~ AC_WA_547 ~ C00009429
Southern Health - Hospital unknown ~ 03Jul2005 ~ AC_ES_566 ~ C00009430
Fremantle Hospital ~ 30Aug2011 ~ AC_WA_411 ~ C00009426
Southern Health - Hospital unknown ~ 03Jul2005 ~ AC_ES_565 ~ C00009431
[redacted]
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064c ~ C00009438
John Hunter Hospital ~ 04Oct2011 ~ AC_ES_497 ~ C00009435
Unknown GP clinic - WA ~ 21Sep2011 ~ AC_WA_456 ~ C00009428
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064d ~ C00009439
Austin Hospital ~ 18Jan2012 ~ AC_ES_545 ~ C00009425
Mona Vale Hospital ~ 29Oct2011 ~ AC_ES_498 ~ C00009424
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064e ~ C00009432
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064b ~ C00009437
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064a ~ C00009436
Prince of Wales Hospital ~ unknown_date ~ AC_ES_482 ~ C00009434
Oxford GP ~ 27Feb2009 ~ 1802b ~ C00002515
CDRN London ~ C00009695
Acetlion Trial USA ~ C00009691

Is *Clostridium difficile* a threat to Australia's biosecurity?

Thomas V Riley

Australia can benefit from lessons learned in the epidemic of C. difficile *infection in Europe and North America*

MJA • Volume 190 Number 12 • 15 June 2009

Every effort should be made to stop epidemic *C. difficile* from becoming established in our production animals. Unfortunately, the mere perception of *C. difficile* infection as a foodborne disease will damage the industry.

However, if cephalosporin use is driving *C. difficile* infection in animals overseas, then additional efforts to target cephalosporin use in veterinary medicine may be needed in Australia.



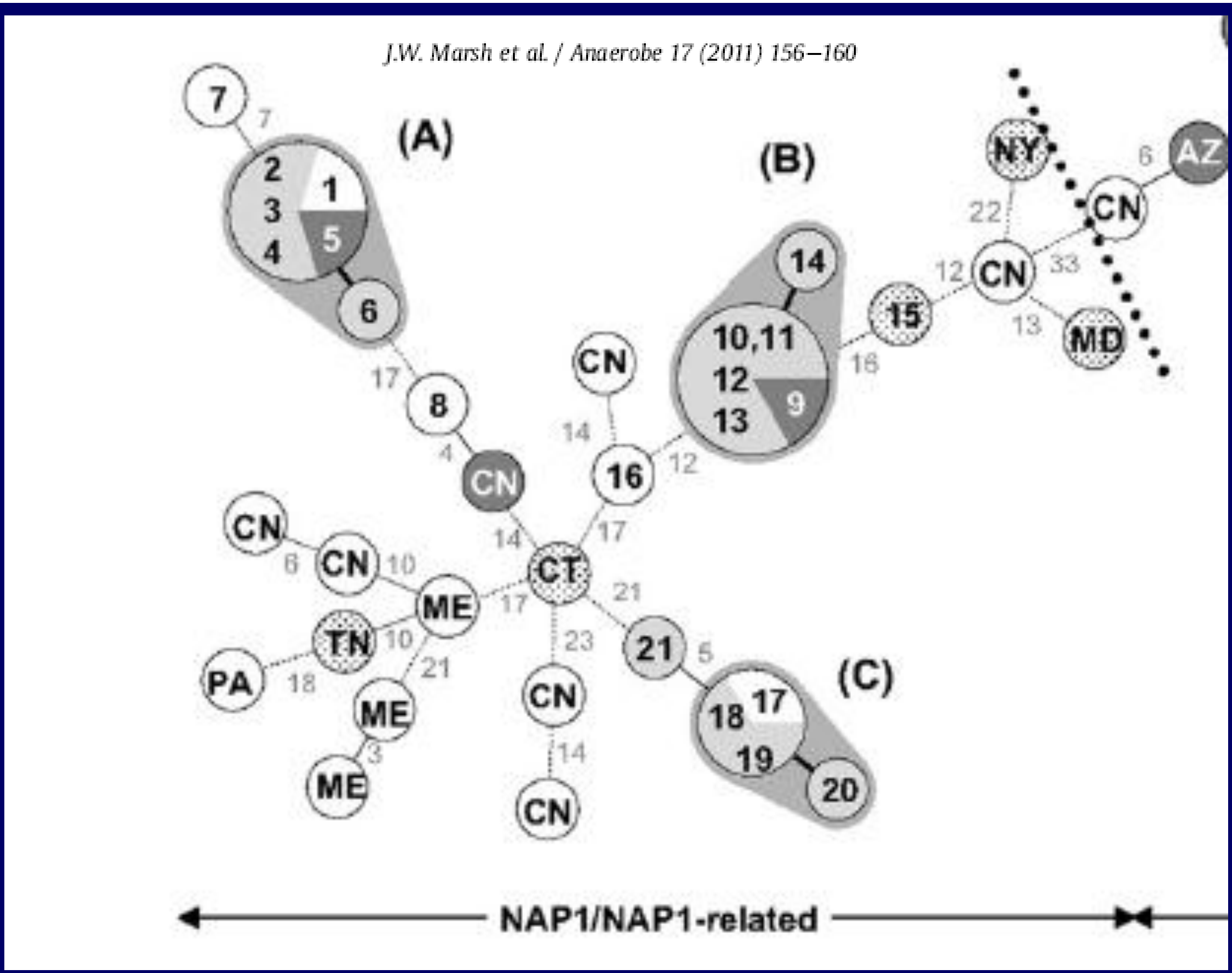



Table. Source and characteristics of *Clostridium difficile* isolates obtained from retail meats sold in Tuscon, Arizona, USA, 2007*

Meat product	No. samples cultured	Total no. (%) positive	Ribotype	Toxinotype	Δ*tcdC*, bp†	PFGE type	No. (%) pos
Ground beef (uncooked)	26	13 (50)	027	III	18	NAP1	1 (3.8)
						NAP1-related	2 (7.7)
			078	V	39	NAP7	8 (30.8)
						NAP8	2 (7.7)
Summer sausage (ready to eat)	7	1 (14.3)	027	III	18	NAP1	1 (14.3)
Ground pork (uncooked)	7	3 (42.9)	027	III	18	NAP1-related	1 (14.3)
			078	V	39	NAP7	2 (28.6)
Braunschweiger (ready to eat)	16	10 (62.5)	027	III	18	NAP1	2 (12.5)
						NAP1-related	1 (6.2)
			078	V	39	NAP7	7 (43.8)
Chorizo (uncooked)	10	3 (30.0)	027	III	18	NAP1-related	1 (10.0)
			078	V	39	NAP7	2 (20.0)
Pork sausage (uncooked)	13	3 (23.1)	027	III	18	NAP1-related	1 (7.7)
			078	V	39	NAP7	2 (15.4)
Ground turkey (uncooked)	9	4 (44.4)	078	V	39	NAP7	4 (44.4)
Totals	88	37 (42.0)	027	III	18	NAP1	4 (4.4)
						NAP1-related	6 (6.7)
			078	V	39	NAP7	25 (27.8)
						NAP8	2 (2.2)

*All samples were positive for *cdtB*, which encodes the binding component of binary toxin. PFGE, pulsed-field gel electrophoresis.
†Deletions in *tcdC* regulatory gene.

Songer *et al*. *Emerg Infect Dis* 2009; 15: 819-821

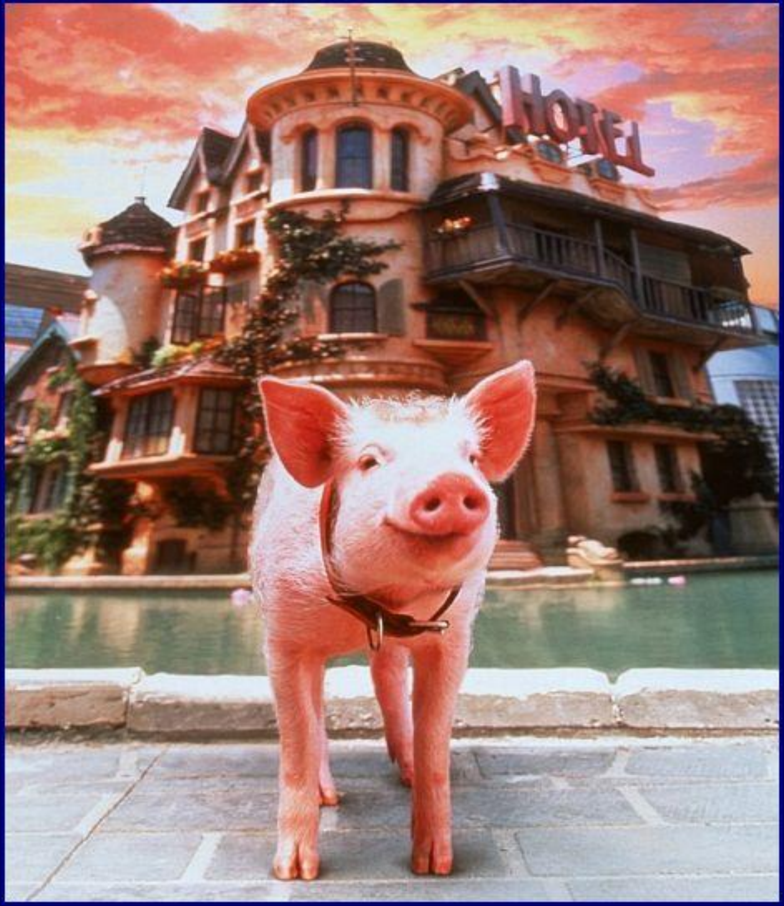


Molecular and epidemiologic information of selected study *C. difficile* isolates.

Cluster	No.	Source	Location	CDR4	CDR5	CDR6	CDR9	CDR48	CDR49	CDR60	tcdC	PFGE
A	1	Human	NJ	18	3	20	15	9	12	10	1	NAP1
	2	Braunschweiger	AZ	18	3	20	15	9	12	10	1	NAP1
	3	Ground beef	AZ	18	3	20	15	9	12	10	1	NAP1
	4	Braunschweiger	AZ	18	3	20	15	9	12	10	1	NAP1
	5	Bovine	AZ	18	3	20	15	9	12	10	1	NAP1

C. difficile in pigs

- Early this century outbreaks of CDI in 5d old piglets in USA - high mortality (16%)
- Since 2000, *C. difficile* the major & most common cause of enteritis in neonatal piglets in USA
- Economic losses
- Pig ribotype 078
- 078 now infecting people in Europe and USA, 3rd most common
- ? Food source or environment



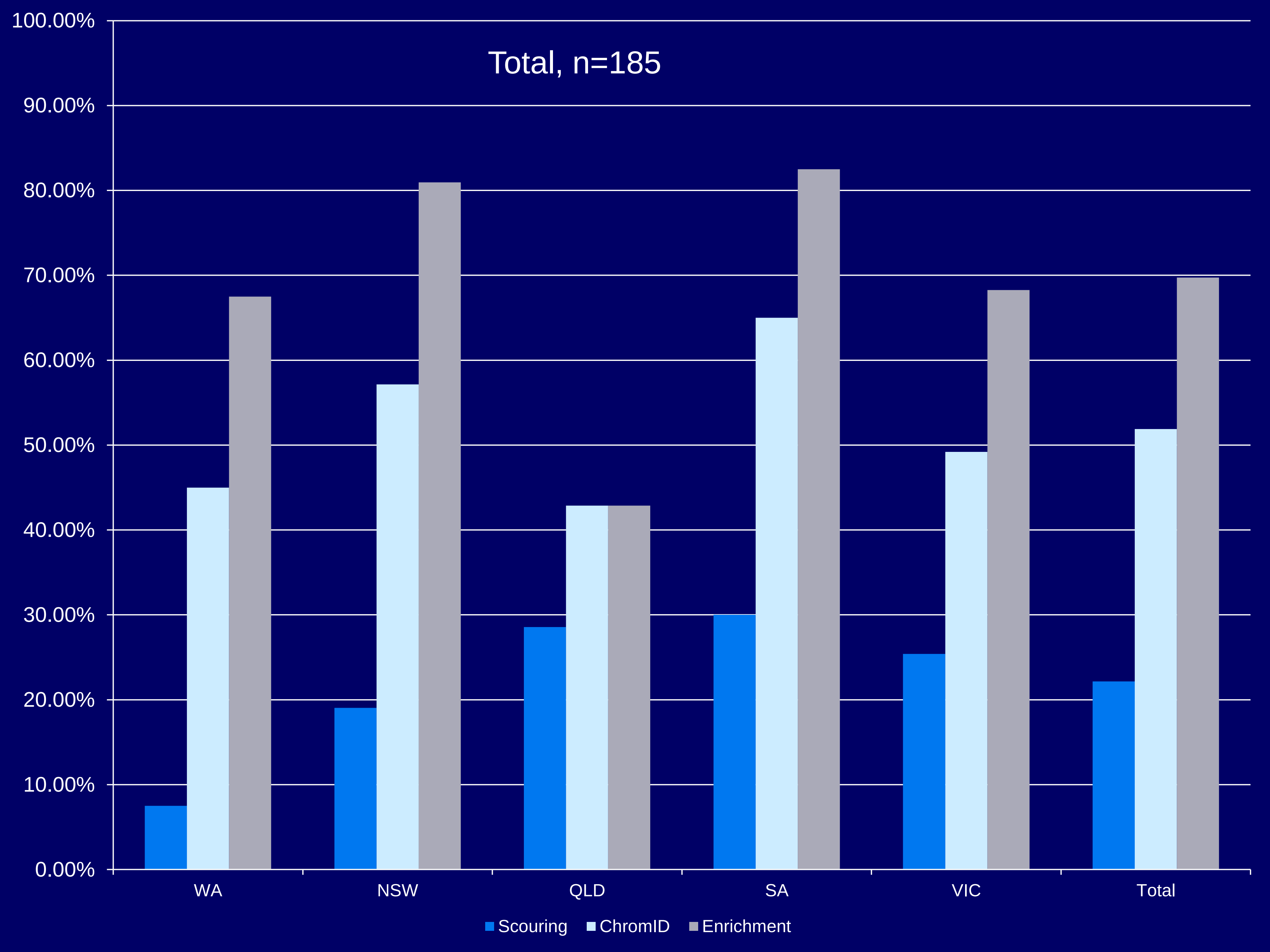
Clostridium difficile infection in Europe: a hospital-based survey

*Martijn P Bauer, Daan W Notermans, Birgit H B van Benthem, Jon S Brazier, Mark H Wilcox, Maja Rupnik, Dominique L Monnet, Jaap T van Dissel, Ed J Kuijper, for the ECDIS Study Group**

Lancet 2011; 377: 63-73

Methods We set up a network of 106 laboratories in 34 European countries.

Microbiological characteristics	
Most frequent PCR-ribotypes of toxigenic isolates	
014/020	61/389 (16%)
001	37/389 (10%)
078	31/389 (8%)
018	23/389 (6%)
106	20/389 (5%)
027	19/389 (5%)
002	18/389 (5%)
012	17/389 (4%)
017	14/389 (4%)



Total, n=185
100.00%
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
WA
NSW
QLD
SA
VIC
Total
Scouring
ChromID
Enrichment

Rates of detection of *C. difficile* in Australian sheep and lambs

Faecal samples	Sheep	Lambs
	No. positive / No. tested (% positive)	No. positive / No. tested (% positive)
Batch 1 (n=50)	1/27 (3.7%)	3/23 (13%)
Batch 2 (n=100)	0/47	1/53 (1.8%)
Batch 3 (n=50)	0/24	0/26
Batch 4 (n=100)	0/58	2/42 (4.2%)
Total (n=300)	1/156 (0.6%)	6/144* (4.2%)

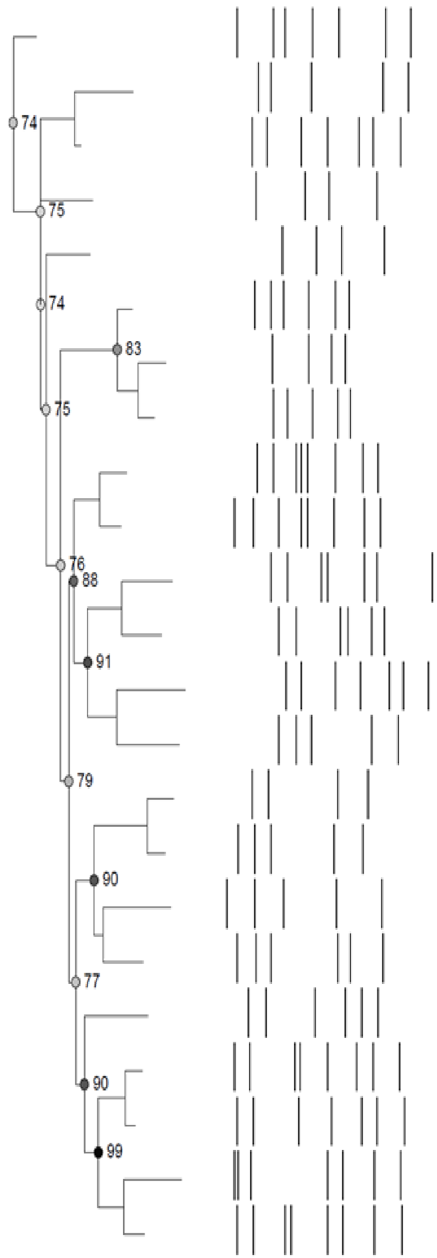
*p=0.04

C. difficile in chickens

- No *C. difficile* in chickens – relatively small sample (~60)
  - 4-5 day old chicks
  - 4 weeks old
  - At slaughter – 8 weeks

C. difficile in cattle in Australia

- 2008/9: adult cattle, 151 carcass washings and 151 gut contents from WA
  - No *C. difficile*
- 2009/10: 280 faecal samples from adults E Australia
  - 5 positives (1.8%)
- 2012: 360 <7 day old veal calves, several abattoirs in Vic and Queensland (4% in 2-6 month old calves)
  - 56% positive



	Toxin gene profile						
PCR Ribotype	tcdA	tcdB	cdtA/cdtB	n (%)	Specimen	Age distribution (n)	Abattoir distribution (n)
RT027*	+	+	+	-	-	-	-
QX022	-	+	-	1 (0.5)	Faeces	<7 day old calf (1)	V5[‡] (1)
RT103	+	+	-	3 (1.4)	Faeces	<7 day old calf (3)	V6[‡] (3)
QX058	-	+	+	2 (1.0)	Faeces	<7 day old calf (2)	V6[‡] (2)
RT033[ΦLK-]	-	-	+	41 (19.6)	Faeces	<7 day old calf (41)	Q12[Ω] (6), V5[‡] (4), V6[‡] (23), V6α[‡] (8)
RT078*[Φ]	+	+	+	-	-	-	-
RT127[Φ]	+	+	+	105 (50.2)	Faeces	<7 day old calf (104), [±](1)	Q12 [Ω] (10[±]), V5[‡] (30), V6[‡] (54), V6α[‡] (11)
RT126[Φ]	+	+	+	12 (5.7)	Faeces	<7 day old calf (12)	Q12 [Ω] (11), V6[‡] (1)
QX010	+	+	-	2 (1.0)	Faeces	<7 day old calf (2)	V6[‡] (1), V6α[‡] (1)
AU095	-	-	-	1 (0.5)	Faeces	Adult cow (1)	V4[‡] (1)
QX025	+	+	-	2 (1.0)	Faeces	<7 day old calf (2)	V6[‡] (2)
QX030	+	+	-	4 (1.9)	Faeces	<7 day old calf (4)	V6[‡] (3), V6α[‡] (1)
QX017	+	+	-	1 (0.5)	Faeces	<7 day old calf (1)	V6[‡] (1)
QX018	+	+	+	2 (1.0)	Faeces	<7 day old calf (2)	V6[‡] (1), V6α[‡] (1)
AU179	-	-	-	1 (0.5)	Faeces	Adult cow (1)	N2[§] (1)
RT002	+	+	-	2 (1.0)	Faeces	<7 day old calf (2)	V6[‡] (1), V6α[‡] (1)
AU171	-	-	-	1 (0.5)	Faeces	Adult cow (1)	Q5 [Ω] (1)
RT137	+	+	-	1 (0.5)	Faeces	<7 day old calf (1)	Q12 [Ω] (1)
AU147	-	+	+	1 (0.5)	Faeces	Adult cow (1)	N1[§] (1)
RT056	+	+	-	16 (7.7)	Faeces	Adult cow (1), calf (15)	Q4 [Ω] (1), V6[‡] (14), V6α[‡] (1)
RT064	+	+	-	1 (0.5)	Faeces	<7 day old calf (1)	V6[‡] (1)
RT014	+	+	-	3 (1.4)	Faeces	<7 day old calf (3)	V6[‡] (3)
RT087	+	+	-	7 (3.3)	Faeces	<7 day old calf (7)	V5[‡] (1), V6[‡] (6)
			Total	209			

Contaminated vegetables

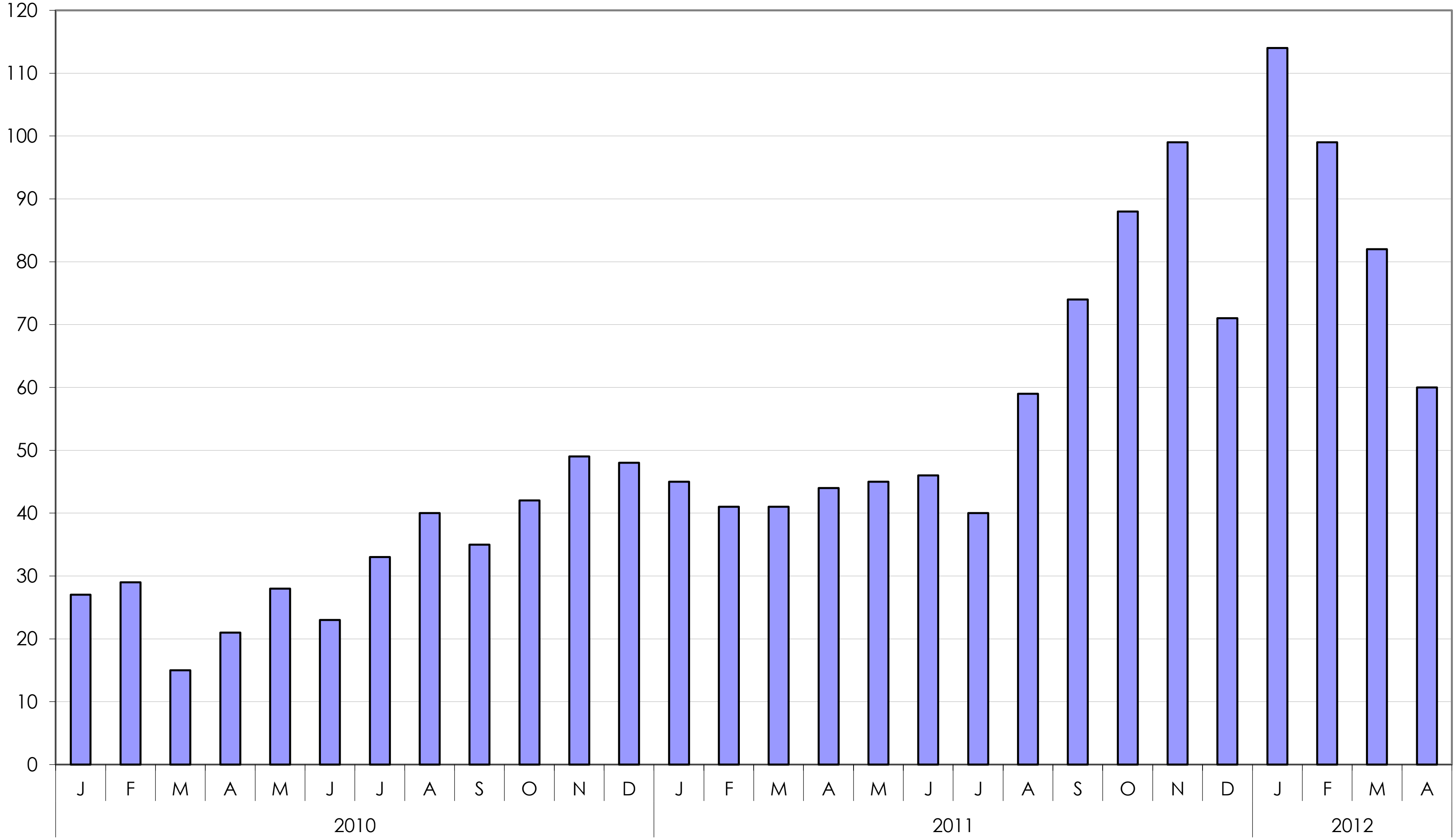
- Bakri *et al*. *Clostridium difficile* in ready-to-eat salads, Scotland. Emerg Infect Dis 2009;15: 817-8. (3/40 [7.5%] positive)
- Metcalf *et al*. *Clostridium difficile* in vegetables, Canada. Letts Appl Microbiol 2010; 51: 600-2. (5/111 [4.5%] positive)
- Al Saif and Brazier. The distribution of *Clostridium difficile* in the environment of South Wales. J Med Microbiol 1996; 45: 133-7.(7/300 [2.3%] positive)

- MUSHROOMS!

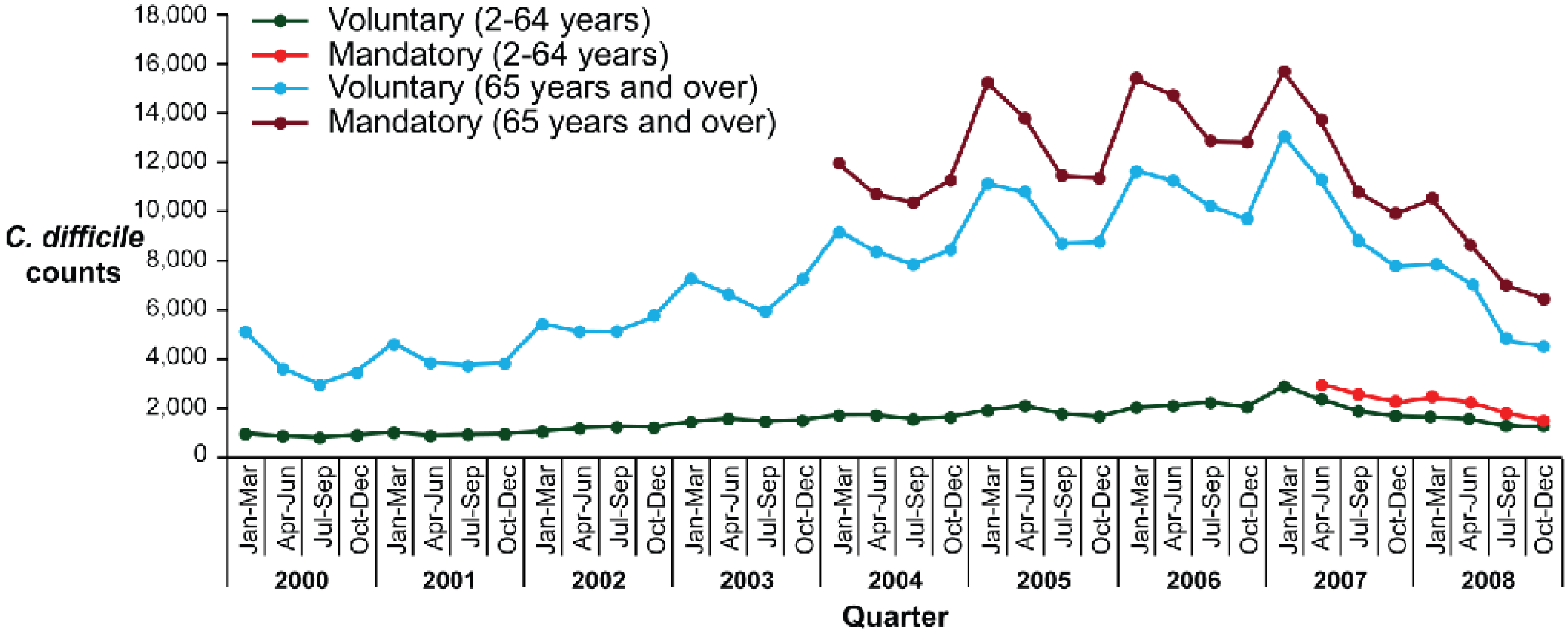
Our 1st theory

- Contaminated Australian meat or vegetables
- Driven by flu season
- But can’t find RT 244 in any animals!
- Doesn’t account for all the increase
- Briony Elliott thinks RT 244 comes from North America

CDI CASES 2010 - 2012



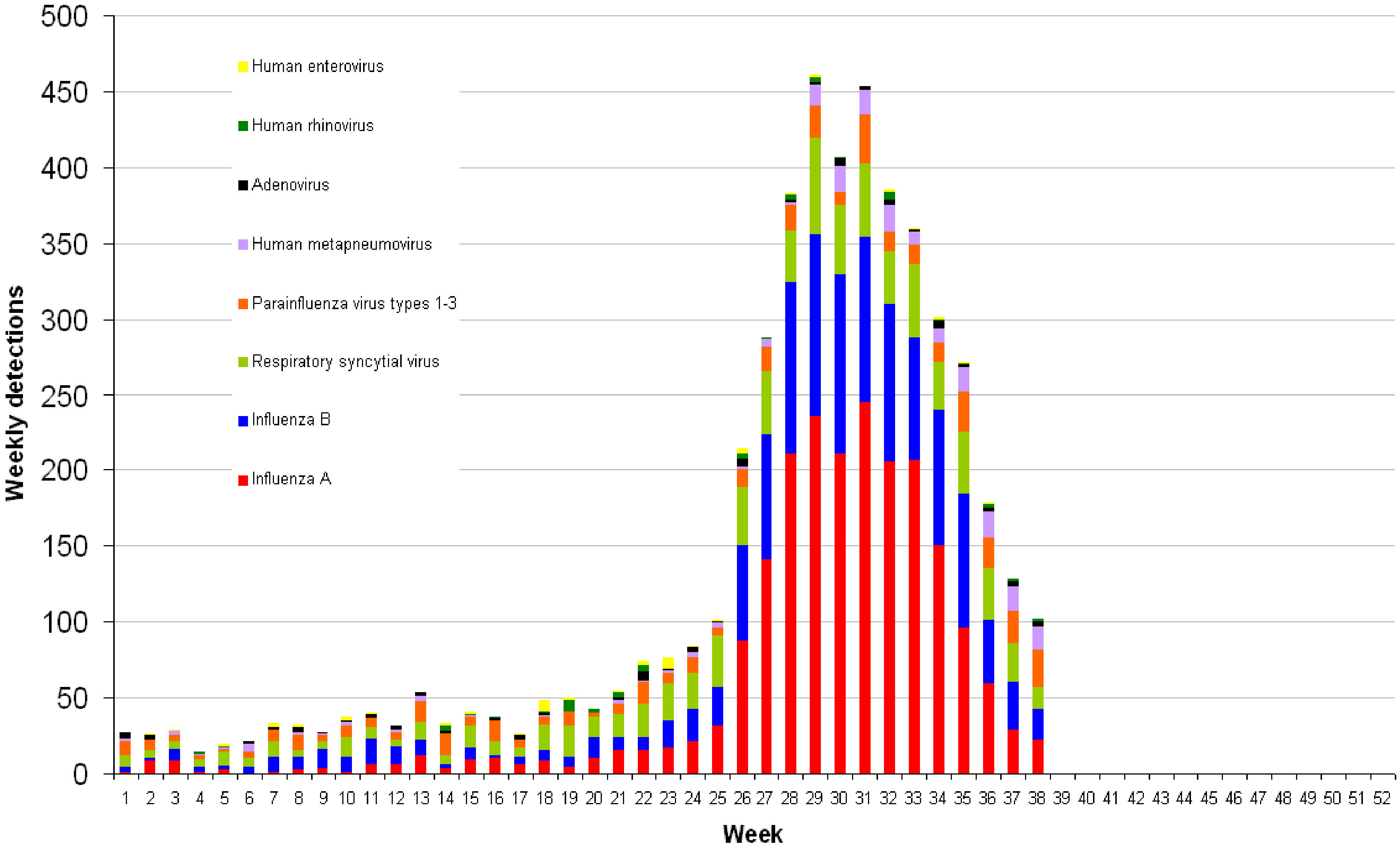
Quarterly counts of *C. difficile:* comparison of mandatory and voluntary quarterly reporting



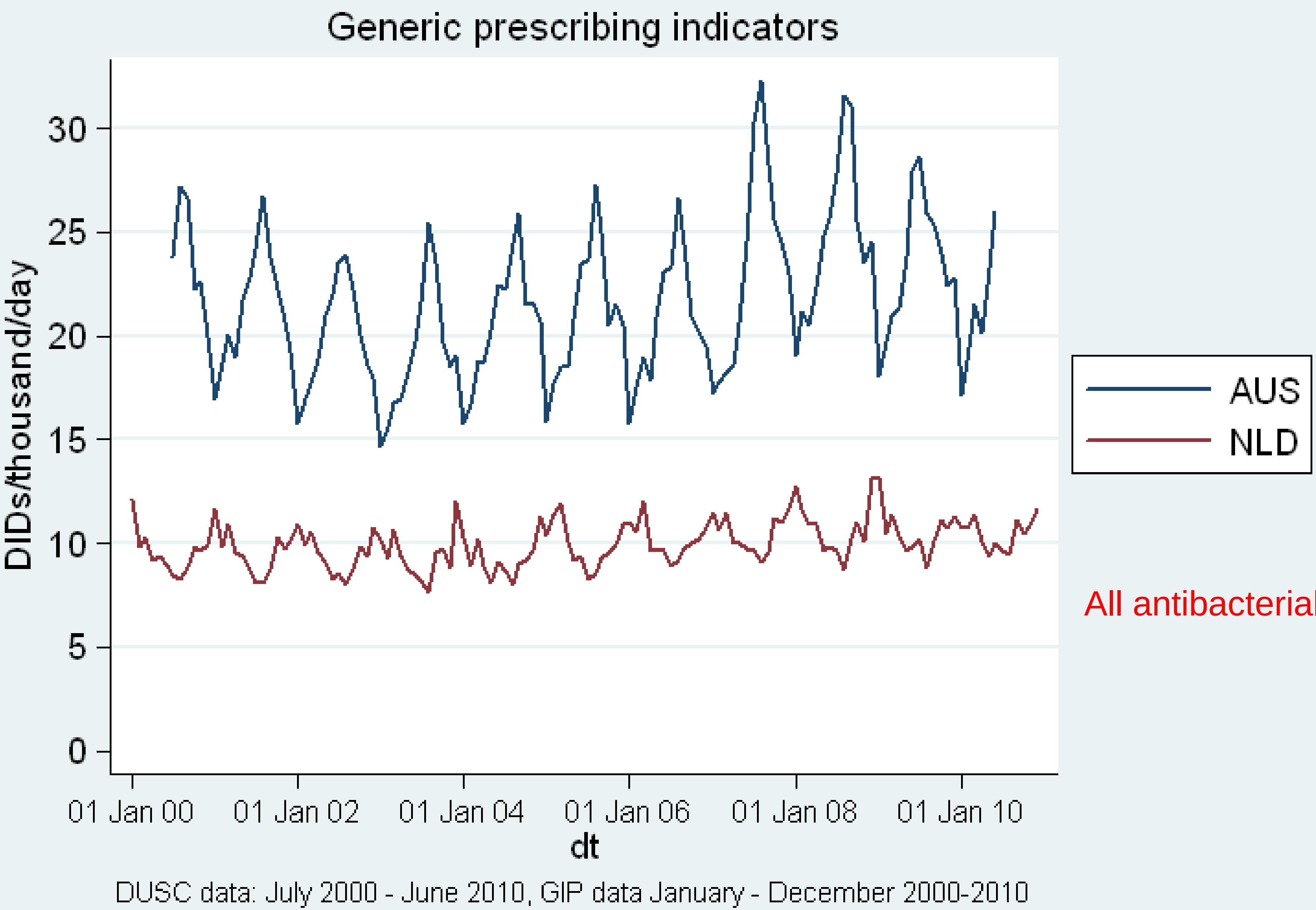
Please note that the voluntary *C. difficile* 2008 data at time of extraction may be under completed.
C. difficile voluntary data includes toxin negative reports.
Extraction date 26.01.2009

Courtesy Andrew Pearson

PathWest QEII 2012 Respiratory Virus Detections



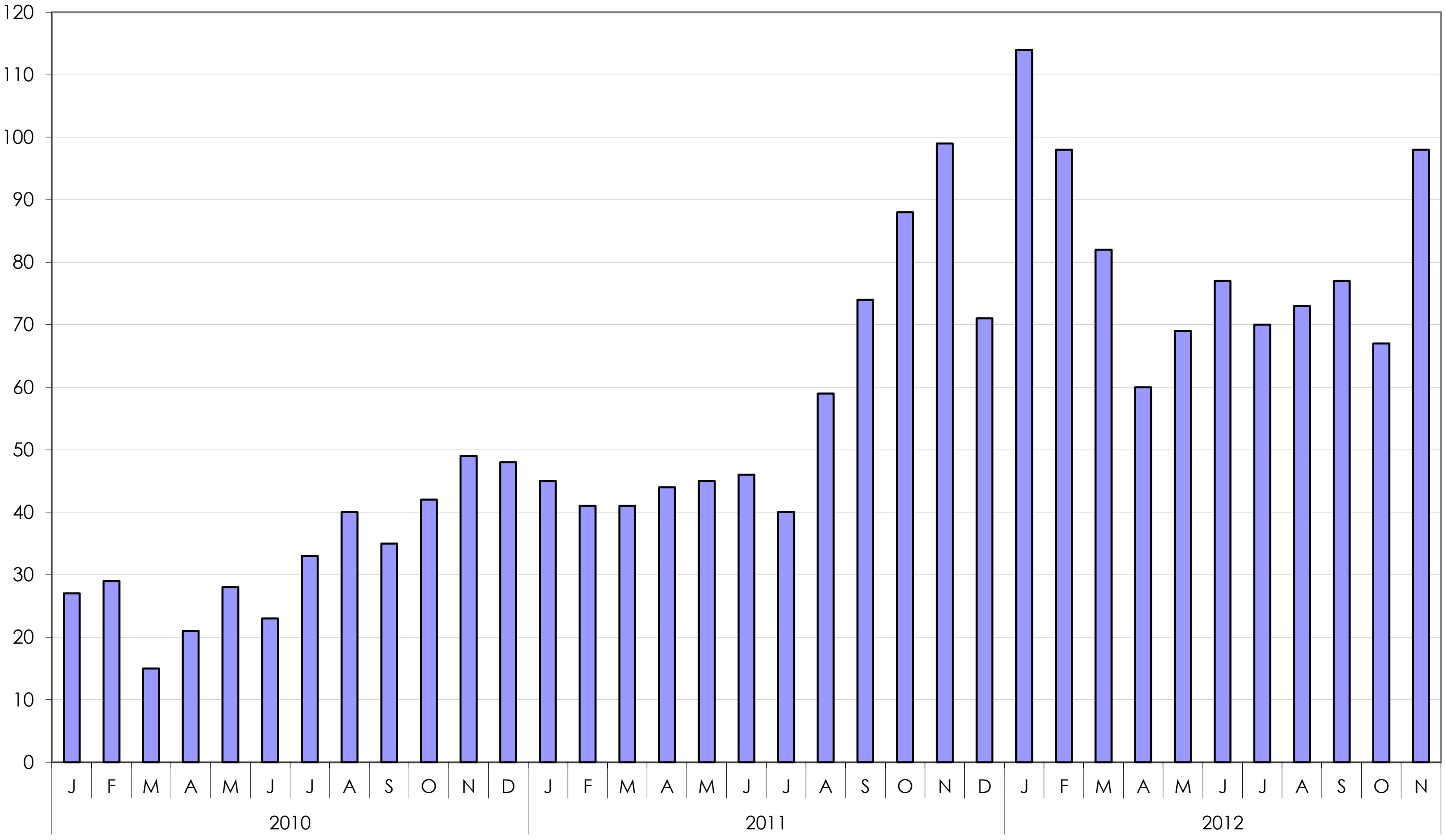
1a: J01: AUS vs NLD



All antibacterials

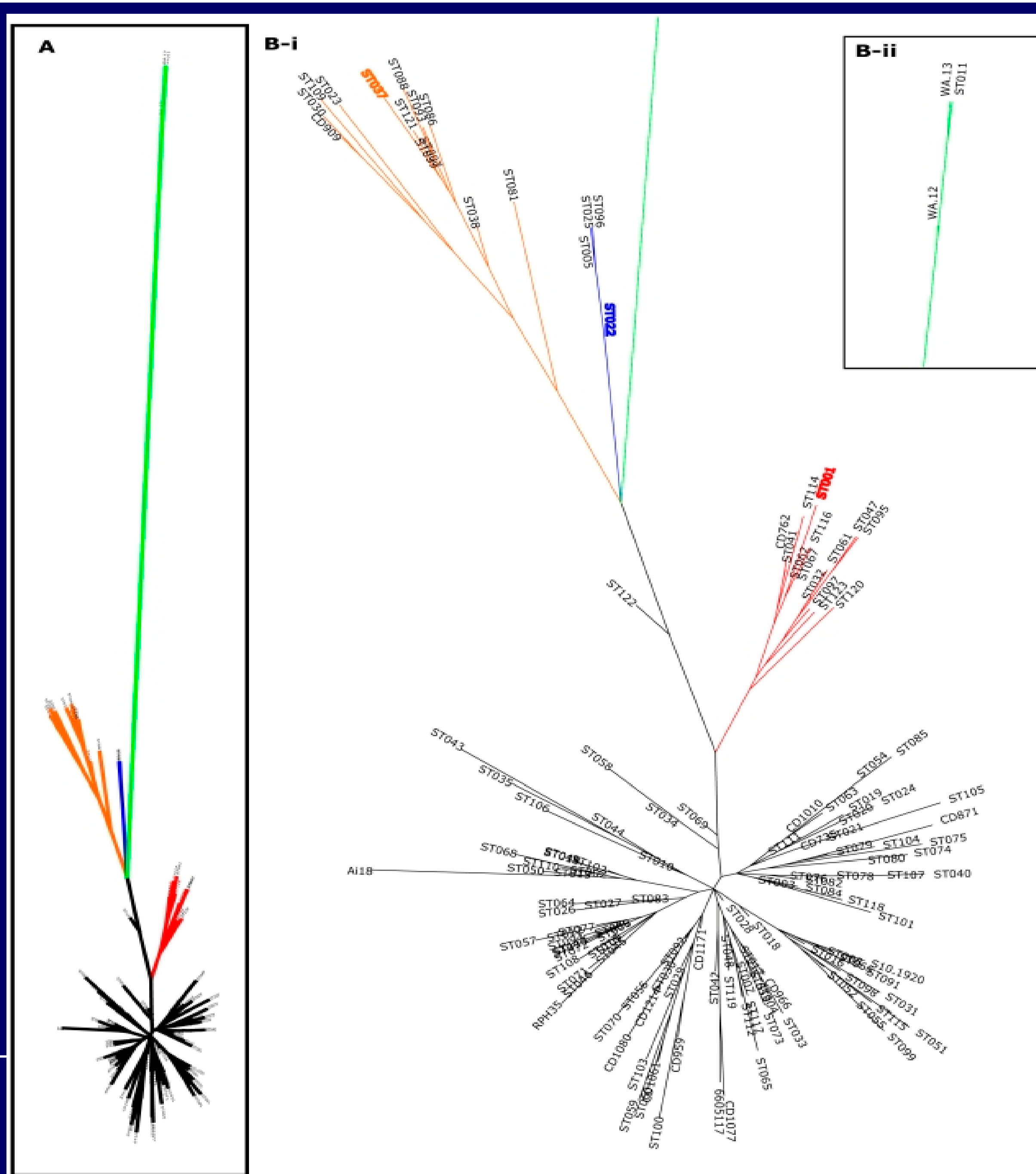
Courtesy of John Turnidge

CDI CASES 2010 - 2012



Relative evolutionary relatedness of five main subgroups and demonstration of microdiversity of subgroups.

Stabler R.A. et al. Macro- and micro diversity of *Clostridium difficile* isolates from diverse sources and geographical locations. *PLoS One* 2012;7:e31559



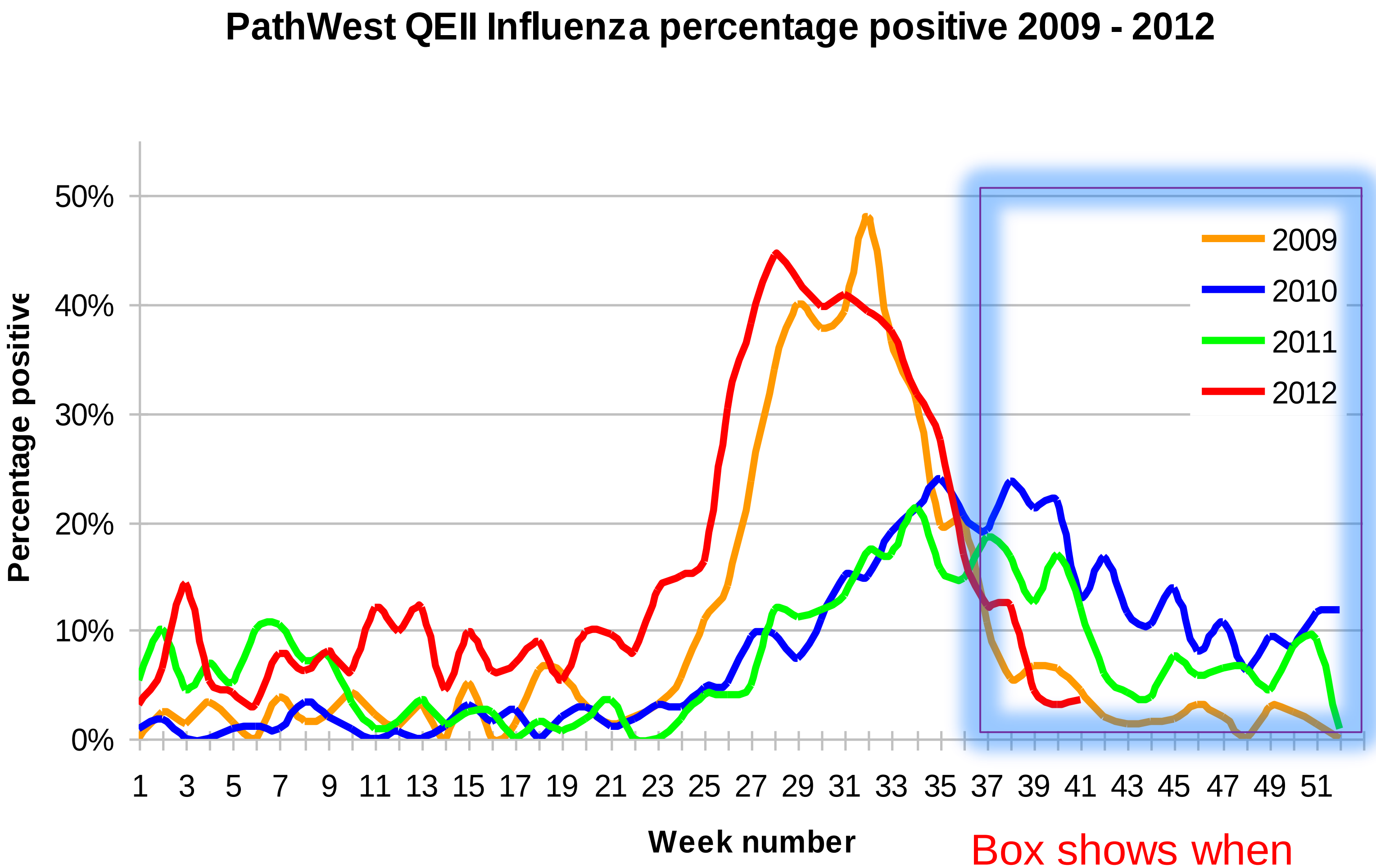
Branch colouring; black = clade 1, red = clade 2 (inc ST-1/RT027), blue = clade 3 (inc ST-22/RT023), orange = clade 4 (inc ST-37/RT017), green = clade 5 (inc ST-11/RT078).

Ribotype 251

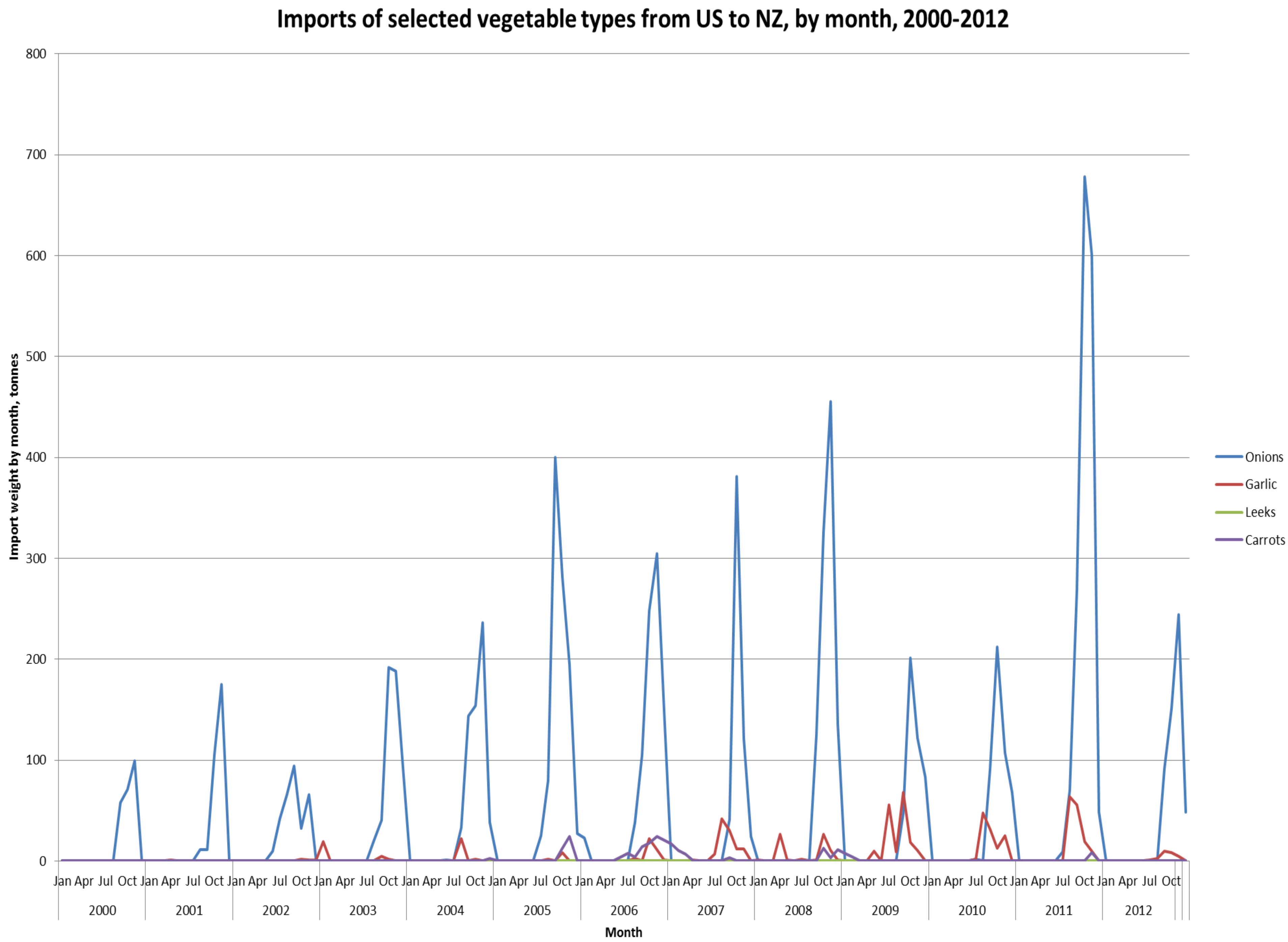
- 2nd major new RT emerged in Australia
- Similar to RT 244
- Community acquired, severe disease
- Binary toxin positive
- Groups with 027 by PFGE
- Cluster found in USA along with a cluster of 244

Our 2nd theory

- Contaminated food imported from North America
- 96% of Australian food local
- Possibly onions
- Exactly the same problem occurring in NZ with the same food importation patterns as Australia
- But probably endemic local food-borne disease also



Box shows when onions/garlic are imported from the USA/Mexico


Imports of selected vegetable types from US to NZ, by month, 2000-2012
800
700
600
500
400
300
200
100
0
Import weight by month, tonnes
Jan Apr Jul Oct
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Month
Onions
Garlic
Leeks
Carrots

Animal/human connections

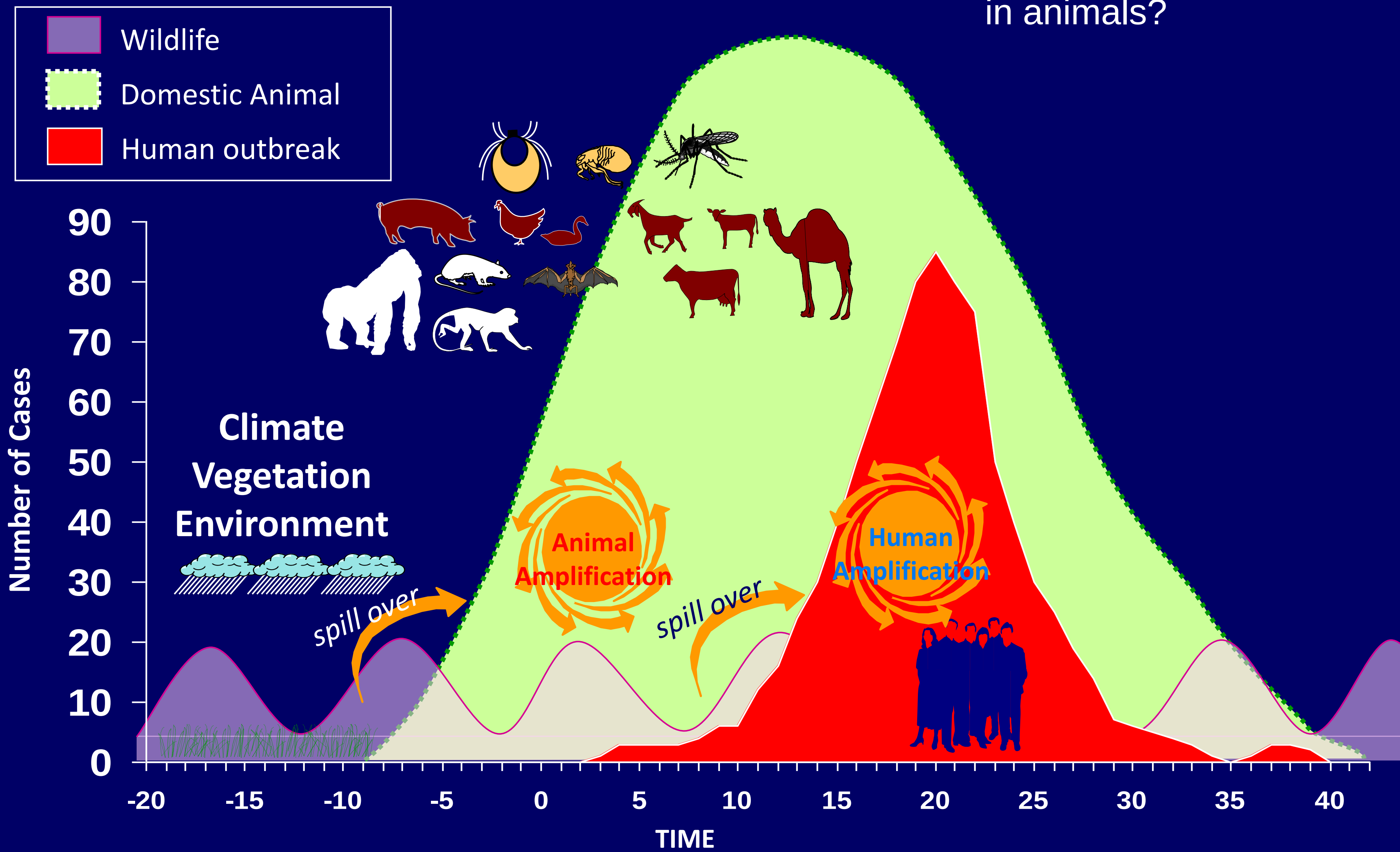
- Ribotype 126
- Ribotype 127
- Ribotype 033

cattle

- Ribotype 237 - pigs
- Ribotype ??? – horses
- Many other new ribotypes from animals: usually binary toxin positive, that are starting to appear in humans

Emerging infectious diseases

But what is driving the emergence of *C. difficile* in animals?



Slide kindly provided by Dr Pierre Formenty

Table 1. Production of food animals (including export of live animals) and the production of meat and milk, Denmark

DANMAP 2006

Year	Broilers		Turkeys a)		Cattle (slaughtered)		Dairy cows		Pigs		Farmed fish	
											Fresh water	Salt water
	1,000 heads	mill. kg	1,000 heads	mill. kg	1,000 heads	mill. kg	1,000 heads	mill. kg milk	1,000 heads	mill. kg	mill. kg	mill. kg
1990	94,560	116	571	2.5	789	219	753	4,542	16,425	1,260	-	-
1992	107,188	137	761	5.4	862	236	712	4,405	18,442	1,442	35	7
1994	116,036	152	1,091	8.6	813	210	700	4,442	20,651	1,604	35	7
1996	107,895	149	961	9.3	789	198	701	4,494	20,424	1,592	32	8
1998	126,063	168	1,124	11.6	732	179	669	4,468	22,738	1,770	32	7
2000	133,987	181	1,042	10.3	691	171	636	4,520	22,414	1,748	32	7
2001	136,603	192	1,038	12.6	653	169	623	4,418	23,199	1,836	31	8
2002	136,350	190	965	11.5	668	169	610	4,455	24,203	1,892	32	8
2003	129,861	181	510	7.4	625	161	596	4,540	24,434	1,898	34	8
2004	130,674	181	55	1.0	632	165	563	4,434	25,141	1,965	34	9
2005	120,498	180	158	0.5	549	145	558	4,449	25,758	1,988	31	8
2006	105,888	163	32	0.1	509	140	563	4,492	25,763	1,957	-	-

Data from Statistics Denmark (www.dst.dk) and The Danish Directorate for Fisheries

a) From 2002, the export of live turkeys for slaughter increased. By 2004, 95% of all turkeys raised in Denmark were slaughtered abroad. For turkeys, data on export of live animals is not included in the table

Approx. 50% increase in numbers

Table 4. Trends in the estimated total consumption (kg active compound) of prescribed antimicrobials for production animals, Denmark

DANMAP 2006

ATC_{vet} group b)	Therapeutic group	1990	1992	1994	1996	1998	2000	2001	2002	2003	2004	2005	2006
QJ01AA	Tetracyclines	9,300 a)	22,000	36,500	12,900	12,100	24,000	28,500	24,500	27,300	29,500	30,050	32,650
QJ01CE	Penicillins, β–lactamase sensitive	5,000	6,700	9,400	7,200	14,300	15,100	16,400	17,400	19,000	20,900	22,250	22,600
QJ01C/QJ01DA	Other penicillins, cephalosporins	1,200	2,500	4,400	5,800	6,700	7,300	8,800	9,900	11,100	12,900	12,300	11,550
QJ01EW	Sulfonamides + trimethoprim	3,800	7,900	9,500	4,800	7,700	7,000	9,200	10,600	10,600	11,500	12,200	13,800
QJ01EQ	Sulfonamides	8,700	5,900	5,600	2,100	1,000	1,000	950	900	850	850	750	750
QJ01F/QJ01XX	Macrolides, lincosamides, pleuromutilins	10,900	12,900	11,400	7,600	7,100	15,600	18,400	19,200	20,700	24,200	22,350	22,050
QJ01G/QA07AA	Aminoglycosides	7,700	8,500	8,600	7,100	7,800	10,400	11,600	11,700	11,700	11,600	10,800	10,500
	Others c)	6,700	6,800	4,400	600	650	300	900	1,600	1,500	1,000	1,950	1,250
Total		53,400	73,200	89,900	48,000	57,300	80,700	94,700	95,900	102,500	112,500	112,650	115,150

1990-2000: Data based on reports from the pharmaceutical industry of total annual sales. (Data 1990-1994: Use of antibiotics in the pig production. Federation of Danish pig producers and slaughterhouses. N. E. Rønn (Ed.). 1996-2000: Danish Medicines Agency). Data 2001-2006: VetStat. For comparability between VetStat data and previous data, see DANMAP 2000. Only veterinary drugs are included. Veterinary drugs almost exclusively used in pets (tablets, capsules, ointment, eye/ear drops) are excluded. Dermal spray with tetracycline, used in production animals, is the only topical drug included

a) Kg active compound rounded to nearest 50 or 100

b) Only the major contributing ATC_{vet} groups are mentioned

c) Consumption in aquaculture was not included before 2001

Approx. 400% increase in penicillins, β-lactamase sens.
Other penicillins, cephalosporins 1000% increase

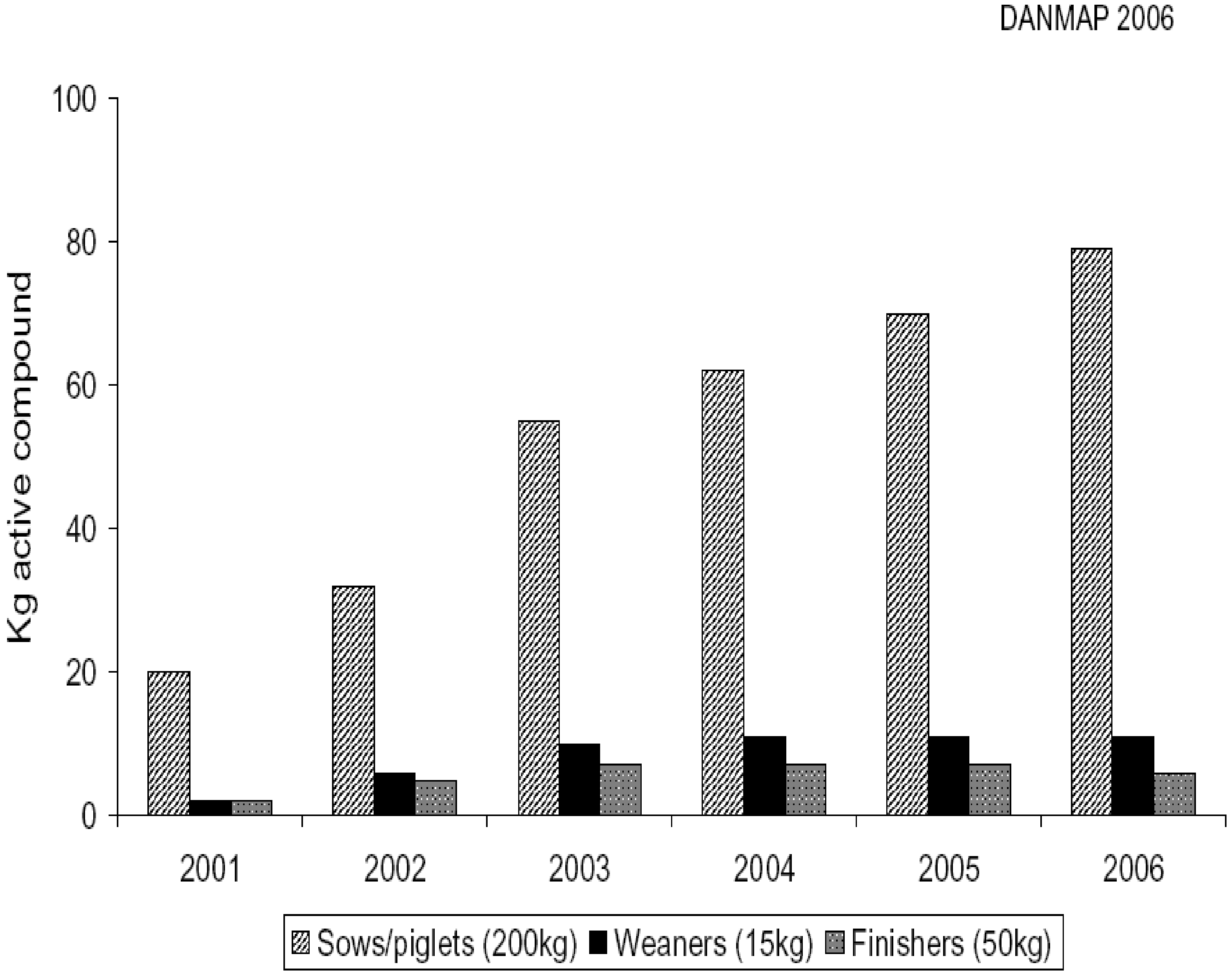


Figure 4 . Consumption of cephalosporins in pigs given as kg active compound from 2001 to 2006, Denmark

DanMap 2007

“This change in prescription habits suggests that the consumption of cephalosporins in pigs is changing from occasional prescription to more systematic prescription in herds producing 14-29% of the weaned pigs.”

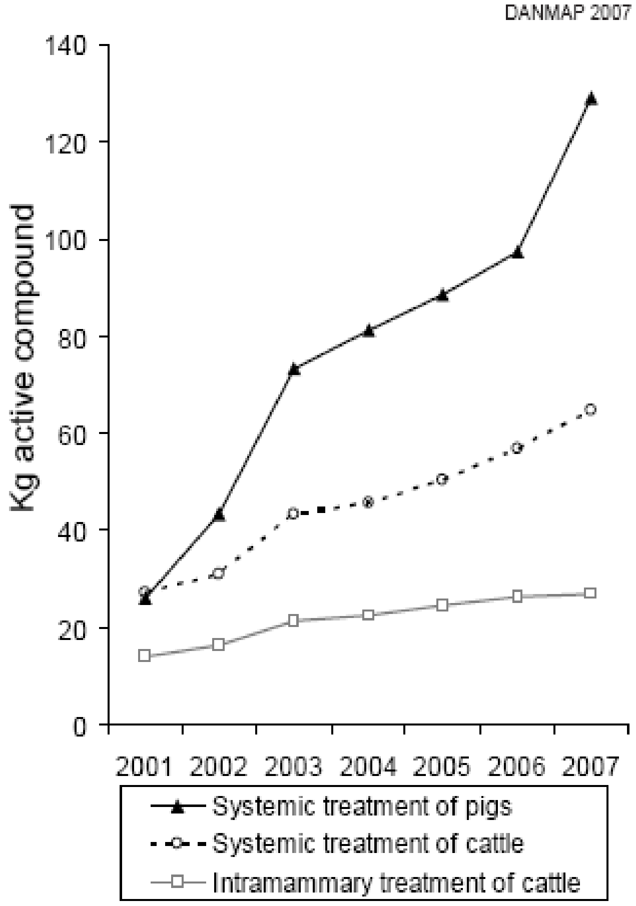
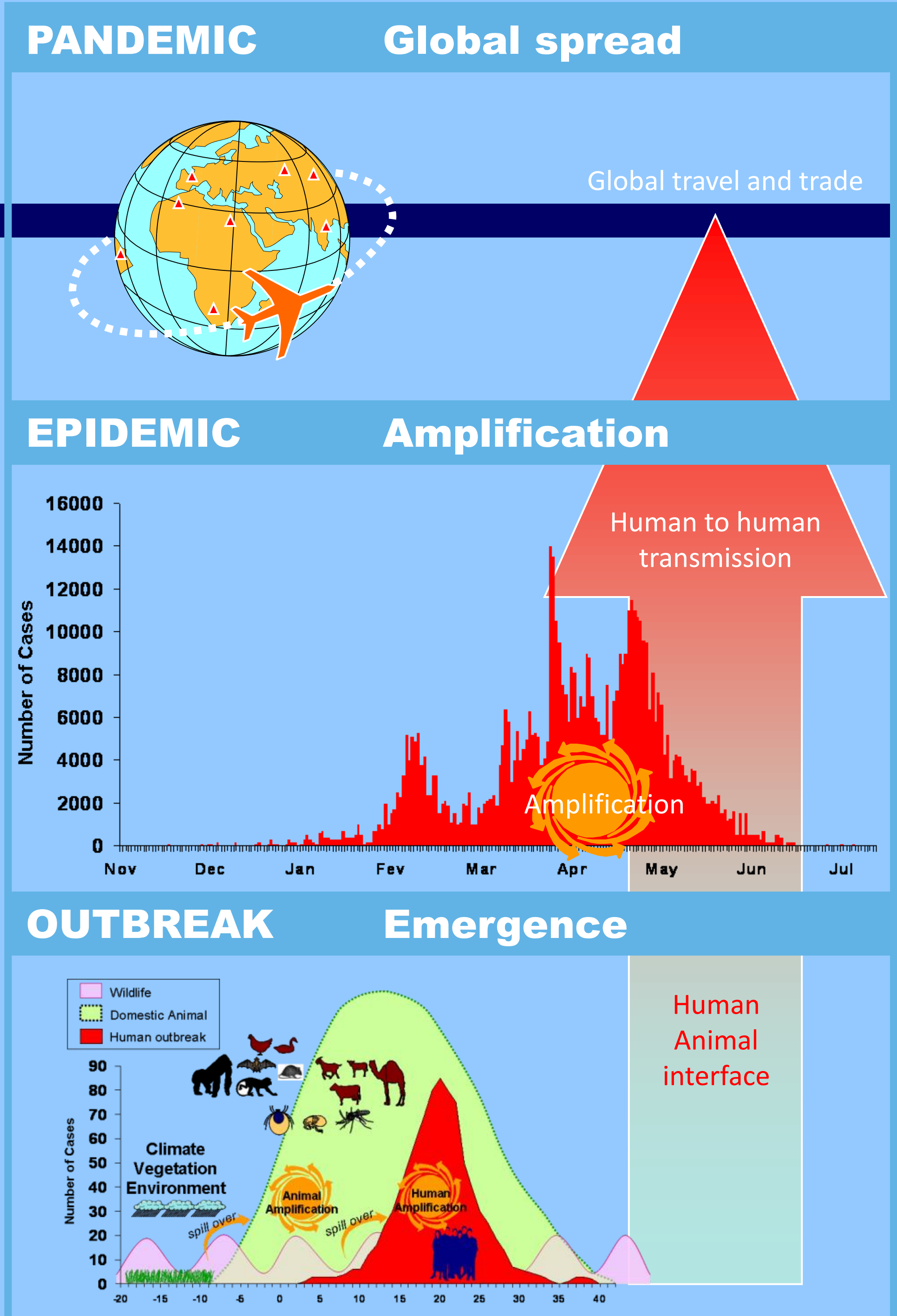


Figure 7. Use of 3rd and 4th generation cephalosporins in pigs and cattle, 2001-2007, Denmark

To summarise the issues

- Major new human health problem in Australia (and NZ) – community CDI
- Need to find the source/reservoir
- Need to prevent establishment of RTs 244/251 in hospitals
- Now a major animal health problem (pigs/horses)
- Gross contamination of the environment OUTSIDE hospitals - probable contamination of food
- CDI is a zoonosis
- Will require a One Health approach to resolve



Global Alert &Response: the need for global surveillance

Globalization of pathogens

- Global travel: people, animals, vectors
- Global trade: animal and their products, vaccines, medical products, etc.

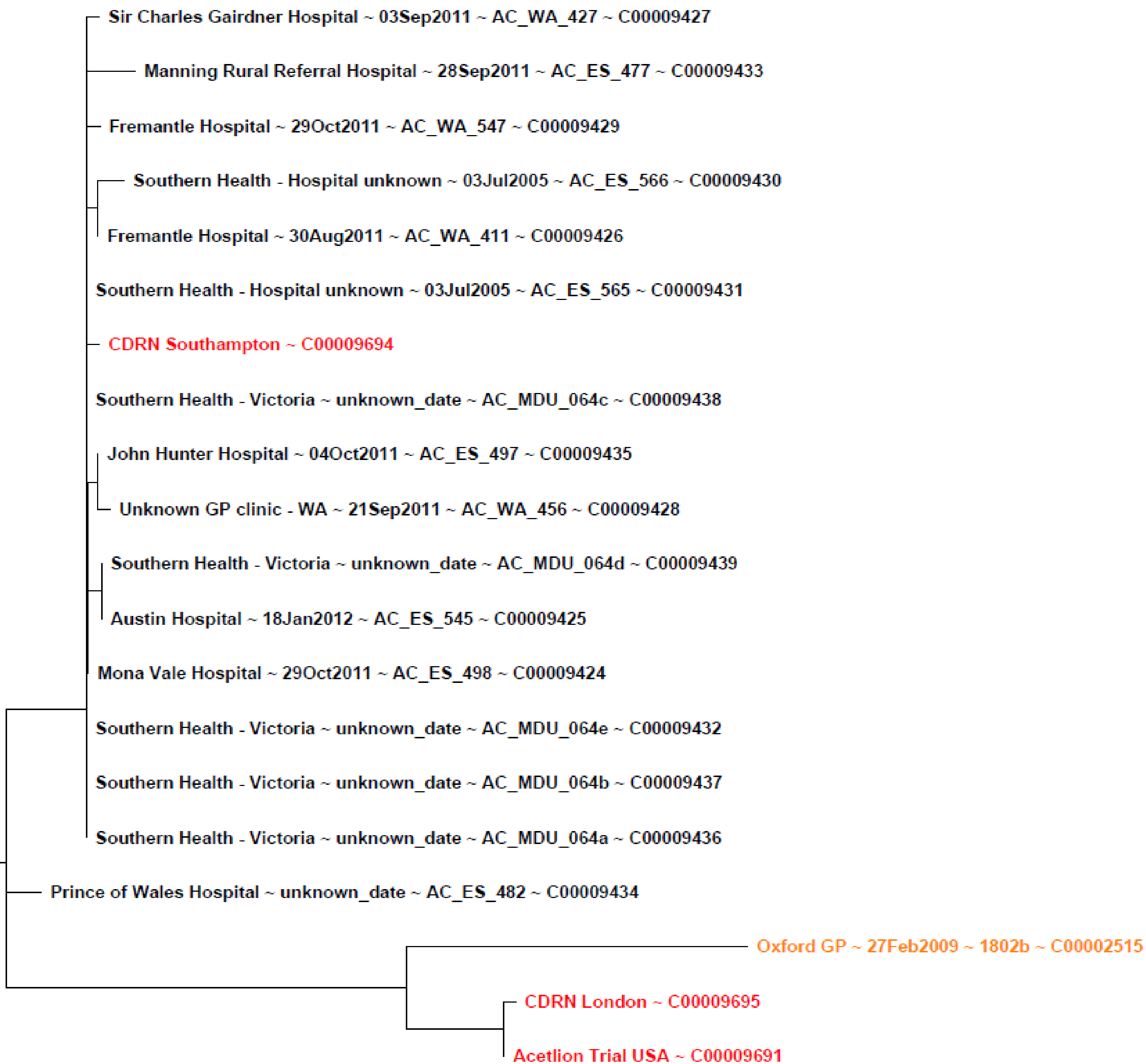
Amplification of pathogens

- Successful H2H transmission,
- Nosocomial transmission in health care centers
- New introduction from animals
- Urbanization
- Agricultural Intensification
- Technology And Industry

Emergence of pathogens

- Encroachment introduction, “Spill over”
- At-risk behaviour
- Human encroachment, Ex situ contact, Ecological manipulation
- Translocation of wildlife

Slide courtesy of Dr Pierre Formenty , WHO



Sir Charles Gairdner Hospital ~ 03Sep2011 ~ AC_WA_427 ~ C00009427
Manning Rural Referral Hospital ~ 28Sep2011 ~ AC_ES_477 ~ C00009433
Fremantle Hospital ~ 29Oct2011 ~ AC_WA_547 ~ C00009429
Southern Health - Hospital unknown ~ 03Jul2005 ~ AC_ES_566 ~ C00009430
Fremantle Hospital ~ 30Aug2011 ~ AC_WA_411 ~ C00009426
Southern Health - Hospital unknown ~ 03Jul2005 ~ AC_ES_565 ~ C00009431
CDRN Southampton ~ C00009694
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064c ~ C00009438
John Hunter Hospital ~ 04Oct2011 ~ AC_ES_497 ~ C00009435
Unknown GP clinic - WA ~ 21Sep2011 ~ AC_WA_456 ~ C00009428
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064d ~ C00009439
Austin Hospital ~ 18Jan2012 ~ AC_ES_545 ~ C00009425
Mona Vale Hospital ~ 29Oct2011 ~ AC_ES_498 ~ C00009424
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064e ~ C00009432
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064b ~ C00009437
Southern Health - Victoria ~ unknown_date ~ AC_MDU_064a ~ C00009436
Prince of Wales Hospital ~ unknown_date ~ AC_ES_482 ~ C00009434
Oxford GP ~ 27Feb2009 ~ 1802b ~ C00002515
CDRN London ~ C00009695
Acetlion Trial USA ~ C00009691

CDI control strategies

- Prevent ingestion of *C. difficile* spores from environment
  - Cleaning hospitals
  - Vaccinating animals
- Prevent development of CDI if spores are ingested
  - Antibiotic stewardship

Acknowledgments

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Rural Industries R & D Corporation
Australian Commission on Safety & Quality in Healthcare
WA Department of Health
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Sanger Institute (Trevor Lawley)
LSTMH (Brendan Wren)
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