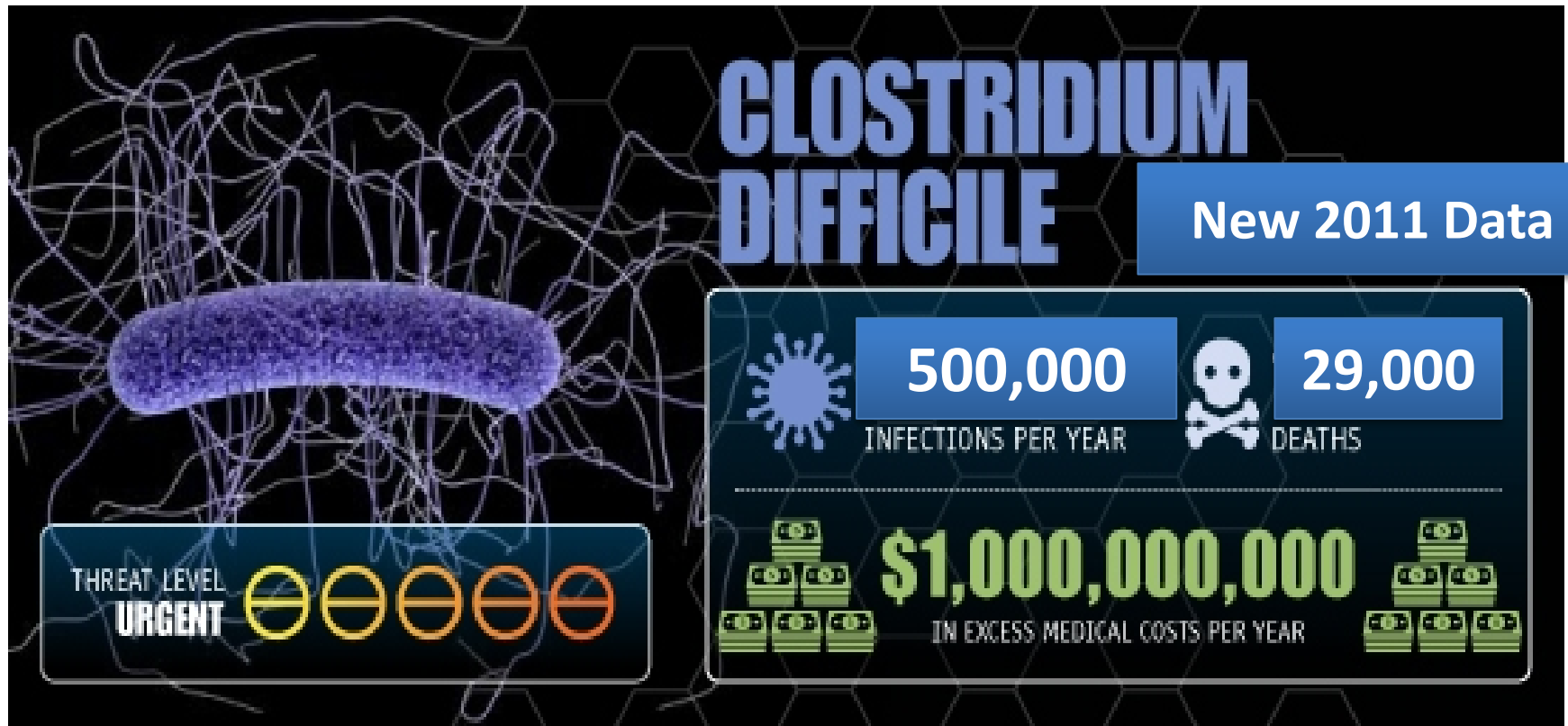


An Update on *Clostridium difficile* Infection:

From Infection Control to Treatment

Kevin W. Garey, PharmD, MS. Professor and Chair
University of Houston College of Pharmacy



Lessa et al, N Eng J Med 2015: 34.2% of CDI cases were considered community-acquired

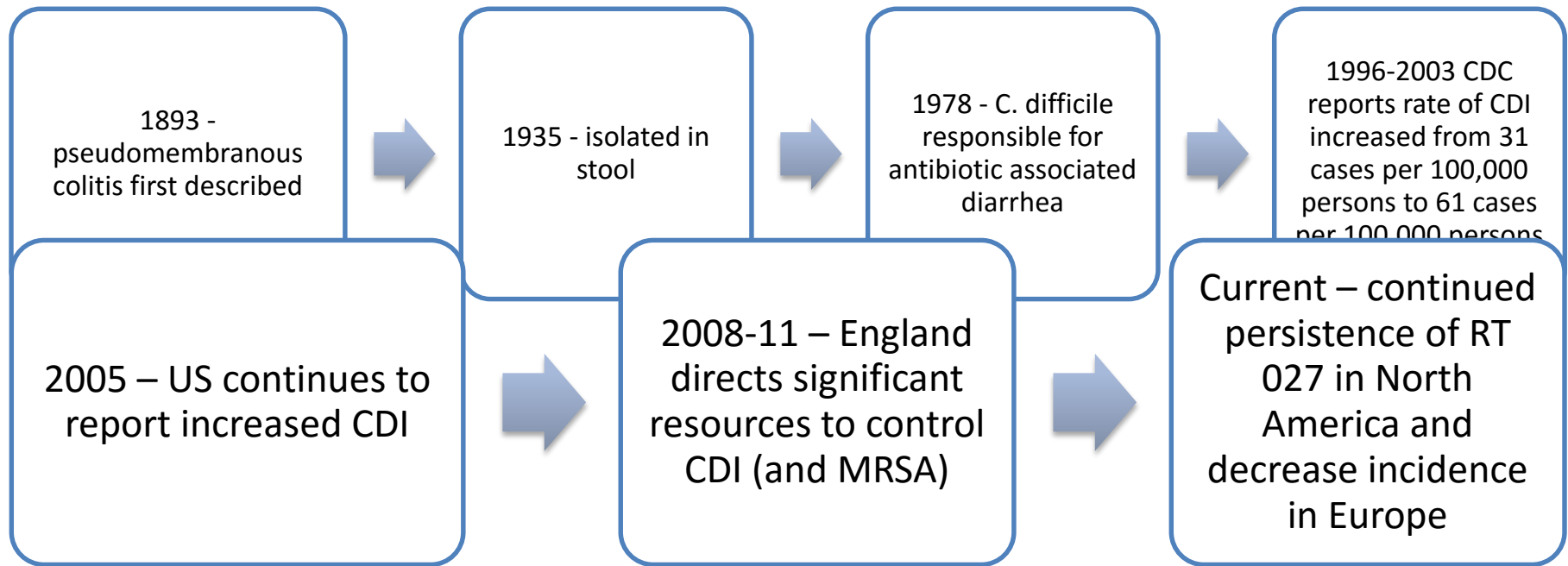
Source: CDC Report "Antibiotic Resistance Threats in the United States, 2013"

Lessa CF et al. NEJM 2015;372:825-34.

Objectives

- Provide a state of the art update on *C. difficile* infection
- Focus on environmental contamination of *C. difficile*
- How do we treat this ubiquitous pathogen?

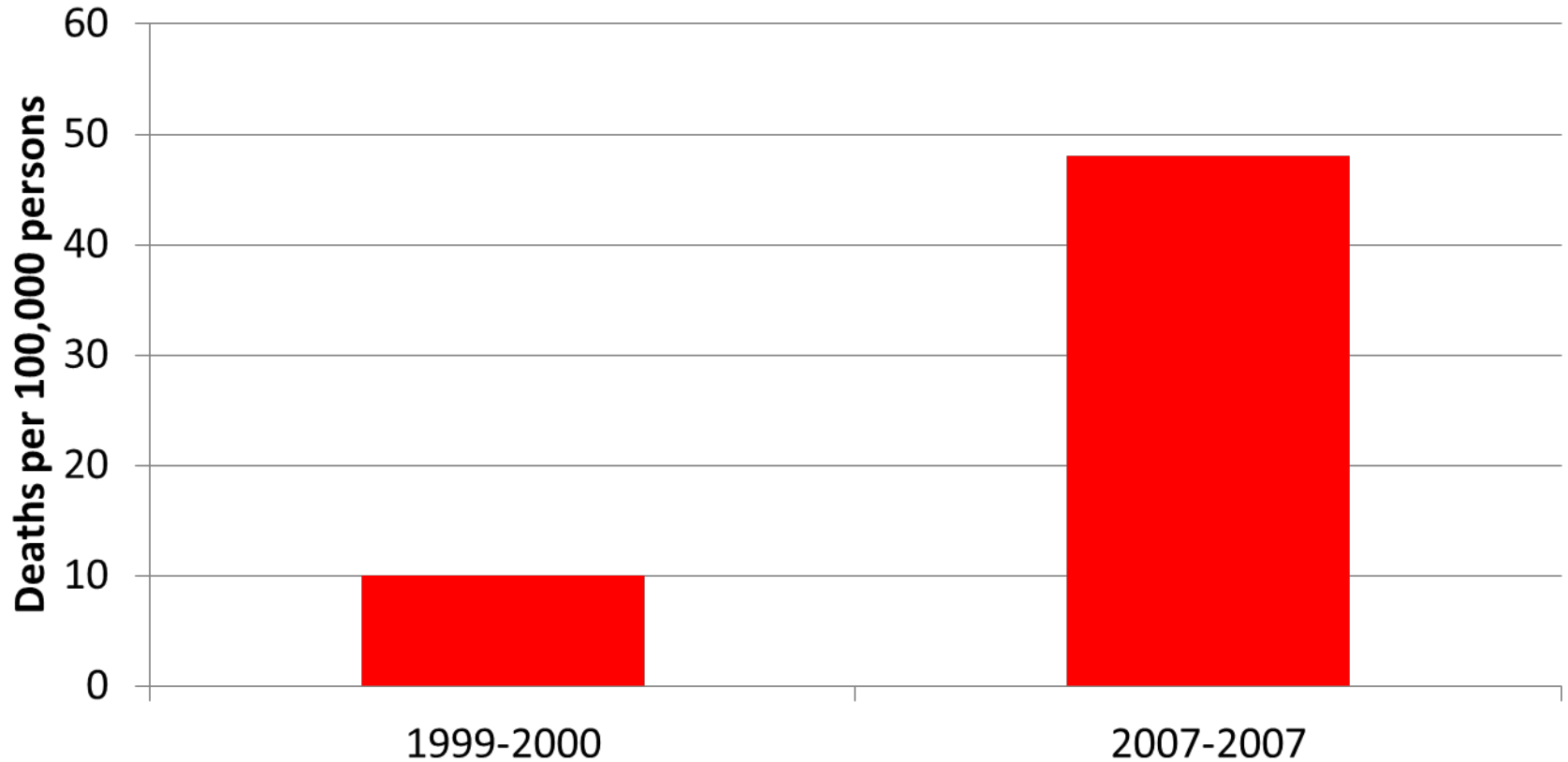
A History of *C. difficile*



1. Heinlen L, Ballard JD. *Clostridium difficile* Infection. *The American journal of the medical sciences*. 2010;340(3):247-252. doi:10.1097/MAJ.0b013e3181e939d8.
2. The *Clostridium difficile* PCR ribotype 027 lineage: a pathogen on the move Valiente, E. et al. *Clinical Microbiology and Infection* , Volume 20 , Issue 5 , 396 - 404

C. difficile is the main contributor to gastroenteritis-associated deaths in the USA

Mortality attributed to CDI

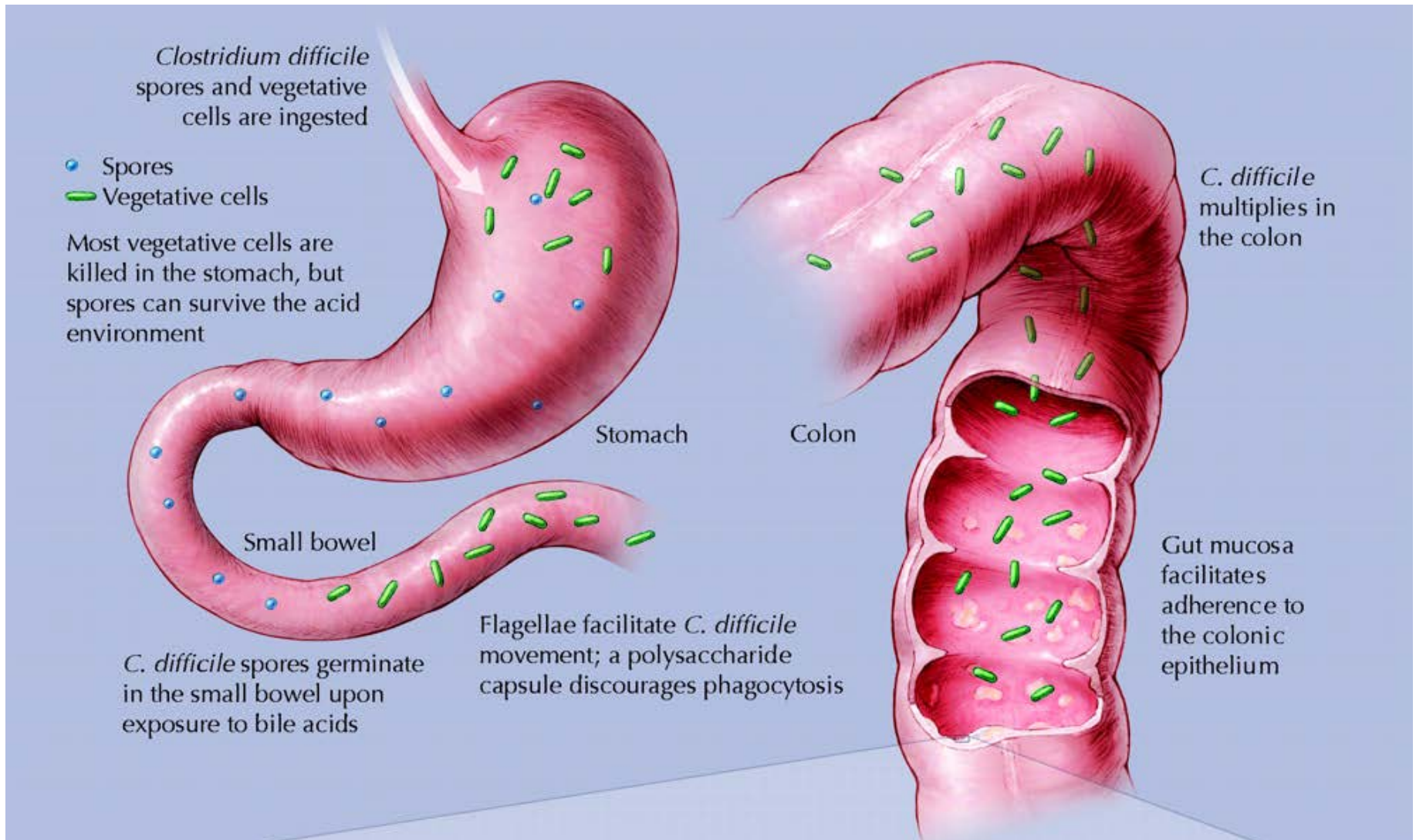


Analysis of National Center for Health Statistics (NCHS) multiple-cause-of-death mortality data for the years 1999–2007, a 5-fold increase in mortality attributed to CDI was noted

How did we get here?

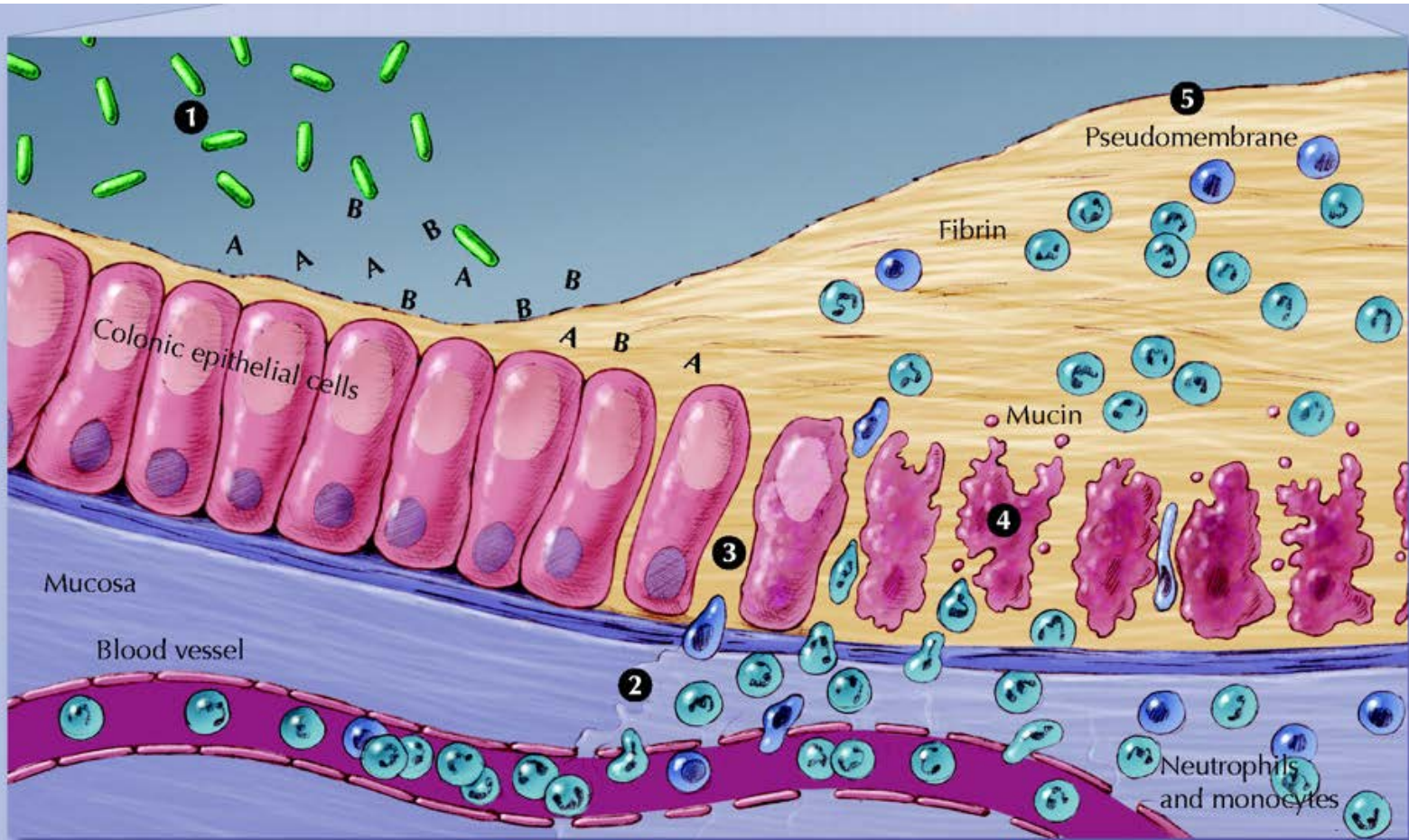
- Let's review a few key concepts on CDI to get everyone up to speed
 - Pathogenesis
 - Emergence of 'hypervirulent' strains

Pathogenesis of *Clostridium difficile*-associated diarrhea in adults



Poutanen, S. M. et al. CMAJ 2004;171:51-58

Pathogenesis of *Clostridium difficile*-associated diarrhea in adults



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (1). Local production of toxins A and B leads to production of tumour necrosis factor- α and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (2),

opening of epithelial cell junctions (3) and epithelial cell apoptosis (4). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (5) and watery diarrhea.

Hypervirulent *C. difficile*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 8, 2005

VOL. 353 NO. 23

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

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

Incidence of hypervirulent strains of *C. difficile*, 2005

Table 1. Isolates of *Clostridium difficile* According to Health Care Facility and the Proportion of Isolates Belonging to the BI/NAP1 Strain.

Health Care Facility	Date of Onset of Outbreak	No. of Isolates Tested	BI/NAP1 Strain
			no. (%)
Georgia	Oct. 2001	46	29 (63)
Illinois	July 2003	14	6 (43)
Maine, Facility A	March 2002	13	9 (69)
Maine, Facility B	July 2003	48	30 (62)
New Jersey	June 2003	12	9 (75)
Oregon*	April 2002	30	3 (10)
Pennsylvania, Facility A	2000–2001	18	7 (39)
Pennsylvania, Facility B	Oct. 2003	6	3 (50)
Total		187	96 (51)

* Isolates were not collected until after the peak of the outbreak.

Increasing mortality and complications due to CDAD

Table 1: Patients with *Clostridium difficile*-associated diarrhea (CDAD) in the Estrie region of Quebec who died within 30 days after diagnosis or who had complicated CDAD, 1991–2003

Period	No. of patients with CDAD*	No. (%) who died within 30 days after diagnosis	Adjusted OR (95% CI)†	No. (%) who had complicated CDAD‡	Adjusted OR (95% CI)†
1991–1992	169	8 (4.7)	1.0	12 (7.1)	1.0
1993–1994	217	11 (5.1)	1.7 (0.5–5.3)	14 (6.5)	1.0 (0.4–2.7)
1995–1996	215	13 (6.0)	1.6 (0.5–5.0)	17 (7.9)	0.9 (0.3–2.2)
1997–1998	192	11 (5.7)	1.1 (0.4–3.7)	13 (6.8)	0.6 (0.3–1.7)
1999–2000	248	19 (7.7)	1.5 (0.5–4.6)	28 (11.3)	1.2 (0.5–2.9)
2001–2002	244	21 (8.6)	1.6 (0.5–4.7)	28 (11.5)	1.1 (0.5–2.5)
2003	390	54 (13.8)	3.0 (1.1–8.4)	71 (18.2)	2.2 (1.0–4.9)
<i>p</i> value		< 0.001§	< 0.001¶	< 0.001§	0.001¶

Note: OR = odds ratio, CI = confidence interval.

*Includes only patients for whom enough information was available to assess these outcomes.

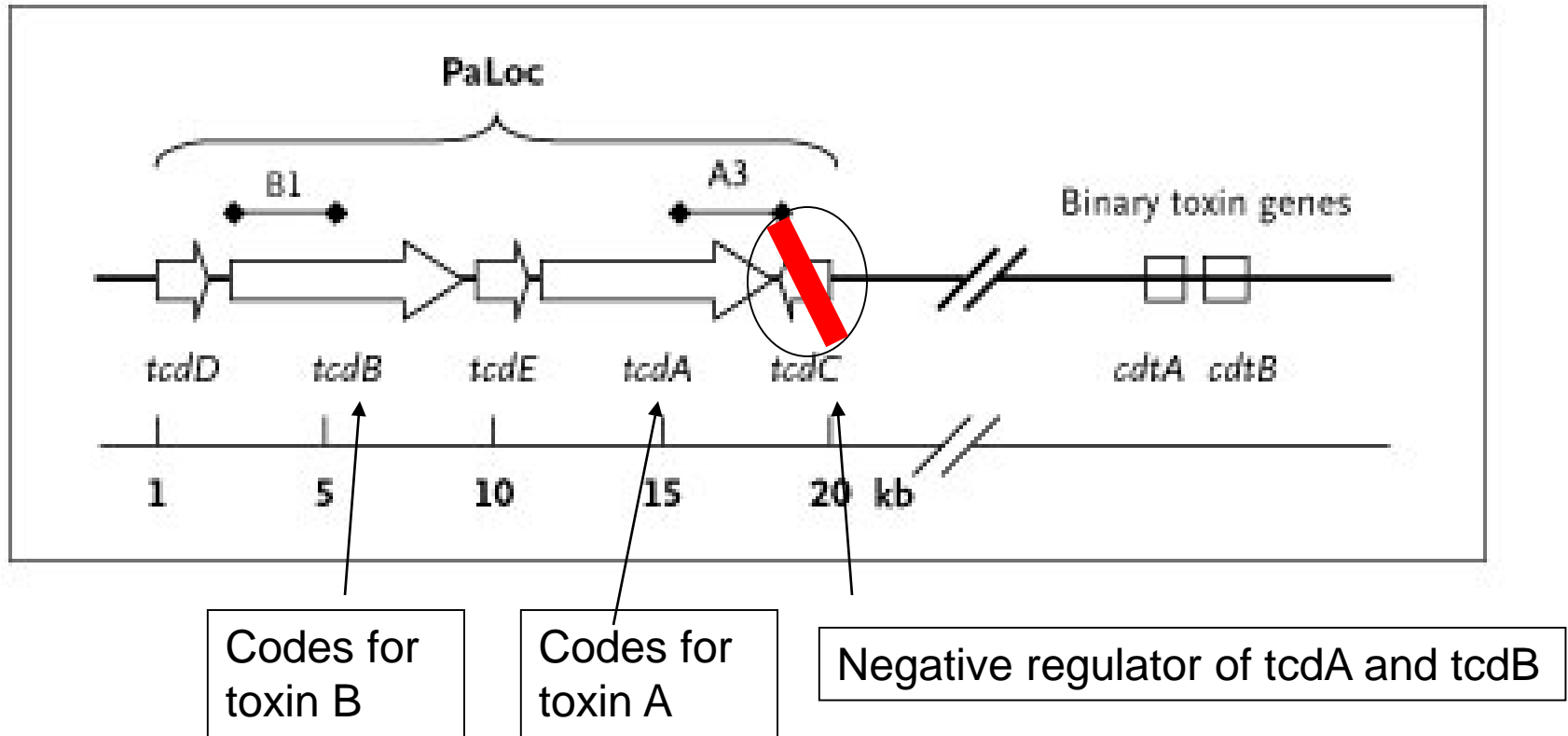
†Adjusted for age, sex, initial treatment, immune status, and tube feeding and surgery in the 2 months preceding diagnosis; 1991–1992 was used as the baseline period.

‡Presence of one or more of the following: megacolon, perforation, colectomy, shock requiring vasopressor therapy, death within 30 days after diagnosis.

§ χ^2 test for trend.

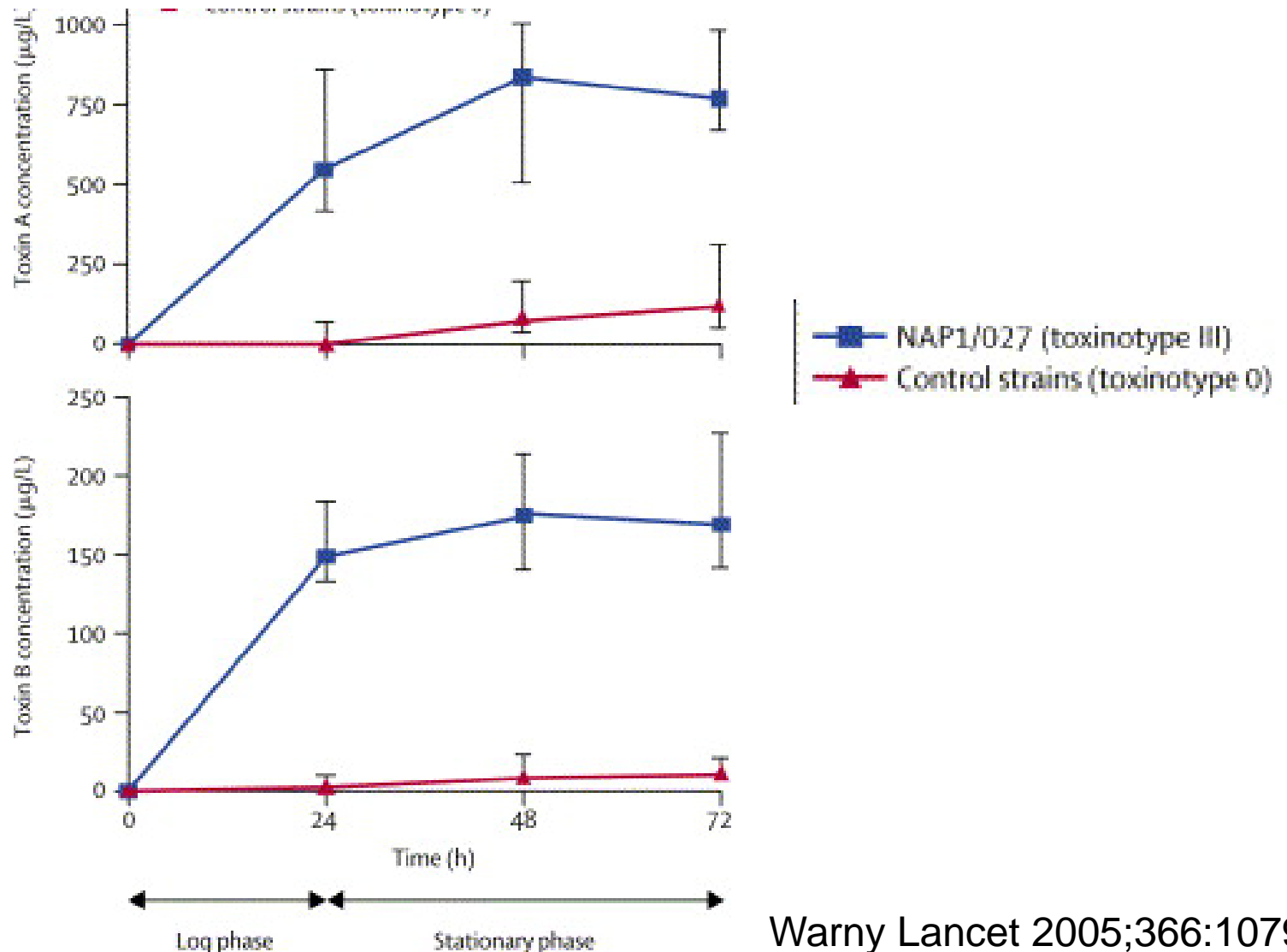
¶ χ^2 test, comparing 2003 with all other years.

Toxins A and toxin B are produced in the Pathogenicity Locus (PaLoc) of *C. difficile*

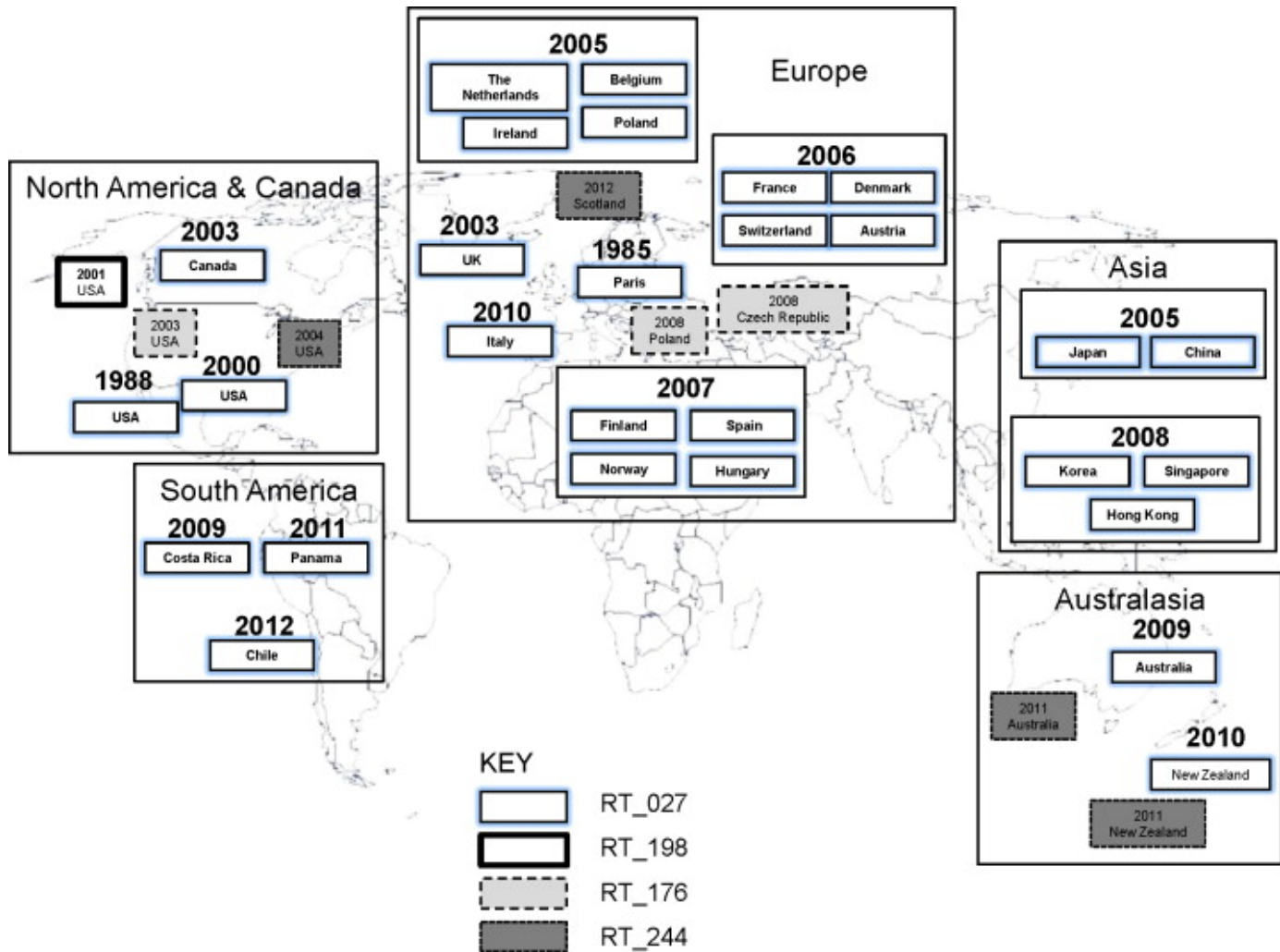


tcdC deficient strain = Lots more production of toxins A and B!

Time course of toxin production by hypervirulent strain compared to control



The *C. difficile* Epidemic



RT 027 FQR1 in North America and RT 027 FQR2 responsible for worldwide epidemic¹

1. Trends in Microbiology August 2014, Vol. 22, No. 8

2. The *Clostridium difficile* PCR ribotype 027 lineage: a pathogen on the move Valiente, E. et al. Clinical Microbiology and Infection, Volume 20, Issue 5, 396 - 404

C difficile nomenclature

- All these are synonymous terms:
 - Toxinotype III: PCR analysis of PaLoc
 - PCR ribotype 027: European typing method
 - REA Group BI (bee eye): Typing method by Dale Gerding (Hines, IL)
 - PFGE: Nap-1: CDC typing method
- Work currently being conducted to make ribotyping the preferred typing method in the USA and Europe

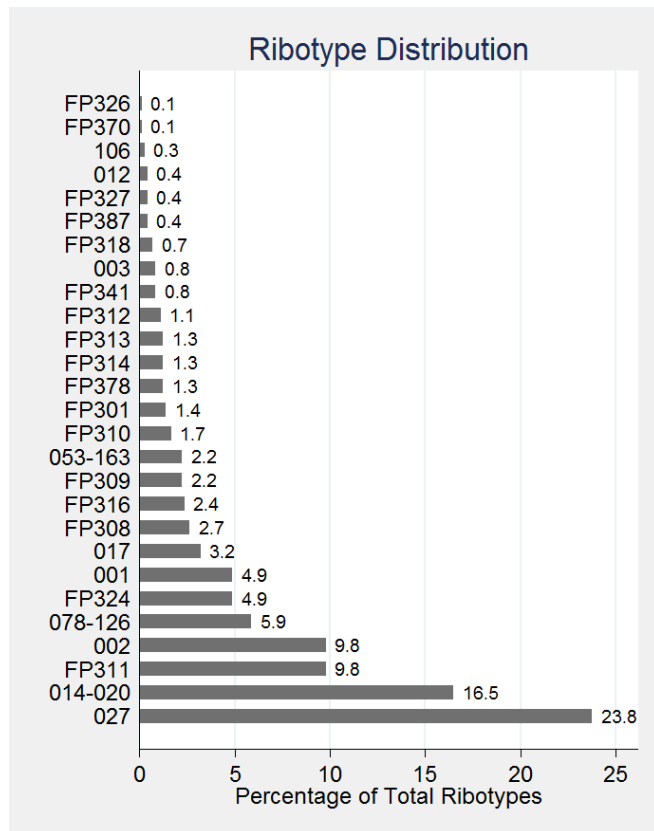
Who you calling “hypervirulent”

Michigan: Derivation (n=310/34 severe) and validation (n=433/45 severe) of predictors of severe CDI (ICU admission, colectomy, or death). After accounting for disease presentation severity, ribotype did not predict outcome

Predictor ^a	Derivation OR (95% CI)	P Value	Validation OR (95% CI)	P Value
Hypervirulent ribotype:				
027/078 vs non-027/078 (reference)	0.82 (.07–10.0)	.874	1.34 (.53–3.16)	.516
White blood cell count: Leukocytosis (>12 000 cells/mL) or leukopenia				
(<4000 cells/mL) vs normal (reference)	4.27 (1.14–19.46)	.041	2.32 (1.07–5.18)	.035
Low albumin level (g/dL)	0.25 (.07–.77)	.025	0.47 (.25–.87)	.018

..and there are more ribotypes than just 027

A lot of ribotypes are associated with CDI



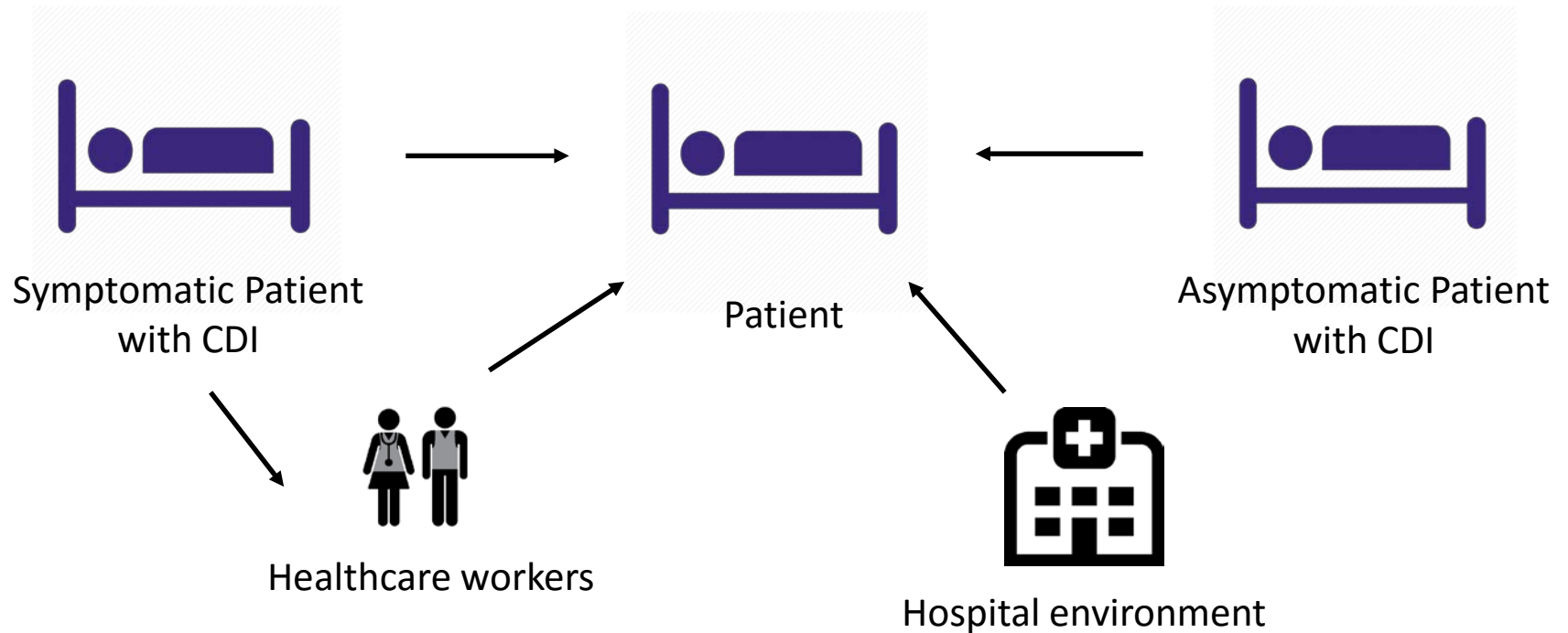
Many ribotypes are virulent, including 027

Ribotype	Severe CDI presentation	Severe CDI outcome
027 (n=170)	54.7%	18.9%
014-020 (n=118)	22.9%	4.2%
FP11 (n=70)	31.4%	8.6%
078-126 (n=42)	21.4%	9.5%
001 (n=35)	42.9%	8.6%
FP24 (n=35)	37.1%	22.9%
17 (n=23)	39.1%	17.4%
FP8 (n=19)	36.9%	10.5%
053-163 (n=16)	37.5%	6.25%
FP16 (n=16)	35.3%	11.8%
FP9 (n=16)	25.0%	18.8%

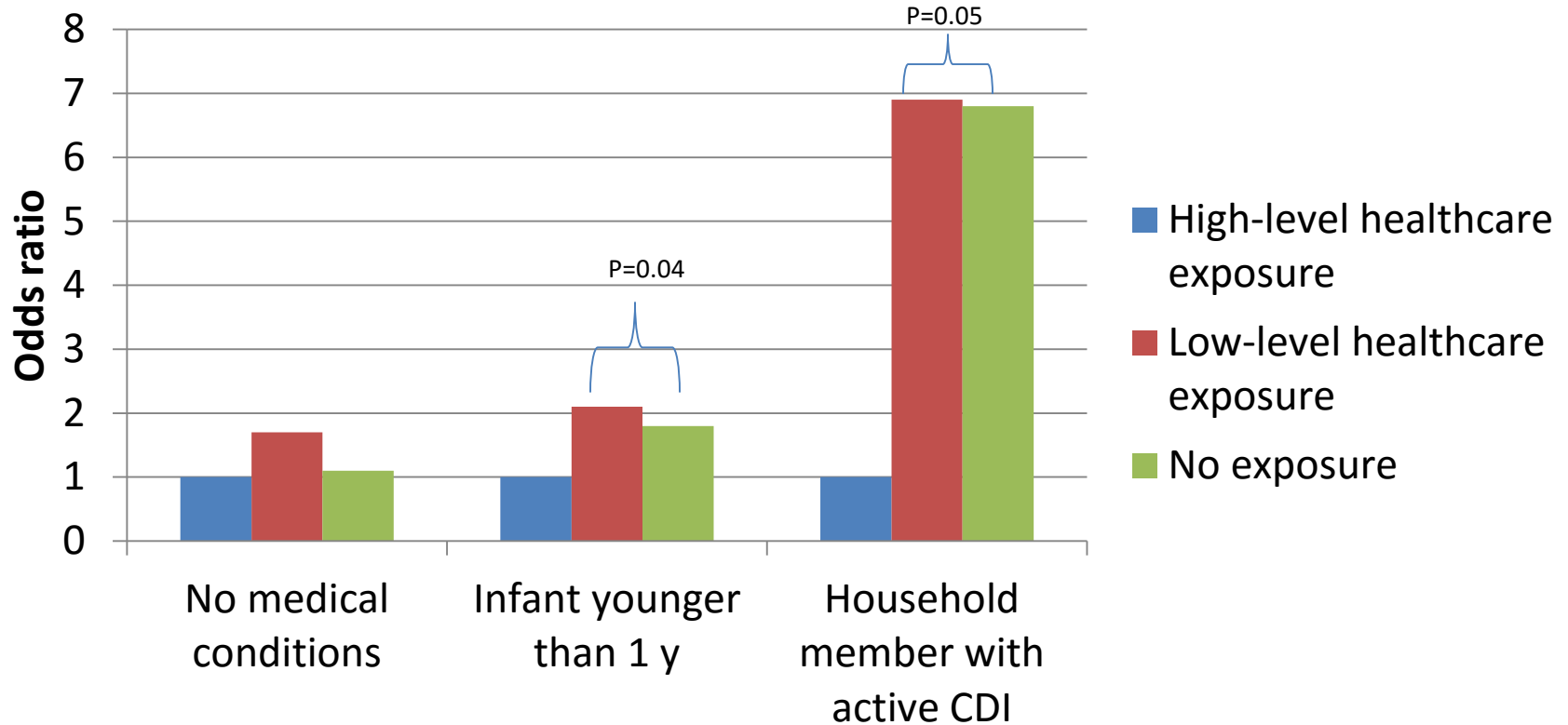
You are all now expert C diff ribotypers

- 027 is definitely a virulent ribotype
-but, there are lots of ribotypes that are equally virulent
- Without a doubt, the ribotype 027 strain has put a large focus on the value of strain typing in *C. difficile*.
- Now, let's use this technology to understand where C. diff may be coming from
 - (answer: everywhere)

Standard view of CDI transmission

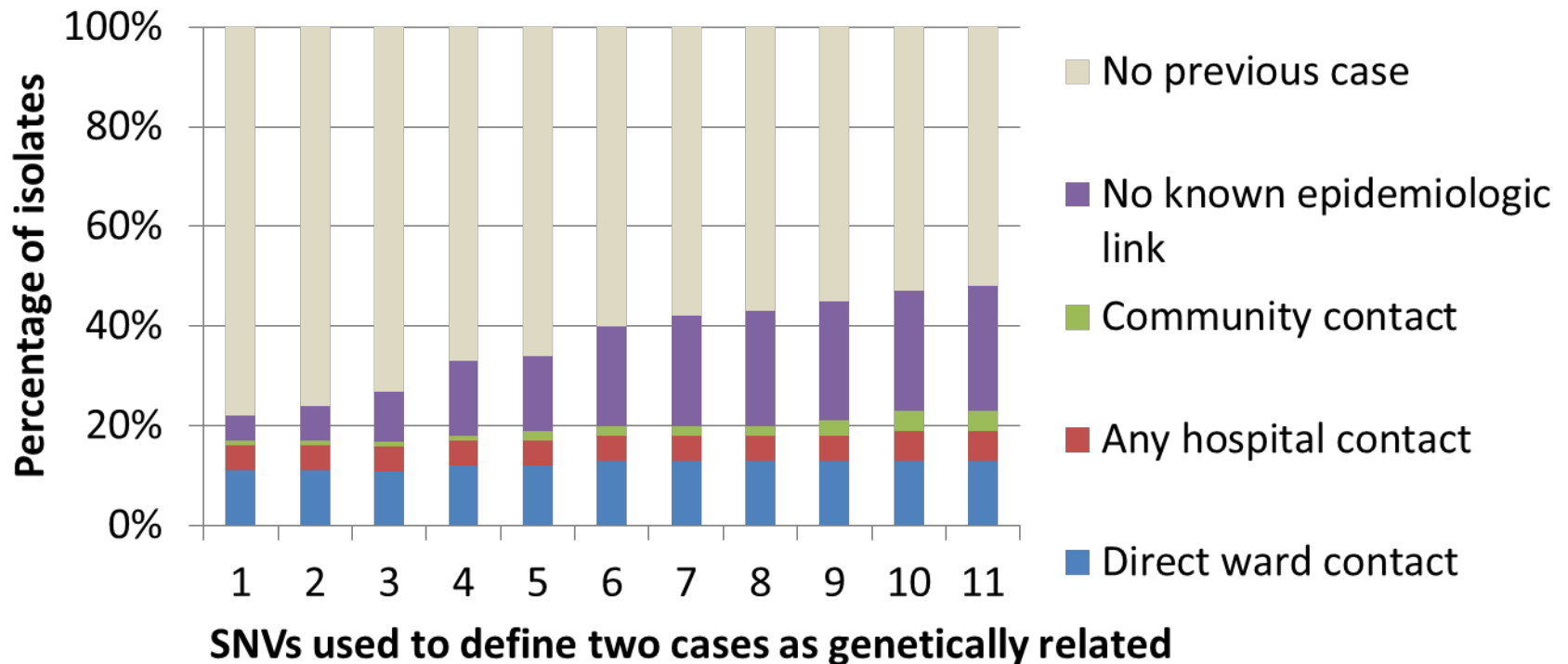


C. difficile is becoming more common in the community setting



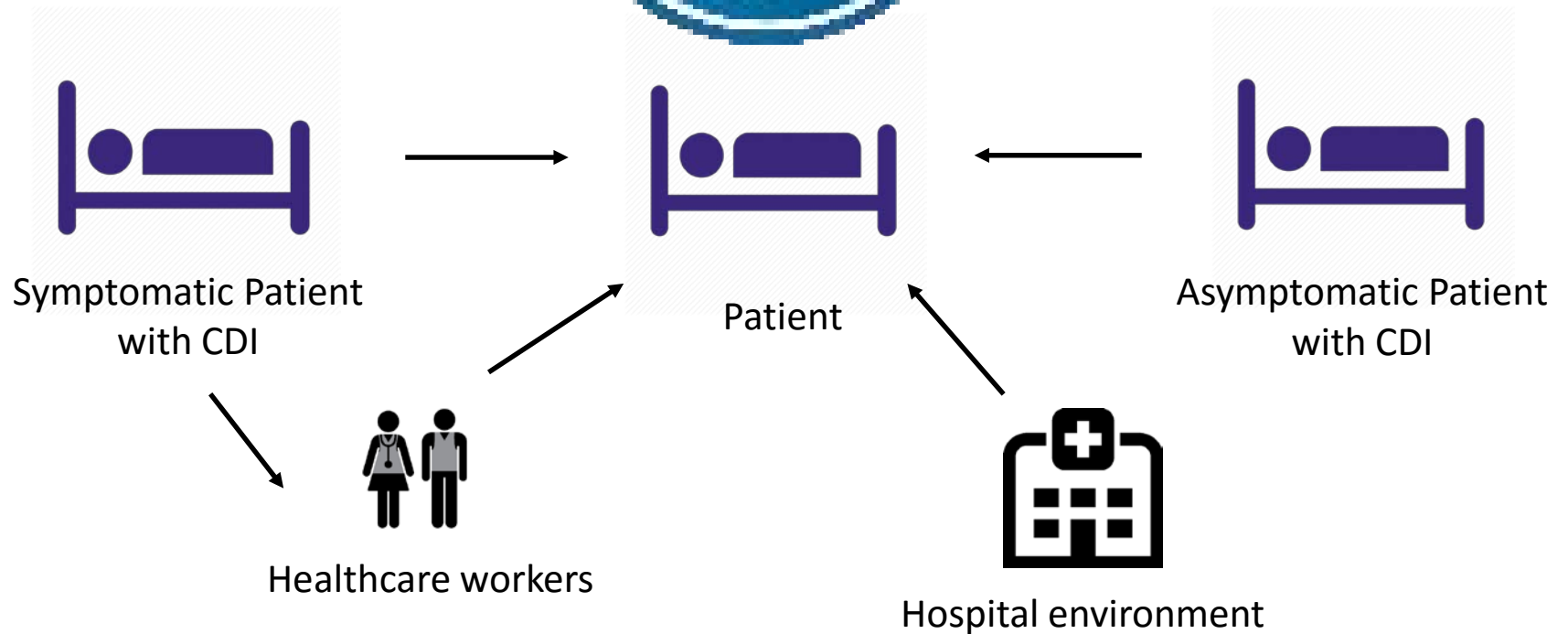
- CDC: 10 US states identified 984 patients with community-acquired CDI (No previous antibiotics: 36%; No outpatient healthcare exposure: 18%).

How do patients get infected in the first place? Where are C diff strains coming from?

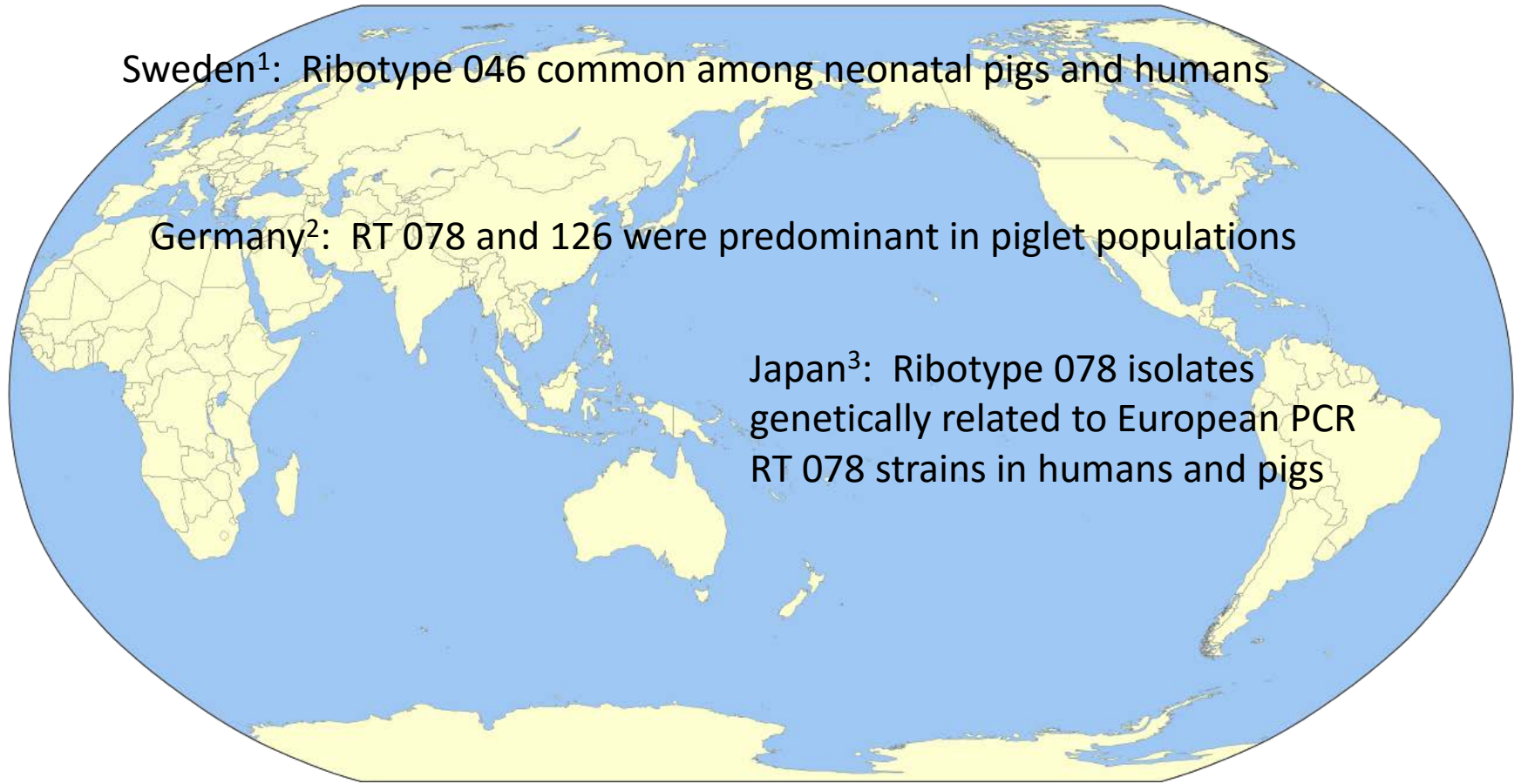


- Leeds, England: Whole genome sequencing of 1223 cases of CDI. This allows for a highly discriminatory way to see where C diff strains are coming from.

New thoughts on CDI transmission

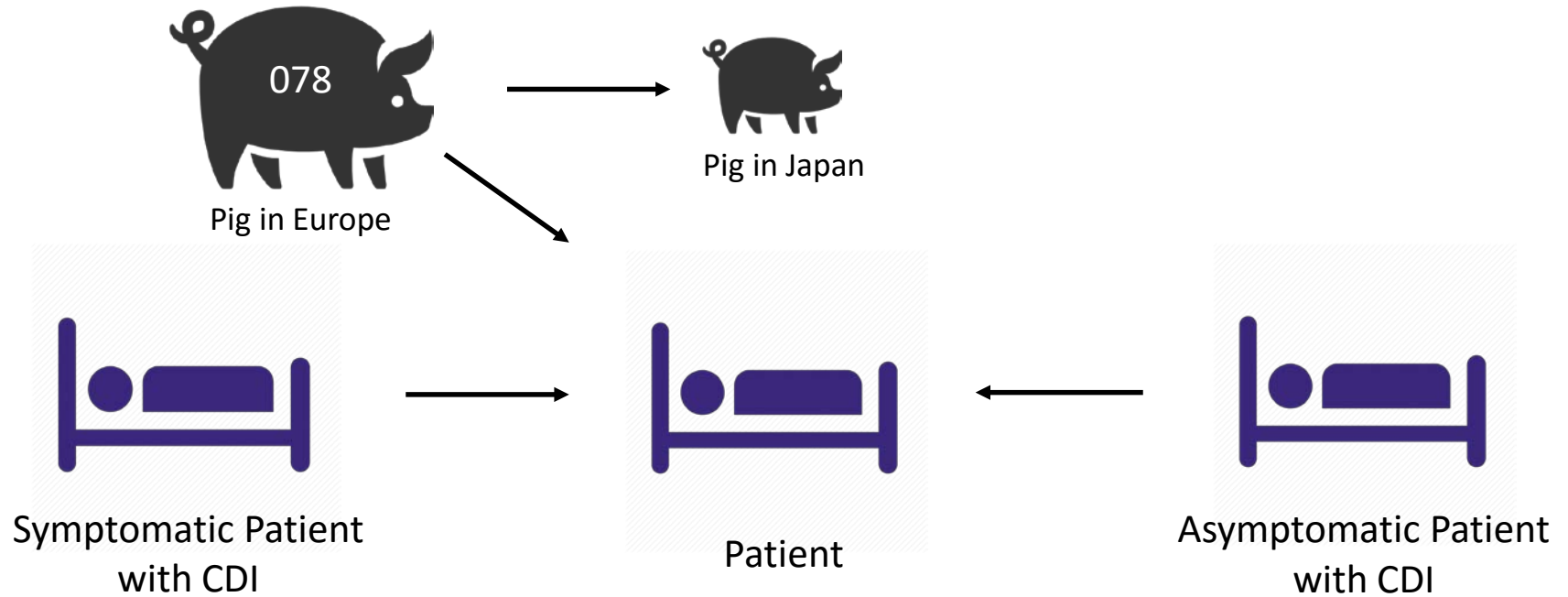


Animals can be colonized with *C. difficile*



1. Clin Microbiol Infect 2014;20:02-6
2. J Clin Microbiol 2013;51:3796-3803
3. Frontiers in Microbiology 2014;5:513.

New thoughts on CDI transmission



Water and soil can also be a reservoir for *C. difficile*

Slovenia 2008-2010: 786 isolates, 90 isolates of *C. difficile* isolated

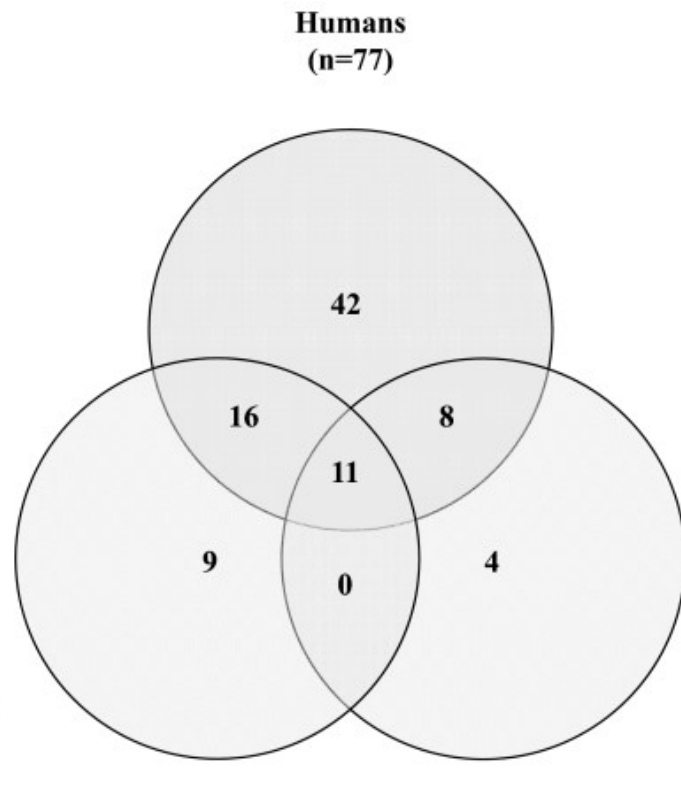
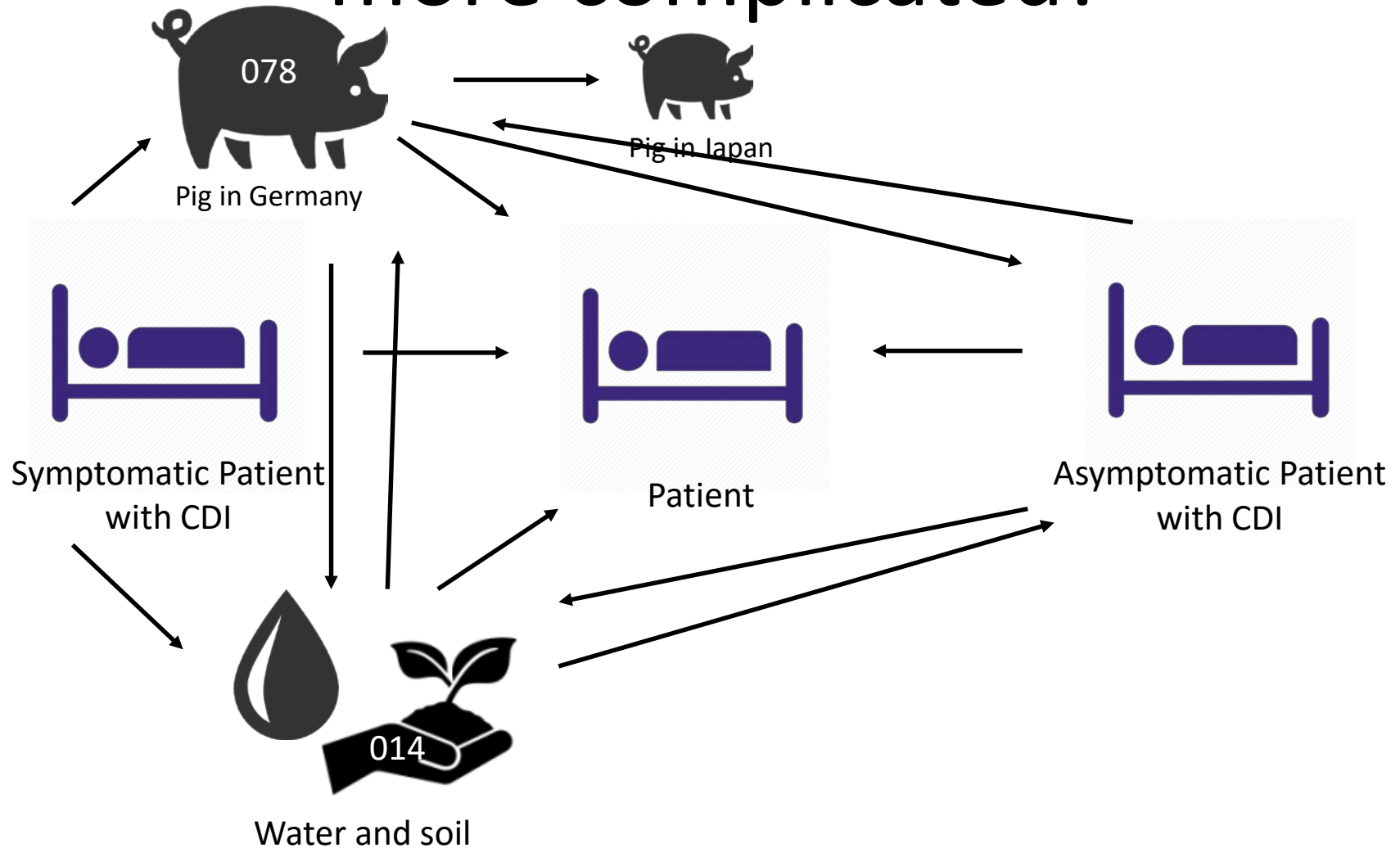


Table 1

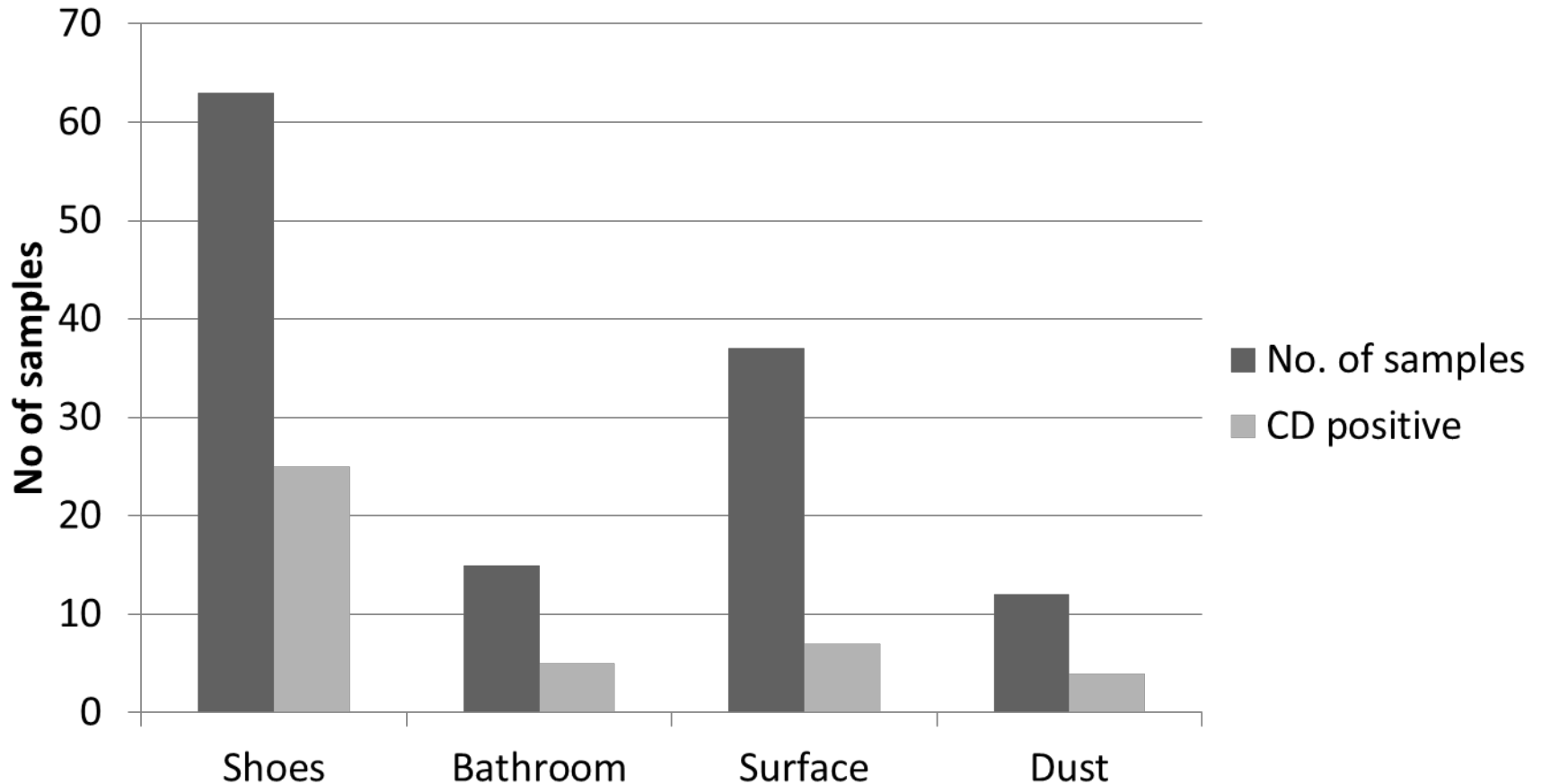
Most prevalent PCR ribotypes in humans, animals and the environment isolated between 2008 and 2010

PCR ribotype/toxinotype	Humans (n = 601)	Animals (n = 104)	Environment (n = 81)
014/020/0 or I	121 (20.1%)	25 (24.0%)	16 (19.8%)
002/0	49 (8.2%)	24 (23.1%)	5 (6.2%)
001/072/0, tox- or XXIV (CDT+ [§])	42 (7.0%)	8 (7.7%)	2 (2.5%)
012/0	30 (5.0%)	/*	1 (1.2%)
023/IV (CDT+)	30 (5.0%)	/*	3 (3.7%)
018/0	27 (4.5%)	/	2 (2.5%)

CDI transmission is getting a lot more complicated!



Prevalence of *C. difficile* (CD) from various environmental samples. Samples collected from 30 households throughout Houston, TX



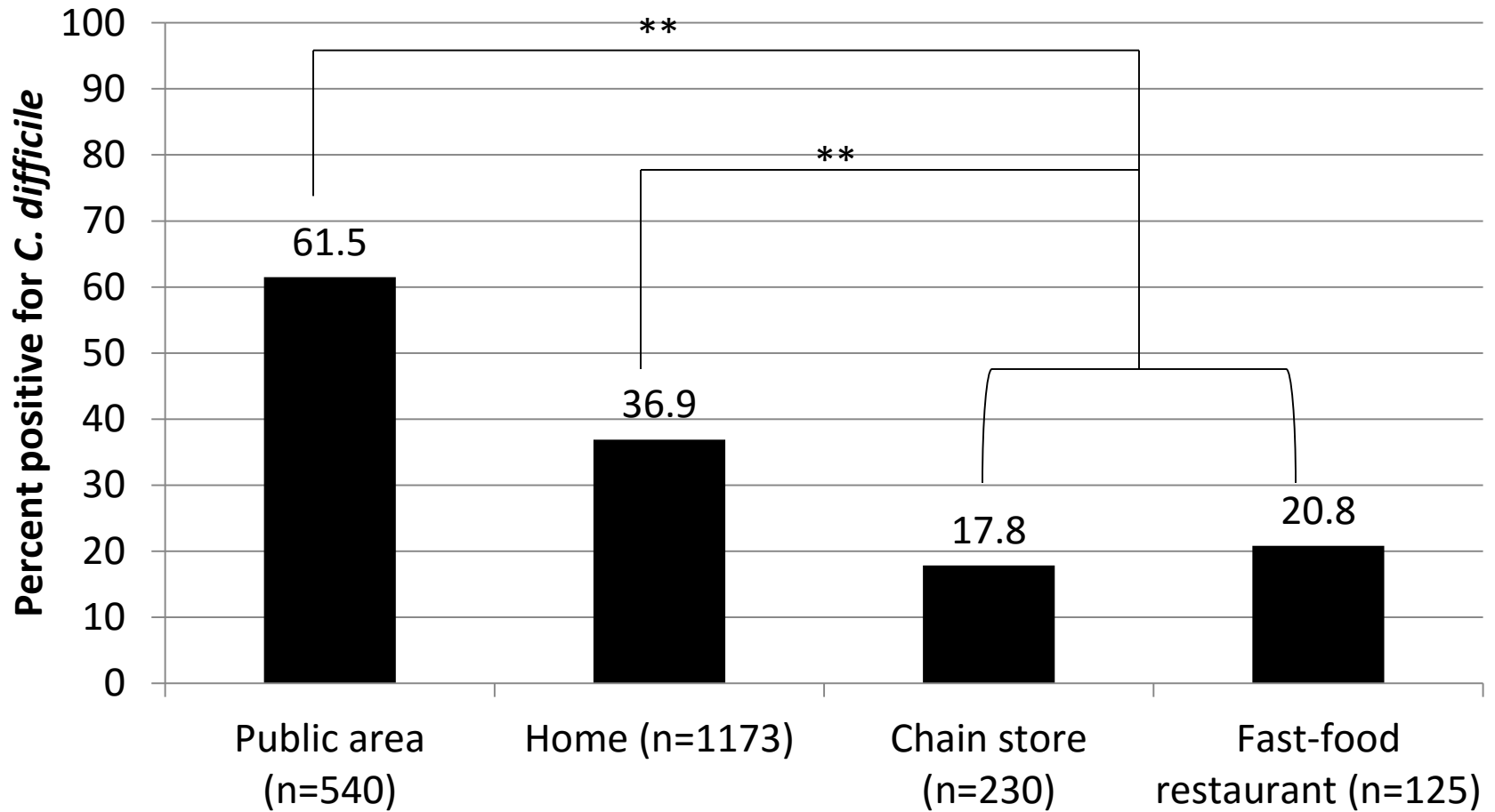
Is *C. diff* ubiquitous in our environment?

- We hypothesized the community environment may contain a large burden of *C. difficile* contamination.
- The objectives of the study was to assess community environmental contamination of toxigenic *Clostridium difficile*
 - Sub-aims
 - compare strain relatedness to clinical strains (ribotype)
 - assess virulence in a mouse model.

Results, number of samples

Isolate source	Number
Environmental	
Home	1173
Chain stores	230
Fast-food restaurants	125
Public Area	540
Clinical isolates	613

Figure 1. Community environmental contamination of *C. difficile*



**p<0.001 compared to either chain stores or fast-food restaurants

Figure 2. Home environmental contamination of *C. difficile*

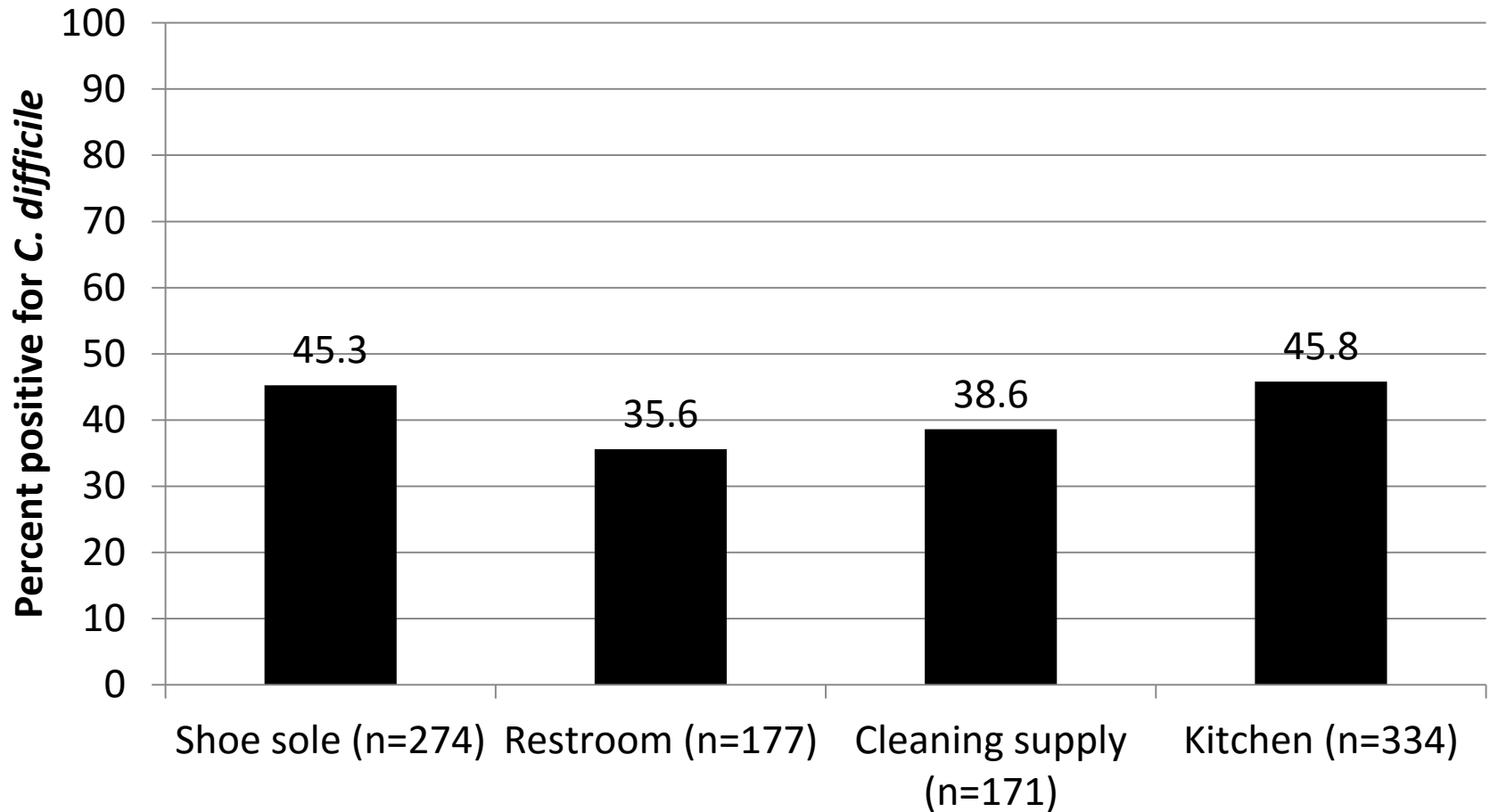
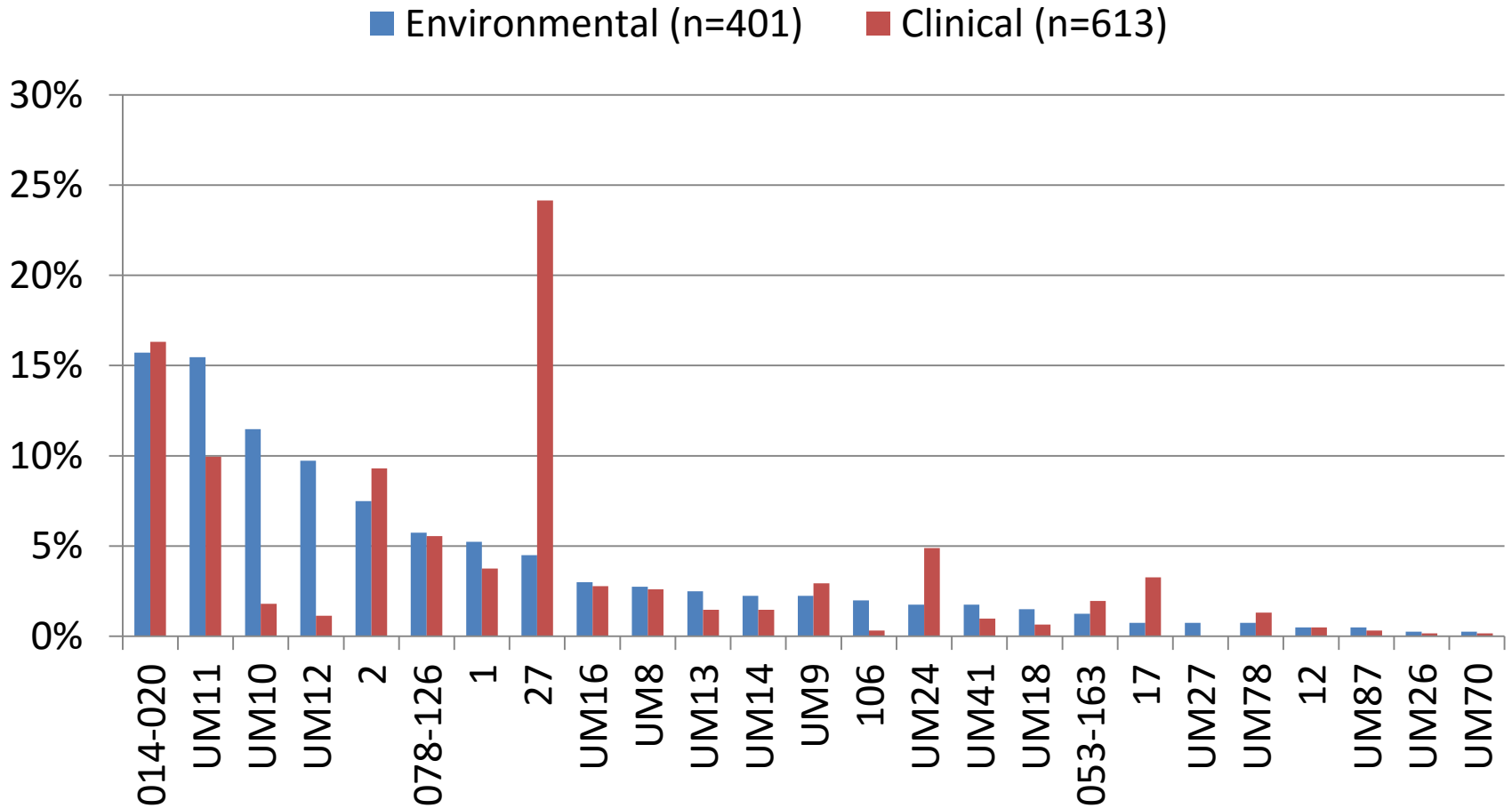


Table 1. Risk factors for home contamination with *C. difficile*

	C diff positive	C diff negative	P value
Home type			
House	41 (36%)	71	>0.3
Apartment	162 (43%)	215	
Pet in home			
Yes	41 (65%)	22	<0.001
No	144 (38%)	233	
Number of persons in home	3.6±1.9	3.2±1.3	>0.3
Age of oldest person in home	42±16	44±16	>0.3
Age of youngest in home	20±7	21±11	>0.3
Any child in daycare	10 (5%)	11 (4%)	>0.3

Ribotype distribution of clinical vs. environmental *C difficile* isolates



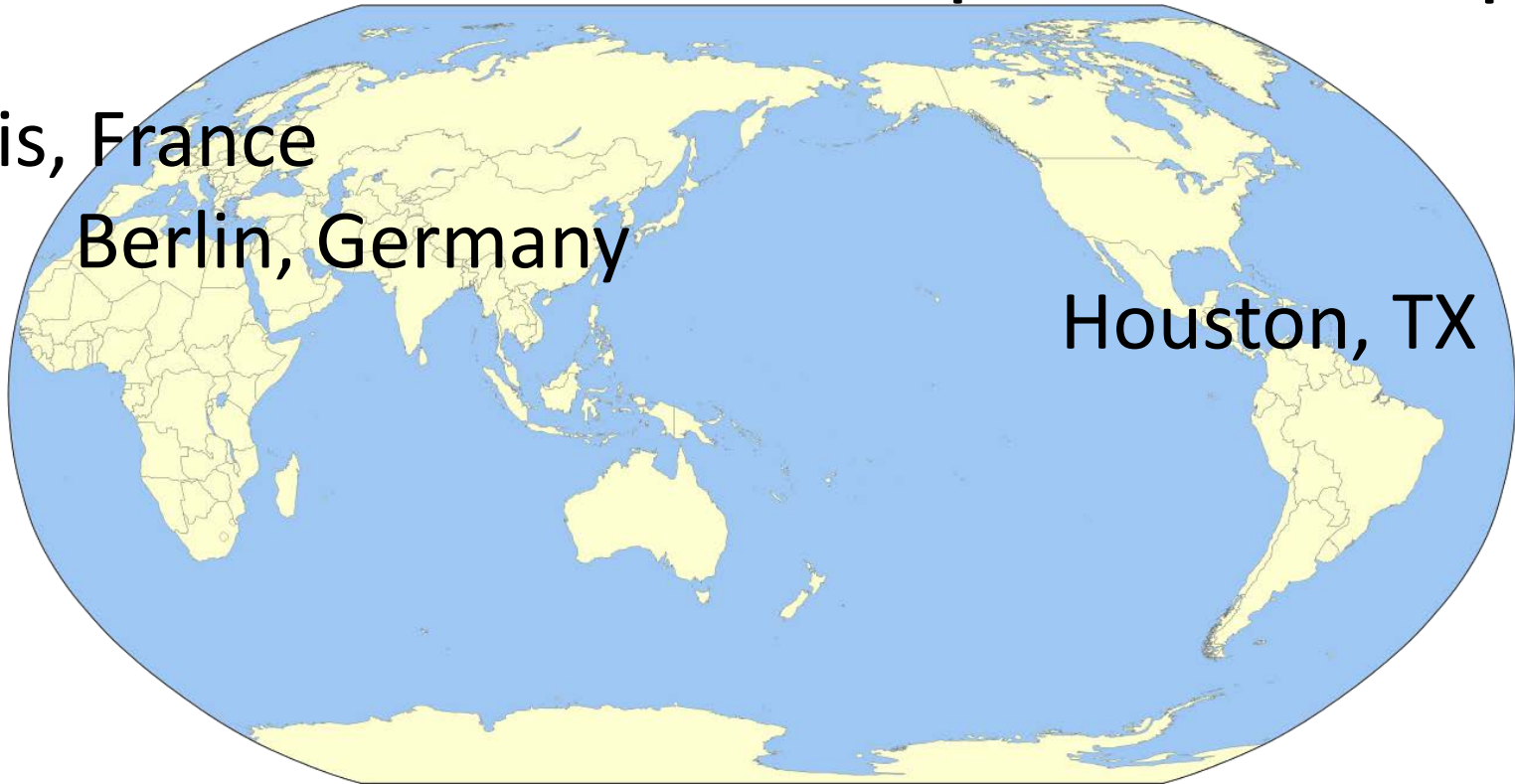
Most of the other environmental samples
have been conducted in Europe.

How do our results compare to Europe?

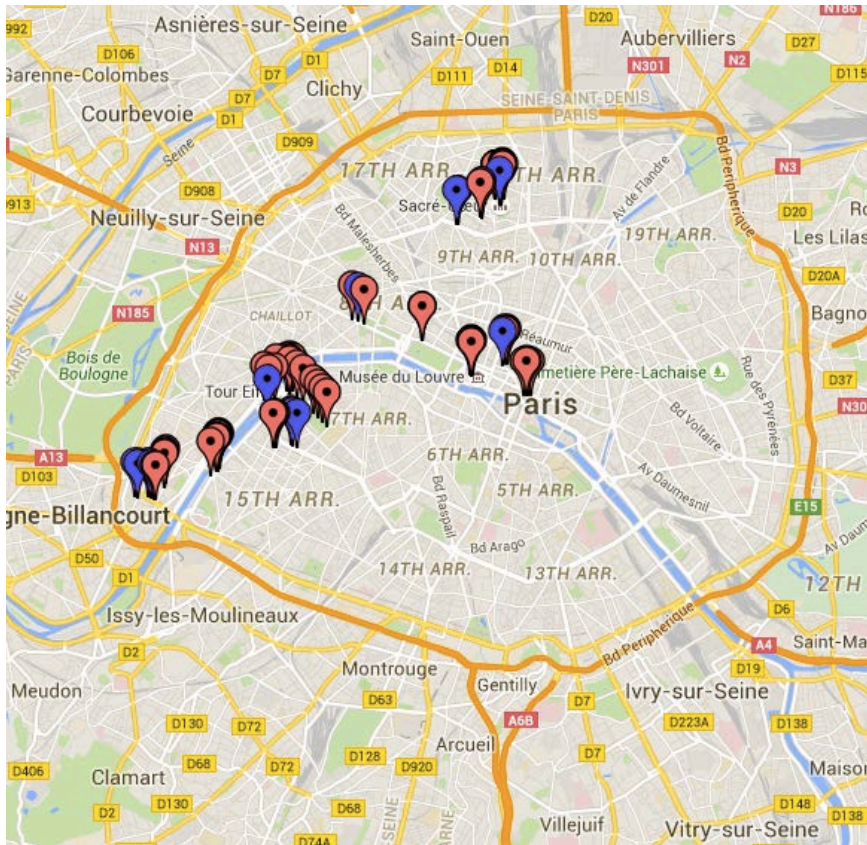
Paris, France

Berlin, Germany

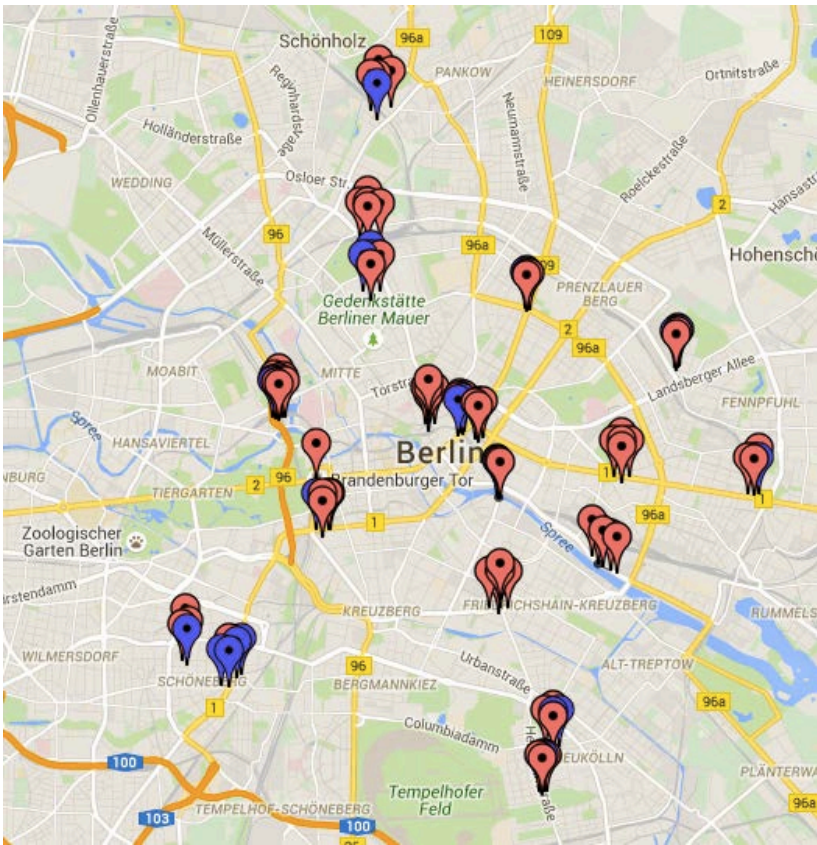
Houston, TX



Lucky for me, I had a student do an internship in Paris and Berlin last Summer!



Area swabbed
No *C. difficile* found



C. difficile isolated

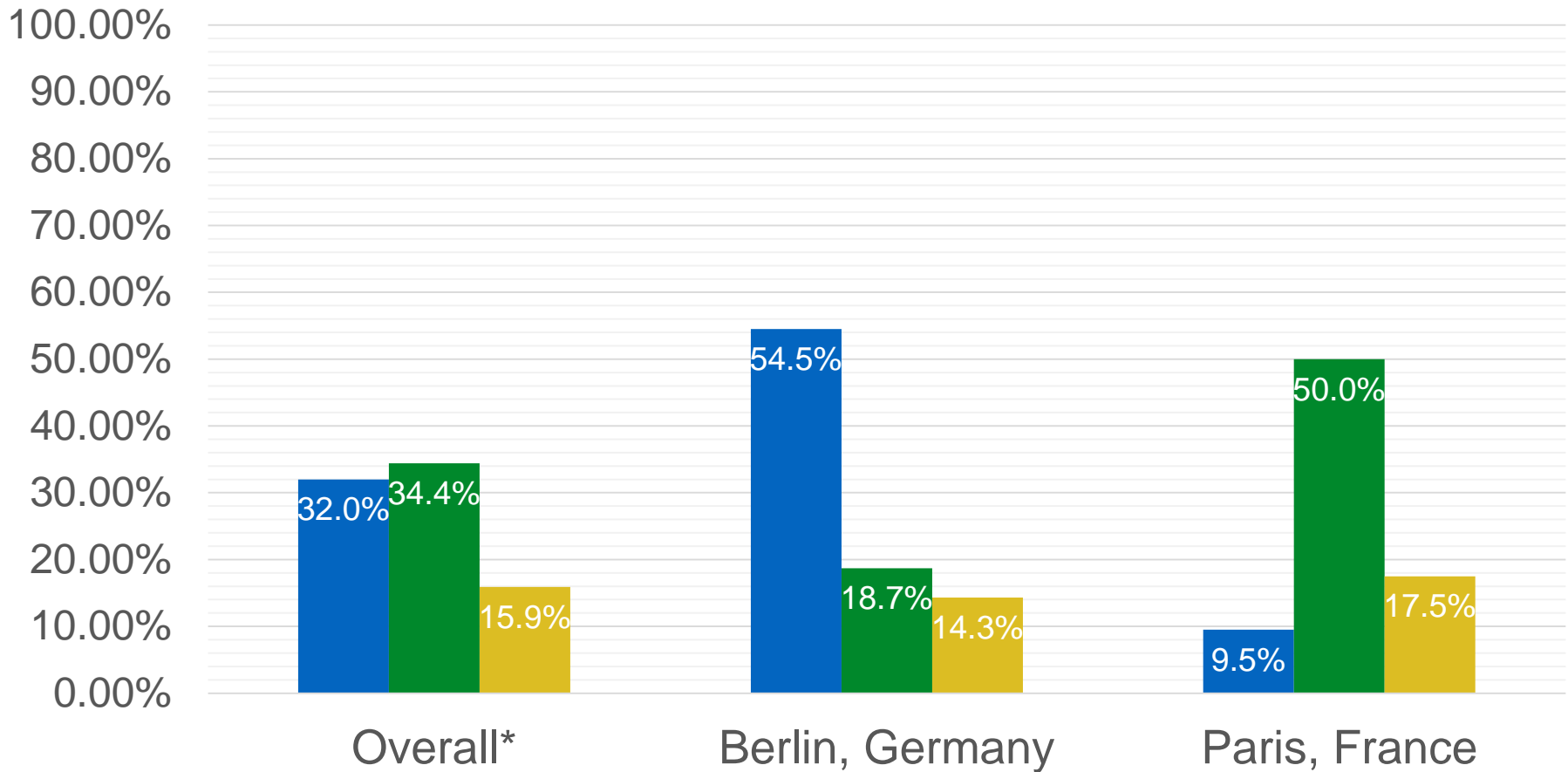
Environmental *C. difficile* in Berlin and Paris

	Berlin (n=100)	Paris (n=100)
Overall Prevalence	22/100 (22%)	20/100 (20%)
Surface swabbed		
Floor	19/85 (22%)	14/37 (38%)
Bench	3/15 (20%)	4/53 (8%)
Other**		2/10 (20%)
Location		
Parks	6/11 (55%)	4/42 (10%)
Metro/bus	14/75 (19%)	9/18 (50%)
Public areas***	2/14 (14%)	7/40 (18%)
Ribotype		
078-126	0/22 (0%)	0/20 (0%)
014-020	10/22 (46%)	1/20 (5%)
27	0/22 (0%)	1/20(5%)
2	1/22 (5%)	1/20(5%)
UM9	0/22 (0%)	2/20 (10%)
UM10	1/22 (5%)	1/20 (5%)
UM11	0/22 (0%)	5/20 (25%)
UM12	4/22 (18%)	3/20 (15%)
UM13	3/22 (14%)	2/20 (10%)
UM16	0/22 (0%)	2/20 (10%)
UM18	3/22 (14%)	0/20 (0%)
UM26	0/22 (0%)	2/26 (8%)

Other defined as bike handle station release button, board, and side rails, *excluding parks and metro/bus areas

Environmental *C. difficile* Prevalence in Berlin and Paris

■ Parks ■ Metro/bus ■ Public areas***



***defined as bike handle station release button, board, and side rails

Texas vs. Europe

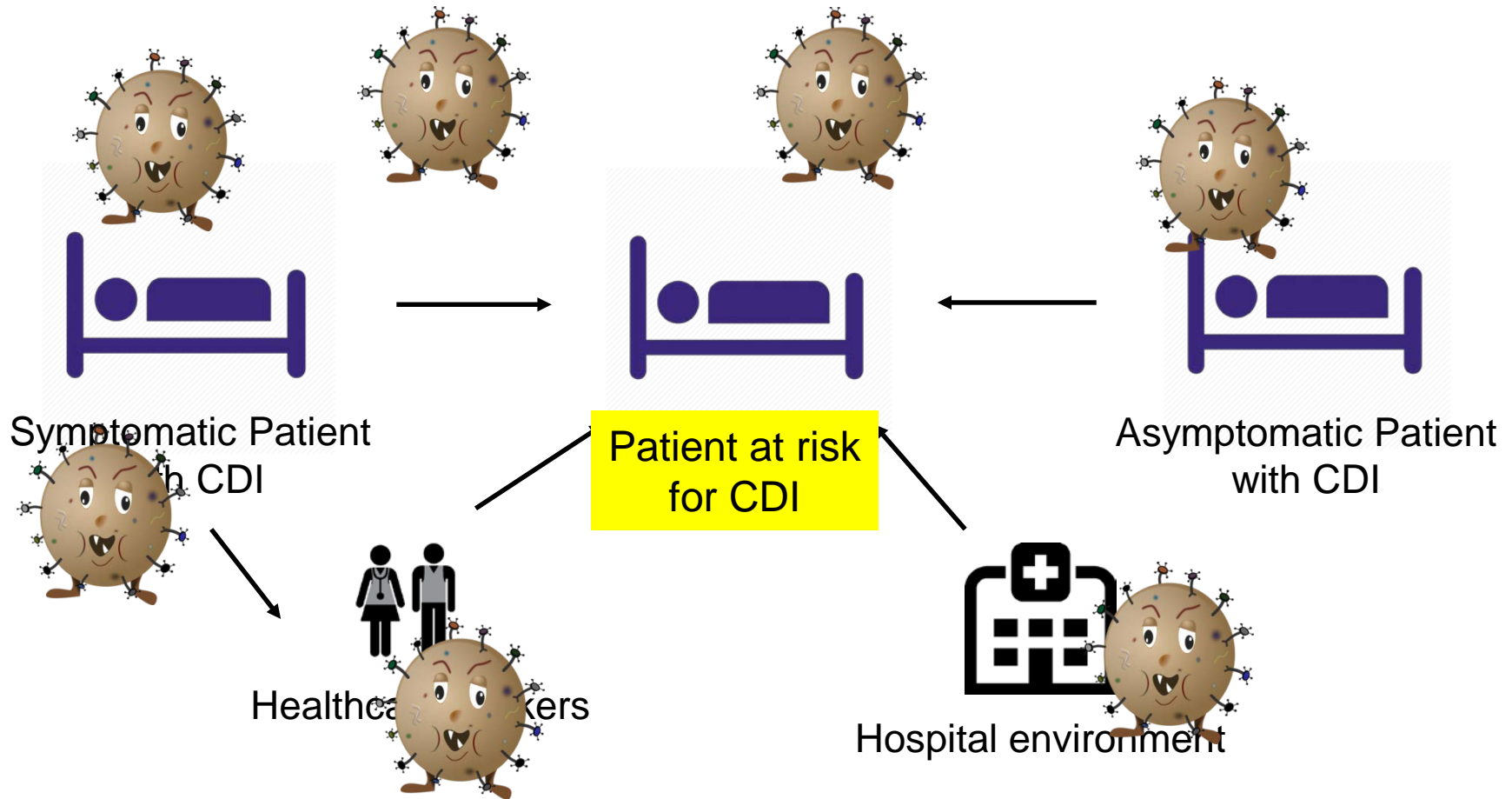
C. difficile environmental prevalence

An Epidemiological Survey of Environmental <i>Clostridium difficile</i> in Berlin and Paris	
Overall*:	21%
Parks:	32%
Houses:	n/a
General Public:	16%
Fast Food:	n/a
Chain Stores:	n/a

Community environmental studies on potentially pathogenic <i>Clostridium difficile</i>	
Overall:	219/1040 (21%)
Parks:	97/235 (41%)
Houses:	61/175 (35%)
General Public:	27/200 (14%)
Fast Food:	10/125 (8%)
Chain Stores:	21/250 (8%) ¹

Emerging view of CDI transmission

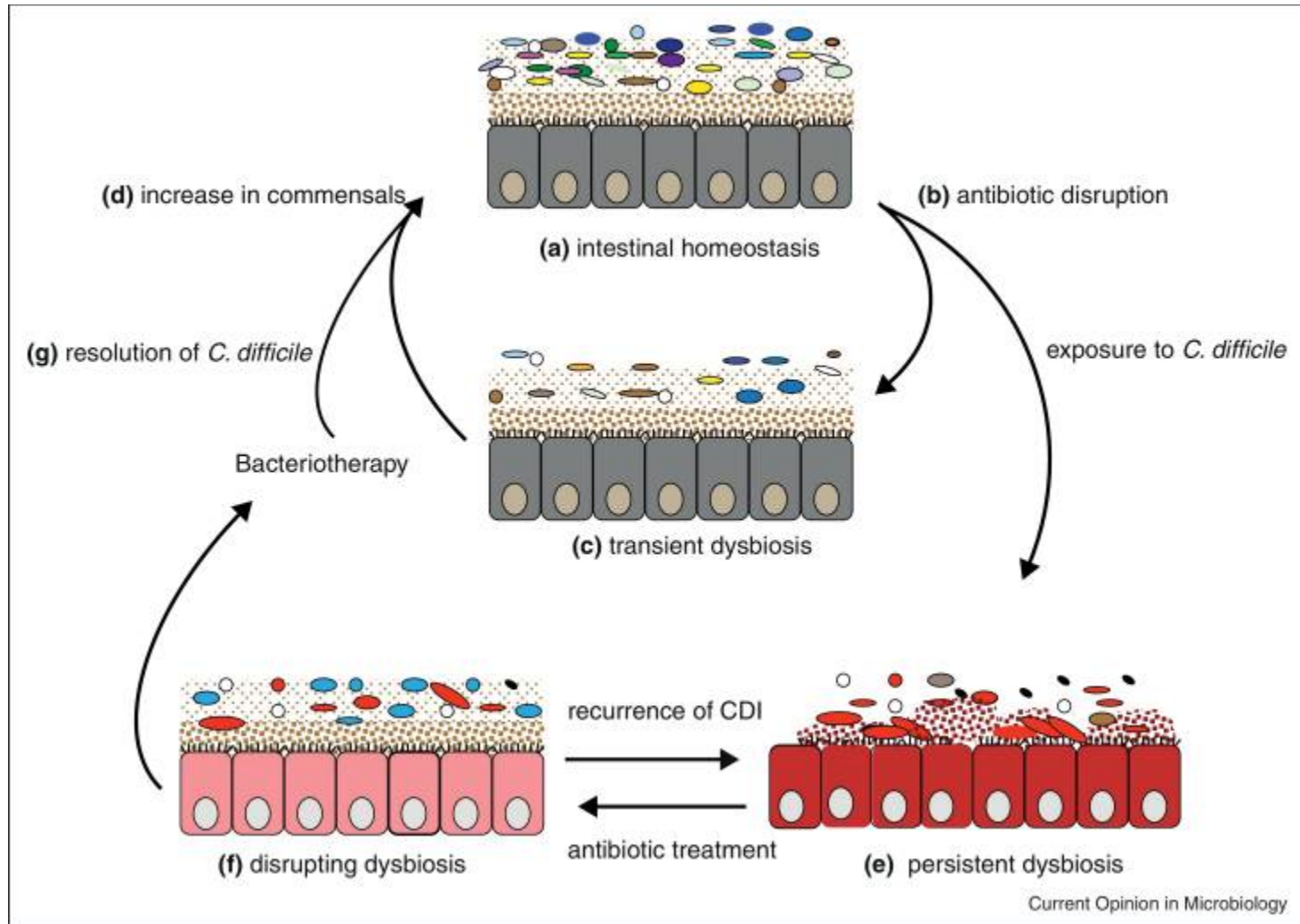
Host factors that increase vulnerability to CDI might be of more importance than increased exposure to *C. difficile*



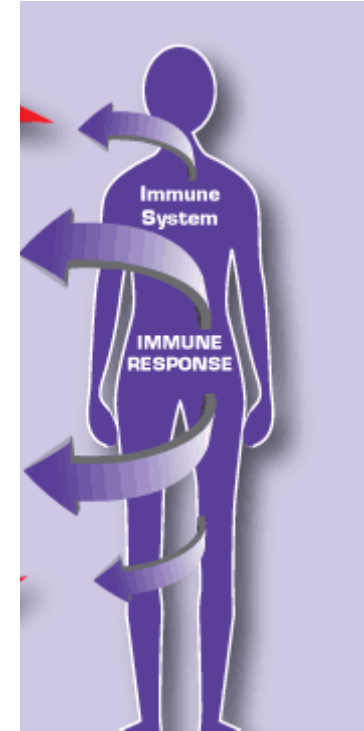
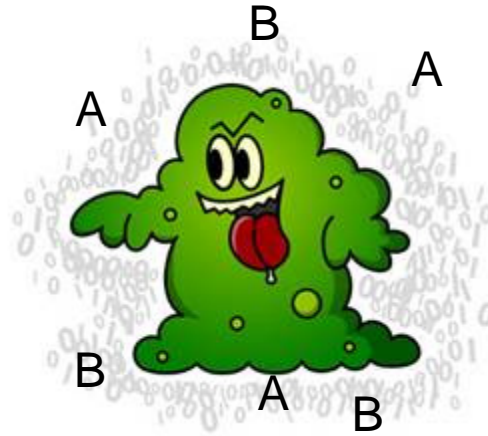
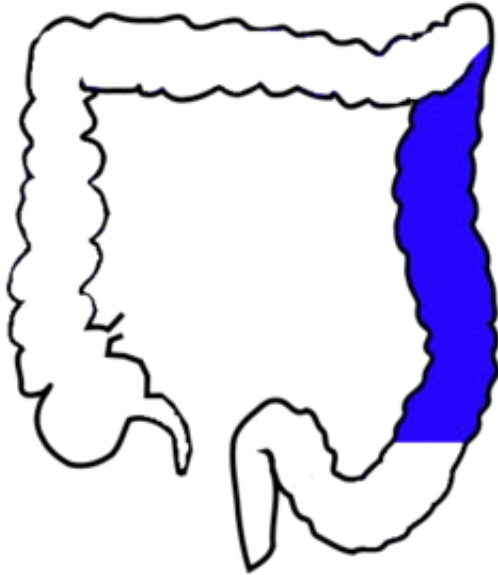
Now that I've totally rocked your C. diff infection control world!!

- How should we treat this ubiquitous pathogen?
- Current practice
 - Metronidazole (40-60% of total use)
 - Oral vancomycin (20-40% of total use)
 - Fidaxomicin (<10% of total use)
- Is this the correct use of these drugs?

Treatment of *Clostridium difficile* infection. Kill the bug and treat the patient



Expanding treatment goals for CDI



Essential: Correct dysbiosis

Kill the organism

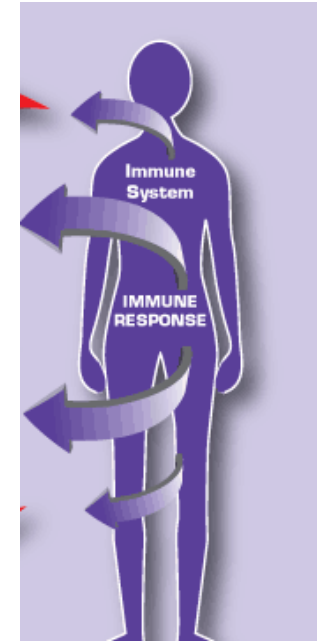
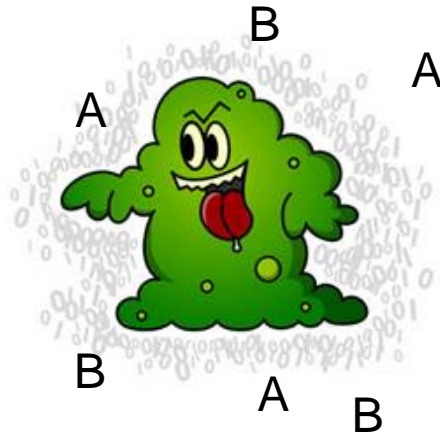
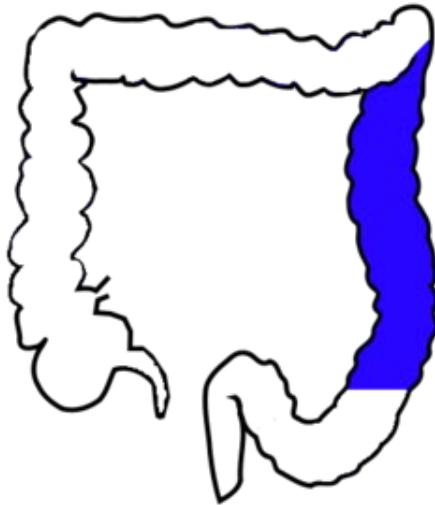
Adaptive immunity

Optional but nice: Safe and convenient

Also affects toxins and spores

Short vs. long-term

There has been an explosion in treatment possibilities for CDI



Current: Probiotics
FMT

Metronidazole
Vancomycin
Fidaxomicin

IVIG

Future: 2nd generation FMT
non-tox C diff M3
Ecobiotics

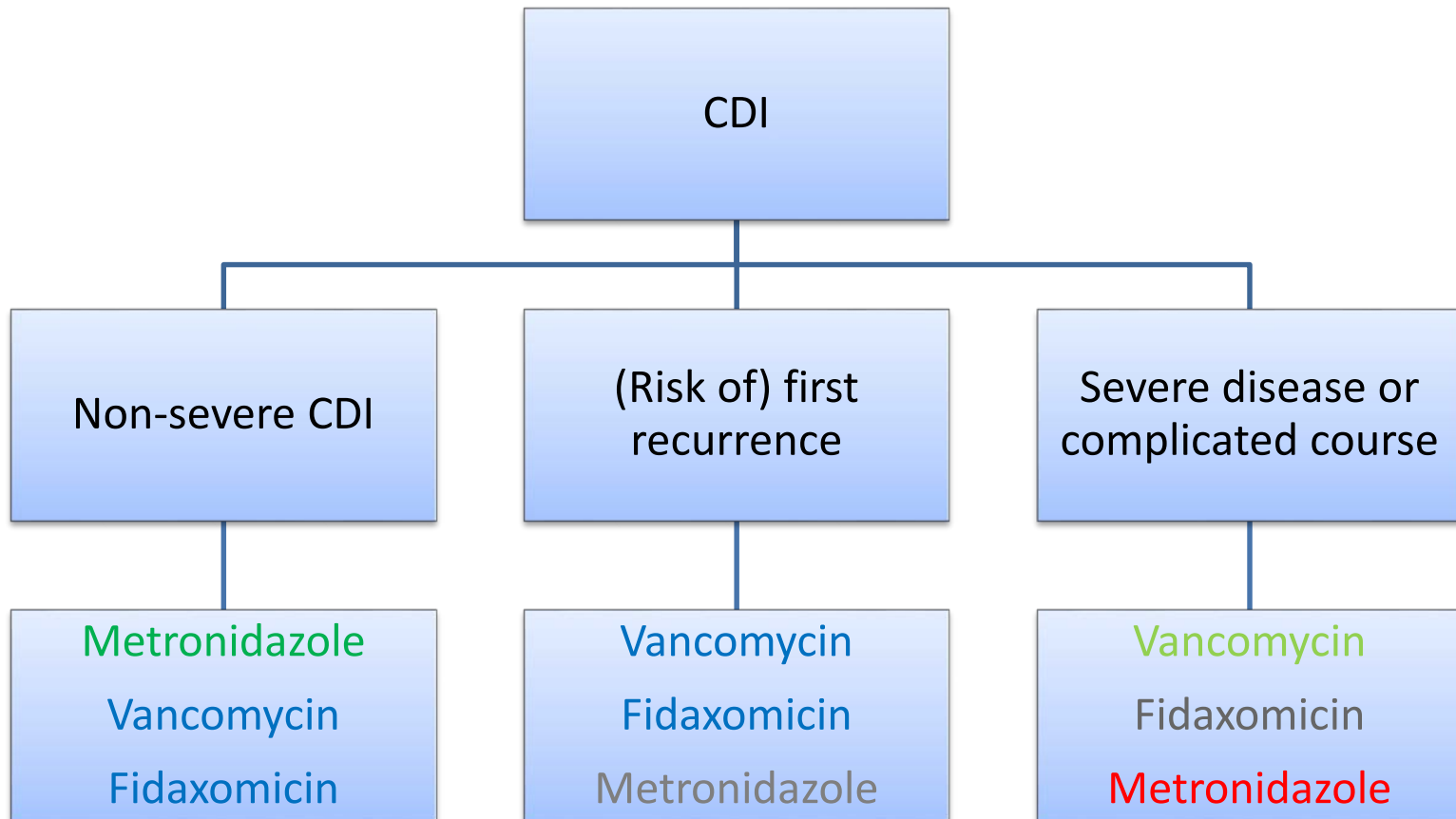
Surotomycin
Cadazolid
SMT-19969

Monoclonal antibodies
vs. C diff toxins
Toxoid vaccines

Current US IDSA CDI guidelines 2010

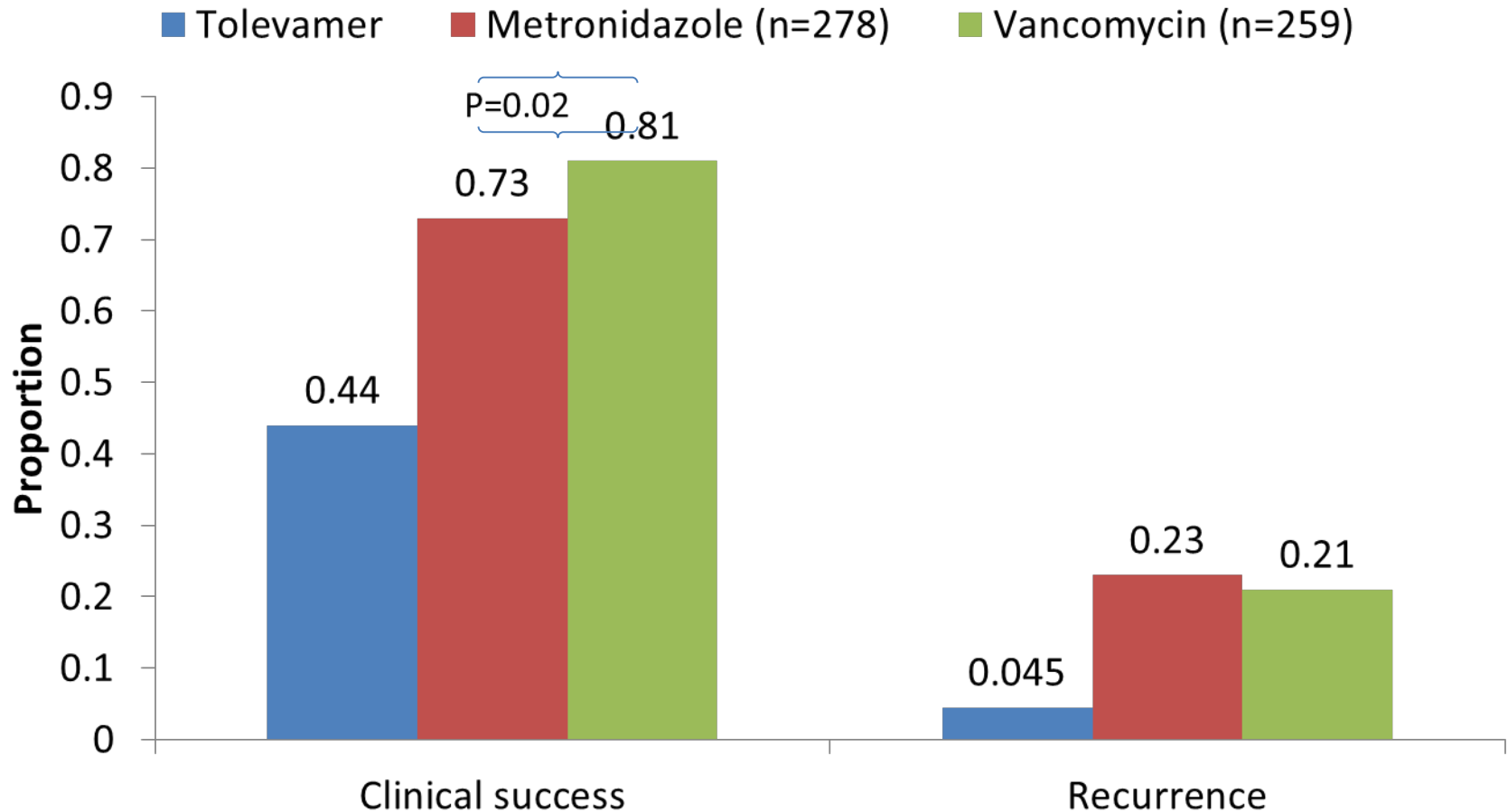
Episode	Clinical Signs	Severity	Recommended agent	Dosing Regimen	Strength of Recommendation
Initial	WBC < 15,000 and SrCr < 1.5 X premorbid level	Mild or moderate	Metronidazole	500 mg PO three times daily 10-14 days	A-I
Initial	WBC ≥ 15, 000 or SrCr ≥ 1.5 X premorbid level	Severe	Vancomycin	125 mg PO four times daily 10-14 days	B-I
Initial	Hypotension, shock, ileus, megacolon	Severe, complicated	Vancomycin + metronidazole IV	Vancomycin: 500 mg PO or NG four times daily + Metronidazole: 500 mg IV q8hours. For ileus, consider adding rectal instillation of vancomycin	C-III
Second (1 st recurrence)	-----	-----	Same as initial	Same as initial	A-II
Third (2 nd recurrence)	-----	-----	Vancomycin	PO tapered and/or pulsed	B-III

Current European CDI guidelines

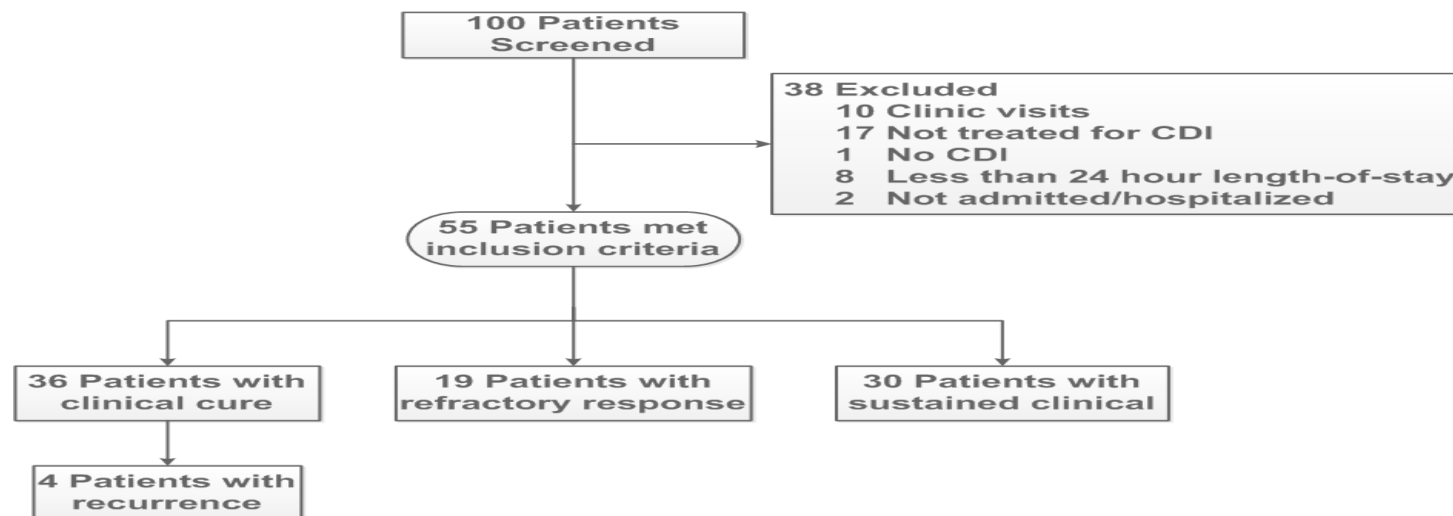


Green: strongly supports use; Blue: moderately supports use; Grey: Minimally supports use; Red: recommend to not use

More recently, metronidazole has been shown to be globally inferior to vancomycin (tolevamer phase III RCT)



Why are patients failing metronidazole?



	Age			
	<50 (n=72)	50-70 (n=97)	>70 (n=73)	P value
Continued use of antibiotics	38 (53%)	61 (63%)	45 (62%)	0.38
CDI severity	21 (29%)	59 (61%)	48 (66%)	<0.01
Horn's index > 2	14 (19%)	29 (30%)	28 (38%)	0.043

Summary of metro vs. vanco clinical studies

Study	Year	Location	n	Single center	Blinded	Randomized	Metro dose	Vanco dose	Clinical failure		Recurrence	
									metro	vanco	metro	vanco
Teasley, 1983	82-83	MN	101	yes	no	yes	250 mg QID	500 mg qid	2 of 37 (5.4%)	0 of 45 (0%)	2 of 37 (5.4%)	6 of 45 (13%)
Wenisch, 1996	93-95	Austria	62	yes	no	yes	500 mg TID	500 mg tid	2 of 31 (6%)	2 of 31 (6%)	5 of 31 (16%)	5 of 31 (16%)
Musher, 2006	02-04	USA (Houston)	34	no	yes	yes	250 mg QID	125 mg qid	6 of 34 (17%)	N/A	9 of 28 (32%)	N/A
Zar, 2007	94-02	Chicago	150	Yes	yes	yes	250 mg QID	125 mg qid	13 of 79 (16%)	2 of 71 (3%)	9 of 66 (14%)	5 of 69 (7%)
Johnson, 2013	05-07	World	552	no	yes	yes	375 mg QID	125 mg qid	76 of 278 (27%)	49 of 259 (19%)	48 of 202 (23%)	43 of 210 (21%)

There may have been a MIC creep with metronidazole over the decades

Author	Location	Time period	Isolates	Metronidazole		
				MIC50	MIC90	Range
All strains						
Hecht et al	Various	1983–2004	110	0.125	0.25	0.025–0.5
Edlund et al	Sweden	1998	50	0.125	0.25	0.125–0.25
Betriu et al	Spain	2001	55	0.5	1	≤0.06–1
Citron et al	USA	2003	18	0.5	1	0.25–1
Finegold et al	USA (CA)	2003	72	0.5	1	0.25–2
Karlowsky et al	Canada (Manitoba)	2007	208	0.5	1	0.25–4
Debast et al	Europe	2008	398	0.25	0.5	<0.06-2
Reigadas et al	Spain	2013	100	0.25	0.5	0.06-1
Snydman et al	USA	2011-12	925	1	2	<0.06-4
BI/027/Nap1 strains						
Citron et al	USA	2004–2005		NR	2	0.5–2
Debast et al	Europe	2008		0.5	1	0.5-1
Snydman et al	USA	2011-12		2	2	<0.06-4

There is a possibility that higher MICs of metronidazole may have often gone unnoticed

- MIC increased 2-4 fold after exposure to 1-2 passages of sub-MIC metronidazole (Moura, JAC 2013)
- The addition of hemin to media decreased metronidazole susceptibility of *C. difficile* (Wu, ICAAC 2015)
- We don't test for MIC susceptibility very often

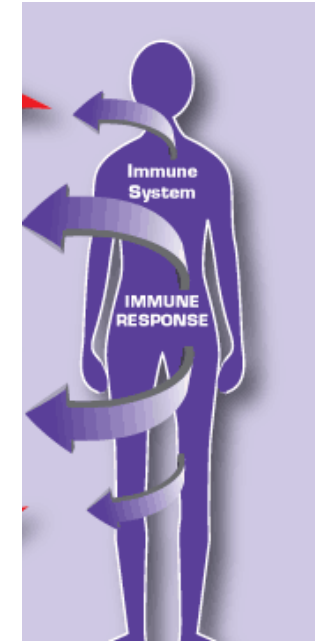
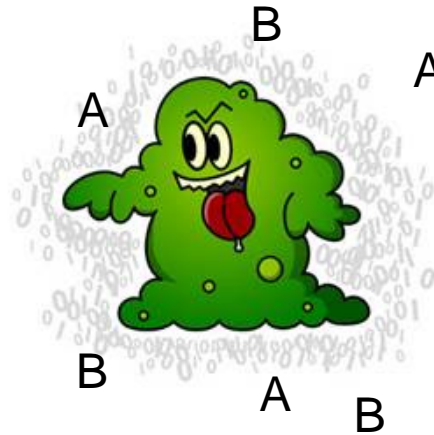
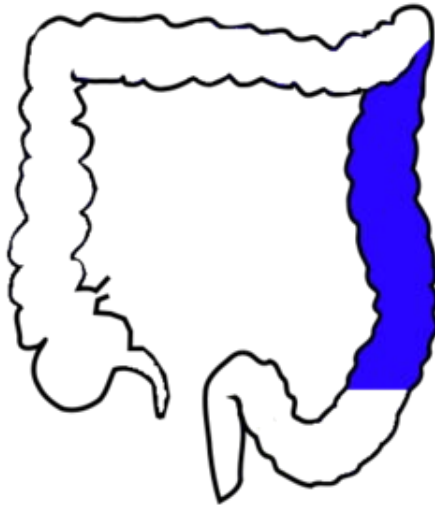
Bottom line:

this may simply be a PK/PD problem

- Mean concentrations of metronidazole in stool: <0.25-9.5 ug/g
- MIC50: 1 ug/ml MIC90: 2 ug/ml
 - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

Explosion in treatment possibilities for CDI minus

1



Current: Probiotics
FMT



Vancomycin
Fidaxomicin

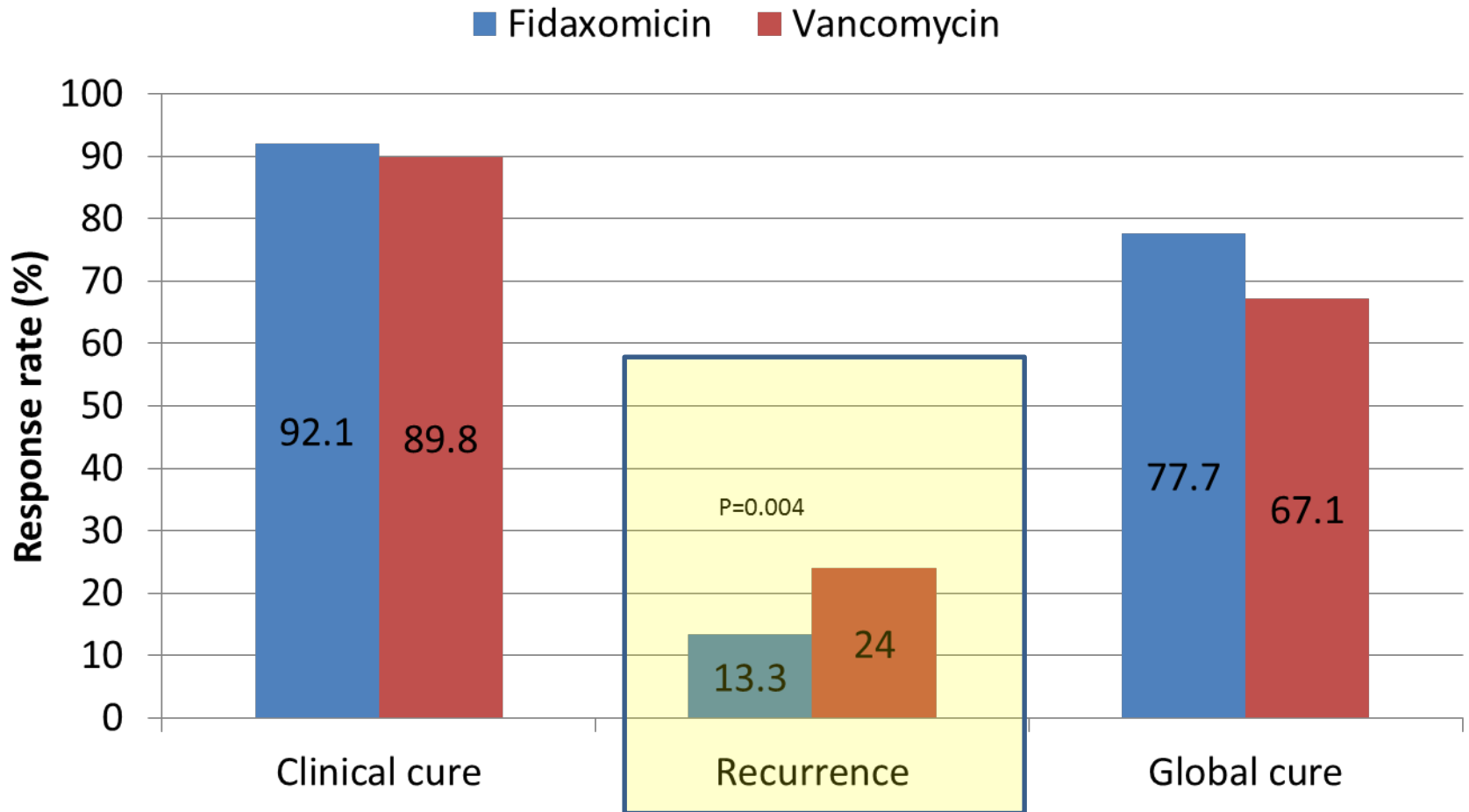
IVIG

Future: 2nd generation FMT
non-tox C diff M3
Ecobiotics

Surotomycin
Cadazolid
SMT-19969

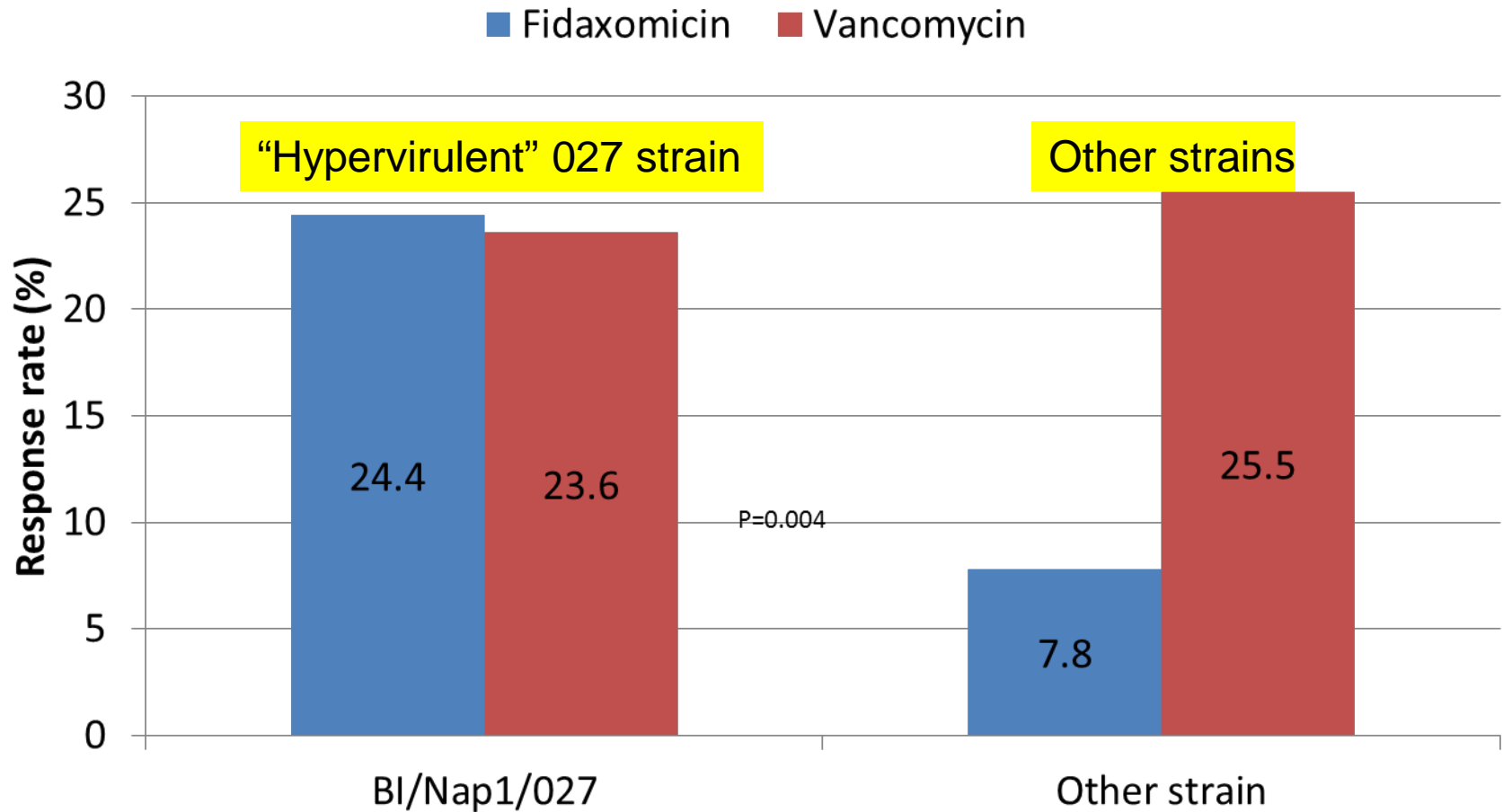
Monoclonal antibodies
vs. C diff toxins
Toxoid vaccines

Fidaxomicin: Equal efficacy at vancomycin to cure patients and lessens the risk of recurrence



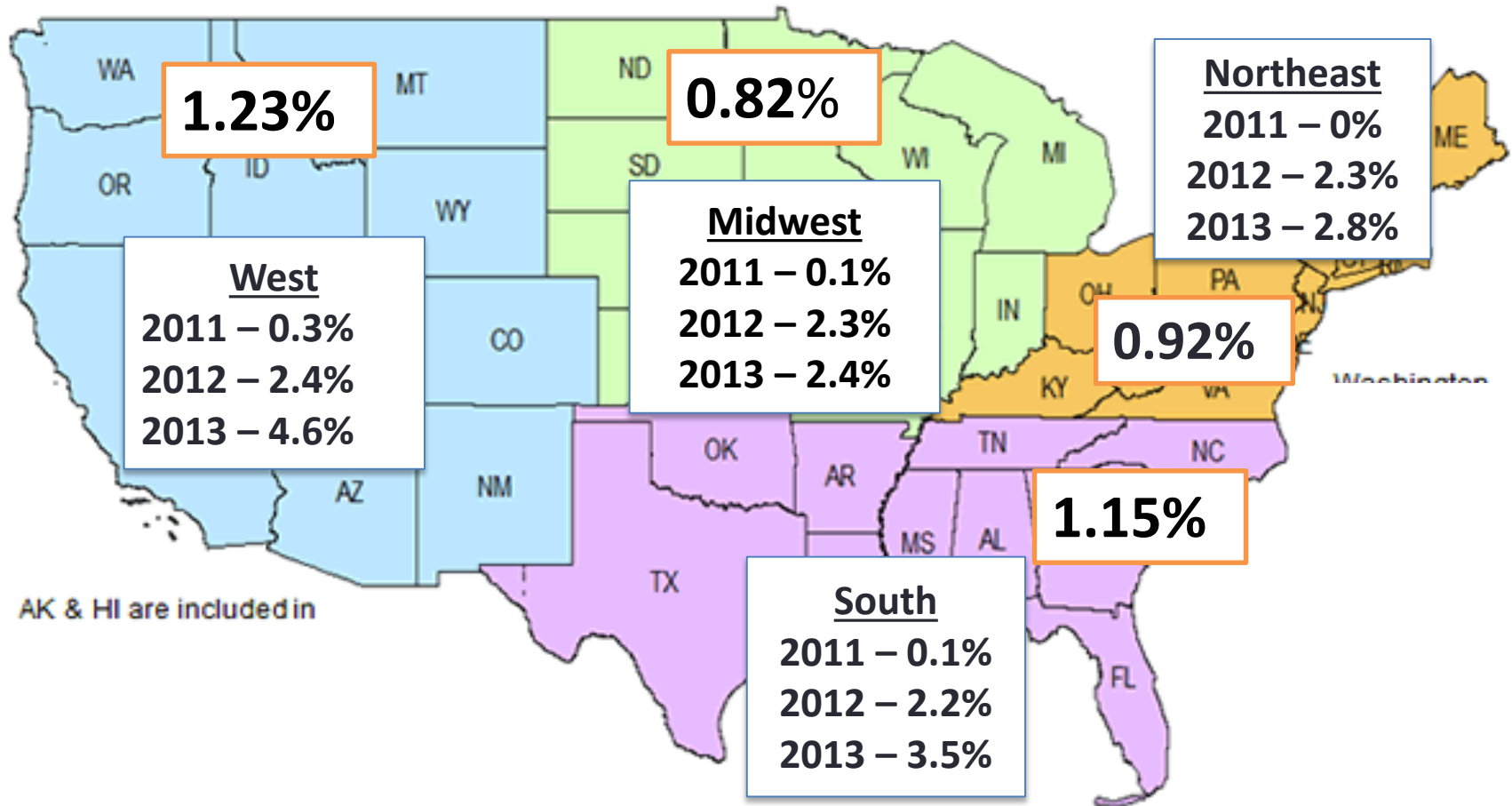
The second phase III study showed similar results (Crook et al. Lancet ID)

Recurrence rates of CDI in patients given fidaxomicin vs. vancomycin in the phase III study. Results from the per protocol analysis shown below.



The second phase III study showed similar results
Recurrence with 027: Fidaxo: 22% Vanco: 38%

However, this drug is quite costly: Fidaxomicin Use By Region



Appropriate use of fidaxomicin

- Because of high acquisition cost, fidaxomicin has been reserved for a very select patient population (my best guess)
- Remember: fidaxomicin's primary MOA is its narrow spectrum of activity preserving host microbiota
- Has reserving fidaxomicin for the worst cases been a good idea?
- Answer: No

We really have to do a better job of using fidaxomicin correctly

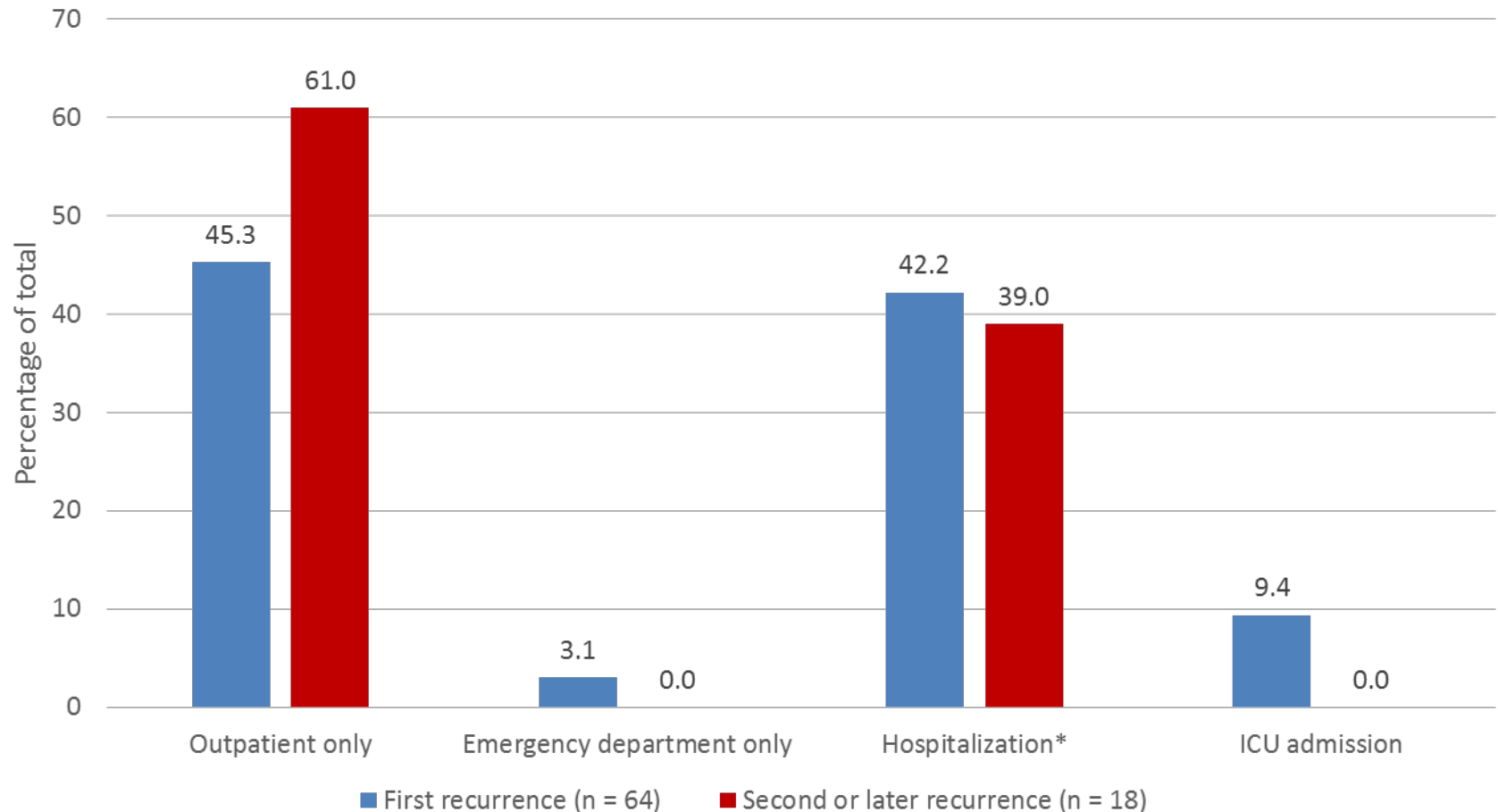
	Early episodes			Later episodes	Overall (n=102)
	Episode 1 (n=37)	Episode 2 (n=32)	Total (n=69)	Episode ≥ 3 (n=33)	
Mild-Moderate CDI; n(%)	10 (27%)	12 (37.5%)	22 (32%)	N/A	22/69 (32%)
Severe CDI; n(%)	27 (73%)	20 (62.5%)	47 (68%)	N/A	47/69 (68%)
1. FDX monotherapy; n (%)	3 (8%)	4 (12.5%)*	7 (12%)	6 (18%)	13 (13%)
2. Other CDI therapy; n (%)	34 (92%)	27 (84%)	61 (88%)	27 (82%)	88 (86%)
I. Subsequent; n	18	14	32	16	48
II. Subsequent and combination; n	8	6	14	2	16
III. Combination; n	2	1	3	1	4
IV. Unable to categorize; n	6	6	12	8	20
Concomitant non-CDI antibiotics; n (%)	25 (68%)	10 (31%)	35 (51%)	13 (39%)	48 (47%)

Multicenter, 11 hospital chart review study of hospitalized patients with CDI that received fidaxomicin between 2011 and 2013.

How do we decide who to give fidaxomicin to?

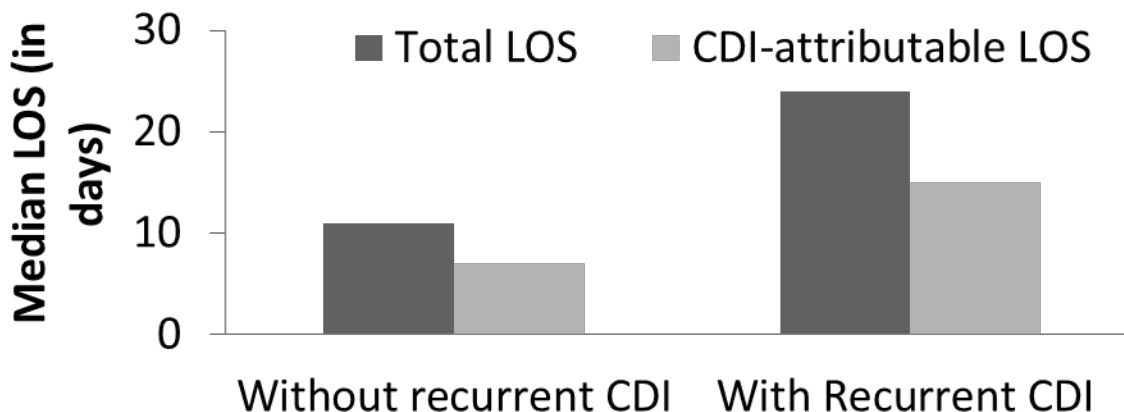
- As far as I can tell, 100% of the money we have used on fidaxomicin has been a waste of money (only kind of kidding).
- Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?

Recurrent CDI is costly: Healthcare utilization for recurrent CDI



* Of disease-attributable readmission, 85% returned to the initial hospital for care

Increased healthcare utilization = increased healthcare costs

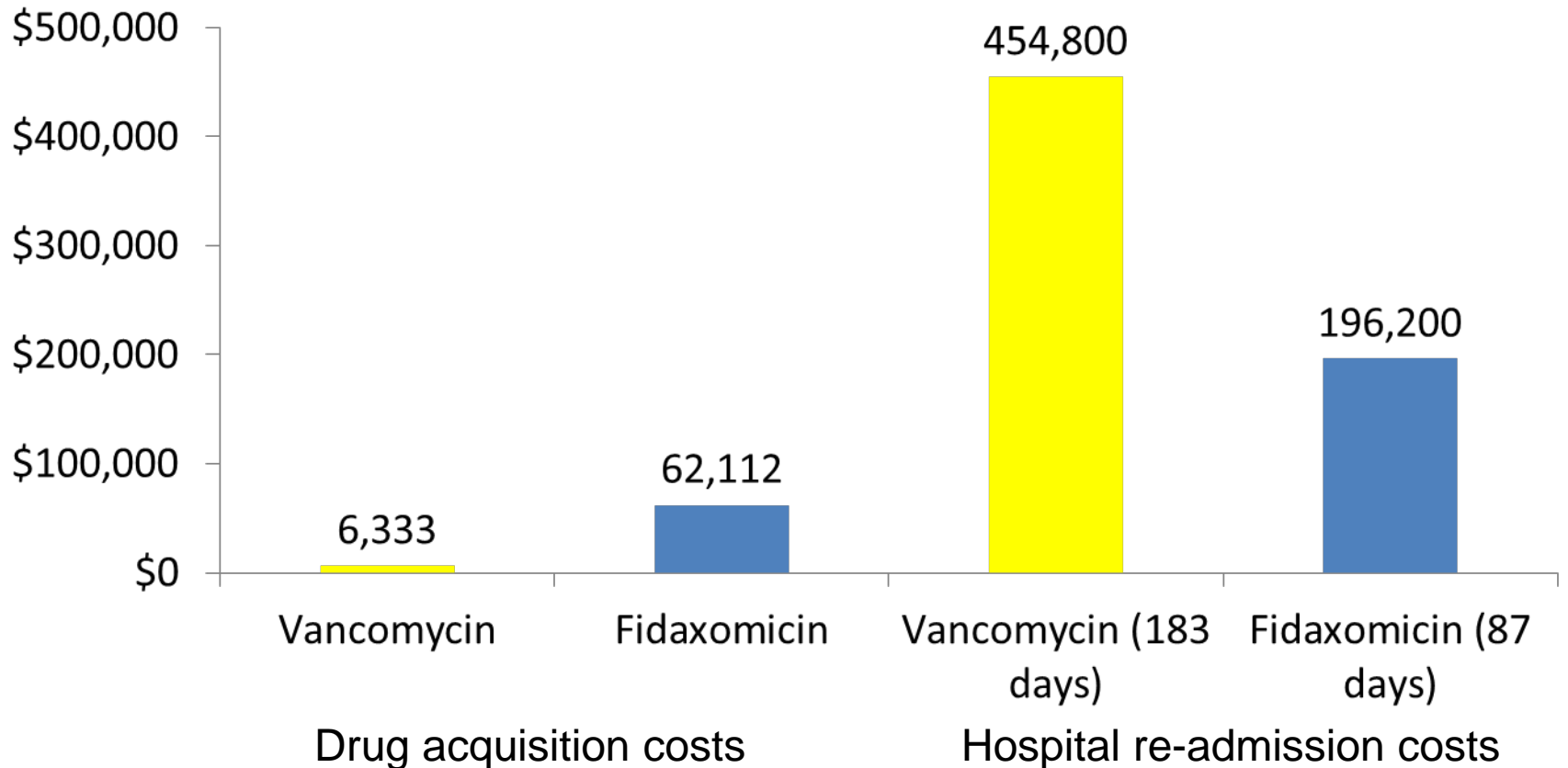


Cost in US dollars; median (IQR)	Without recurrent CDI	With recurrent CDI
CDI pharmacologic treatment*	\$60 (23 - 200)	\$140 (30 - 260)
CDI-attributable hospitalization^	\$13,168 (7,525 - 24,455)	\$28,218 (15,049 - 47,030)
Total hospitalization^	\$20,693 (11,287 - 41,386)	\$45,148 (20,693 - 82,772)

Any evidence that fidaxomicin may reduce these costs?

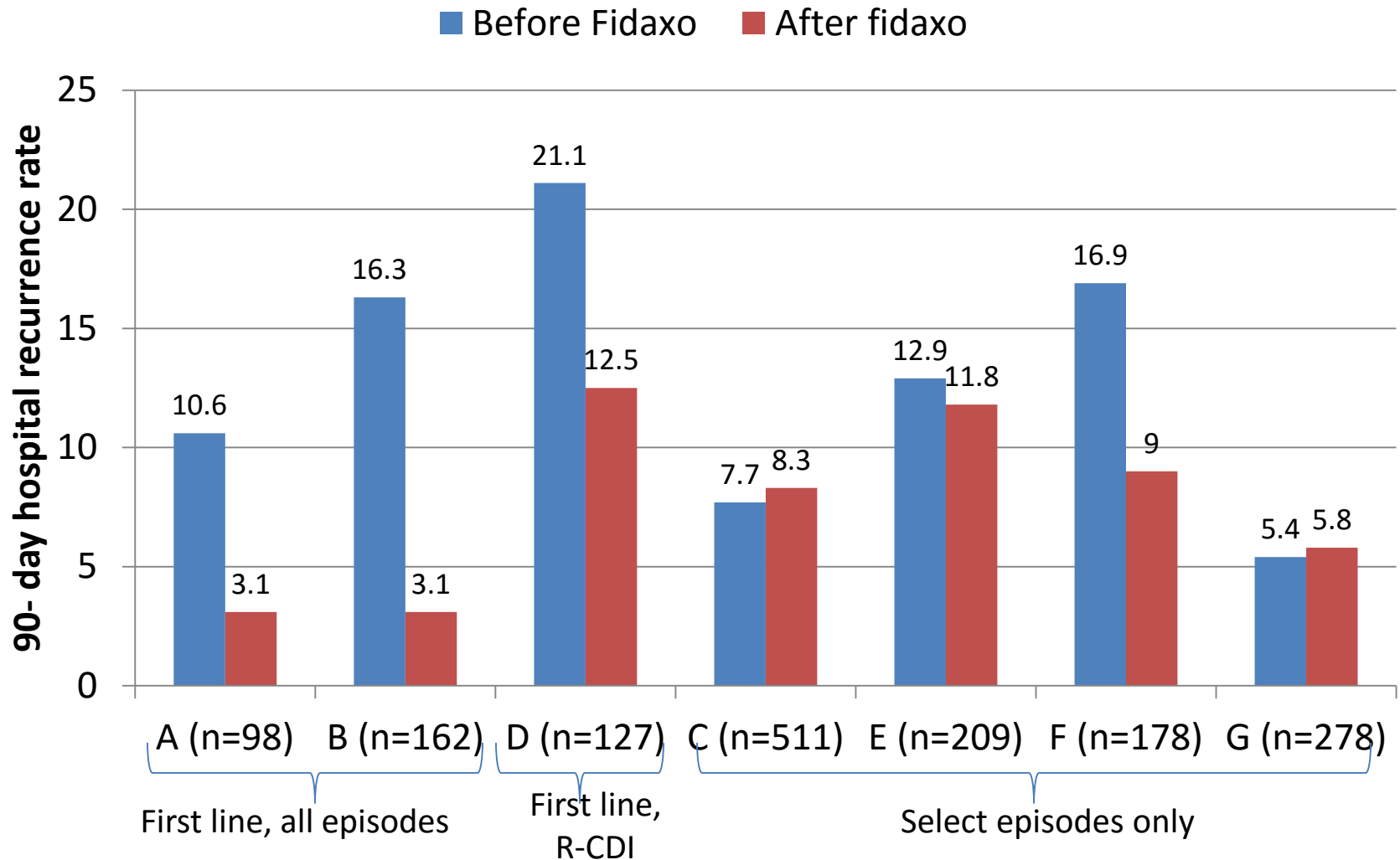
Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients.

CDI-related re-admissions: Fidaxo: 20.4%; Vanco: 41.3%



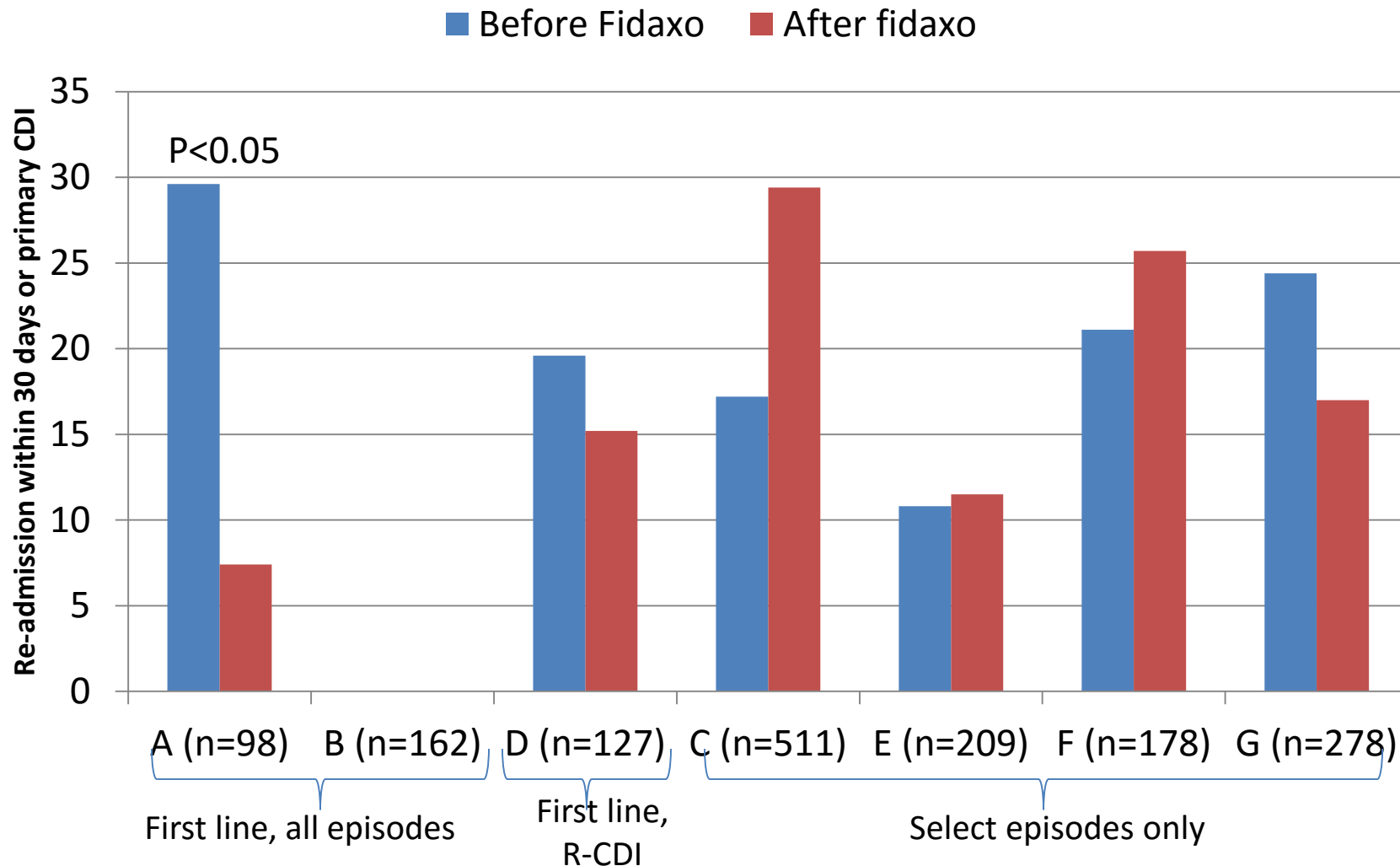
Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13: seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals

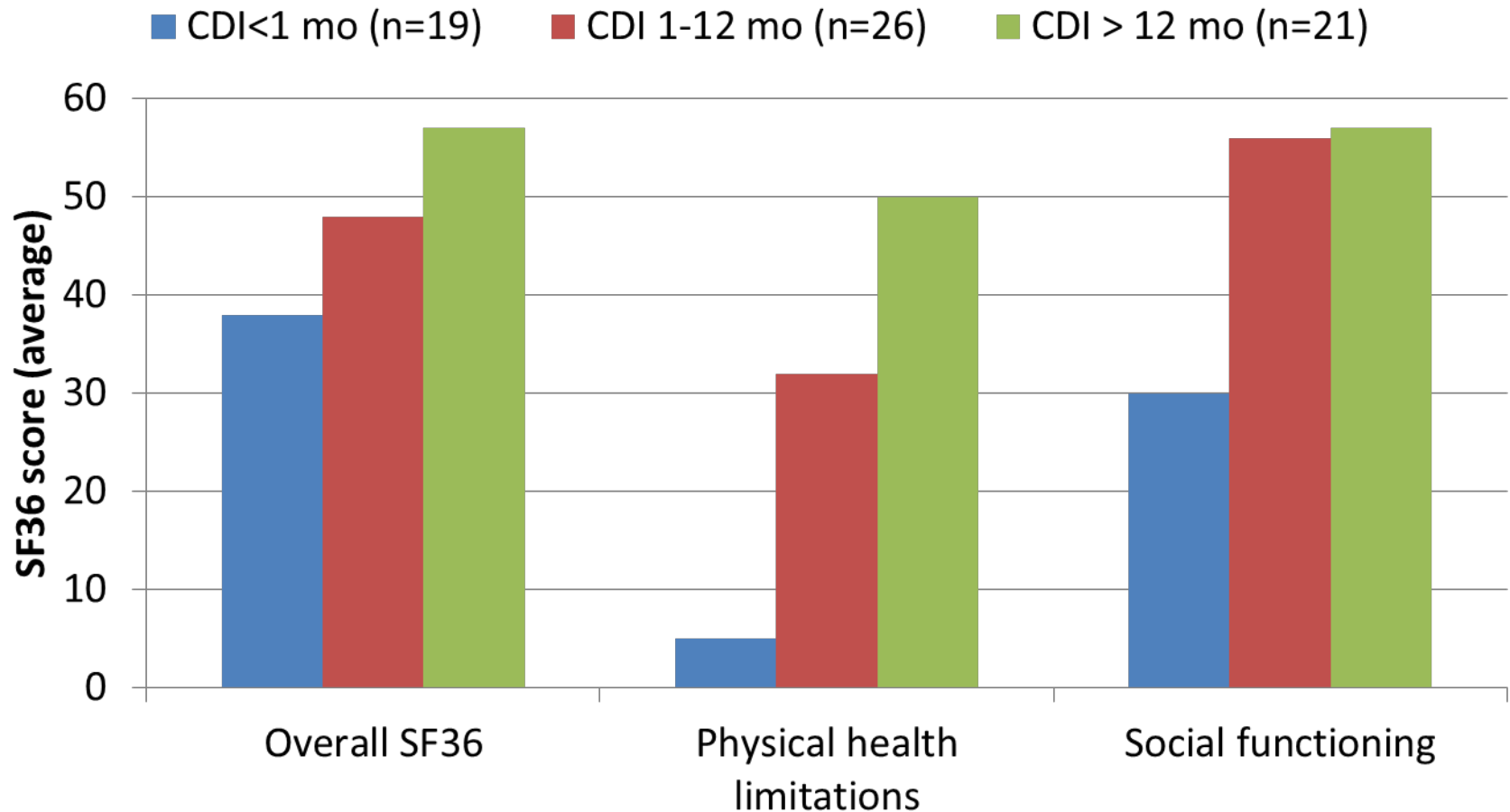


Real-world evidence that fidaxomicin may reduce these costs?

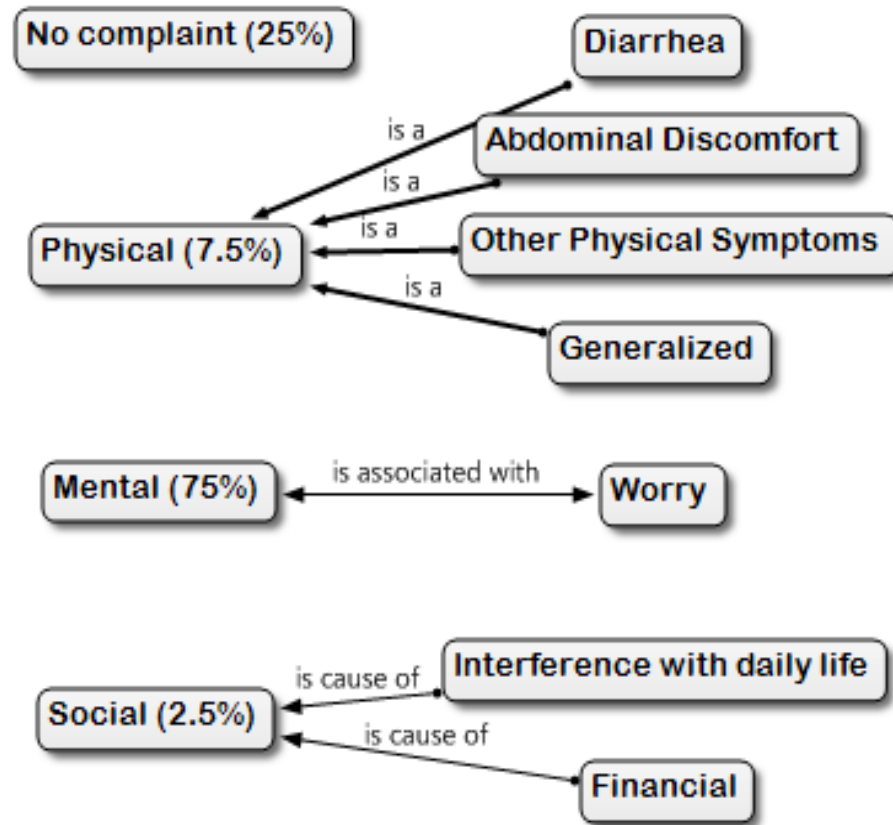
UK, 2012-13 : seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively ($p < 0.05$, each)



I do also wonder if we are missing the most important endpoints?



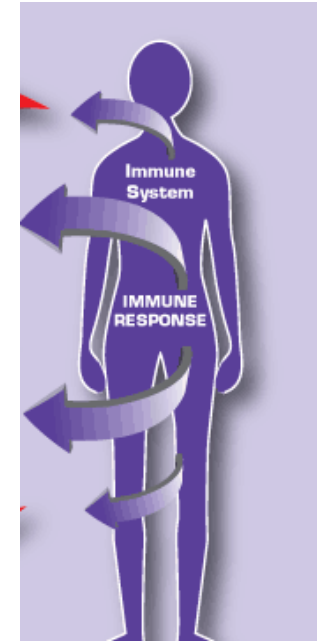
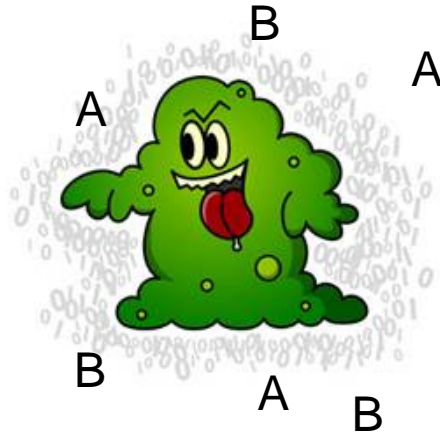
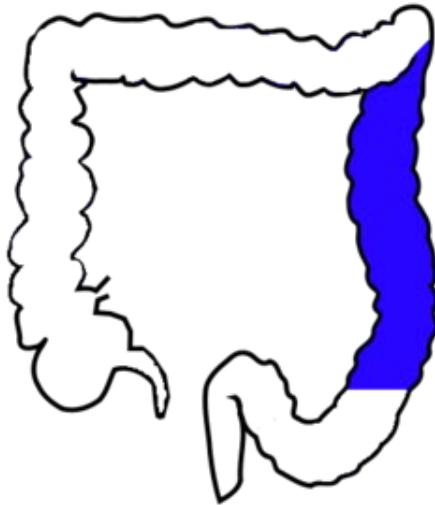
The driver for decreased QOL is not so much physical as a worry/anxiety of transmissibility or persistence of symptoms



Final thoughts on antibiotic treatment

- Limit use of metronidazole as alternative agent
- Consider a certain budget that you can afford to prove the worth of fidaxomicin and then use it for that purpose (first recurrence?).
- As more narrow-spectrum branded drugs become available, may have to prove themselves in other pharmacologic niches (decreased toxin expression).
 - This assumes similar phase III results

Explosion in treatment possibilities for CDI: Augment immune response!



Current: Probiotics
FMT



Vancomycin
Fidaxomicin

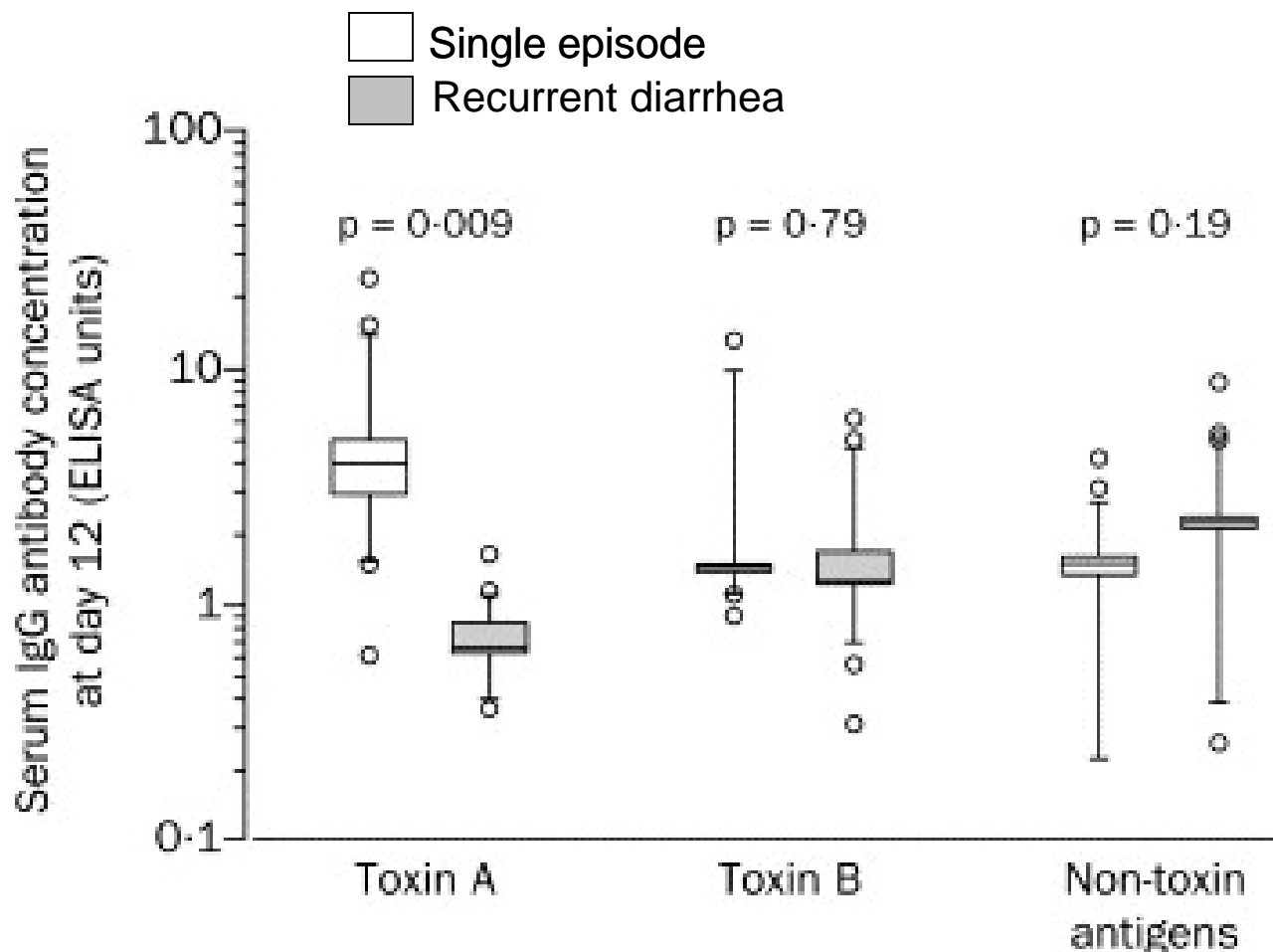
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Future: 2nd generation FMT
non-tox C diff M3
Ecobiotics

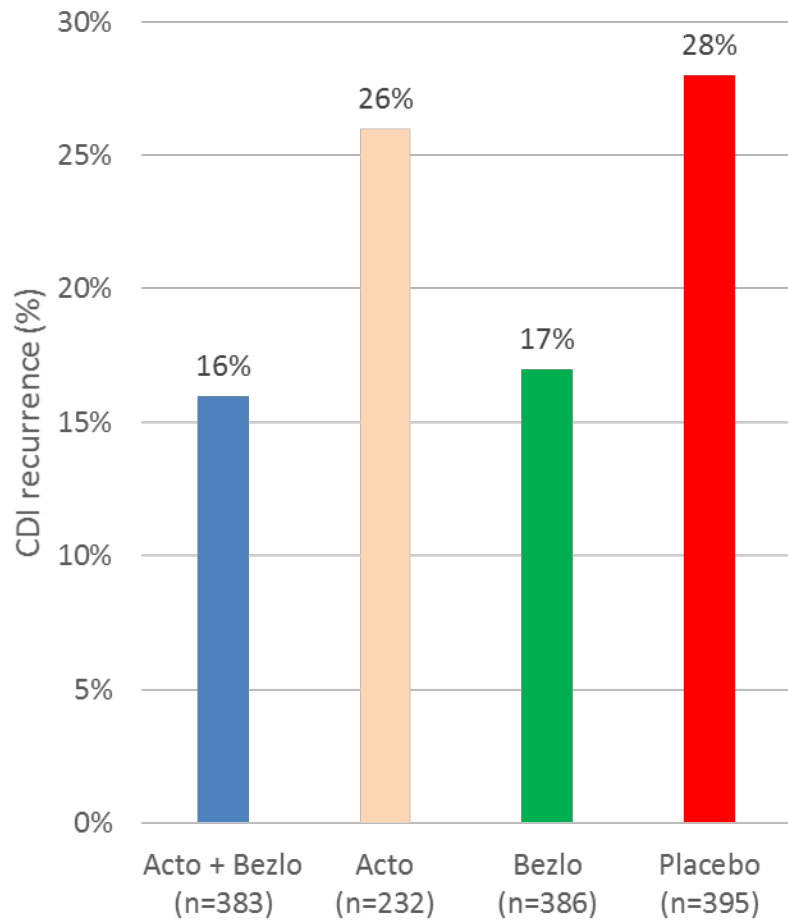
Surotomycin
Cadazolid
SMT-19969

Monoclonal antibodies
vs. C diff toxins
Toxoid vaccines

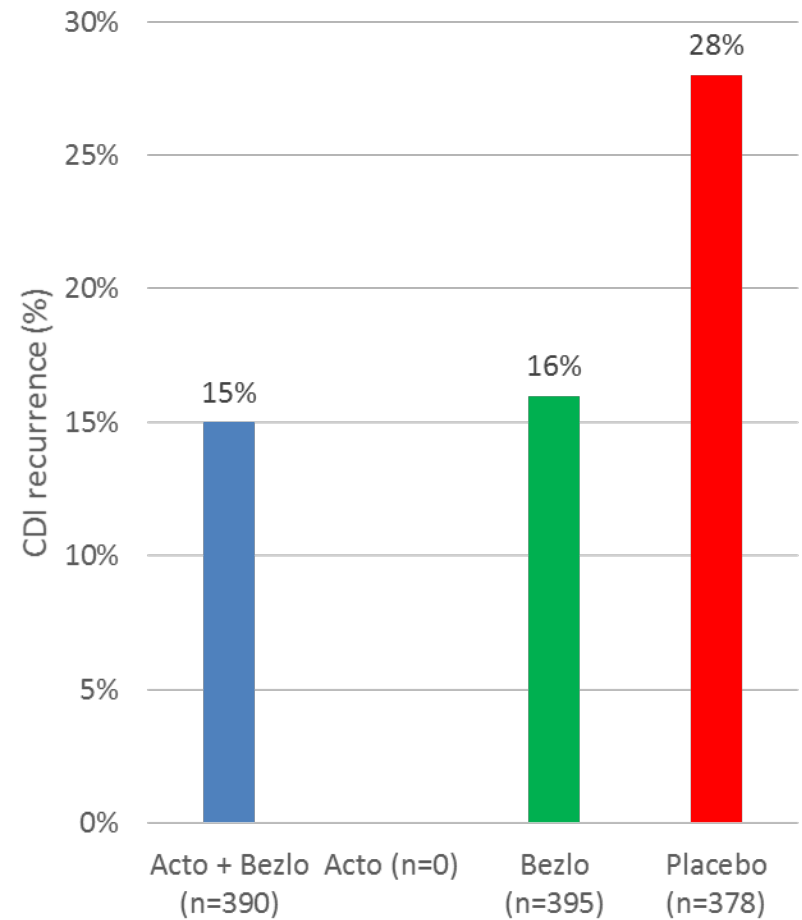
Serum concentrations of IgG antibodies against toxin A, toxin B, and non-toxin antigens



Phase III studies of actoxumab (acto) and bezlotoxumab (bezlo): Overall



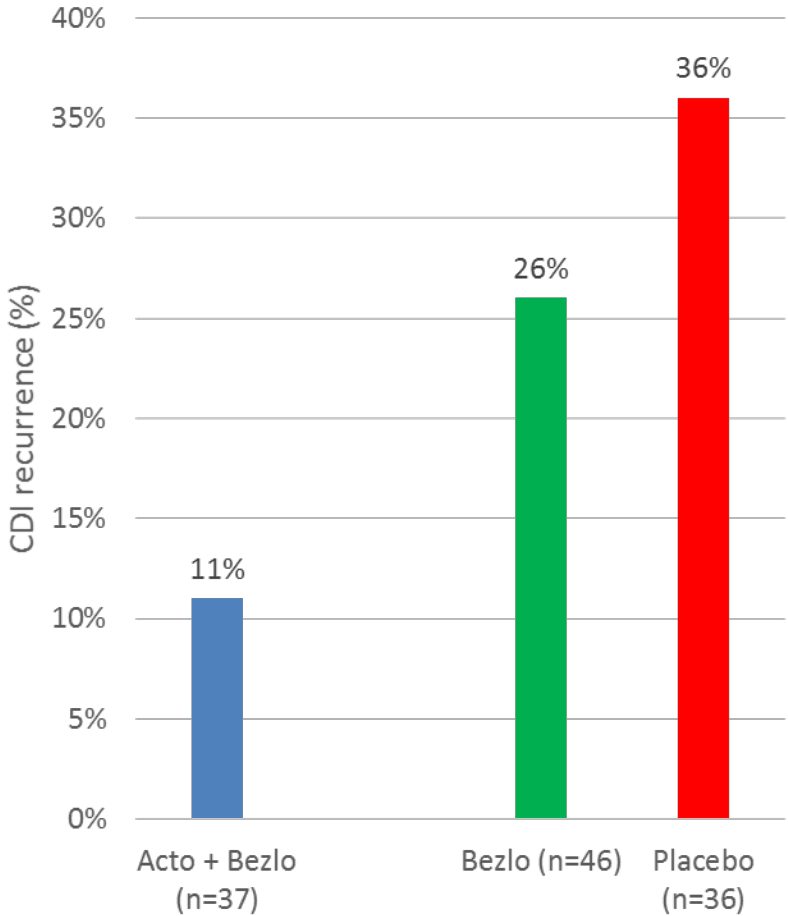
Modify I



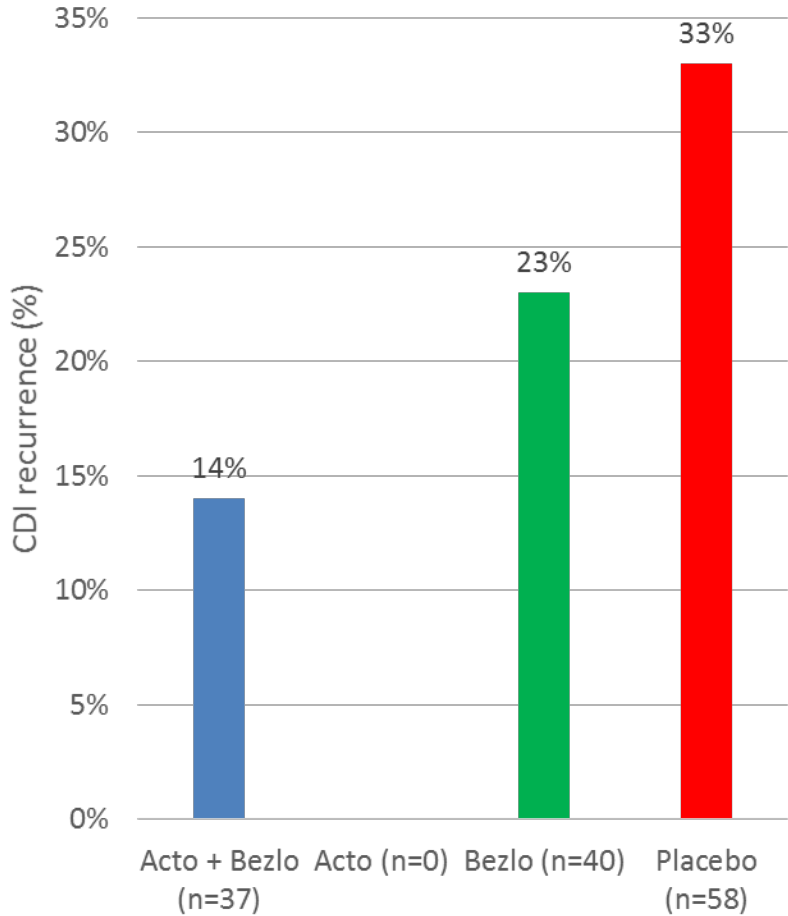
Modify II

Wilcox et al. ICAAC 2015
Gerding et al. ICAAC 2015

Phase III studies of actoxumab (acto) and bezlotoxumab (bezlo):027/Nap1/BI strain



Modify I



Modify II

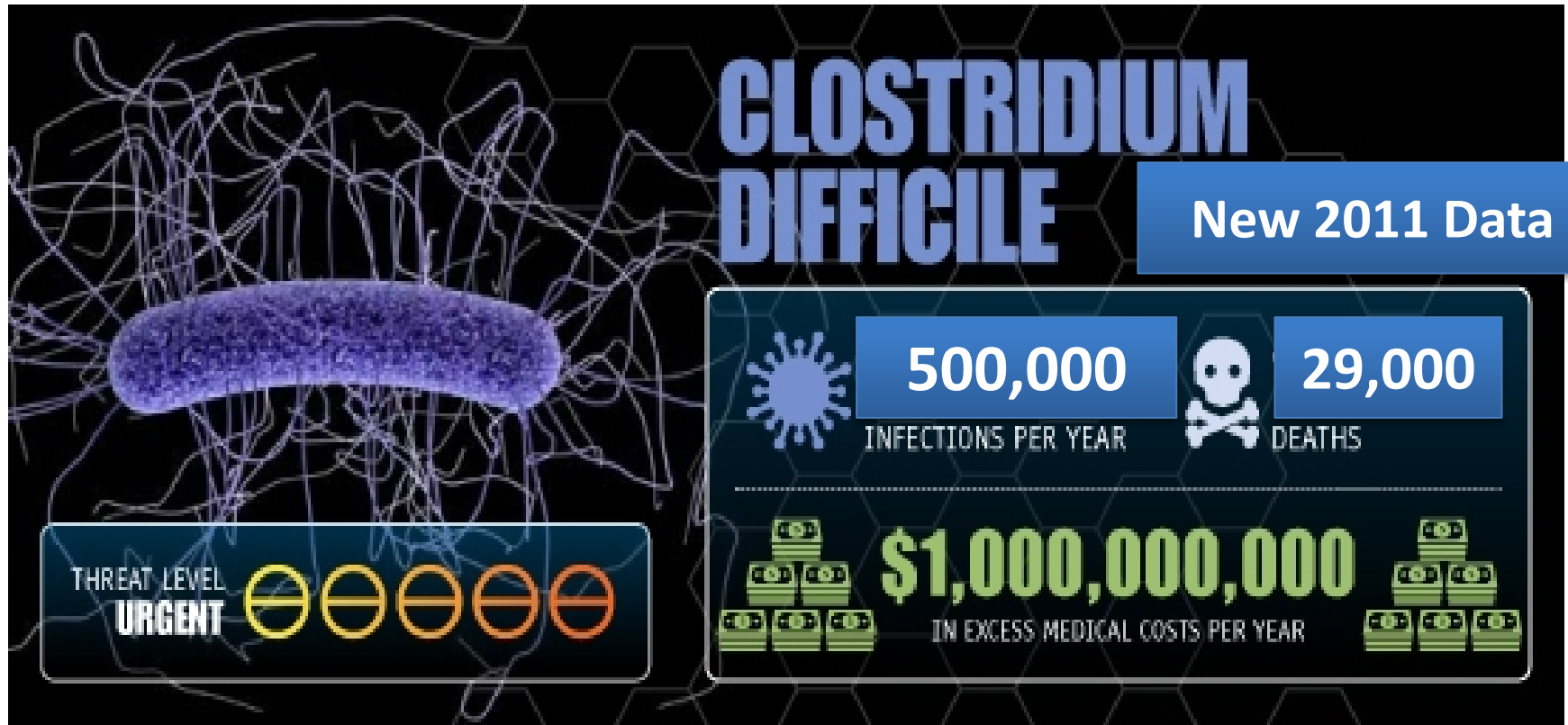
Conclusion

- As long as we live in a world of elderly, hospitalized patients given broad spectrum antibiotics, CDI is here to stay
- With a coordinated effort and contemporary epidemiologic techniques, we can likely control and respond to future changes in the pathogenesis of CDI
- With a little luck and good science, we may also be able to discover new insights into strategies to prevent and control CDI.

An Update on *Clostridium difficile* Infection:

From Infection Control to Treatment

Kevin W. Garey, PharmD, MS. Professor and Chair
University of Houston College of Pharmacy



Lessa et al, N Eng J Med 2015: 34.2% of CDI cases were considered community-acquired

Source: CDC Report "Antibiotic Resistance Threats in the United States, 2013"

Lessa CF et al. NEJM 2015;372:825-34.