C difficile 2021 and Beyond

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IDAC April 15,2022 Virtual Meeting

Conflicts of Interest 2021

- **Advisory Boards:**
- **Acurx Pharmaceuticals LLC**
- **Bio K +**
- **Merck Pharmaceuticals**
- **Shionogi**
- **Speakers Bureau: Merck**

Outline

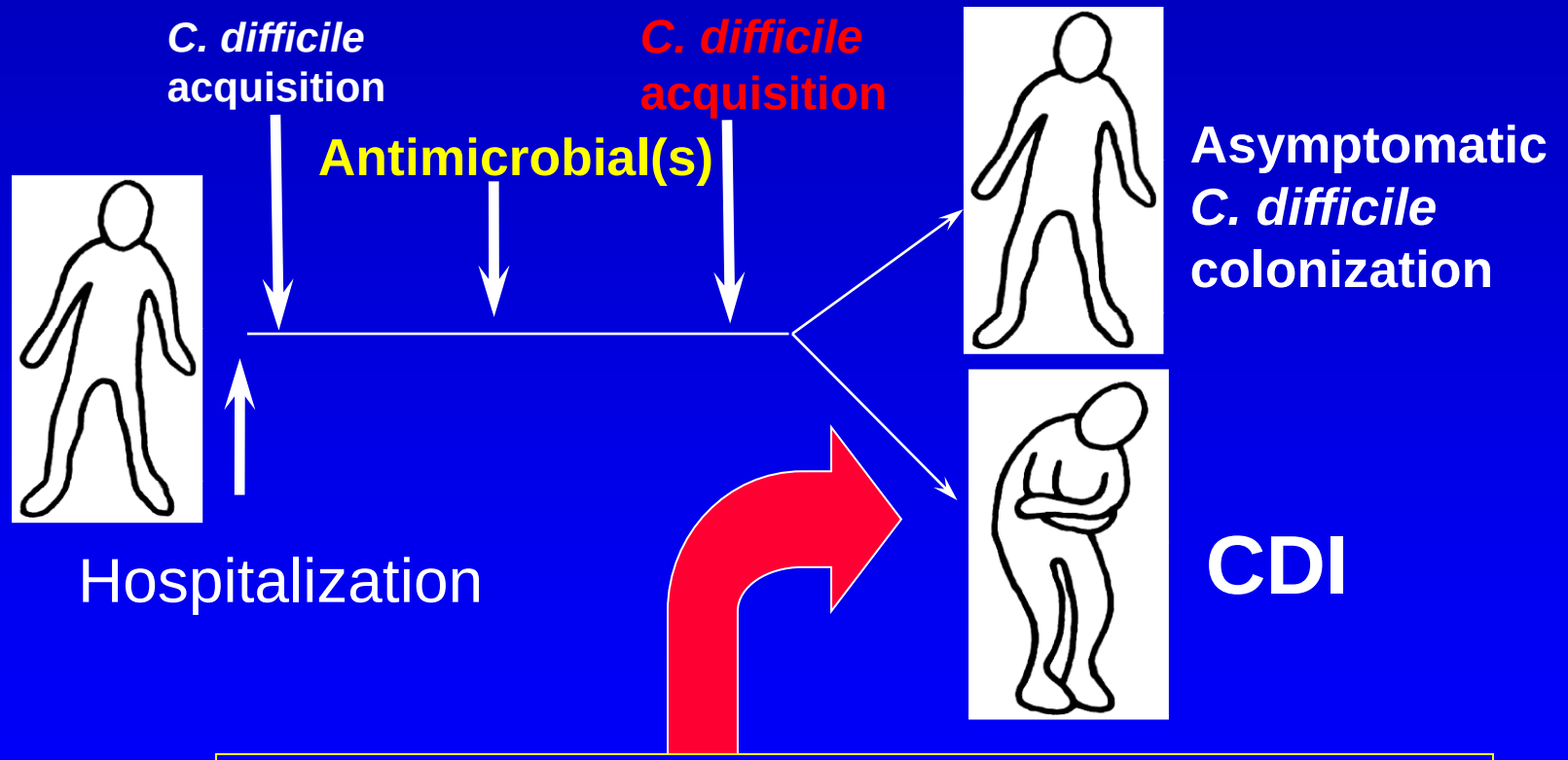
- Epidemiology
- Pathogenesis
- Testing
- COVID Effect?
- Therapy IDSA recommendations & Potential NEW changes
  - **FDX vs Vanco**
  - **Bezoltoxomab**
- New Agents
  - **Research Drugs** Ridinilazole, Ibezapolstat (ACX-362E), Ribaxamase, DAV 132
  - Vaccines
  - Fecal Transplants

Epidemiology of CDI

Over the past 15 years

- **Increased Incidence 147.2/ 100,000 pop.**
  7.4/10,00 pt. days
- **Increased Severity 027 & 078 strains**
- **237% increase in CDI related hospitalizations**
- **In 2013, 250,000 pts. Hospitalized due to CDI**
- **Attributable Mortality 2.2% → 4.5%**
- **Length of Stay Increased of 55.3%**
- **Cost: $6 billion ($ 3,427-$9,960/ case)**
- **CDC classified CDI as URGENT Global Threat**

Current Pathogenesis Model for *C. difficile* Infection (CDI)



CID, 51: 1306,2010

Acquisition of a toxigenic strain of *C. difficile* and failure to mount anamnestic Toxin A, B IgG antibody response results in CDI.

C difficile carriage in healthy infants - France

- 1 year follow-up study of 10 infants
  - ALL 10 infants acquired C. difficile and were carriers for several months
- Additional 1-point study of 85 infants
  - 38/85 (45%) carried C. difficile
  - 11% had toxigenic isolates
  - Abx use (mother or infant) and “food diversification” had a positive association

Rousseau et al CID 2012; 55:1209

Lower Socio-economic Status linked to Community Assoc CDI

- Up to 20% of those diagnosed with CA-CDI have no hx of recent abx therapy or outpt health care exposure
- CDC studies 35 counties in 10 states; 9,682 cases CA-CDI 2014-2015
- Three factors accounted for 95% of variance
- **<u>Higher Incidence</u>**
  - **Poverty (RR=1.19; 95%; CI 1.15-1.22)**
  - **Foreign born (RR=1,05; CI 1.02-1.08)**
- High Income (RR=0.95; CI 0.92-0.97-) **<u>Lower Incidence</u>**

Skrobarcek KA, CID 2021 doi:10.1093/cid/ciab042

C. difficile Isolates from Retail Meats, United States

Meat product	No. tested	Ribotype 078/ Tox V (%)	Ribotype 027/ Tox III (%)	Total pos. (%)	Total by species of origin (%)
Ground beef	26	10 (38.5)	3 (11.5)	13 (50.0)	14 (42.4)
Summer sausage	7	0	1 (14.3)	1 (14.3)	
Ground pork	7	2 (28.6)	1 (14.3)	3 (42.9)	19 (41.3)
Braunschweiger	16	7 (43.8)	3 (18.8)	10 (62.5)	
Chorizo	10	1 (10)	1 (10)	2 (20)	
Pork sausage	13	2 (15.4)	2 (15.4)	4 (30.8)	
Ground turkey	9	4 (44.4)	0	4 (44.4)	4 (44.4)
TOTAL	90	26 (28.9)	11 (12.2)	33 (36.7)	

Songer JG et al. Unpublished data

Open Forum Infectious Diseases
MAJOR ARTICLE

A Risk Score to Predict *Clostridioides difficile* Infection

Laurie Aukes,[1] Bruce Fireman,[1] Edwin Lewis,[1] Julius Timbol,[1] John Hansen,[1] Holly Yu,[2] Bing Cai,[2] Elisa Gonzalez,[2] Jody Lawrence,[2] and Nicola P. Klein[1]
[1]Kaiser Permanente Vaccine Study Center, Oakland, California, USA, [2]Pfizer, Inc., Collegeville, Pennsylvania, USA

- **Kaiser Permanente Northern CA**
- **May 2011- July 2014 9,986 cases vs 2,230,354 controls**
- **Cases tended to be older (> 65 yo 59% vs 21%) females, 61 % vs 53%**
- **hospitalized (69% vs 10%), ED visits (51 % vs 14%),**
- **ECF stays (25% vs 0.6%) , PPI use (36% vs 7%)**
- **Charlson score 3 (11% vs 2%),with specific Co-morbidities**
  - **PNA (21% vs 1%), CKD (26% vs 4%), CAHD (22% vs 3%),**
  - **CHF (22% vs 2%) DM (23% vs 6%),**
  - **ABX 81% vs 11%)**

- **Using hospital discharge as the IDRSA, our risk score model yielded excellent performance in predicting the likelihood of developing CDI in the subsequent 31–365 days (C-statistic of 0.848)**

Cardiac Surgery Risk factors for CDI

- CDI 3rd most common infection post cardiac surgery
- Of 12,235 pts following cardiac surgery, 143 (1.2%) developed CDI
- Hyperlactatemia and Decreased Lactate Clearance perturbations of the perioperative acid-base balance increase the risk of CDI

Rzucidło-Hymczak A et a (Poland)l. PLOS One 3-17,2021 Poland

Risk Stratification of Antibiotics

High Risk	Intermediate	Low Risk
Fluoroquinolones **Cephalosporins** **Carbapenems** **Clindamycin**	macrolides Intravenous b-lactam/b-lactamase inhibitors	Doxycycline Tigecycline Azithromycin Metronidazole Aztreonam Penicillin Clarithromycin Vancomycin Trimethoprim Nitrofurantoin

[i] Pakyz AL, Jawahar R, Wang Q, Harpe SE. Medication risk factors associated with healthcare-associated Clostridium difficile infection: a multilevel model case-control study among 64 US academic medical centres. J Antimicrob Chemother. 2013 Dec 9. [Epub ahead of print]

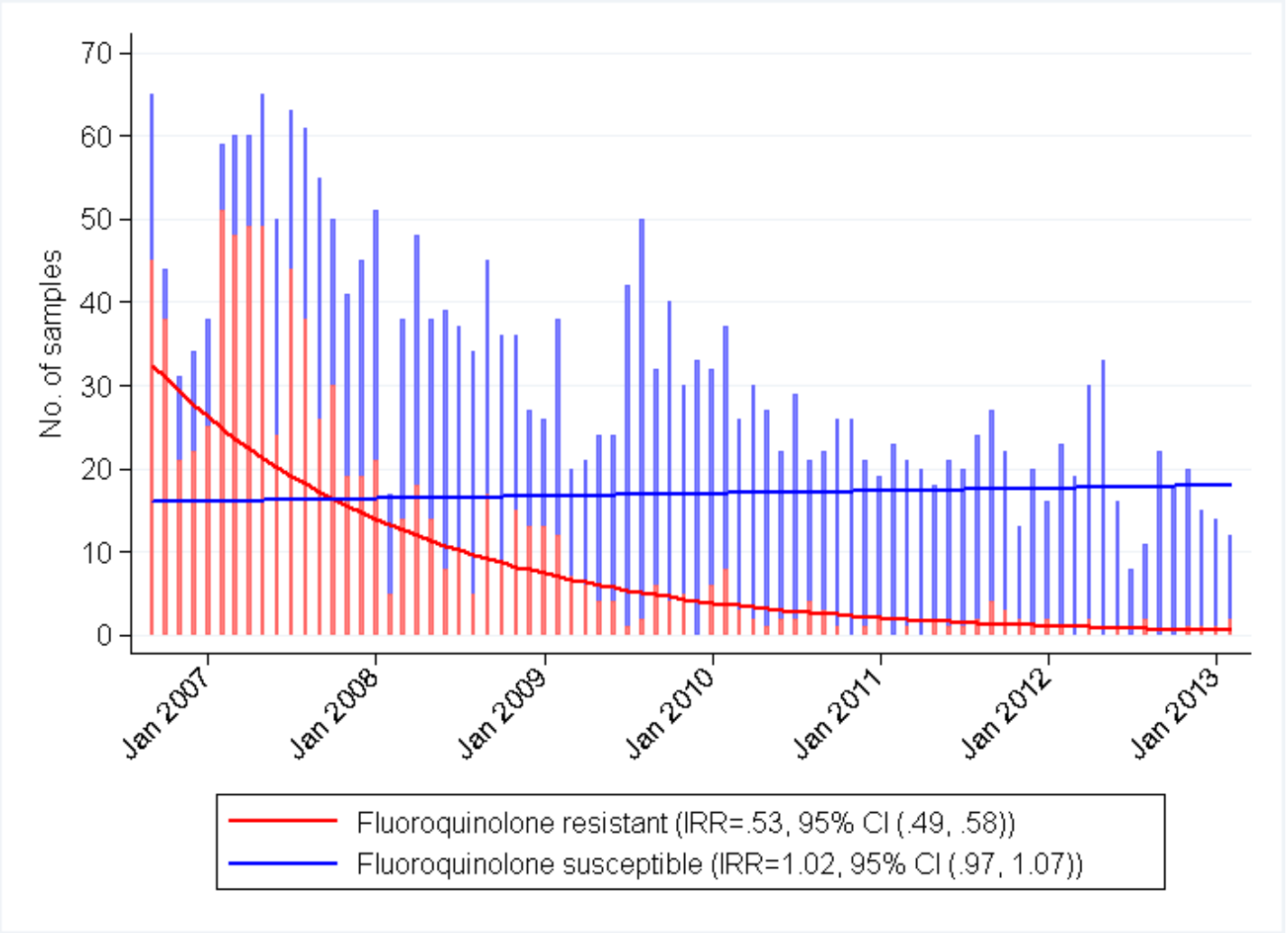
[ii] Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. J Antimicrob Chemother. 2013 Dec 8. [Epub ahead of print]

[iii] van der Kooi TI, Koningstein M, Lindemans A, Notermans DW, Kuijper E, van den Berg R, Boshuizen H, Filius PM, van den Hof S. Antibiotic use and other risk factors at hospital level for outbreaks with Clostridium difficile PCR ribotype 027. J J Med Microbiol. 2008 Jun;57(Pt 6):709-16. doi: 10.1099/jmm.0.47711-0.

[iv] Baxter R, Ray GT, Fireman BH.Case-control study of antibiotic use and subsequent Clostridium difficile -associated diarrhea in hospitalized patients. Infect Control Hosp Epidemiol. 2008 Jan;29(1):44-50. doi: 10.1086/524320.

[v] Talpaert MJ, Gopal Rao G, Cooper BS, Wade P. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of Clostridium difficile infection. J Antimicrob Chemother. 2011 Sep;66(9):2168-74. doi: 10.1093/jac/dkr253. Epub 2011 Jun 14.

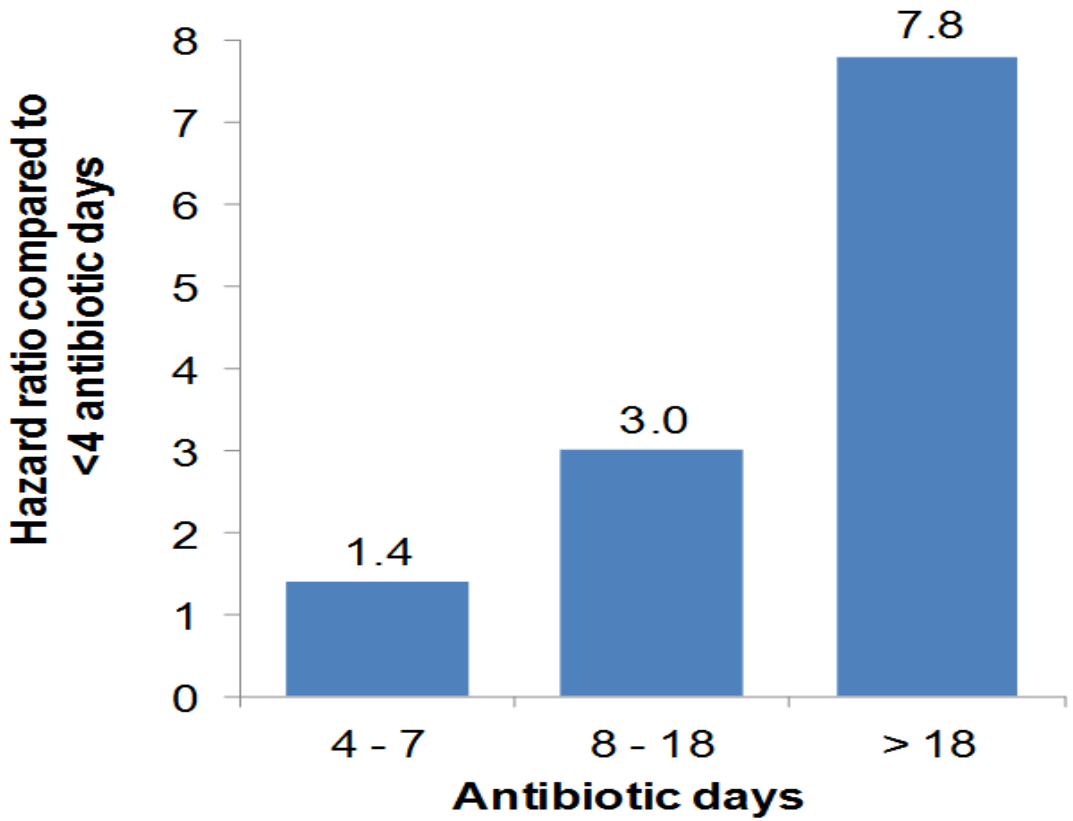
Elimination of healthcare associated fluoroquinolone-resistant, but not fluoroquinolone-susceptible *Clostridium difficile*

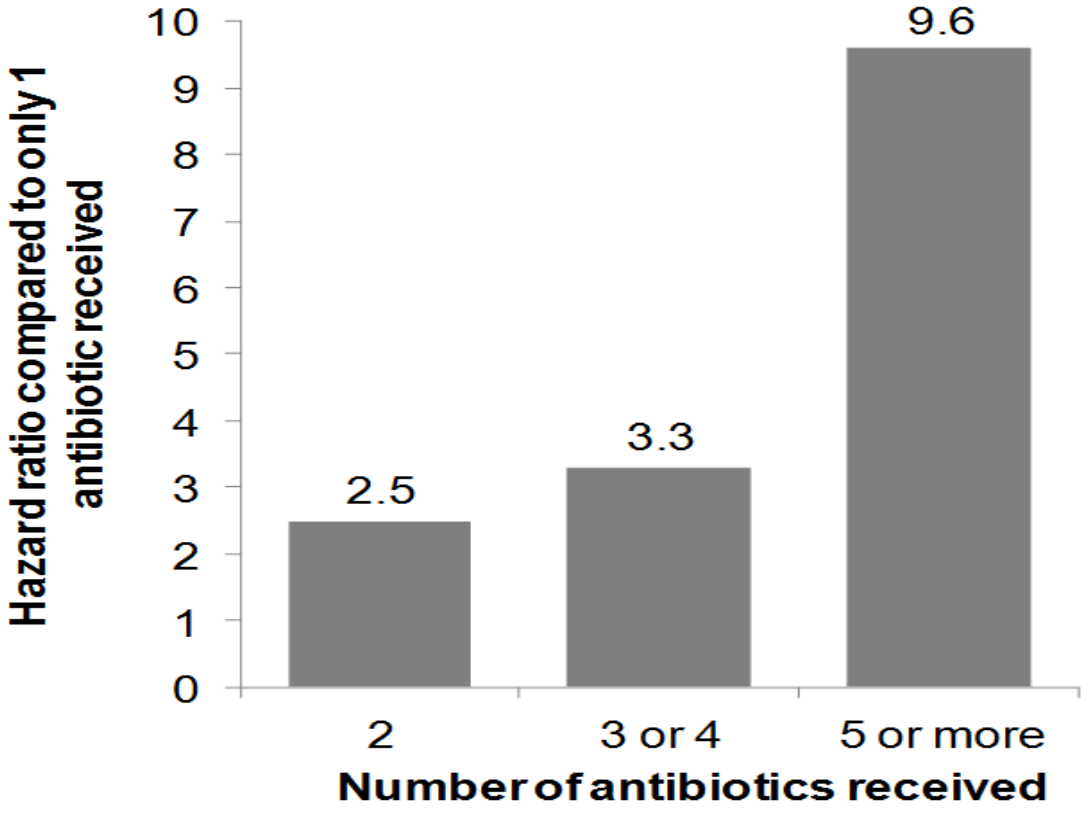


Dingle K et al. Lancet ID **2017**;17:411-421

Populations at Risk: Patients Taking Antibacterial Drugs

Antibiotic Exposure and Risk of CDI[1]





[1]Stevens V et al. *Clin Infect Diseases*. 2011;53(1)42–48.

C difficile associated with poor outcomes in End-Stage Renal Disease

National Inpatient sample Database 2009

20% sample of US hospitals in 44 states

184,139 cases ESRD

2.8% had CDI

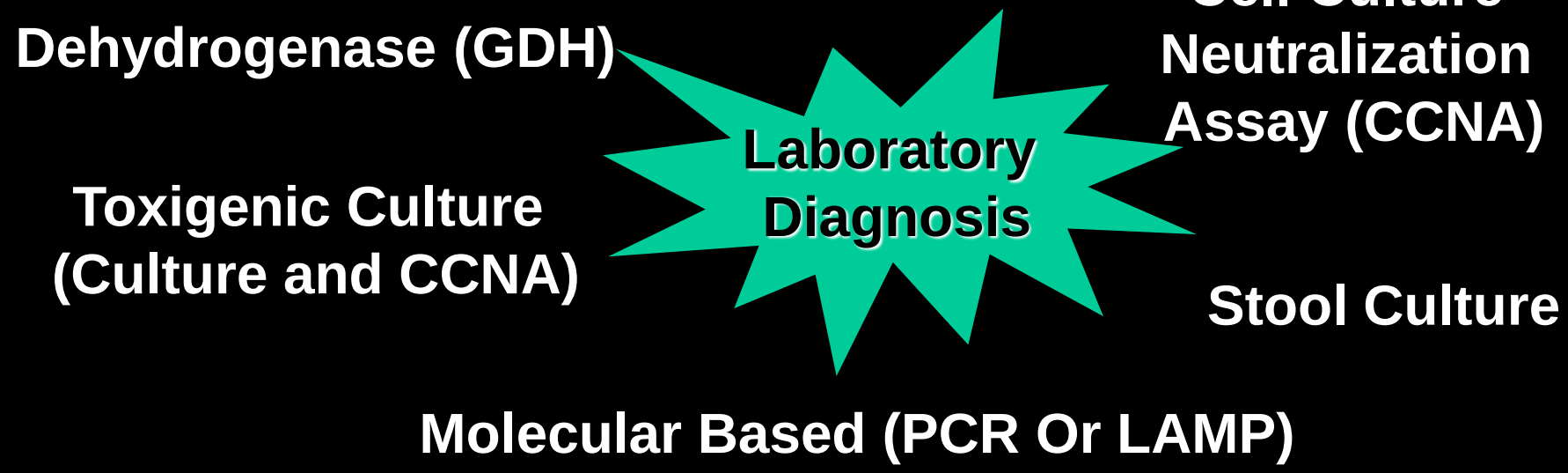
	+ CDI	w/o CDI
In Hosp. Mortality	13.2%	5.3%
Length of Stay	17.3 days	7.1 days
Cost	$124,846	$56,663

CDI is associated with significantly worse out comes in patients with ESRD

Pant et al. J Investig Med 2012; 60:529

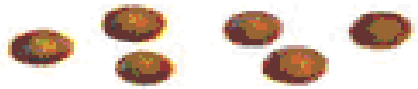
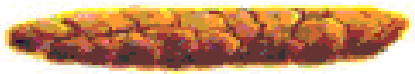
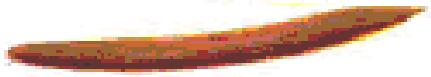
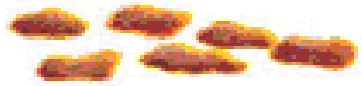
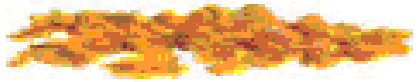
Laboratory Diagnosis of CDI

Enzyme Immunoassay (EIA)



- Test only <u>unformed</u> stools
- Do <u>NOT</u> test asymptomatic pts.
- Stool culture is the most sensitive

THE BRISTOL STOOL FORM SCALE

Type 1		Separate hard lumps, like nuts (hard to pass).
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4 semi-formed		Like a sausage or snake, smooth and soft.
Type 5 Loose stool		Soft blobs with clear cut edges (passed easily)
Type 6 Diarrhoea		Fluffy pieces with ragged edges, a mushy stool.
Type 7 Diarrhoea		Watery, no solid pieces Entirely Liquid

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Guidelines recommend only Grades 5 to 7 should be tested for *C. difficile* toxin

Types of CDI Test 2021

Summary of available tests for CDI in decreasing order of analytical sensitivity

Test	Sensitivity	Specificity	Substance detected
Toxigenic culture	High	Low[a]	*C difficile* vegetative cells or spores
NAAT	High	Low/moderate	*C difficile* nucleic acid (toxin genes)
GDH	High	Low[a]	*C difficile* common antigen
CCNA	High	High	Free toxins
Toxin A/B EIA	Low	Moderate	Free toxins

Adapted from McDonald et al.

Labor Intense

Multiplex Test for enteric Pathogens- <u>Problematic</u>

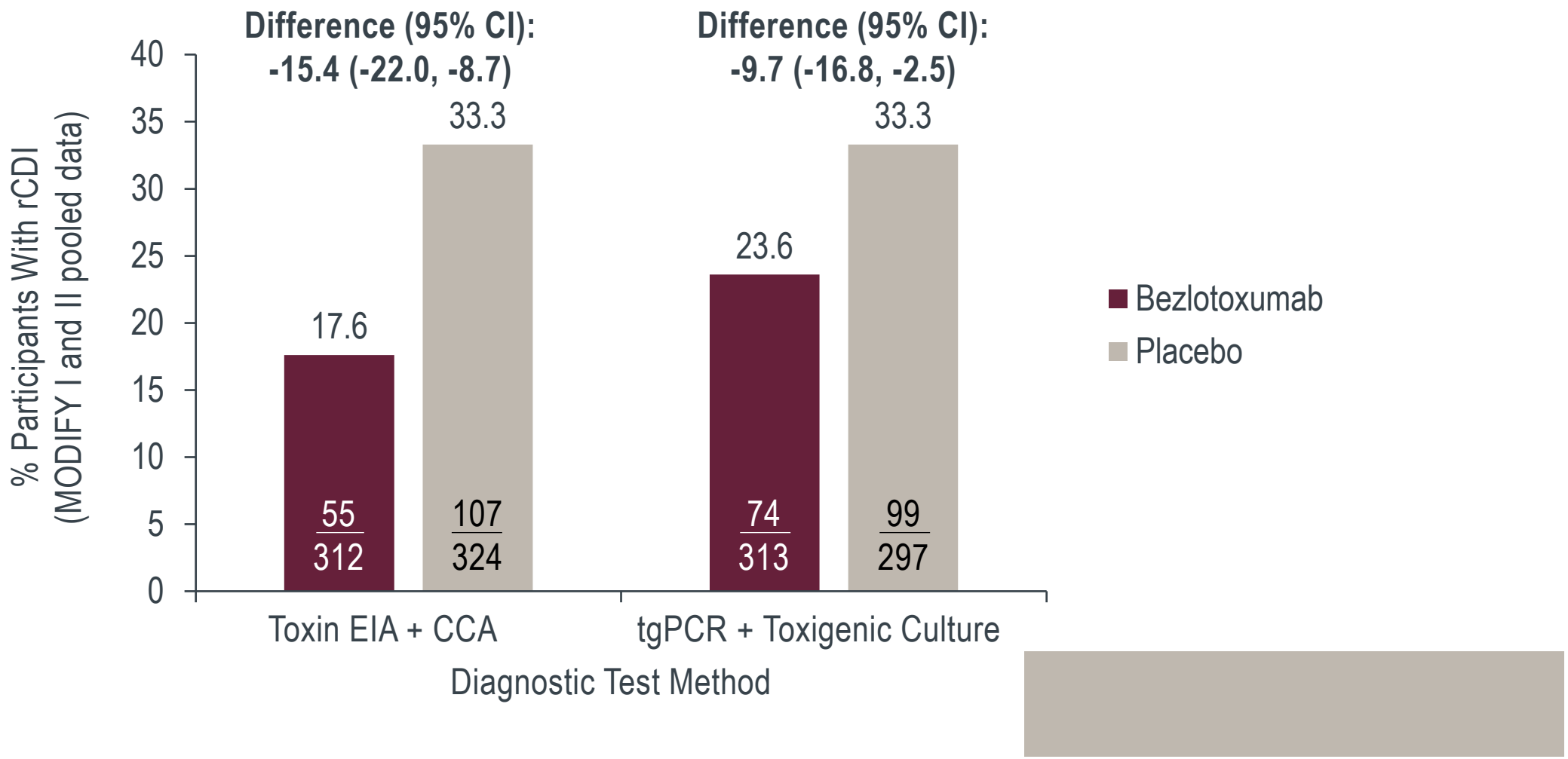
Over diagnosis of CDI in the Molecular Test Era

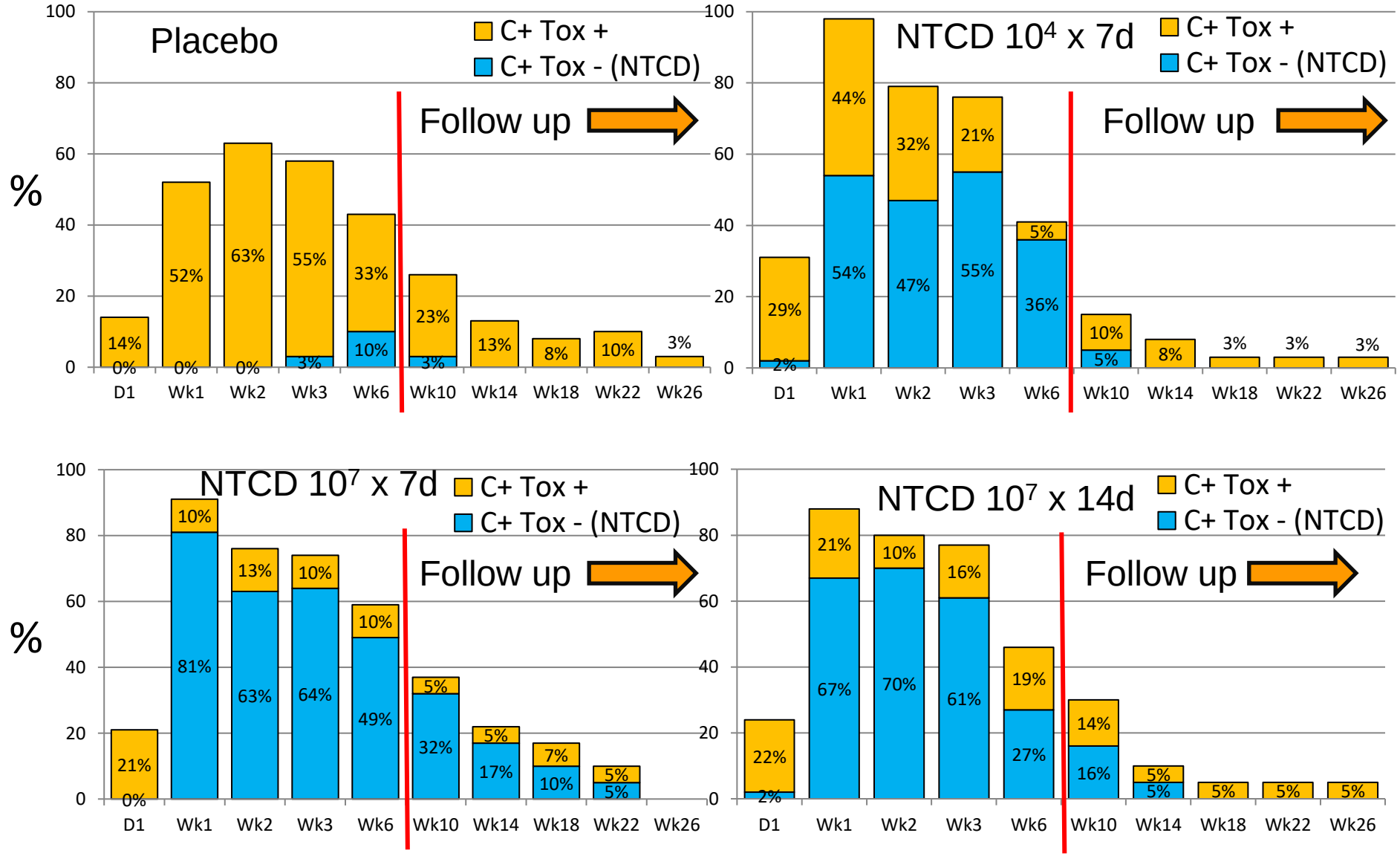
- Prospective observational study [1]
  - 2010-2012 UC Davis
- 293/1416 pts Tested + PCR
- 131/293 (44.7%) + for Toxin
- “Virtually all CDI-related complications and deaths occurred” with + toxin assay
- “Treat the Patient, Not the Test” [2]

1. Polage et al JAMA Intern Med 9-8-15 doi:10:1001/jamainternmed.2015.4114
2. Debberke & Burnham JAMA Intern Med 9-8-15

Impact of Diagnostic Method

Larger difference in patients diagnosed with methods that detect toxin in stool





Monthly Fecal *C. difficile* Detection from Week 6 to 6 Months

Gerding DN et al JAMA 2015;313:1719, May 5, 2015, Supplementary Material

CDI Outcomes

Measure	Comment
Recurrence	10-38%
Colectomy	8.7 per 1,000 CDI cases
30-day mortality	3-9% 90% of CDI deaths in the elderly
Costs	Average cost is approximately $25,000 per episode $4.8 billion in excess costs to US Acute care facilities
Length of Stay	55% increase

Evans C, Safdar N. *Clin Infect Dis*. 2015;60(Suppl 2):S66-S71.

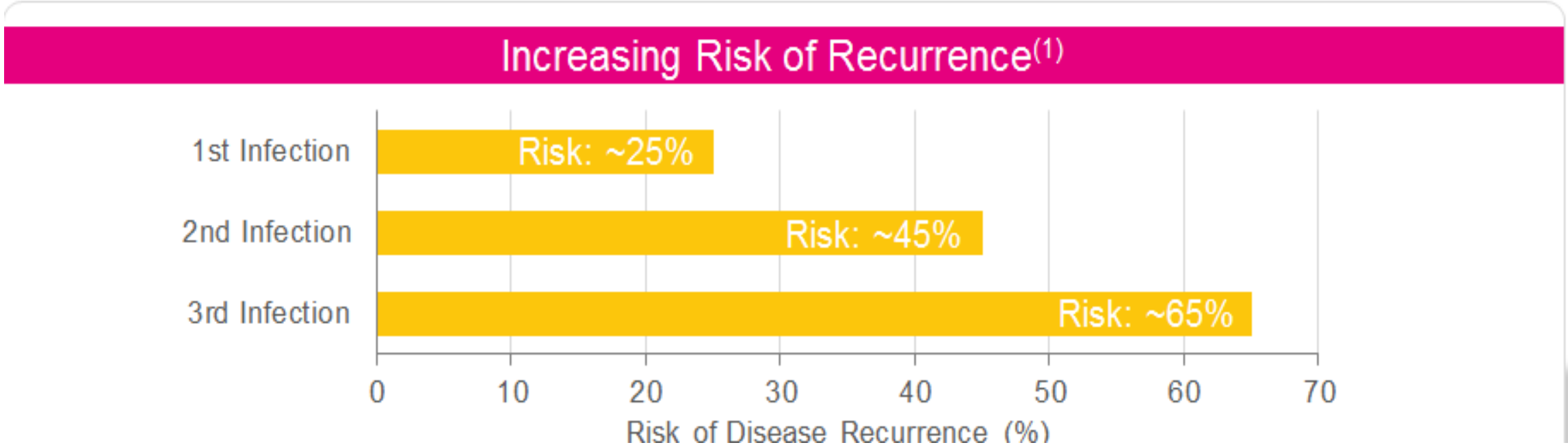
CDI Problems 2019
Increasing Recurrences; Patient PTSD

Each additional episode of CDI associated with:

- Increased morbidity and mortality
- Increased healthcare cost
- Limited treatment options

Recurrent CDI associated with increased perturbation of the gut microbiota

- Mainstay therapy (metronidazole and vancomycin) associated with increased dysbiosis



2017 IDSA Update Rx of CDI

Initial Episode Non-severe	**Vanco 125 QID or FDX 200 bid MTZ if only available**	**Strong/ High Strong/High Weak/ High**
Initial Episode Severe	**Same except NOT MTZ**	**Same**
Initial Episode Fulminant	**Vanco 500 QID po/ng Rectal if Ileus MTZ + Vanco**	**Strong /Moderate Strong/Low Strong/Moderate**
First Relapse	**Taper Vanco 2-8 weeks FDX x 10 days**	**Weak/Low Weak/ Moderate**
Second or later relapse	**Vanco + rifaximin taper FDX Fecal Transplant**	**Weak/Low Weak/Low**

“Metronidazole is medicine for your mother-in-law Vancomycin is for your mother”

Prof. Sherwood L Gorbach
Tufts Univ School of medicine

Co-discoverer of *C. difficile*

Inf Dis Clin Practice 1992

“ Medicines for your mother-in-law ”

Review article

Review of high dose vancomycin in the treatment of *Clostridioides difficile* infection >

Mazen S. Bader , John Hawboldt , Cheryl Main , Dominik Mertz , Mark Loeb , Alison Farrell & Joanna Joyce

Infectious Diseases, Volume 52, 2020 - Issue 12

Summarizes the current evidence on the efficacy and adverse

No evidence supports the use of high dose oral vancomycin in the treatment of severe *CDI*

Weak evidence from observational studies supports the use of **high dose oral vancomycin in addition to intravenous metronidazole**

Weak evidence for high dose vancomycin retention enema in fulminant *CDI*.

Vancomycin retention enema can be used in severe *CDI* when oral administration is not possible, or in conditions when the oral formulation cannot reach the colon such as Hartman's pouch, ileostomies, or colon diversions.

Focused Update on *C. difficile* Infection Treatment Guidelines: Fidaxomicin and Bezlotoxumab

Session 55: IDSA Case-based Clinical Guideline Overview and Update

ID Week 2020 *Virtual Meeting*

October 23, 2020

Stuart Johnson, MD
Hines VA Hospital
Loyola University Medical Center
Chicago, IL

Background

- Since publication of the 2017 Clinical Practice Guidelines for CDI in early 2018, new relevant evidence for fidaxomicin and bezlotoxumab was published
- Literature reviewed (all CDI treatment) through May 2020
  - Fidaxomicin vs vancomycin
    - 3,609 articles screened, 18 full text review, 5 kept for qualitative analysis
  - Bezlotoxumab
    - 239 articles screened, 12 full text review, 7 kept for qualitative analysis
- Focus of review limited to adult patients
- Did not reassess recommendations for FMT but noted the FDA safety alerts documenting transmission of pathogenic *E. coli* from donor to FMT recipients and concern for transmission of SARS-CoV-2

Summary

- Additional RCTs since publication of the 2017 Clinical Practice Guidelines for CDI support the **superiority of fidaxomicin over vancomycin for sustained clinical response after treatment**.
- This effect was evident for patients with primary CDI as well as patients with recurrent CDI, although **the certainty of evidence was low for patients with recurrent CDI.**
- **Extended-pulsed dosing of fidaxomicin shows promise** for treatment of recurrent CDI although additional studies with more appropriate comparators are needed to clarify the role of this dosing strategy.
- **Bezlotoxumab given as adjunctive therapy can improve outcomes** in patients at high risk for recurrence, including age ≥65, immunocompromise, severe CDI, and prior CDI episodes.
- Once approved, these recommendations will be incorporated into the previous over all recommendations (2017) for treatment of CDI.

Evidence summary for patient-important outcomes, PICO 1 (patients with an initial CDI episode): Vanco vs Fidaxo

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with vancomycin	Risk difference with fidaxomicin (95% CI)
Sustained response of CDI (follow up: 4 weeks after EOT)	1,673 (4 RCT)	⊕⊕⊕◯ MODERATE [a,b]	**RR 1.16 (1.09 to 1.24)**	631 per 1,000	**101 more per 1,000 (57 more to 151 more)**
CDI initial clinical cure * (follow up: 2 days after EOT)	1,673 (4 RCT)	⊕⊕⊕◯ MODERATE [a,b,c]	RR 1.00 (0.96 to 1.04)	856 per 1,000	0 fewer per 1,000 (34 fewer to 34 more)
Drug-related adverse events (follow up: 4 to 12 weeks)	1,721 (4 RCT)	⊕⊕◯◯ LOW [a,b,d]	RR 1.02 (0.76 to 1.36)	95 per 1,000	2 more per 1,000 (23 fewer to 34 more)
All-cause mortality (follow up: 4 to 12 weeks)	1,721 (4 RCT)	⊕⊕⊕◯ MODERATE [a,b,d]	RR 0.90 (0.66 to 1.23)	87 per 1,000	9 fewer per 1,000 (30 fewer to 20 more)

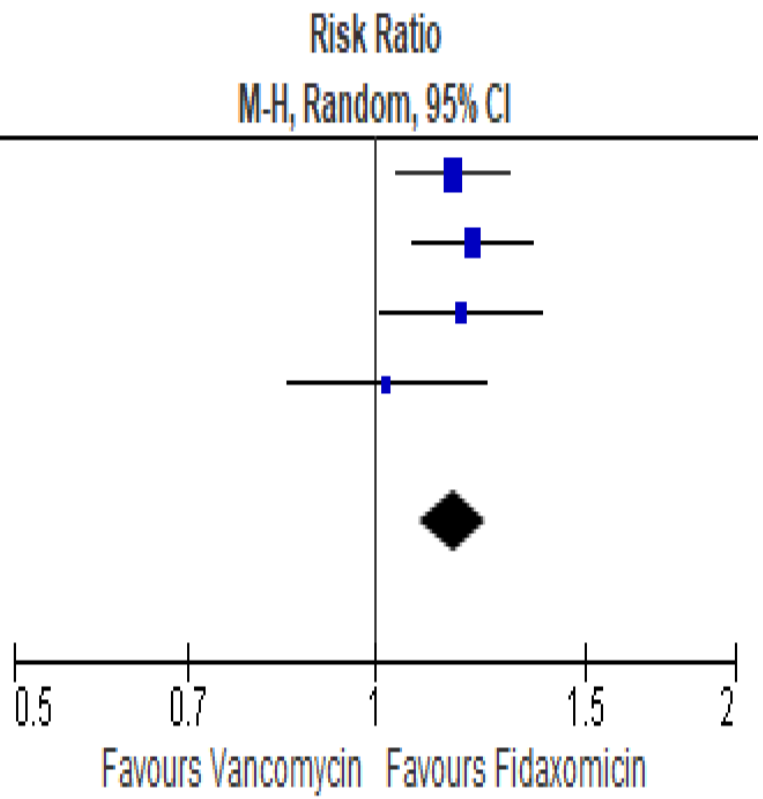
Pooled analysis from 4 RCTs: Louie TJ, et al. N Engl J Med 2011; Cornely OA, et al. Lancet Infect Dis 2012; Guery B, et al. Lancet Infect Dis 2018; Mikamo H, et al. J Infect Chemother 2018

Forest plot, PICO 1: Sustained response 1 month after end of treatment (patients with an initial CDI episode)

Study or Subgroup	Fidaxomicin Events	Fidaxomicin Total	Vancomycin Events	Vancomycin Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Louie	214	287	198	309	37.5%	1.16 [1.05, 1.30]	2011
Cornely	193	252	163	257	32.6%	1.21 [1.08, 1.36]	2012
Guery	124	177	106	179	18.0%	1.18 [1.01, 1.38]	2018
Mikamo	70	104	71	108	11.9%	1.02 [0.85, 1.24]	2018
Total (95% CI)		**820**		**853**	**100.0%**	**1.16 [1.09, 1.24]**	
Total events	601		538				

Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%

Test for overall effect: Z = 4.51 (P < 0.00001)



Pooled analysis from 4 RCTs: Louie TJ, et al. N Engl J Med 2011; Cornely OA, et al. Lancet Infect Dis 2012; Guery B, et al. Lancet Infect Dis 2018; Mikamo H, et al. J Infect Chemother 2018

PICO 2: In patients with recurrent CDI episode(s), should fidaxomicin be used rather than vancomycin?

- Previous guidelines included 3 options for treatment of a first CDI recurrence (vancomycin, fidaxomicin, tapered-pulsed vancomycin); rationale for choice was based on treatment used for initial episode
- We considered evidence in subgroup analyses from 3 RCTs comparing fidaxomicin with vancomycin; randomization was stratified for the number of previous episodes. 1 study compared an extended-pulsed fidaxomicin regimen with a standard vancomycin regimen
- Patient important outcomes considered:
  - sustained response (1 mo after EOT)
  - sustained response (3 mo after EOT)
  - initial clinical cure (2 d after EOT)
  - Serious AEs
  - all-cause mortality

Extended-pulsed fidaxomicin regimen

- Regimen studied (*Guery B, et al. Lancet Infect Dis 2018*):
  - **Day 1 to 5: fidaxomicn 200 mg twice daily**
  - **Day 6 to 26: fidaxomicin 200 mg once every other day**
- Strategy supported by an *in vitro* human gut model (*Chilton CH, et al. Antimicrob Chemother 2015*)
- Has only been compared to standard vancomycin dosing
- Some data suggest that the initial treatment phase (twice daily dosing for 5 days) might be suboptimal in duration

- *Poster presentation #797 Xing Tan, et al.: Management of Patients with Multiple Clostridioides difficile Infection Recurrences using a Tapered-Pulsed Fidaxomicin Strategy ('IDWeek Trainee Award')*

Evidence summary for patient-important outcomes, PICO 2 (patients with one or more recurrent CDI episodes):

Outcomes (follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with vancomycin	Risk difference with fidaxomicin (95% CI)
Sustained response of CDI (follow up: 30 days after EOT)	253 (2 RCT)	⊕⊕◯◯ LOW [a,b]	**RR 1.40** (1.11 to 1.77)	450 per 1,000	**179 more per 1,000** (from 59 more to 300 more)
Sustained response of CDI (follow up: 90 days after EOT)	75 (1 RCT)	⊕◯◯◯ VERY LOW [a,c]	**RR 1.56** (0.99 to 2.44)	410 per 1,000	**229 more per 1,000** (9 more to 449 more)
CDI initial clinical cure * (follow up: 2 days after EOT)	253 (2 RCT)	⊕⊕◯◯ LOW [a,d]	**RR 1.02** (0.91 to 1.14)	822 per 1,000	**17 more per 1,000** (75 fewer to 109 more)
Serious adverse events (follow up: 90 days)	75 (1 RCT)	⊕◯◯◯ VERY LOW [a,e]	**RR 0.68** (0.35 to 1.29)	410 per 1,000	**132 fewer per 1,000** (from 345 fewer to 80 more
All-cause mortality (follow up: 90 days)	75 (1 RCT)	⊕⊕◯◯ LOW [e]	**RR 0.81** (0.20 to 3.38)	103 per 1,000	**19 fewer per 1,000** (from 150 fewer to 112 more)

Pooled analysis from 3 RCTs: Guery B, et al. Lancet Infect Dis 2018; Cornely OA, et al. Clin Infect Dis 2012

PICO 3: In patients with a CDI episode, should bezlotoxumab be used as a co-intervention along with standard of care (SOC) antibiotics rather than SOC alone?

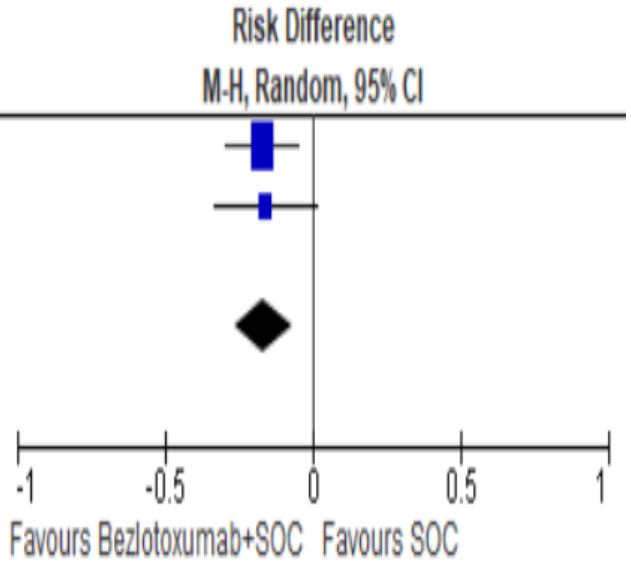
- Bezlotoxumab is a mAb directed against *C. difficile* toxin B and has been studied as an adjunctive therapy in patients receiving SOC antibiotics (metronidazole, vancomycin, or fidaxomicin)
- Evidence was available from 2 large RCTs (>1,000 participants) where bezlotoxumab was administered in conjunction with SOC antibiotics compared with SOC alone; A subgroup analysis was identified for patients at high risk for recurrence defined as age ≥65, immunocompromise, severe CDI, prior CDI episode (w/in 6 mo)
- Patient important outcomes considered:
  - CDI recurrence after ICC (3 mo f/up)
  - CDI-associated hospital readmission (1 mo f/up)
  - Drug-related AEs (1 mo f/up)
  - all-cause mortality (3 mo f/up)

Forest plot, PICO 3: Post-hoc subgroup analysis of CDI recurrence – Number of prior CDI episodes

Study or Subgroup	Bezlotoxumab with SOC Events	Total	SOC Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1 episode of CDI in the past 6 months	31	114	48	109	65.9%	-0.17 [-0.29, -0.04]
≥2 episodes of CDI in the past 6 months	23	56	41	72	34.1%	-0.16 [-0.33, 0.01]
Total (95% CI)		**170**		**181**	**100.0%**	**-0.17 [-0.27, -0.06]**
Total events	54		89			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, $df = 1$ ($P = 0.93$); $I^2 = 0\%$

Test for overall effect: $Z = 3.22$ ($P = 0.001$)



Data provided by trial sponsor (post-hoc analysis of Wilcox MH, et al N Engl J Med 2017; 376(4): 305-17

PICO 3: In patients with a CDI episode, should bezlotoxumab be used as a co-intervention along with standard of care (SOC) antibiotics rather than SOC alone?

Provisional Recommendation

- Recommendation: For patients with a CDI **RECURRENT** episode and at least one risk factor of recurrence, we suggest using bezlotoxumab as a co-intervention along with SOC antibiotics rather than SOC antibiotics alone (conditional recommendation, high certainty of evidence).
- Comment: Risk factors for CDI recurrence (or poor outcome) include age >65 years, immunocompromised host, severe CDI on presentation, and prior episode of CDI in the last six months. The FDA warns that “in patients with a history of congestive heart failure (CHF), bezlotoxumab should be reserved for use when the benefit outweighs the risk”.

Bezlo for the prevention of rCDI

- Bezlo study MODIFY II
- 19 day ½ Life Detectible in serum 6 months
- 130/293 participants stools 6, 9, & 12 months
- Same as any prior ribotype 44%- 6 m; 64% -9 m. **61%- 12 m**.
- rCDI < 2% at 12 months in Bezlo group
- Efficacy due to prevention rather than delayed onset rCDI

Goldstein et al CID 2020;71:1102-5

•. 2019 Jan 14;19(1):51.
•. 2019 Jan 14;19(1):51.
•. 2019 Jan 14;19(1):51.

Preventative Oral Vanco for CDI

- 3 Clinical studies found **Oral Vanco Prophylaxis** reduced the risk of RCDIs and should be considered on a case-by-case basis. Caution is warranted before routine use is implemented because the impact on long-term outcomes has not been assessed and the optimal regimen has not been defined.

  C Brown et al. Ann Clin Pharmacotherapy 2019 Apr;53(4):396-401

- For elderly patients with frequently relapsing C. difficile, prolonged vancomycin once daily at a dose of 125 mg orally was effective in preventing further relapse.

  Zhang K et al. BMC Infect Dis 2019;19:51

Oral Vanco Prevention of CDI

SW Johnson et al. CID 2020;71:1133-9

North Carolina, Randomized Prospective, open label study

100- similar patients except for ABX exposure

(Vanco 125 mg po Q day,
Average 12 doses)

Zero HCFO-CDI for VOP group

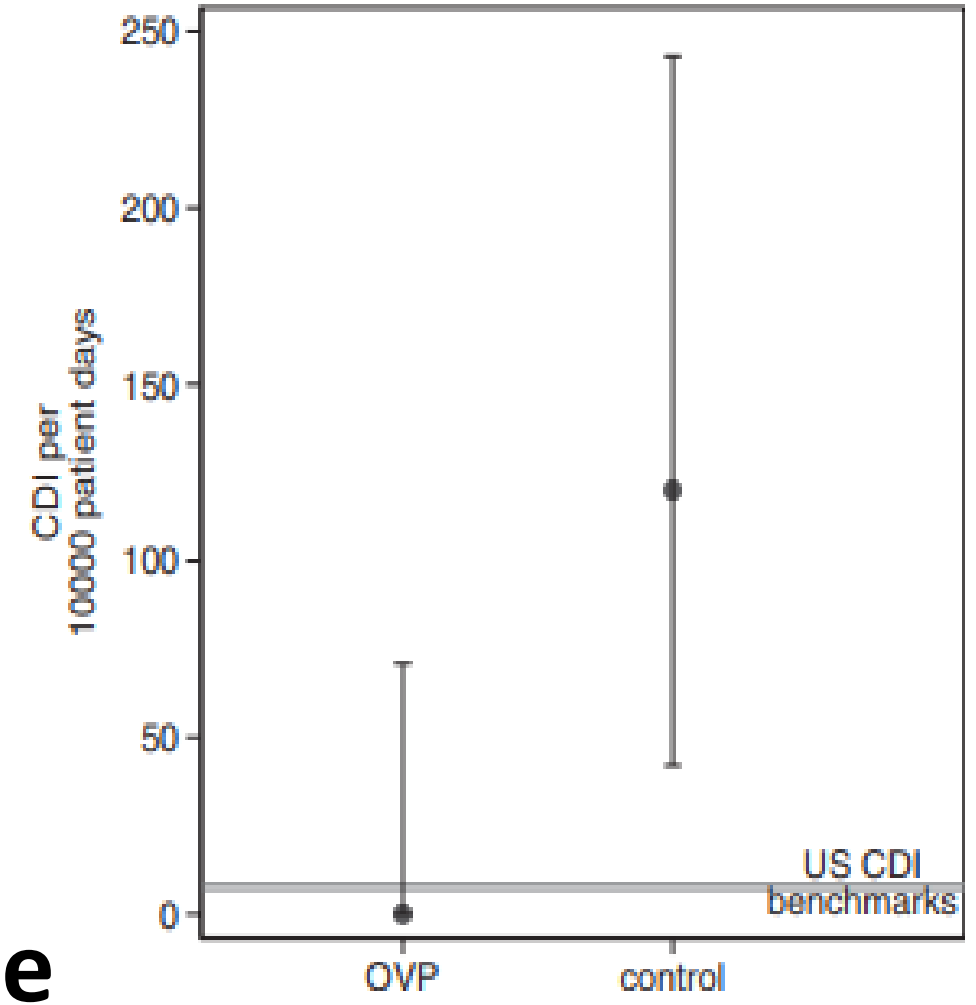
6 (12%) for Control group

<u>Literature review</u> of 8 studies

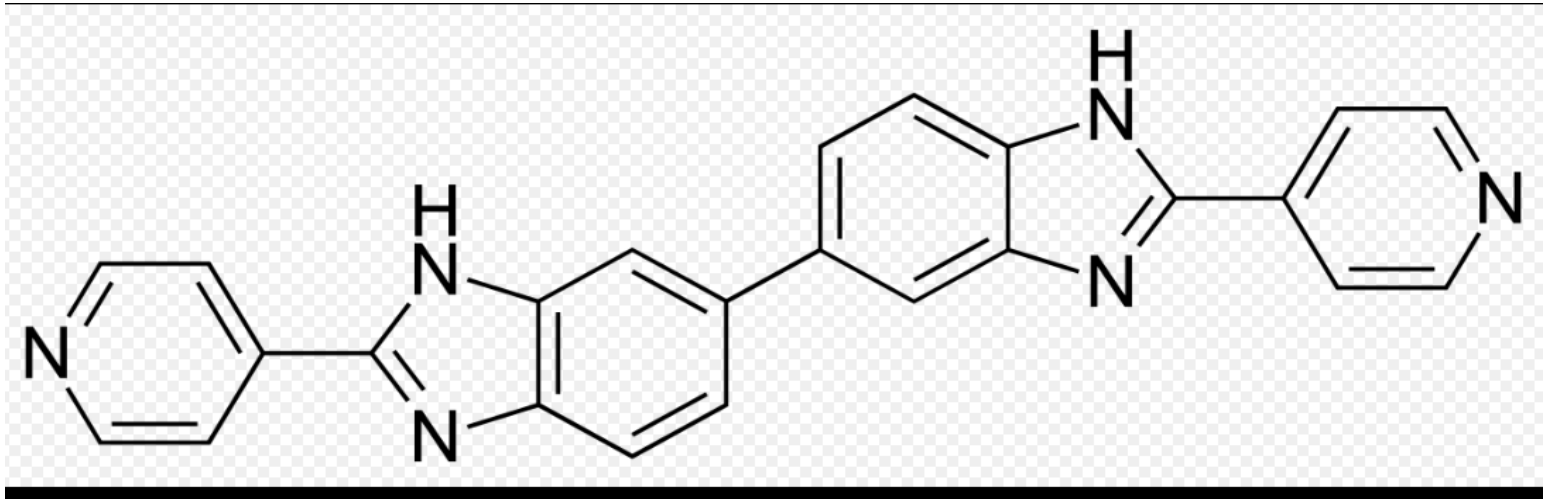
Dosage varied Once daily (3)

Twice daily (3) QID (1)

<u>Five studies showed significance</u>



Ridinilazole

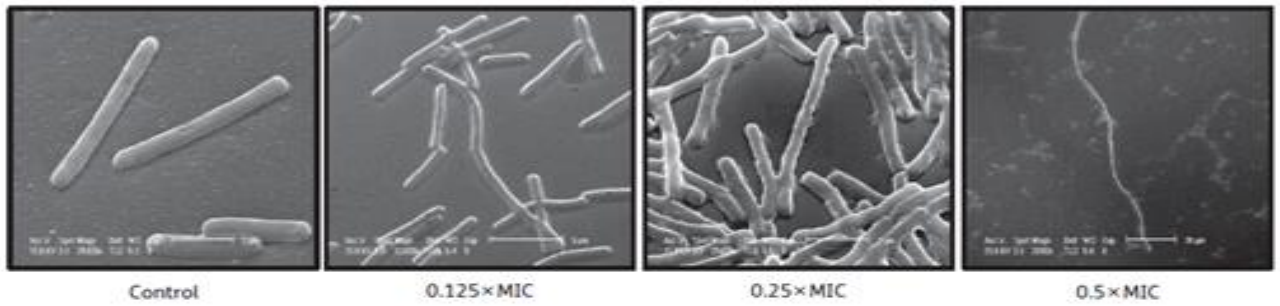


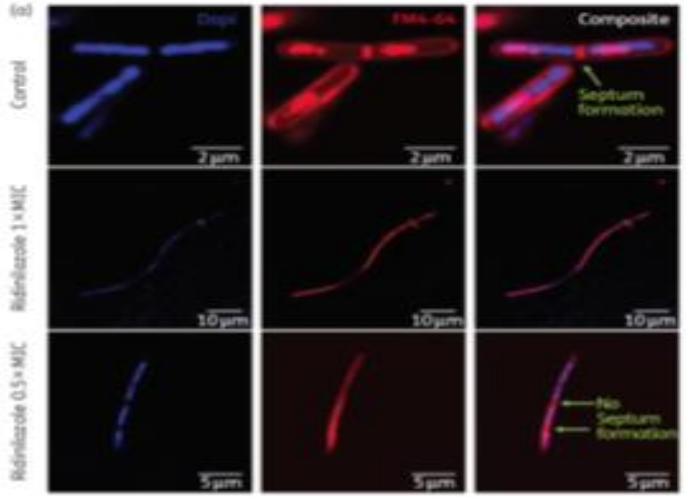
- Non absorbable
- Does not act through cell wall inhibition
- Nor via lipid, protein, RNA or DNA synthesis
- Likely impairs cell division- elongates cells and inhibits sporulation
- Narrow spectrum

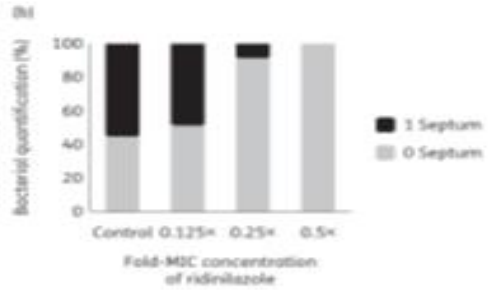
Less Microbiome change compared to vancomycin

Bactericidal with Inhibition of Toxin Production

Ridinilazole arrests *C. difficile* cell division[1]

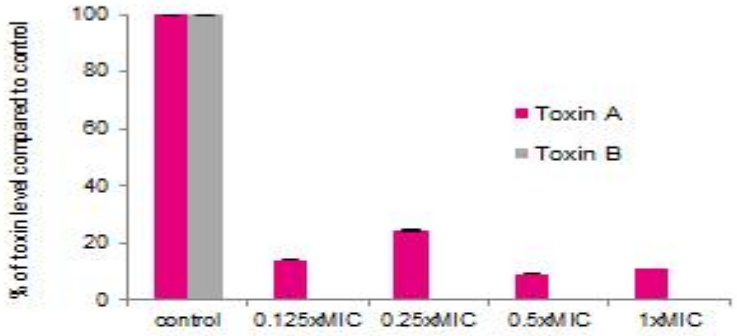




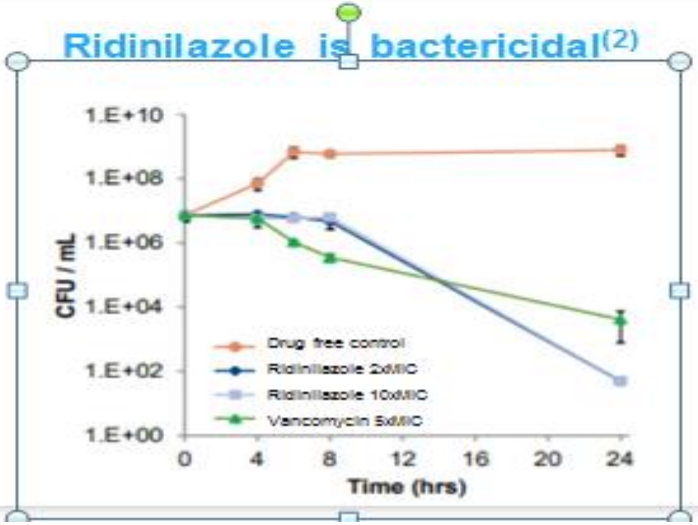


Dose dependent inhibition of septum formation

Ridinilazole inhibits toxin production[1]



Ridinilazole is bactericidal[2]



Direct attachment to C diff spores

(1)Basseres *et al*: JAC 2016; Anaerobe 2021
(2)Corbett *et al*. JAC 2015

No Safety Concerns Identified

Comparable rates of adverse events across the two treatment groups

Adverse Events	Ridinilazole n patients (%)	Vancomycin n patients (%)
Total number of AEs	*180*	*183*
TEAEs	41 (82)	40 (80)
Severe drug related TEAEs	2 (4)	1 (2)
Deaths	0	2 (4)
SAEs	8 (16)	9 (18)
TE SAEs	8 (16)	9 (18)
Drug related TE SAEs	1 (2)	2 (4)
Withdrawals due to AEs	2(4)	1(2)
SOC Preferred Term		
Gastrointestinal disorders	20 (40)	28 (56)
General disorders and administration site conditions	12 (24)	10 (20)
Infections and infestations	12 (24)	12 (24)
Metabolism and nutrition disorders	11 (22)	7 (14)
Nervous system disorder	10 (20)	11 (22)
Respiratory, thoracic and mediastinal disorders	9 (18)	3 (6)
Musculoskeletal and connective tissue disorders	6 (12)	8 (16)
Skin and subcutaneous tissue disorders	5 (10)	5 (10)

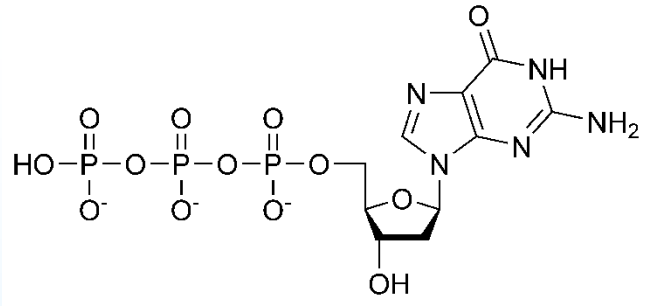
[redacted]

Rationale for Ibezapolstat (ACX-362E) Development

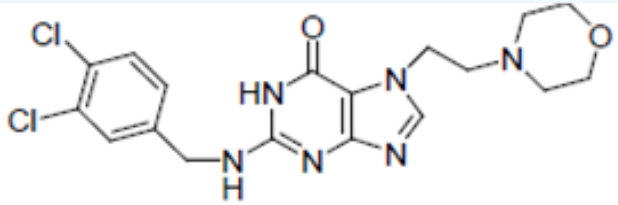
- **A New Class of antibiotic**

Targets DNA Pol IIIC
“pol” for DNA polymerase”; **“stat”** for enzyme inhibitor

- Guiding principles (Tarantino, AAC 1999)
  - **DNA Pol IIIC** essential for replication of low G+C content Gram-positive bacteria
  - DNA Pol IIIC strongly conserved across broad spectrum of low G+C Gram-positive pathogens
  - DNA Pol IIIC possesses a unique active site which renders it specifically susceptible to inhibition
- ACX-362E designed as inhibitor based upon competitive inhibition of dGTP



dGTP



ACX-362E

[redacted]

Phase 2 Trial

- Transition to Segment 2B: Double-blind, vancomycin-controlled
- **Expectation of ibezapolstat therapeutic success supported by:**
  - **In vitro potency against *C difficile***
  - **In vivo efficacy in the hamster model**
  - **Excellent human safety profile to date**
  - **High human fecal concentrations (3 logs above MIC)**
  - **Favorable microbiome effects**
  - **100% 1º efficacy (clinical cure) in 10 Phase 2A patients**
  - **100% 2º efficacy (sustained clinical cure) in 10 Phase 2A patients**

[redacted]

Ibezapolstat Mechanism of Action*: Association with DNA Pol IIIC

Template-directed elongation is blocked by the inhibitor through simultaneous binding to the cytosine of the DNA strand and near the active site of DNA Pol IIIC

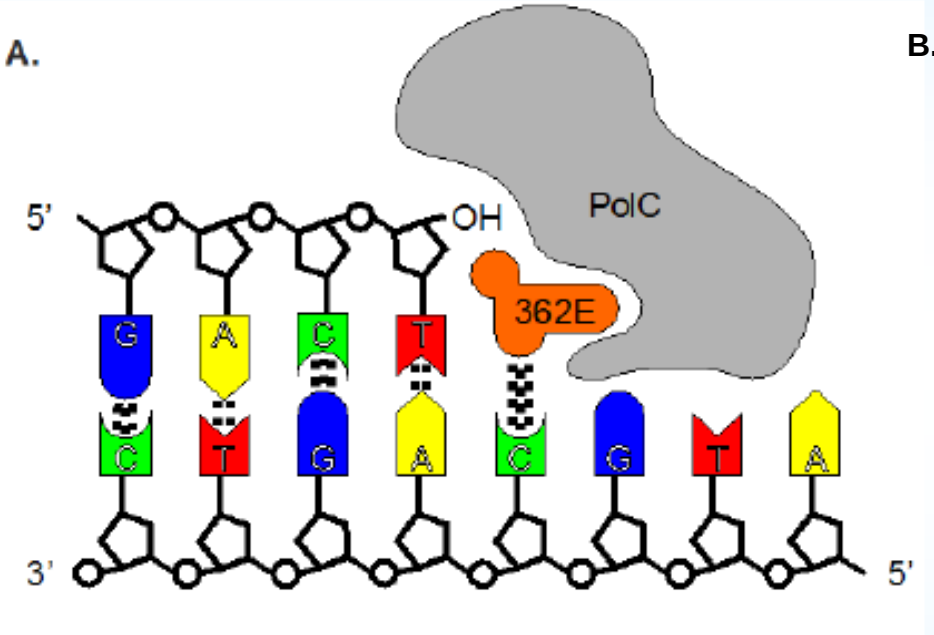


Figure A: Ternary complex of inhibitor ACX-362E, DNA ,and PolC.

*Van Eijk, ECCMID 2012

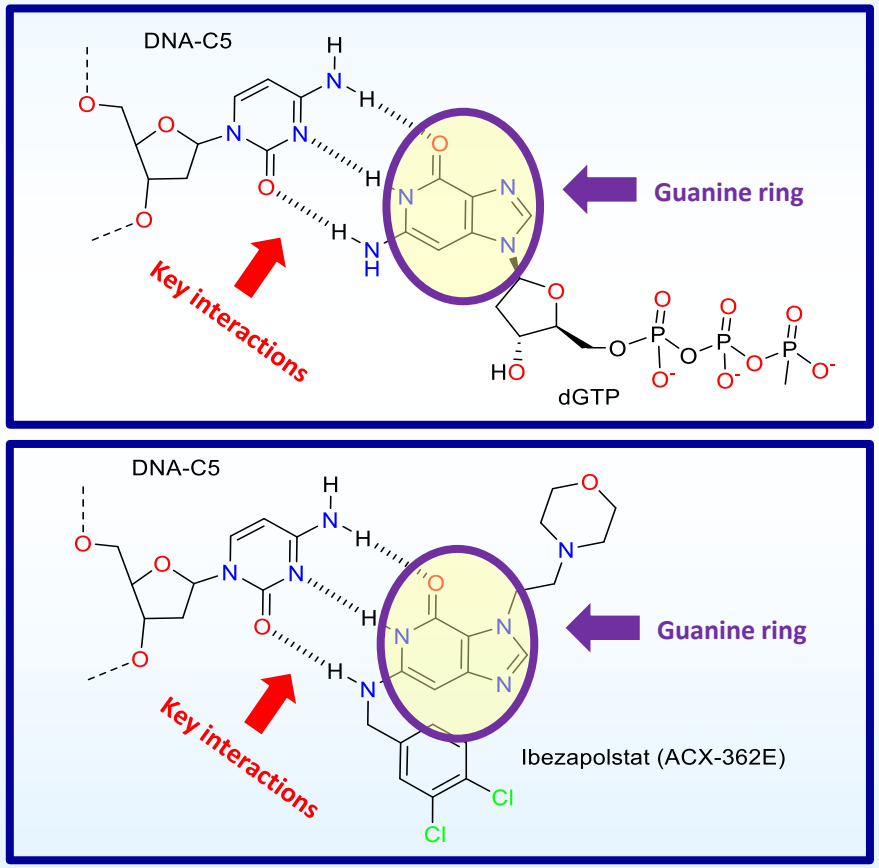
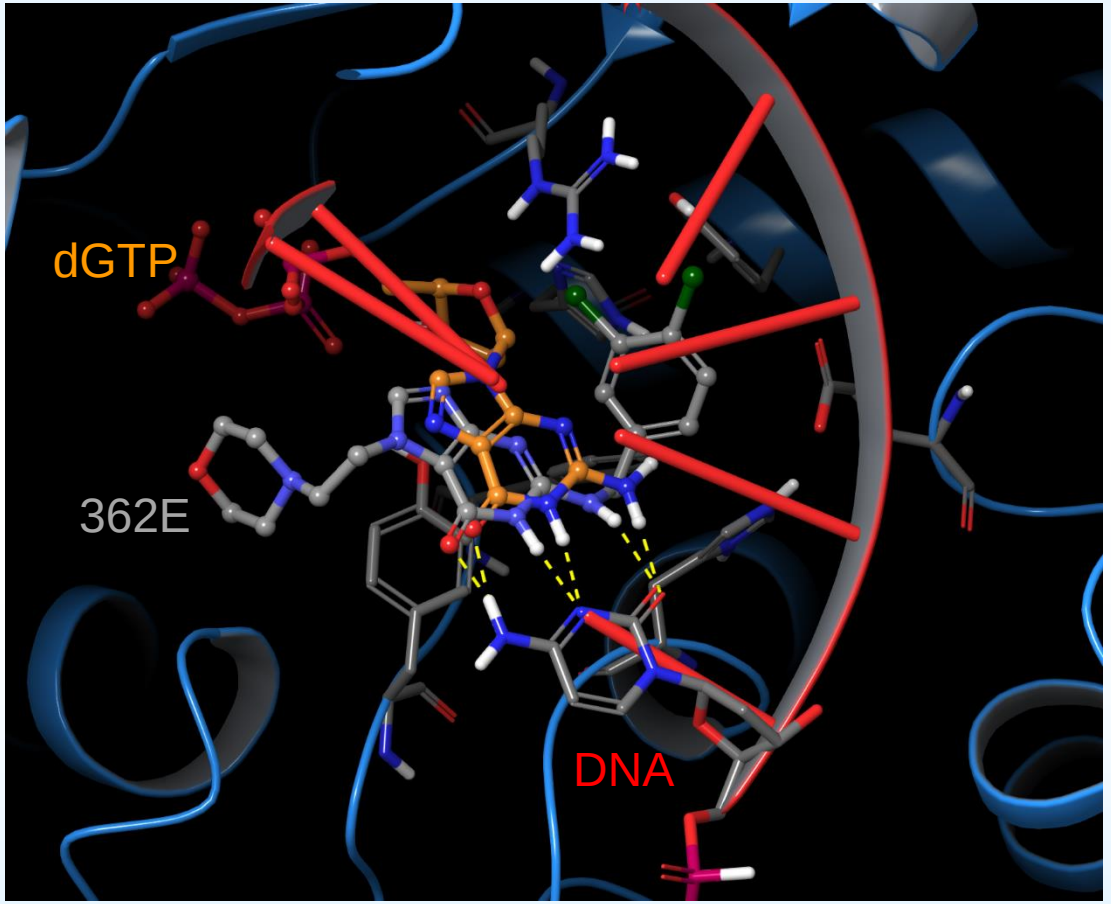


Figure B (2D Interactions): H-bonding between inhibitor molecule dGTP/362E and a cytosine residue of DNA (DNA-C5).

Docking of dGTP vs Ibezapolstat (ACX-362E)

- Superimposition of dGTP and ACX-362E docking positions
- dGTP has its guanine positioned similarly to that of ACX-362E, interacting with DNA-C5
- Phosphate tail of dGTP leads to different direction of other parts of ACX-362E, forming different interactions with protein residues



Phase 2A Adverse Event Profile (450 mg BID x 10 days)

Ibezapolstat was vey well-tolerated, with 7 AEs in 4 subjects

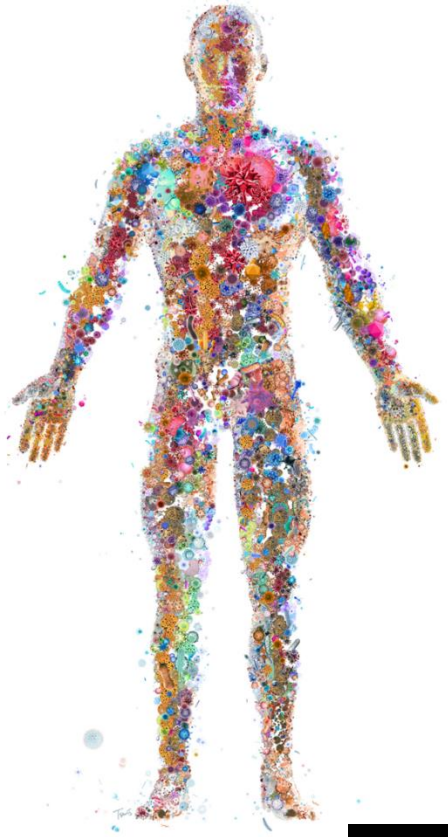
AE DESCRIPTION	INTENSITY	RELATIONSHIP
HEADACHE	MILD	UNRELATED
TEMPORAL HEADACHE	MILD	UNRELATED
MIGRAINE HEADACHE EXACERBATION*	SEVERE	UNRELATED
INTERTRIGINOUS CANDIDIASIS*	MODERATE	UNRELATED
VOMITING*	MODERATE	UNRELATED
NAUSEA*	MODERATE	UNRELATED
NAUSEA	MODERATE	PROBABLY RELATED

*4 AEs reported in the same subject

Ribaximase (SYN 004)

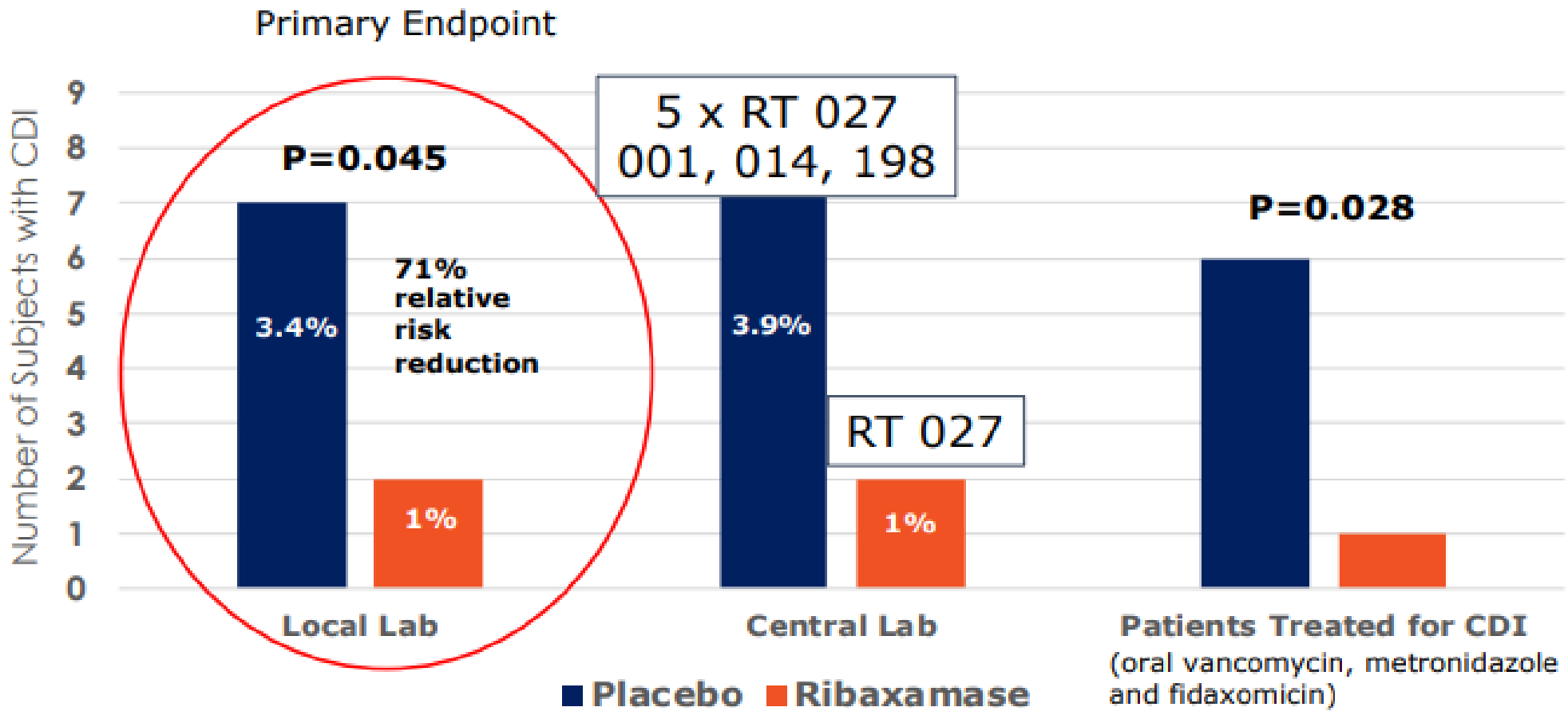
A Therapy to protect the Microbiome from antibiotic collateral damage

- **Ribaxamase a Class A β-lactamase - single amino acid modification**
- **Formulated for oral pH- dependent delivery at pH > 5.5 (proximal small intestine)**
- **For use with selected IV beta-lactam antibiotics (Ceftriaxione)**
- **Intended to degrade excess antibiotics excreted into the intestine via the bile**



[redacted]

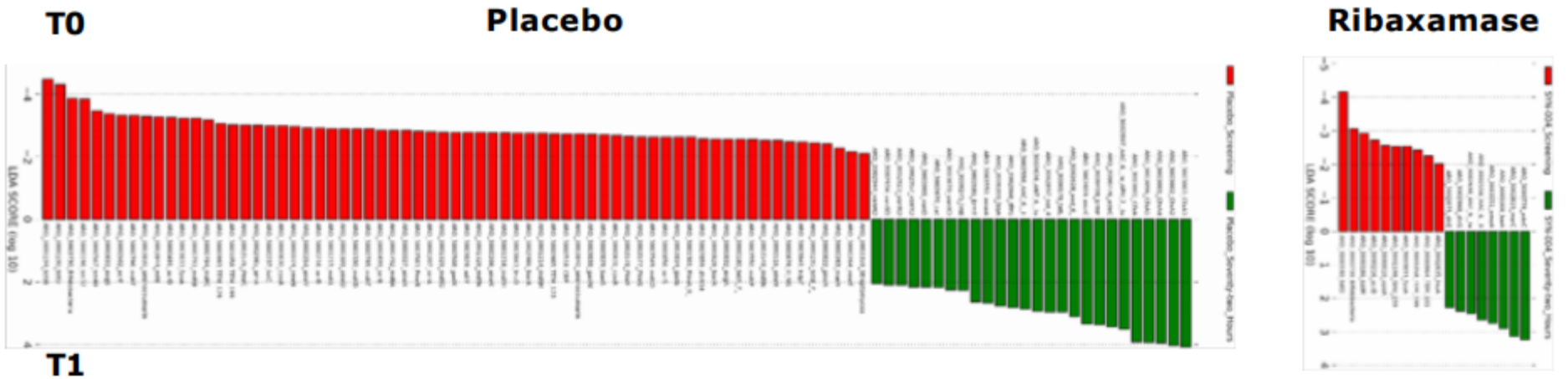
Clostridium difficile Infection (CDI)



- No CDI patients reported previous CDI
- P-values are 1-sided based on the pre-specified Z-test
- The study was powered at 80% with 1-sided alpha=0.05

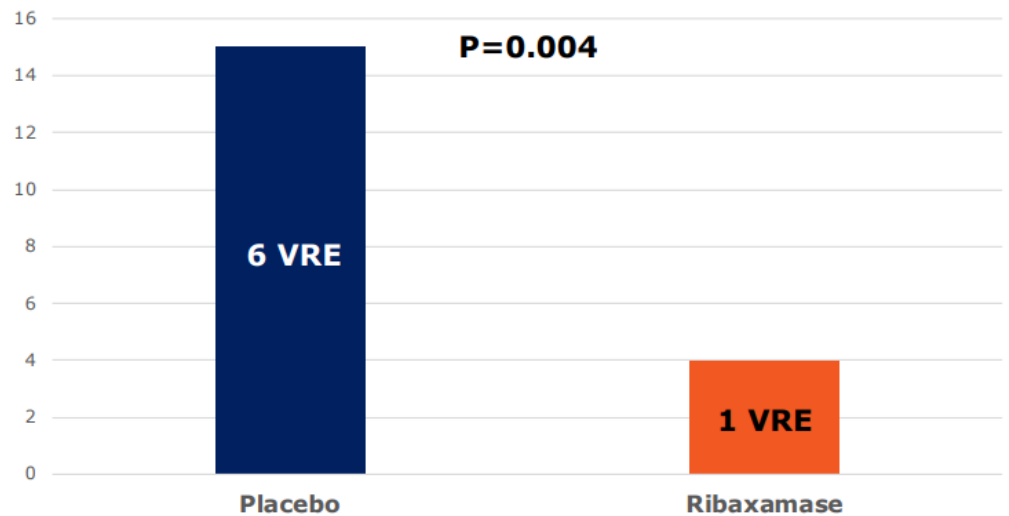
Analysis of the Change in Relative Abundance of AMR Genes

Collection point T0 to T1, Placebo vs. Ribaxamase-treated patients



Comparison of Patients with Enterococcal Mono-domination

> 30% of taxa present were enterococci at T1 or T2 based on 16S sequencing



COVID-19 and CDI- Co-Infection?
With all the Abx used do we expect an Increase ?

- Rawson et al[1]:
  - **72% of 2,010 COVID-19 patients received antibiotics** in the hospital
  - Only 8% actually had a bacterial and fungal co-infection.
- Italy[2]:
  - Among 16,654 patients who died of COVID-19, 'superinfections' were reported in 11% of cases.
- Wuhan[3]:
  - 191 patients
  - 15% of patients developed secondary bacterial infections, and half of those who did died.
  - Most common antibiotics used were respiratory quinolones

[1] Rawson TM, et al. *Clin Infect Dis*. 2020
[2] https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_9_aprile.pdf
[3] Zhou F, et al. *The Lancet* 2020; 395(10229): 1054-1062

CDI in COVID-19 patients

Detroit Medical Center Hospitals, Mar-Apr 2020

9 cases of co-infection with SARS-CoV-2 and *C. difficile*

- 3 had prior CDI
- 2 had diarrhea & positive for *C. diff* on admission; 7 developed CDI after COVID-19 diagnosis (median lag in diagnosis, 6 days)
- All had received antibiotics (mean duration prior to CDI, 5 days)
- 4 patients died & 1 was discharged to hospice
- Underlying characteristics:
  - Median age, 75; F, 78%; median ATLAS score, 6
  - Required ICU & vasopressors, 4
  - Median ferritin, 1,459.4 ng/mL
  - mean WBC 12.0 10^9/L
  - mean Cr 4.22 mg/dL (3 were on HD)

Sandhu A et al Emerg Infect Dis 2020;Sep Ahead of Print

Clostridioides difficile in the COVID-19 Era

- 311/4,973 inpatients tested for **GI infections** 204 COVID +; 107 -
-

	COVID +	COVID -	
– Overall	10%	22%	
– **CDI**	**5.1%**	**8.2 %**	**p =0.33**
– Non CDI	11%	22%	p= 0.44

CDI and non-CDI decreased during the pandemic

Laszkowska et al. Dig Dis Sci 2021 Jan 22;1-8. **doi: 10.1007/s10620-020-06760-**
NYC: Columbia, Mt. Sinai & Sloan Kettering

Italy- during the pandemic (2020) HA-CDI incidence was significantly lower with respect to the previous years **Bentivegna E et al Amer J Inf Control Oct 5, 2020**

Ireland- NYC Decrease in HA-CDI in the pandemic year. Hazel K et al. ICHE 2021;

❖ **Seems Infection Prevention measures work**

DAV 132 (**Da Volterra)** Microbiota Protector

- "first-in-class microbiota protector," patented **colon-targeted adsorbent**
- orally administered formulation that **releases 5 gm of activated charcoal** from a 7.5gm dosage into, or after passage through the ileum.
- Phase 2 Trial (SHIELD) multicenter, randomized, parallel-group comparative trial in 4 European countries (Germany, Romania, Bulgaria, and Serbia)
- 7.5gm of DAV132 **three times daily**
- 260 elderly patients (median age 71) **receiving oral or IV fluoroquinolone** for the treatment of
  - LRTI
  - cUTI
  - Prophylaxis for febrile neutropenia
  - for a mean duration of 7.5 days.
- demonstrated **protection against antibiotic-induced disruption of intestinal microbiota.**

DAV 132 (**Da Volterra) Microbiota Protector**

- DAV132 while developed for the prevention of *Clostridioides difficile* infections,
- and for the prevention of intestinal colonization by multi-drug resistant organisms and their dissemination.
- Is anticipated to provide a significant clinical benefit, in combination with antibiotics, for
  - Patients undergoing allogeneic hematopoietic stem-cell transplantation (HSCT) in collaboration with the European-based COMBACTE-NET consortium
  - Cancer patients treated with immune checkpoint inhibitors.

Vaccines for Primary CDI Prevention

	Valneva VLA 84	Pfizer	Sanofi	?
?	**Recombinant Protein**	**Toxoids A and B**	**Toxoids A and B**	**Replicating Single-Cycle Adenovirus**
Development Stage	Phase I & II completed, Phase III on hold	Phase I & II completed, Phase III ongoing	Phase III Suspended due to "futility"	
Group	50+ years	65+ years	50+ years	**Chandrabali Ghose, Symbiotic Health, Rockefeller University**

Clinical Trial > Lancet Infect Dis. 2021 Feb;21(2):252-262. doi: 10.1016/S1473-3099(20)30331-5. Epub 2020 Sep 15.

Safety, immunogenicity, and efficacy of a Clostridioides difficile toxoid vaccine candidate: a phase 3 multicentre, observer-blind, randomised, controlled trial

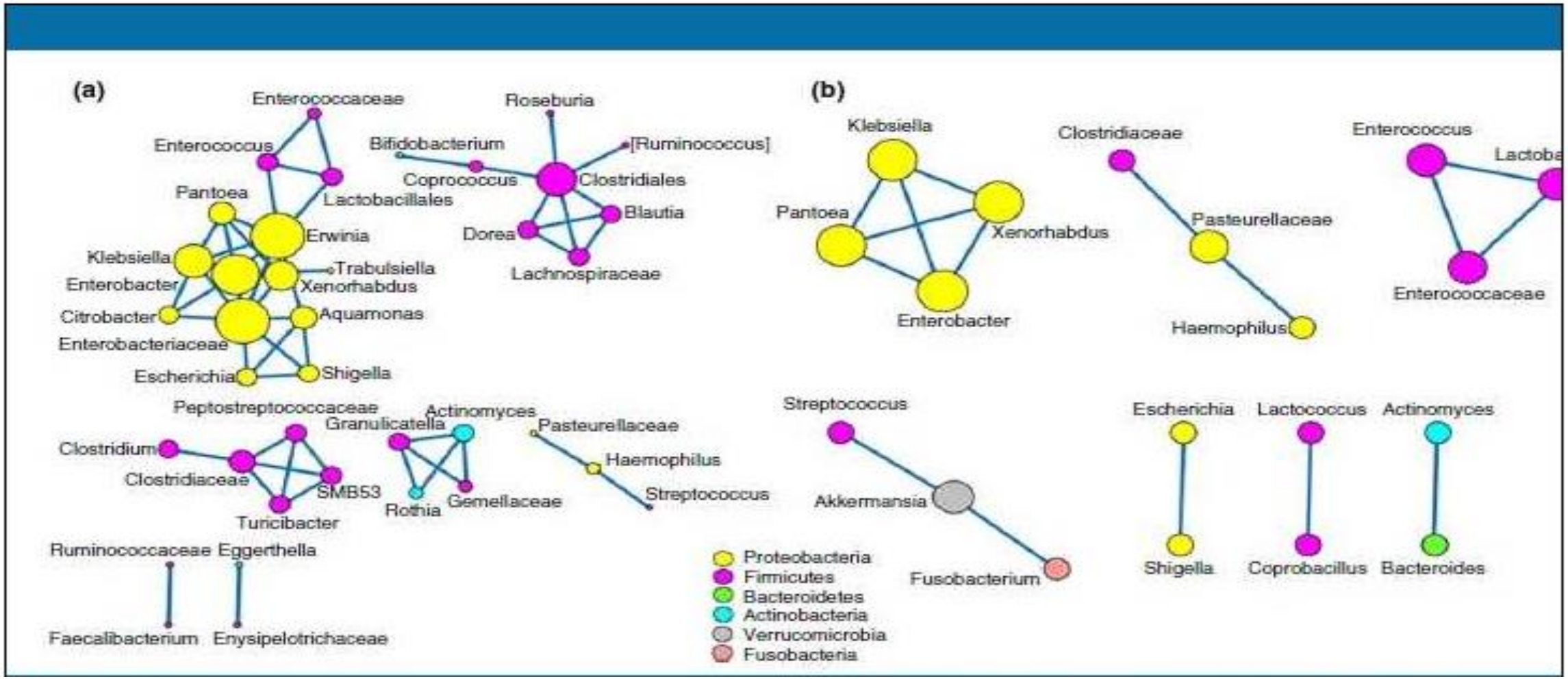
- **Sanofi** 27 countries
- 7-30-2013 to 11-17-2017 9,302 Participants (6,201Vaccine gp)
- > 50 years, 2 Hosp stays + abx or planned surgery + abx
- **Vaccine IM <u>Day 0, 7 and 30</u> 100 µg toxoid**
- **Highly purified TcdA & TcdB <u>ATCC 43255</u>**
- 3 loose stools **PCR +** followed for 3 years
- Terminated at first planned interim analysis due to **<u>"futility"</u>**
- Adverse events 4.8 % both groups

Clinical Trial > Clin Infect Dis. 2020 Jan 1;70(1):1-10. doi: 10.1093/cid/ciz153.

A Phase 2 Study Evaluating the Safety, Tolerability, and Immunogenicity of Two 3–Dose Regimens of a Clostridium difficile Vaccine in Healthy US Adults Aged 65 to 85 Years

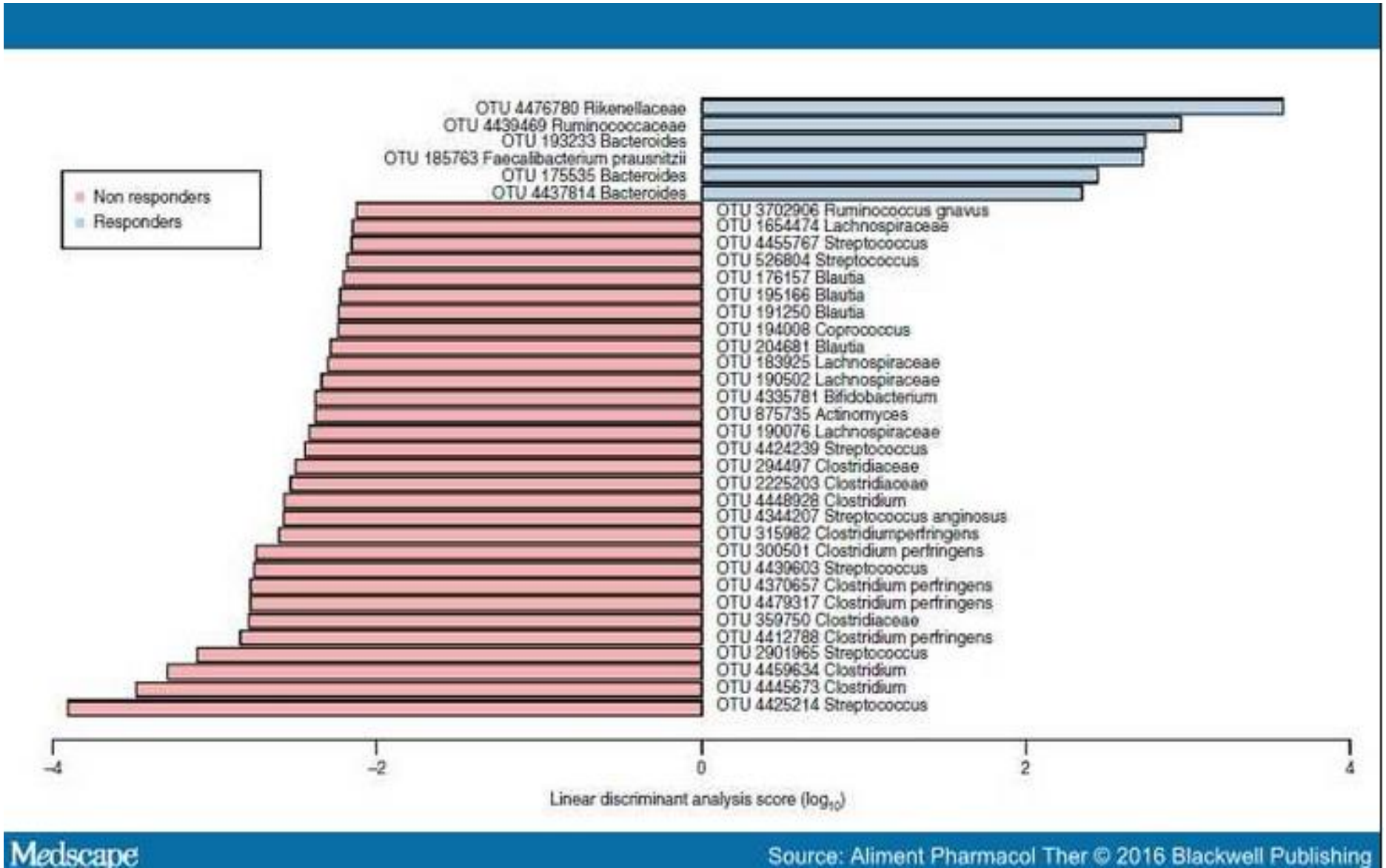
- **Pfizer July 2013 to March 2017 855 adults 65-85 y.o.**
- **15 US Centers 3:3:1 randomization IM toxoid 2 strains**
- **100 or 200 µg or placebo 0,1 & 6 mos. Or 1,8 & 30 days**
- **Serum Toxin A & B specific neutralizing Antibodies**
- **200 >100 µg dose response remained elevated for 12 mos.**
- **Response peaked 7 mos. (month) vs 37 days (day) regimen**

The Gut Microbiome



Khanna S, Montassier B et al Ailment Pharmacol Ther 2016;44:715-27

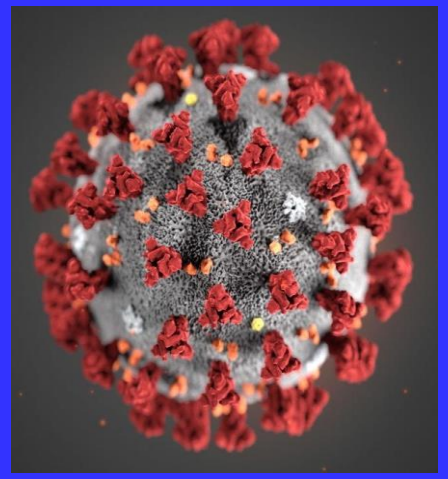
The Gut Microbiome Predicts Treatment Response & Relapse



Medscape

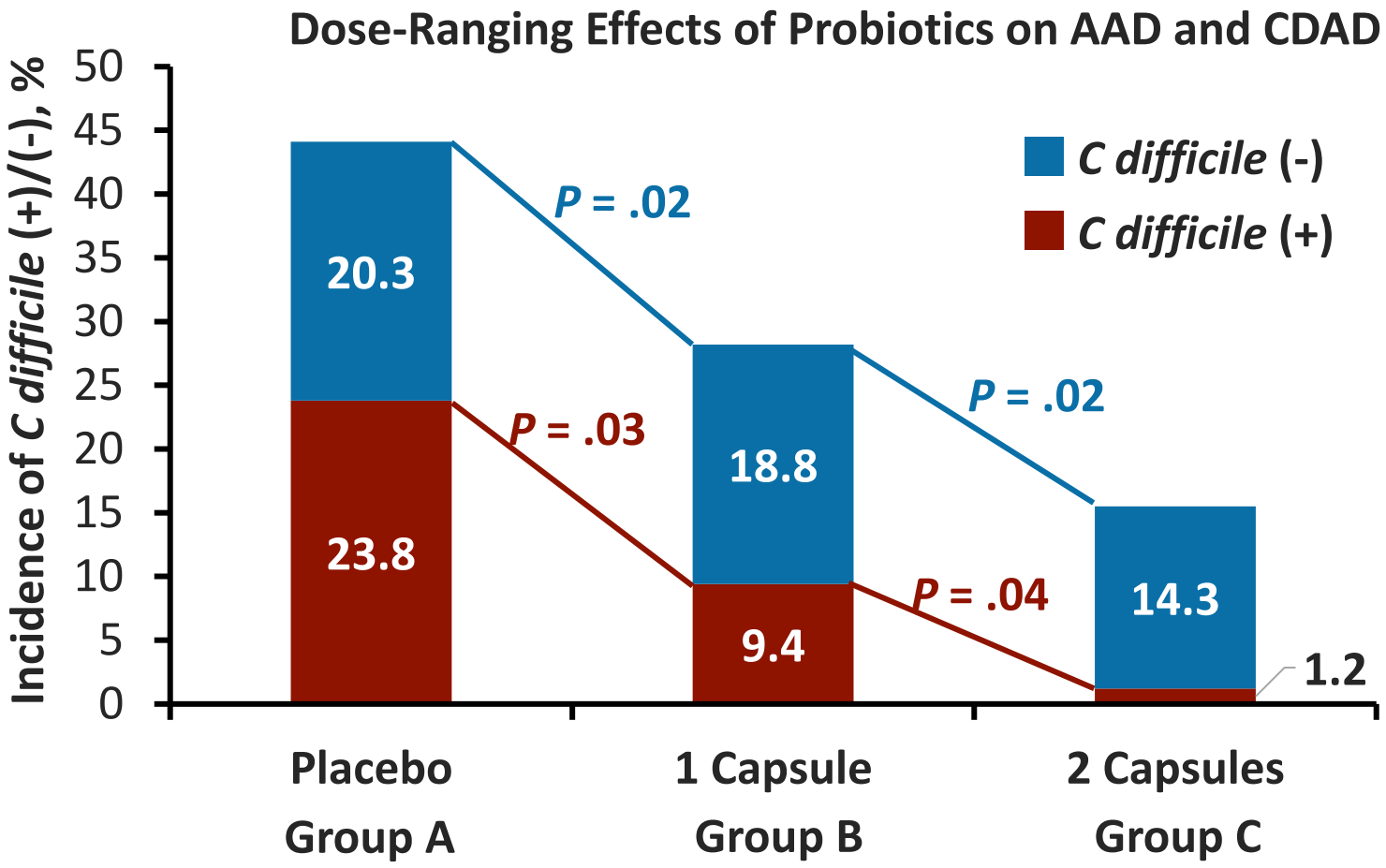
Source: Aliment Pharmacol Ther © 2016 Blackwell Publishing

Probiotics in the Coronavirus Era



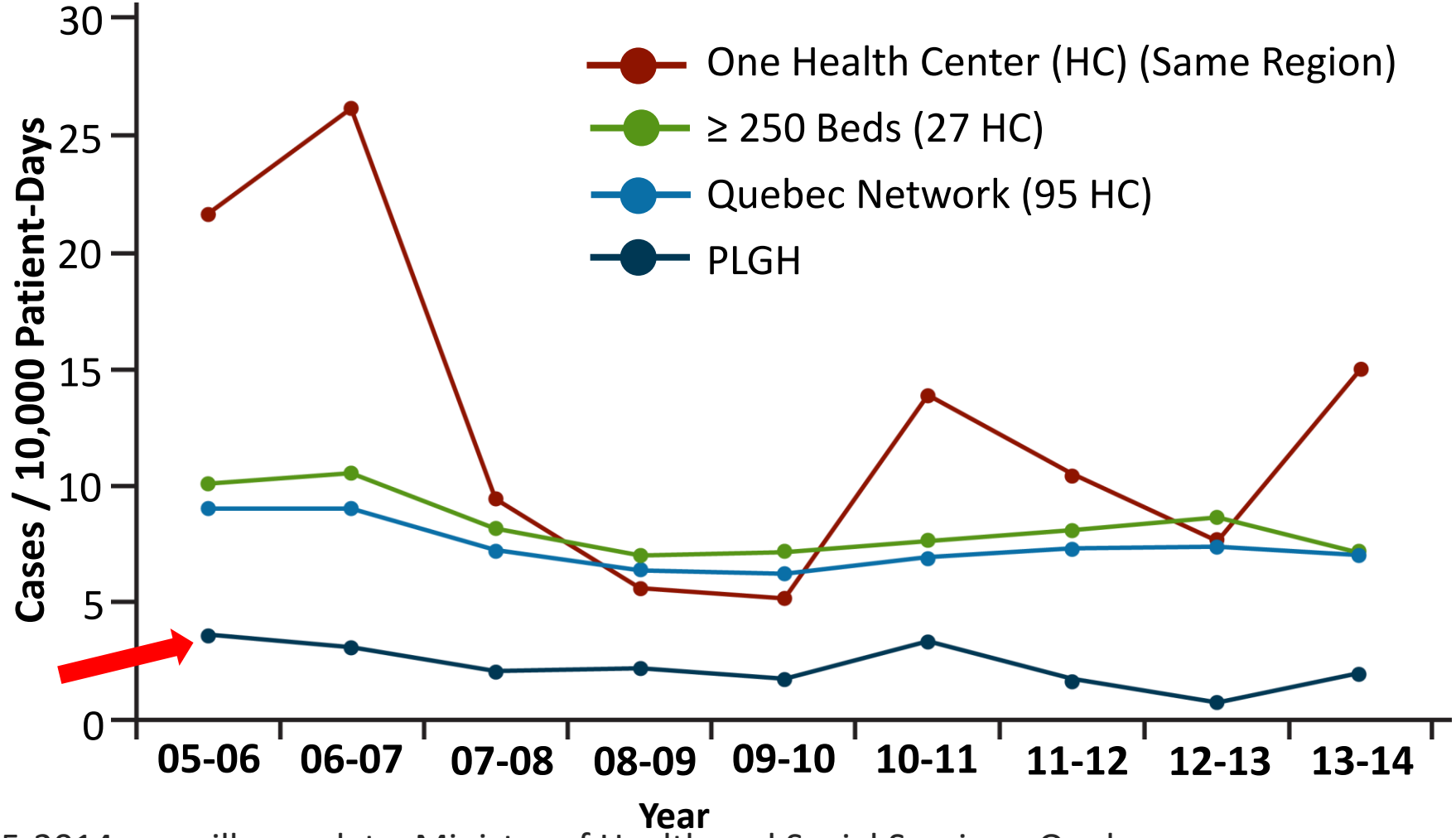
Lynne V. McFarland, PhD
Seattle, Washington

Dose-Response Study of a Lactobacillus Combination Probiotic in Prevention of AAD and CDI



Gao XW, et al. *Am J Gastroenterol*. 2010;105:1636-1641.

Comparative CDI Rates Pierre-LeGarde Hospital vs Similar Hospitals in Quebec



2005-2014 surveillance data, Ministry of Health and Social Services, Quebec.

Mazaide JP et al. *Clin Infect Dis*. 2015;60(Suppl.2) S146.

Enhanced *CDI* prevention with a pharmacy controlled policy that adds a 3-strain *Lactobacillus* probiotic to most antibiotic users

Mazaide et al. CID **In Press 2021**

- Pierre-Le Gardeur Hospital, in the outskirts of Montreal, Quebec, Canada 2016-2019
- quinolone antibiotic use restricted azithromycin → doxycycline
- Adult inpatients prescribed two or more days of antibiotics were flagged by the hospital pharmacy to receive the probiotic daily within the first 24 hours
- 13922 inpatient hospitalizations of adults Rx antibiotics
- 4383 patients observed 12-months & 6079 18-months
- When 70% of antibiotic users took a probiotic (BioK+) HA-CDI was significantly lower during the **intervention**, 5.2 cases per 10 000 patient day compared to the **observation** period, **8.6, P=.002**

Proposed Mechanisms of Probiotic Action

Product	Proposed Mechanism
Saccharomyces boulardii	• Secretes a protease that degrades Toxins A & B • Inhibits binding receptors
Lactobacillus rhamnosus GG	• Avidity of mucosal cells • Reduction of permeability defects • Enhances intestinal immunity
Bio K + combination *L acidophilus* CL1285 *L casei* LBC808R *L rhamnosus* CLR2	• Inhibits *C difficile in vitro* Bacteriocin activity • Neutralizes Toxin A & B

Goldstein E, et al. *Clin Infect Dis*. 2015:60 (Suppl 2):S99-S107.

2020 AGA Guidelines: Prevention of *C. difficile* infections

:

In adults and children on antibiotic treatment:

- ***S. boulardii*** **CNCM I-745 [Florastor®] (based on 9 RCTs)**
- **2-strain combination of *L. acidophilus* CL1285 and *L. casei* LBC80R [Bio K+]**

  (based on 3 RCTs)
- **3-strain combination of *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, and *B. bifidum***

  ***(*only 1 RCT)**

[Su GL et al. 2020 Gastro]

Fecal Biotherapy/ Transplant

Upper or Lower Endoscopy
Home Enemas
Capsules

Fecal Transplants for r CDI

- **Directed Donor**
- **Open Biome** Non profit stool bank www.openbiome.org
  - issues with CRE, Corona virus
  - **will expand availability of FMT preparations for all scheduled patients, May 3, 2021. RT-PCR testing- donors & stools**
- **RBX-2660** (Ferring Pharmaceuticals)
  - Suspension of "human derived" microbiota as rectal enema
  - PUNCHCD3 NCTO3244644
- **SER 109** Donor derived purifies spores
  - 89 pts reduced rates of CDI but did not meet clinical significance Phase 2

  McGovern B et al CID 2020 NCT02437487

  Phase 3 underway, 289 pts enrolled 88.9% sustained response preliminary analysis Contagion Feb 2021

Thank you Any Questions?