Current developments in *Clostridioides difficile* prevention, therapy and R&D

Guest speakers: Benedikt Huttner, Paul Feuerstadt, Kerrie Davies & Mark Wilcox

Moderator: Christian John Lillis

Host: Victor Kouassi

13 March 2026

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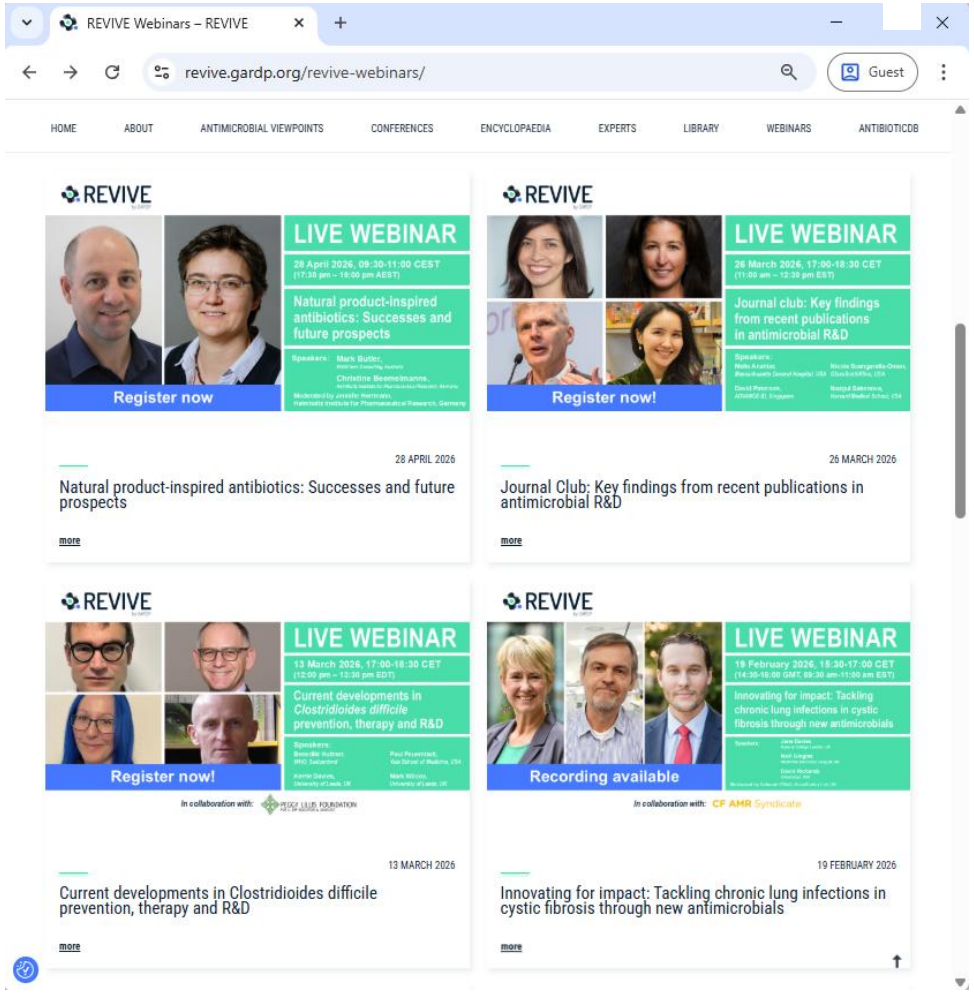

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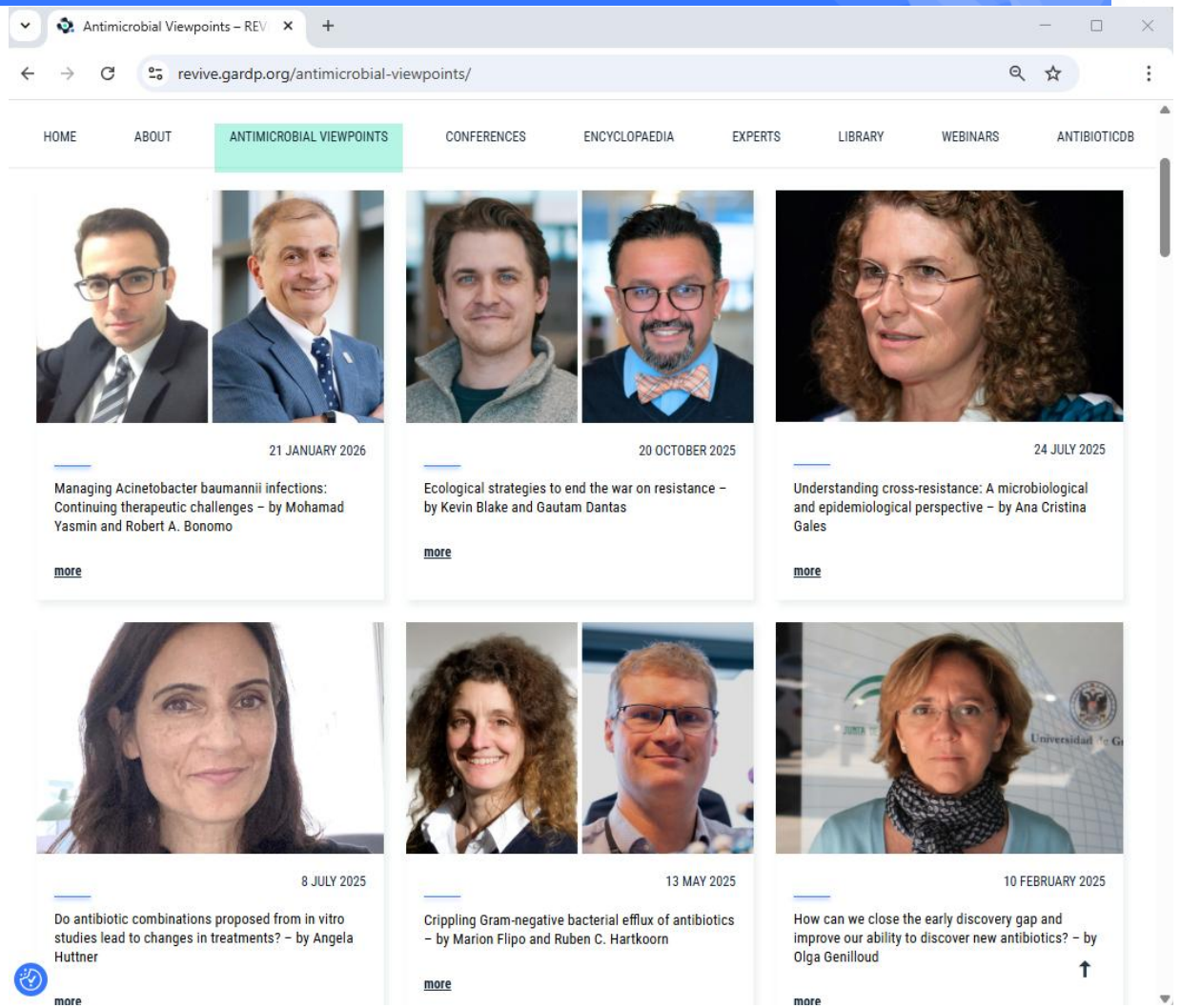

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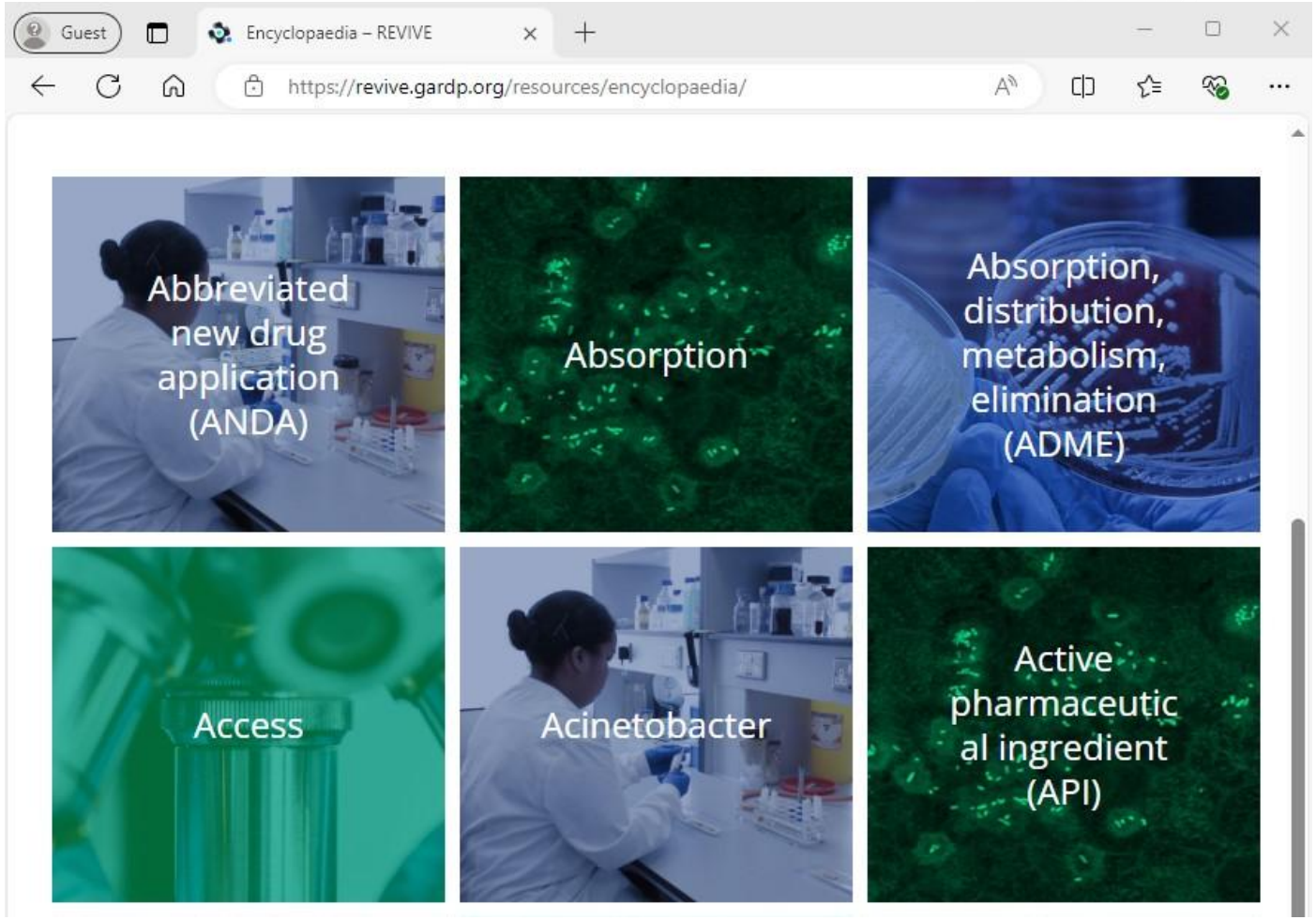

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How to submit your questions

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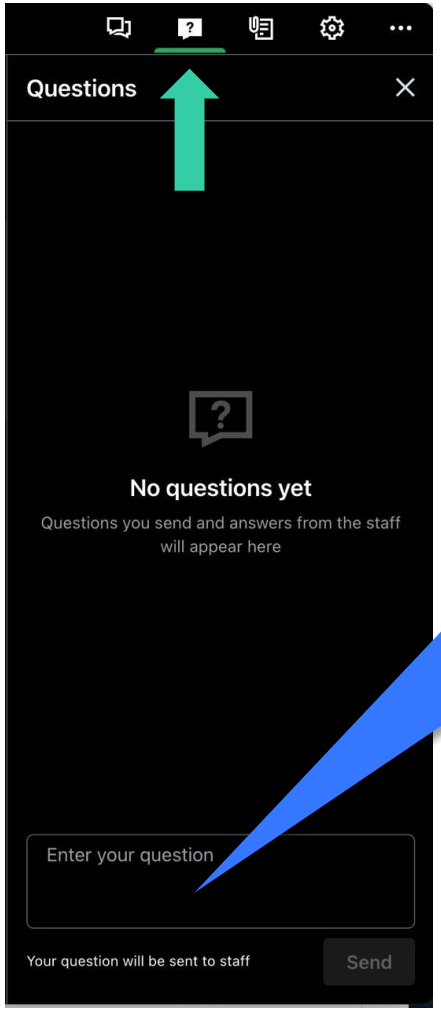
If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

REVIVE
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This webinar was developed in collaboration with

PEGGY LILLIS FOUNDATION
FOR C. DIFF EDUCATION & ADVOCACY

https://cfamr.org.uk/

Today's speakers

REVIVE by GARDP

Current developments in *Clostridioides difficile* prevention, therapy and R&D

Moderator:
Christian John Lillis
Peggy Lillis Foundation, USA

Benedikt Huttner
WHO, Switzerland

Paul Feuerstadt
Yale School of Medicine, USA

Kerrie Davies
University of Leeds, UK

Mark Wilcox
University of Leeds, UK

PEGGY LILLIS FOUNDATION
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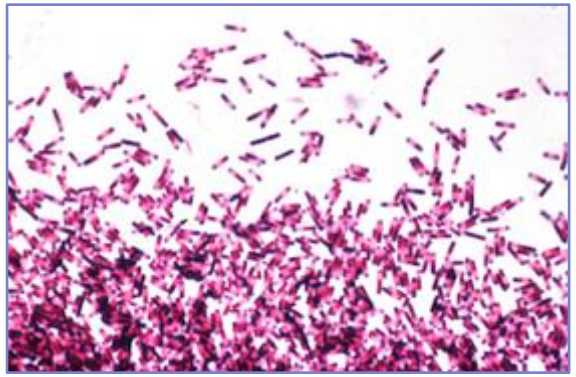
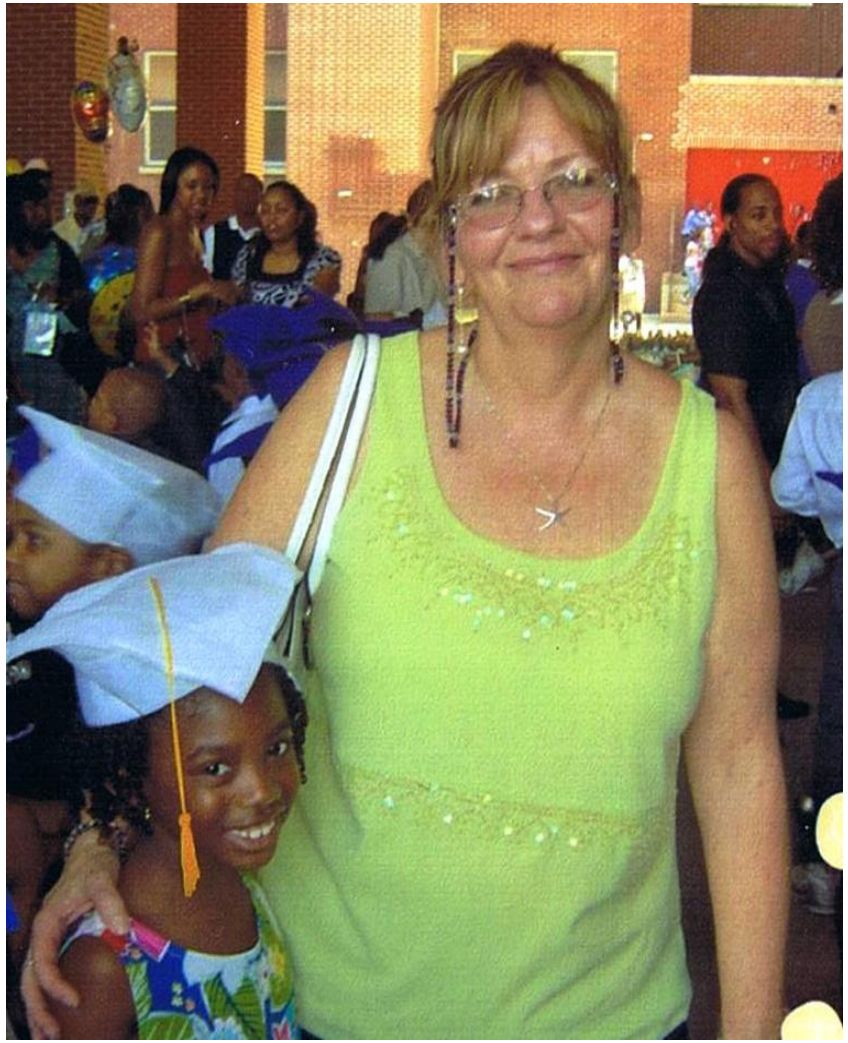
Current developments in Clostridioides difficile prevention, therapy, and R&D



Who Was Peggy?



- Peggy was a 56-year-old Brooklyn, Kindergarten teacher
- Single mother of two adult sons
- Peggy's long-time dentist prescribed clindamycin following a root canal
- 6 days later Peggy died from sepsis related to C. diff infection and toxic megacolon
- Her sons founded PLF in response to her death

PEGGY LILLIS FOUNDATION
FOR C. DIFF EDUCATION & ADVOCACY

Vision

We envision a world where *C. diff* infections are **rare, treatable, and survivable.**

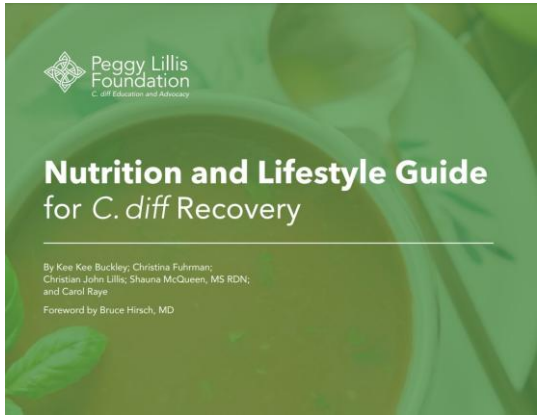
Mission

Peggy Lillis Foundation is **building a** C. diff awareness movement by educating the public, empowering advocates, and shaping policy

PLF's Work

Patient Support

PLF offers a Peer Support program, Care and Nutrition guides, and an array of print and video resources.

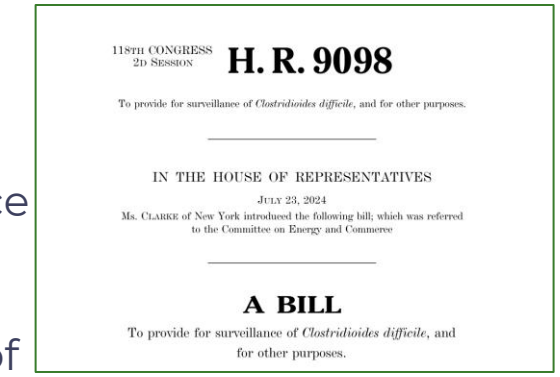


Education

PLF educates patients, healthcare workers, industry and the public through media, webinars,

Policy Advocacy

We worked with Rep. Yvette Clarke to introduce the **Peggy Lillis C. difficile Inclusion Act**, requiring the reporting of all C. diff infections.



118TH CONGRESS
2D SESSION

H. R. 9098

To provide for surveillance of *Clostridioides difficile*, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

JULY 23, 2024

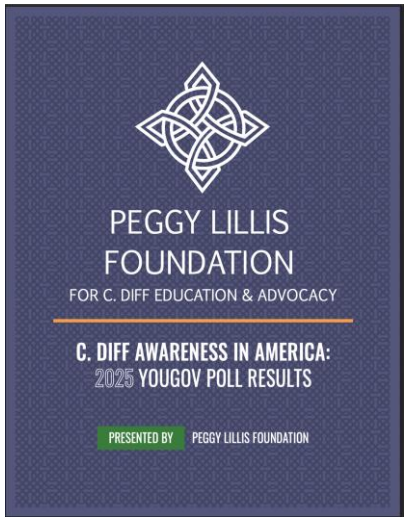
MS. CLARKE of New York introduced the following bill; which was referred to the Committee on Energy and Commerce

A BILL

To provide for surveillance of *Clostridioides difficile*, and for other purposes.

Awareness

PLF's report "C. diff Awareness in America," showed **a 6 percent increase in awareness** from 2021-2025



Benedikt Huttner

Benedikt Huttner is currently the unit head of Access, Stewardship and AMU surveillance in the Department of Antimicrobial Resistance at the World Health Organization (WHO)'s headquarters in Geneva.

Prior to this, Benedikt was team lead of the Essential Medicines in the Division of Access to Medicines and Health Products at WHO where he led the development of the WHO AWaRe antibiotic book. After obtaining his medical degree in 2001, Benedikt then moved to Switzerland to train in infectious diseases. From 2006 to 2021, he worked as a clinician responsible for the local antimicrobial guidelines and antimicrobial stewardship and academic researcher at Geneva University Hospitals. His research focused on antimicrobial resistance, antimicrobial stewardship and appropriate use of medicines in general. From 2010 to 2012, he did a research fellowship at the University of Utah, USA where he also obtained a master's degree in the Science of Clinical Investigation.

Global epidemiology of *Clostridioides difficile* and WHO priorities for prevention

Benedikt HUTTNER

Unit Head

Research, Access, Stewardship and AMR surveillance

Department of Antimicrobial Resistance

World Health Organization

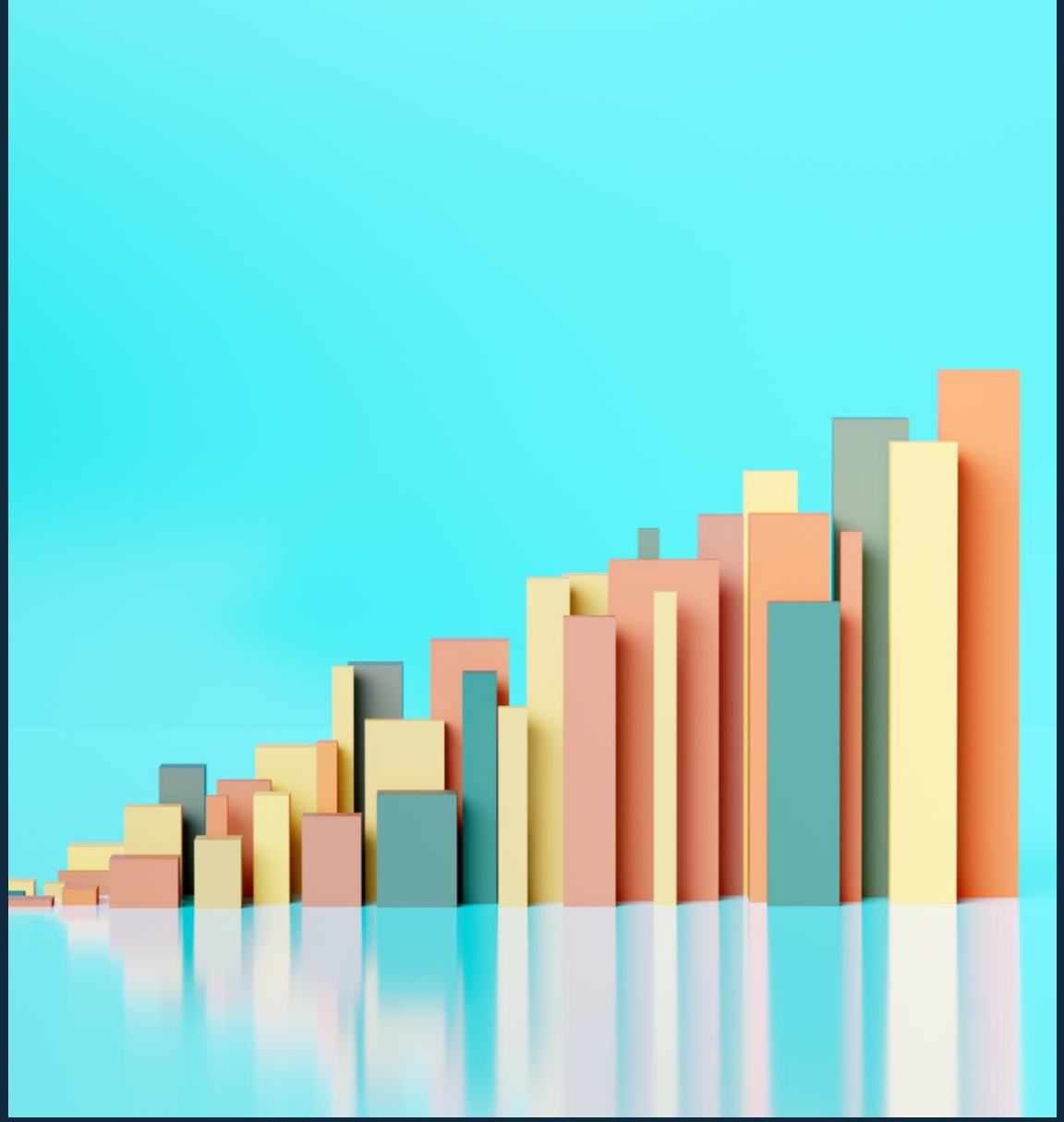
Webinar 13 March 2026

Current developments in *Clostridioides difficile* prevention, therapy and R&D

Declaration of interests

- I am a full-time staff member of WHO
- Otherwise, nothing to declare

Global epidemiology of *Clostridoides difficile*



World Health Organization

GLASS-AMR

GLASS
Global Antimicrobial Resistance and Use Surveillance System

Pathogens currently included in GLASS-AMR are:

- *Acinetobacter* spp.
- *E. coli*
- *Klebsiella pneumoniae*
- *Neisseria gonorrhoeae*
- *Salmonella* spp. (non-typhoidal)
- *Shigella* spp.
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*

Infections covered:

Bloodstream, gastrointestinal, urinary tract and urogenital gonorrhoea

https://www.who.int/initiatives/glass/glass-routine-data-surveillance
https://www.who.int/publications/i/item/B09585

No data on *C. difficile*

World Health Organization

The Global Burden of Clostridioides difficile Infections, 2016–2024: A Systematic Review and Meta-Analysis

- Peer-reviewed papers published in English in from January 2016 to July 2024

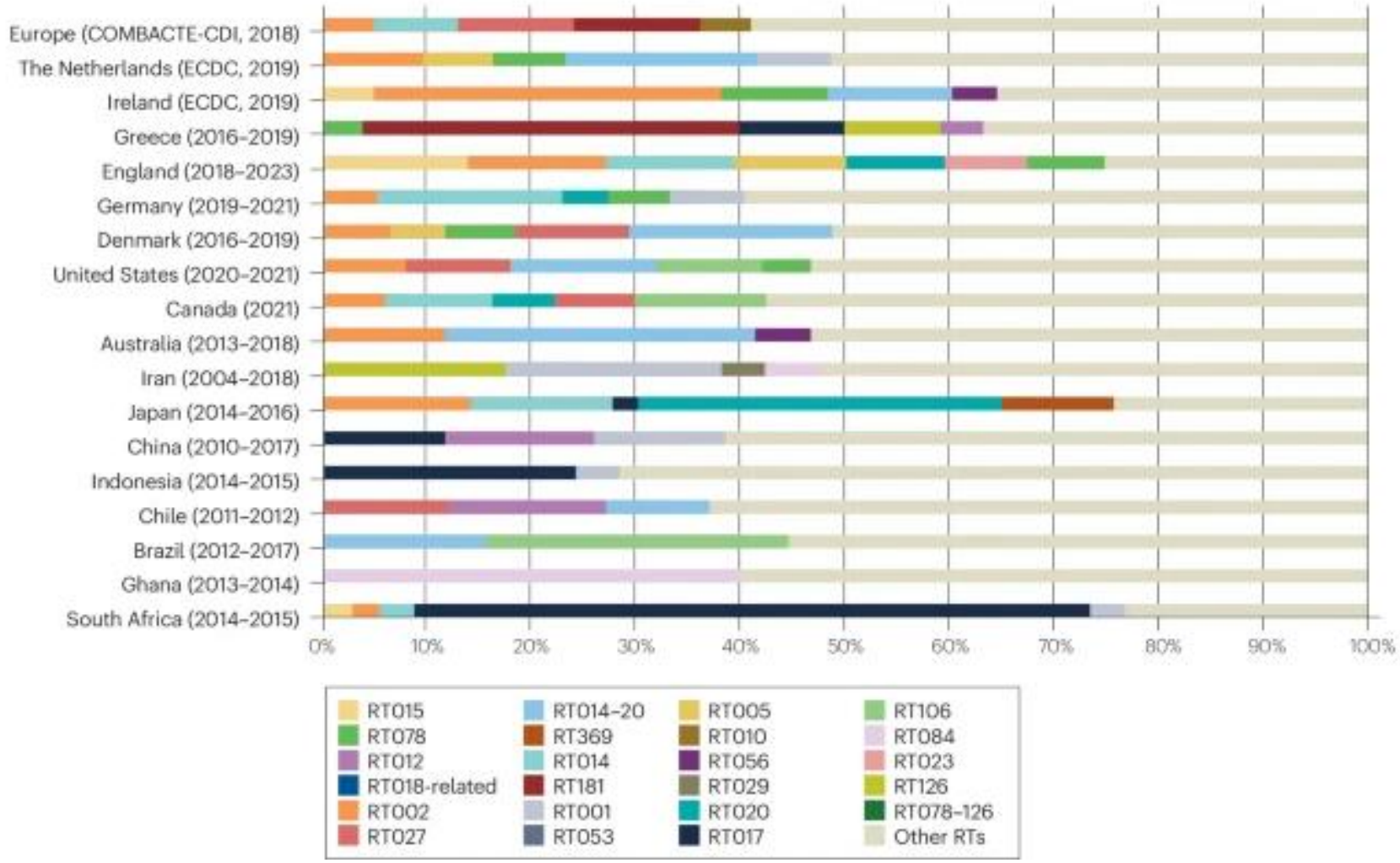
- 59 studies from 24 countries identified
  - About 430’000 CDI cases
  - 71% (42 out of 59) from North America and Europe
  - None from Africa or Southeast Asia

Continent	Incidence of CDI per 1000 Admissions [95% CI]	Incidence of CDI per 10,000 Patient-Days [95% CI]	Incidence of CDI per 100,000 Population [95% CI]
Eastern Mediterranean	1.13 [0.04; 3.64]	1.42 [0.55; 2.70]	-
Europe	2.84 [1.76; 4.18]	3.57 [2.73; 4.52]	36.03 [23.86; 50.68]
Latin America	1.69 [1.54; 1.84]	3.09 [2.82; 3.37]	-
North America	4.85 [4.07; 5.70]	6.23 [5.50; 7.00]	66.02 [1.05; 230.95]
Western Pacific	2.34 [1.68; 3.11]	3.59 [3.10; 4.12]	16.74 [4.30; 37.29]
Pooled Incidence Rate	2.56 [2.18; 2.96]	3.90 [3.34; 4.51]	43.49 [19.51; 76.96]

Akorful et al. Infect Dis Rep 2025 Apr 14;17(2):31.

World Health Organization

C. difficile ribotypes vary across regions (very limited data from LMICs)



Chilton et al. Nature Reviews Microbiology volume 24, pages215–232 (2026)

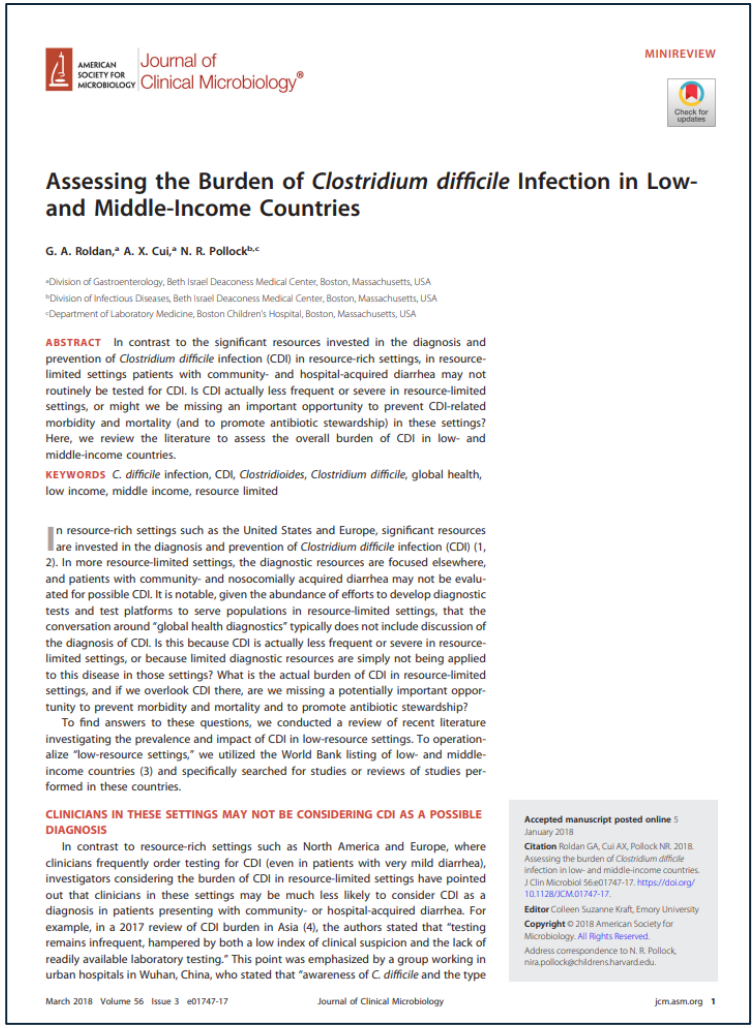
https://www.nature.com/articles/s41579-025-01242-2

World Health Organization

The burden of CDI in LMICs may be underestimated

“Clinicians in these settings may not be considering CDI as a possible diagnosis”

“When you look for CDI, you find it, in rates that are similar to those in the United States and Europe”



AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

MINIREVIEW

Assessing the Burden of *Clostridium difficile* Infection in Low- and Middle-Income Countries

G. A. Roldan,[a] A. X. Cui,[a] N. R. Pollock[b,c]

[a]Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
[b]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
[c]Department of Laboratory Medicine, Boston Children's Hospital, Boston, Massachusetts, USA

ABSTRACT In contrast to the significant resources invested in the diagnosis and prevention of *Clostridium difficile* infection (CDI) in resource-rich settings, in resource-limited settings patients with community- and hospital-acquired diarrhea may not routinely be tested for CDI. Is CDI actually less frequent or severe in resource-limited settings, or might we be missing an important opportunity to prevent CDI-related morbidity and mortality (and to promote antibiotic stewardship) in these settings? Here, we review the literature to assess the overall burden of CDI in low- and middle-income countries.

KEYWORDS *C. difficile* infection, CDI, *Clostridioides*, *Clostridium difficile*, global health, low income, middle income, resource limited

In resource-rich settings such as the United States and Europe, significant resources are invested in the diagnosis and prevention of *Clostridium difficile* infection (CDI) (1, 2). In more resource-limited settings, the diagnostic resources are focused elsewhere, and patients with community- and nosocomially acquired diarrhea may not be evaluated for possible CDI. It is notable, given the abundance of efforts to develop diagnostic tests and test platforms to serve populations in resource-limited settings, that the conversation around “global health diagnostics” typically does not include discussion of the diagnosis of CDI. Is this because CDI is actually less frequent or severe in resource-limited settings, or because limited diagnostic resources are simply not being applied to this disease in those settings? What is the actual burden of CDI in resource-limited settings, and if we overlook CDI there, are we missing a potentially important opportunity to prevent morbidity and mortality and to promote antibiotic stewardship?

To find answers to these questions, we conducted a review of recent literature investigating the prevalence and impact of CDI in low-resource settings. To operationalize “low-resource settings,” we utilized the World Bank listing of low- and middle-income countries (3) and specifically searched for studies or reviews of studies performed in these countries.

CLINICIANS IN THESE SETTINGS MAY NOT BE CONSIDERING CDI AS A POSSIBLE DIAGNOSIS

In contrast to resource-rich settings such as North America and Europe, where clinicians frequently order testing for CDI (even in patients with very mild diarrhea), investigators considering the burden of CDI in resource-limited settings have pointed out that clinicians in these settings may be much less likely to consider CDI as a diagnosis in patients presenting with community- or hospital-acquired diarrhea. For example, in a 2017 review of CDI burden in Asia (4), the authors stated that “testing remains infrequent, hampered by both a low index of clinical suspicion and the lack of readily available laboratory testing.” This point was emphasized by a group working in urban hospitals in Wuhan, China, who stated that “awareness of *C. difficile* and the type

Accepted manuscript posted online 5 January 2018
Citation Roldan GA, Cui AX, Pollock NR. 2018. Assessing the burden of *Clostridium difficile* infection in low- and middle-income countries. J Clin Microbiol 56:e01747-17. https://doi.org/10.1128/JCM.01747-17.
Editor Colleen Suzanne Kraft, Emory University

Address correspondence to N. R. Pollock, nira.pollock@childrens.harvard.edu.

Roldan et al. J Clin Microbiol. 2018 Feb 22;56(3):e01747-17.

World Health Organization

No test for *C. difficile* included in the 2023 version of the WHO EDL

But added in the 2025 edition

https://edl.who-healthtechnologies.org/

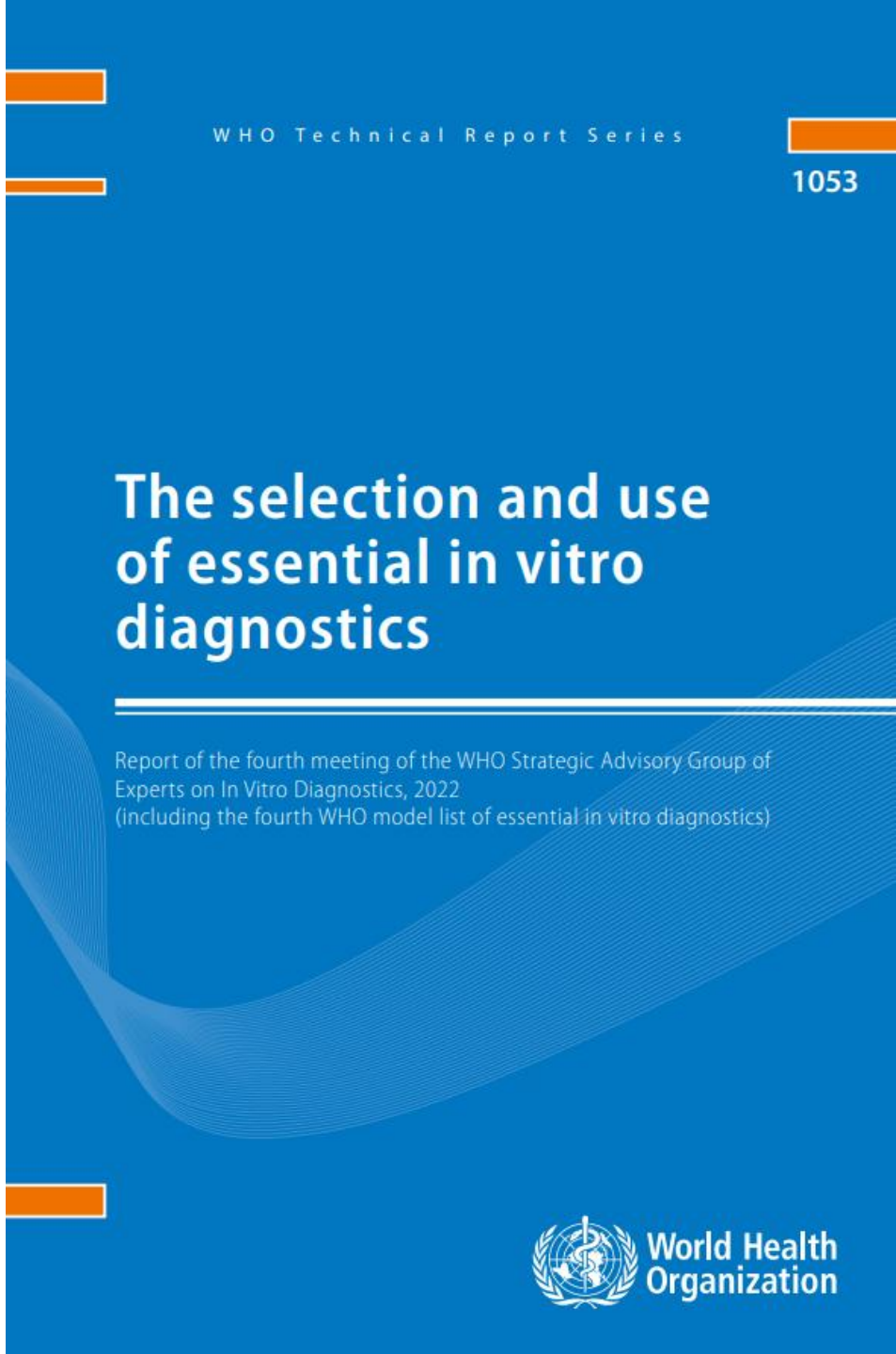
Clostridioides difficile combined Glutamate Dehydrogenase antigen and toxins A and B

Clostridioides difficile combined Glutamate Dehydrogenase antigen and toxins A and B

Clostridioides difficile infection

Setting	Assay format
Laboratory	Lateral flow RDT

https://iris.who.int/server/api/core/bitstreams/69fa4fa6-8830-4e00-a6fc-63257b677f65/content



Anaerobe

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VSI: ICDS2024 – 8th International C. difficile Symposium

Clostridioides difficile is a bacterial priority pathogen

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[b] University of Houston College of Pharmacy, Houston, TX, USA
[c] School of Biomedical Sciences, The University of Western Australia and Department of Microbiology, PathWest Laboratory Medicine (EA), Queen Elizabeth II Medical Centre, Nedlands, 6009, Western Australia, Australia
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ARTICLE INFO

Handling Editor: Sandra Janezic

1. Introduction to the topic

The anaerobic gram-positive enteropathogen *Clostridioides difficile* poses a heavy burden on patients, the healthcare system, the economy and society. Despite introduction of important therapeutic agents such as bezlotoxumab and two microbiome restoration therapies to prevent *C. difficile* infection (CDI) recurrence over the last decade, all are employed in addition to standard-of-care antimicrobial therapy [1–5] and having efficacious antimicrobial therapy is therefore key to patient safety. However, CDI is intimately associated with antimicrobial resistance (AMR), both regarding antimicrobials used to treat other infections that also predispose subjects to CDI, as well as resistance to antimicrobials used to treat CDI [6–8].

The World Health Organization (WHO) recently updated their bacterial priority pathogen list intended to 'guide investment in R&D and form the basis for activities related to surveillance and control of antibacterial resistance' [9]. This list categorizes bacterial pathogens into groups of critical, high and medium importance. The list contains 24 pathogens, spanning 15 families of antimicrobial-resistant bacterial pathogens, but does not mention *C. difficile*. In 2019, a similar list of pathogens that pose AMR threats in the United States was published by the U.S. Centers for Disease Control and Prevention (CDC) and this list included *C. difficile* as an urgent threat [6], although the criteria for inclusion differed somewhat for these two lists. The criteria for inclusion in the WHO list included mortality, incidence, non-fatal health burden, transmissibility, preventability in health care setting and community, trend of resistance, treatability (including resistance), and the pipeline for novel treatment modalities.

Despite exclusion from the WHO bacterial priority pathogen list, we argue based on the WHO criteria that *C. difficile* is a pathogen requiring prioritization for surveillance and control (Table 1 and text below). The present manuscript stems from a panel discussion with leaders in the field of diagnosis, treatment and research on *C. difficile* that took place during the 8th International *C. difficile* Symposium in Bled, Slovenia, on September 19, 2024. We summarize these discussions by briefly reviewing the current epidemiology and impact of CDI worldwide, the development of resistance in agents used or proposed to treat CDI, the pipeline of new drugs for treating CDI and the challenges stemming from *C. difficile* being a One Health pathogen.

2. Epidemiological developments are difficult to forecast

The emergence of the epidemic *C. difficile* strain, PCR ribotype (RT) 027, in North America in the early 2000s heralded a dramatic shift in the epidemiology of CDI, with a marked increase in the incidence and severity of CDI over the subsequent decade [10]. By 2011, over 450,000 incident CDI episodes were estimated to have occurred annually in the US [11], with the incidence of disease highest in older persons [12]. Between 2011 and 2017, the estimated national incidence of CDI dropped from 154.9 to 143.6/100,000 population, representing an adjusted decrease of 24 % [11]. This decrease was driven by a decline in healthcare-associated CDI that persisted through the period of the COVID-19 pandemic, as suggested by a 65 % decrease in the number of hospital-onset CDI events reported between 2015 and 2023 in the USA [13], though practices during the pandemic are difficult to assess. Similarly, among adult patients in Canada, the national rate of

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Available online 25 April 2025

World Health Organization

WHO BPPL 2024 Impact: Essential for research, investment, and public health action.

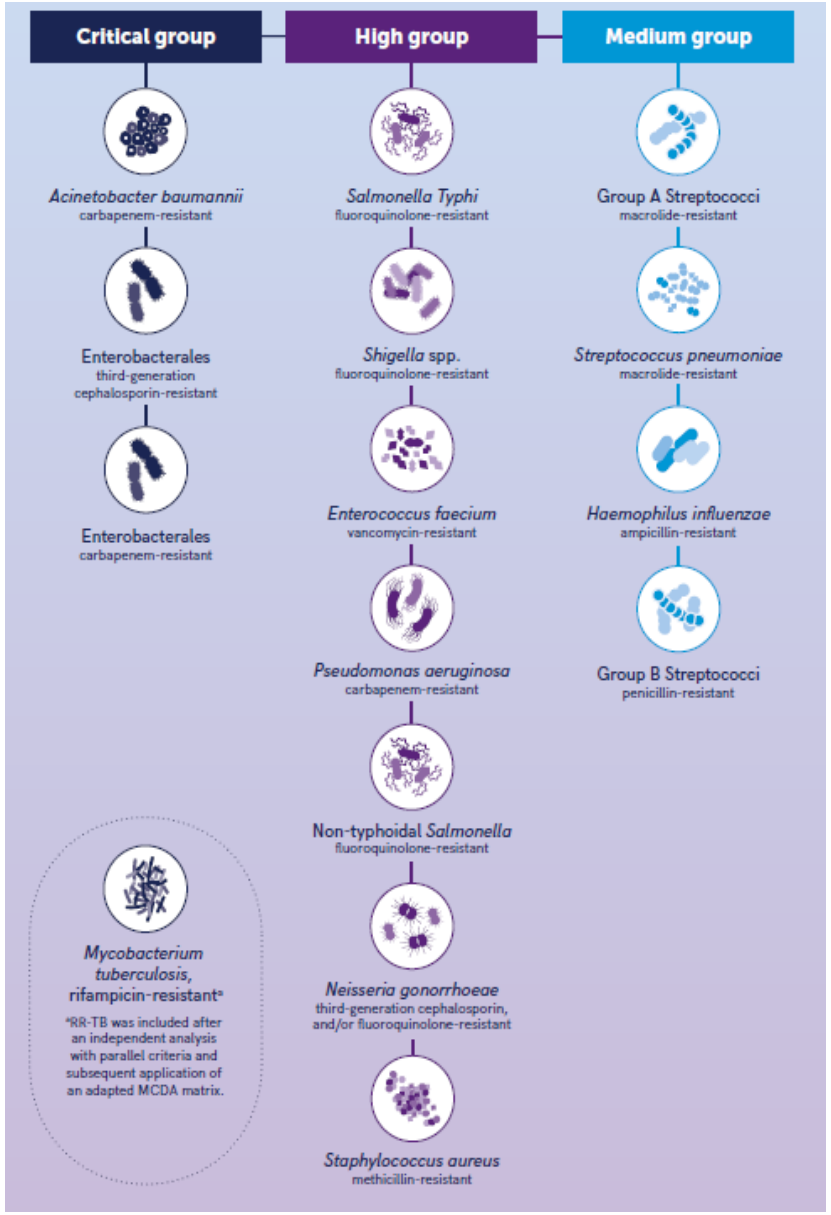
Priority Pathogens: 15 families categorized by critical, high, and medium priority.

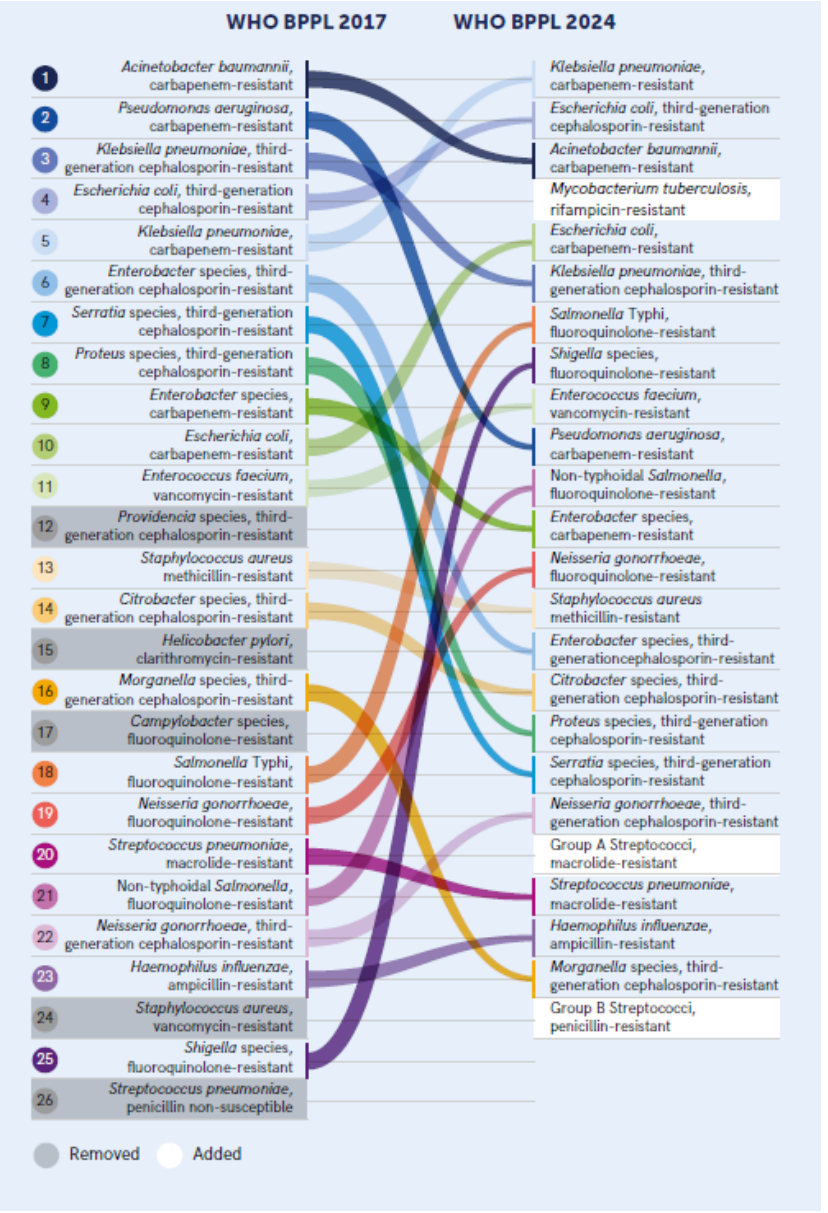
Highlights:

- Focus on LMICs, prioritizing tailored interventions.
- Urgency due to resistance profiles, limited access, and innovation in the pipeline, and the burden and global health impact.

Contextualization is essential

World Health Organization





Methods: Pathogens updates

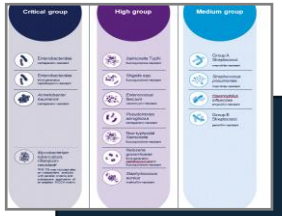
World Health Organization

25 pathogens

Removed from 2017 BPPL

- Clarithromycin-resistant *Helicobacter pylori*
- Fluoroquinolone-resistant *Campylobacter* spp.
- Penicillin-non-susceptible *Streptococcus pneumoniae*
- Third-generation cephalosporin-resistant *Providencia spp.*
- Vancomycin-intermediate and -resistant *Staphylococcus aureus*

24 pathogens



Added in BPPL 2024

- Macrolide-resistant *Group A* Streptococci
- Penicillin-resistant *Group B* Streptococci
- Macrolide-resistant *Streptococcus pneumoniae*
- Rifampicin-resistant TB (RR-TB)-(not new but this time is defined as a Abx-pathogen combination)

Methods: Criteria updates

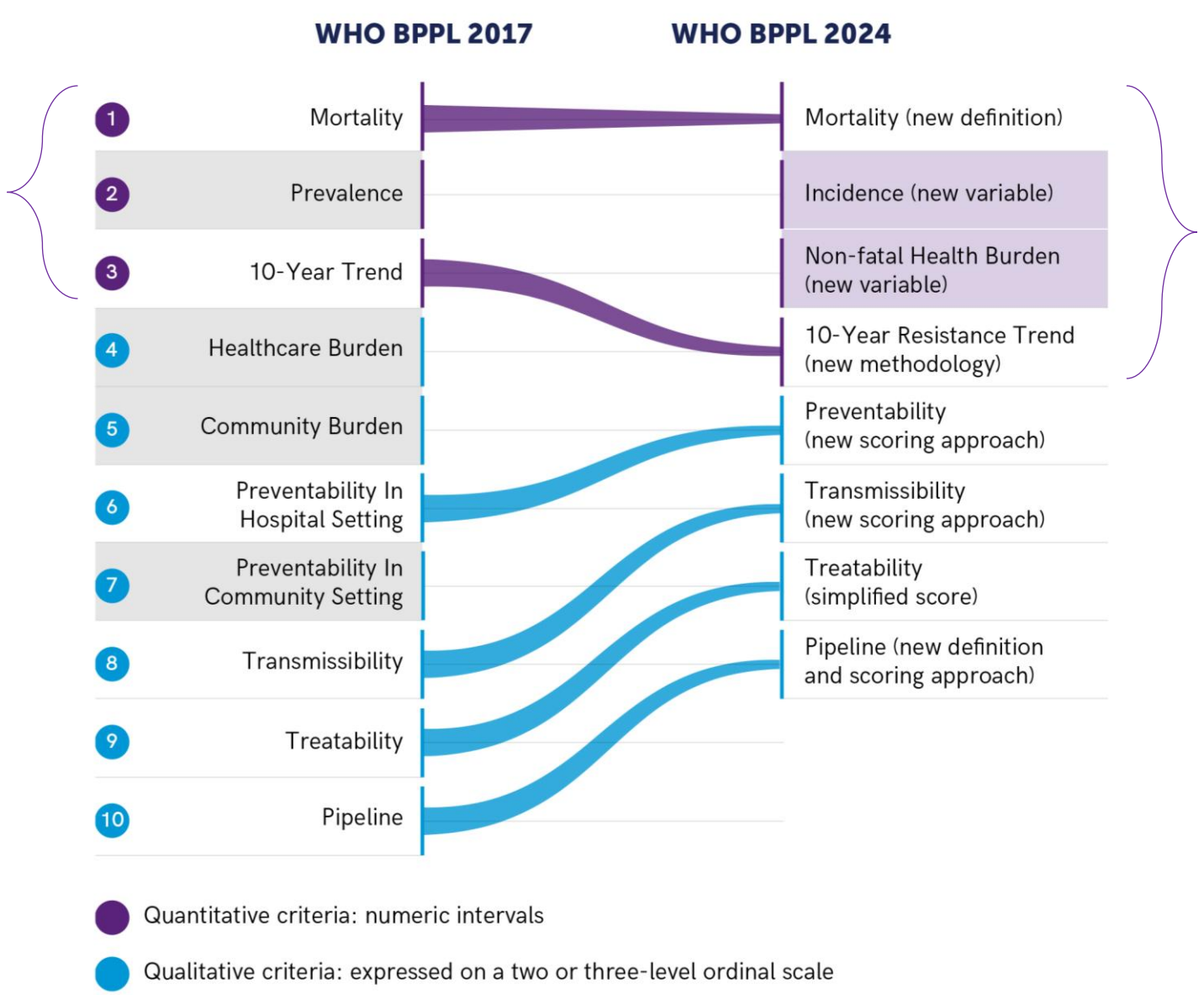
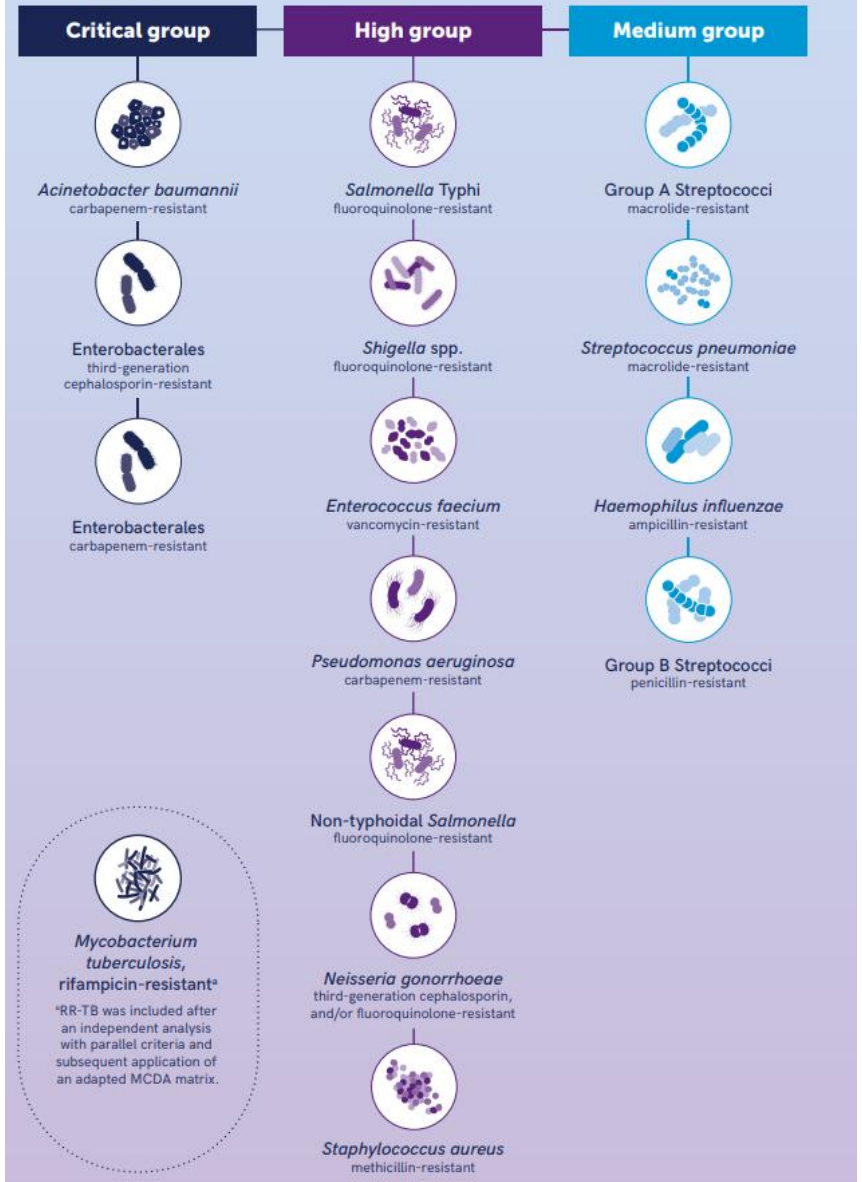


Fig. 1. WHO Bacterial Priority Pathogens List, 2024 update



Criterion	Definition	Scoring system			Survey score*
Mortality	Case Fatality Ratio (Pooled prevalence of all-cause mortality (%) among patients with infections caused by antibiotic-resistant pathogens)	>30%			High
		21-30%			Medium-High
		11-20%			Medium
		5-10%			Medium-Low
		< 5%			Low
Incidence	Global incidence of cases per 1 million population (all ages, all sexes, associate to resistance)	> 10.000 cases per 1 mln population			High
		5001-10.000 cases per 1 mln population			Medium-High
		1001-5000 cases per 1 mln population			Medium
		100-1000 cases per 1 mln population			Medium-Low
		< 100 cases per 1 mln population			Low
Non-fatal health burden	Years Lived with Disability (YLDs) per million inhabitants, including all ages and all sexes, attributable to infections by each resistant pathogen	> 1.5 YLD per 1 mln population			High
		1.1-1.5 YLD per 1 mln population			Medium-High
		0.51-1 YLD per 1 mln population			Medium
		0.11-0.5 YLD per 1 mln population			Medium-Low
		< 0.1 YLD per 1 mln population			Low
Trend of resistance	10-year trend of resistance rate data, where resistant rate is defined as percentage of resistant isolates out of the total number of isolates tested	Increasing trend in ≥ 3 WHO regions (or in most regions with data)			Level 5
		Increasing trend in 2 WHO regions			Level 4
		Increasing trend in one WHO region			Level 3
		Stable trend in all WHO regions			Level 2
		Significantly decreasing trend in at least one WHO region, with no increase in any of the other regions			Level 1
Trans-missibility	Evidence of transmission of the AMR pathogen among different pathways. Two distinct domains considered: Human-to-human transmission: outbreak capability in healthcare/ community settings Transmission between humans and animal, food, and environment compartments	Well documented (OC)	and	High (TP)	High
		Well documented (OC)	and	Moderate (TP)	Medium-High
		Moderately documented (OC)	and	High (TP)	
		Poorly documented (OC)	and	High (TP)	Medium
		Well documented (OC)	and	Low (TP)	
		Moderately documented (OC)	and	Moderate (TP)	
		Moderately documented (OC)	and	Low (TP)	Medium-Low
		Poorly documented (OC)	and	Moderate (TP)	
		Poorly documented (OC)	and	Low (TP)	Low
Preventability in health care setting and community	The existence and effectiveness of preventive measures in containing the transmission of the target AMR pathogen and reducing disease burden. This criterion encompasses two distinct aspects of preventability: 1. Individual-based infectious preventive and control (IPC) measures, including hand hygiene and standard and transmission-based precautions (such as contact, isolation, and barrier precautions). 2. Community-based IPC measures, including vaccination, water sanitation, access to health services, and food safety.	IPC Measures:			> 5 points: High
		• Effective and sufficient		2	
		• Recommended, existing, and effective		1	
		• Not universally recommended due to limited efficacy/feasibility		0	
		Decolonization/Chemoprophylaxis:			5 points: Medium-High
		• Existing and effective		2	
		• Existing and partly effective or restricted to high-risk population		1	4 points: Medium
		• Not existing or non-effective		0	
		Public Health Interventions in Community:			3 points: Medium-Low
		• Existing and effective OR not needed		2	
		• Existing and partly effective		1	< 3 points: Low
		• Not existing or non-effective		0	

Criterion	Definition	Scoring system		Survey score
Treatability	Composite criterion which encompasses: number of molecule(s) listed in the guidelines, their efficacy ranking (1st or lower lines of treatment versus last resort), safety profile, availability of oral/OPAT formulation, presence of pediatric formulation, concomitant resistance, and cost.	Number of 1st line option(s) recommended by evidence-based guidelines:		> 12 points: High
		• One antibiotic class	2	
		• Two or more antibiotic classes	2 for each option	
		Concomitant resistance reported for 1st line option(s):		10-11 points: Medium-High
		• Greater than 20%	-1 for each option	
		• 20% or less	0	
		Availability of alternative option(s) for the most typical infectious syndrome:		8-9 points: Medium
		• No option available OR option(s) available but with a poor toxicity profile AND/OR recommended ONLY in combination	-1	
		• Option(s) available with a fair toxicity profile AND recommended in monotherapy BUT co-resistance > 20%	0	
		• At least one alternative available with a fair toxicity profile AND recommended also in monotherapy AND co-resistance ≤ 20%	1	
		Formulations:		6-7 points: Medium-Low
		• Availability of oral option(s):	1	
		• Availability of OPAT option(s):	1	
		• Available option(s) approved or tested for pediatric population	1	
		Accessibility (cost)		< 5 points: Low
		• High cost[a]	-1	
		• Low cost[b]	0	
Pipeline	The criterion assesses the extent to which the antibacterial pipeline, both currently and over the next 5-7 years, can effectively meet clinical needs for treating each resistant bacterial pathogen. The criterion considers the number of newly approved antibiotics in the last 5-7 years, as well as the number of candidates in the clinical developmental pipeline that meet WHO innovation criteria, such as new chemical classes, novel targets, and absence of cross-resistance. Additionally, it evaluates the availability of oral formulations for both the new candidates and those under development	**Unlikely:** The pathogen has no, or very limited number of potential active candidates in phase X according to WHO clinical pipeline analyses from 2017-2021. Pathogen has no, or very limited number, of candidates with ongoing market authorization application (MAA) and/or new drug application (NDA). No, or very limited number, newly approved antibiotics from July 2017 to 2022.		< 34 points: Unlikely
		Possible: The pathogen has one or more potential active candidates in phase X according to WHO clinical pipeline analyses from 2017-2021. Pathogen has one or more candidates with ongoing market authorization application (MAA) and/or new drug application (NDA). One or more newly approved antibiotics from July 2017 to 2022.		47-34 points: Possible
		Likely: The pathogen has a robust pipeline with multiple potential active candidates in phase X according to WHO clinical pipeline analyses from 2017-2021. Pathogen has multiple candidates with ongoing market authorization application (MAA) and/or new drug application (NDA). Several newly approved antibiotics from July 2017 to 2022. **Note:** A scoring matrix was created for this criterion, and it is presented in the annex for reference.		47 points: Likely

World Health Organization

Antibiotic resistance characteristics of *C. difficile* to CDI treatment agents

Antibiotic (class)	Mode of action	Resistance mechanism	Genes involved	Spread
CDI treatment antimicrobials				
Metronidazole (nitromidazole)	Nucleic acid synthesis	Plasmid-mediated	pCD-METRO[104]	Uncommon
		Haem-dependent	*PnimB*^{G} promoter variant leading to constitutive transcription of *nimB:* production of a haem-binding flavoenzyme that degrades nitroimidazoles[106,107]	Uncommon, however, variation in susceptibility testing methods may have led to underestimation
Vancomycin (glycopeptide)	Bacterial cell wall synthesis	Not well understood	Possible *vanSR*, *vanG*, *vanA*, *vanW* and *vanZ* involvement, possibly plasmid-mediated (Tn*1549*)	Uncommon, some recent reports of elevated MICs
Fidaxomicin (macrolide)	RNA polymerase	Mutations in *RpoB and RpoC*	Ala1143Leu/Gly/Asp in *RpoB*[118,119,120], Gln1149Pro and in *RpoC* leading to Arg89Gly[120]	Very uncommon

Chilton et al. Nature Reviews Microbiology volume 24, pages215–232 (2026)

https://www.nature.com/articles/s41579-025-01242-2

Treatment of *Clostridoides difficile*

AI-generated illustration created with Microsoft Copilot (2026)

World Health Organization

Two options for CDI on the WHO Model List of Essential Medicines (added in 2017)

EML **Model List of Essential Medicines**

export EN FR

Found 2 recommendations for 2 medicines and 0 therapeutic equivalents

clear

Intestinal infections due to Clostridioides difficile ×

Metronidazole General information

Section	Indications
Access group antibiotics Oral > Liquid: 200 mg per 5 mL (as benzoate) Local > Rectal > Suppository: 500 mg; 1 g Parenteral > General injections > unspecified: 500 mg per 100 mL in vial Oral > Solid > tablet: 200 mg; 250 mg; 400 mg; 500 mg	First choice Intestinal infections due to Clostridioides difficile

Vancomycin General information

Section	Indications
Watch group antibiotics Oral > Solid > capsule: 125 mg (as hydrochloride); 250 mg (as hydrochloride)	Second choice Intestinal infections due to Clostridioides difficile

https://list.essentialmeds.org/?indication=425

World Health Organization

33. Intra-abdominal infections – *Clostridioides difficile* infection

Key messages

- Most cases of *Clostridioides difficile* infection occur in patients with current or recent antibiotic use. Good antibiotic prescribing practices – avoidance of antibiotics when not needed, preference for Access antibiotics wherever possible – are key for the control of *Clostridioides difficile* infection.
- If *Clostridioides difficile* infection is confirmed or suspected, all antibiotics that are not necessary should be stopped.
- Use oral antibiotics to treat *Clostridioides difficile* infection wherever possible.
- Adopt infection control measures to prevent transmission.
- *Clostridioides difficile* diarrhoea my resolve slowly over days, but a clinical deterioration of a patient on appropriate antibiotics should lead to escalation of treatment and a surgical referral.

Other relevant WHO resources (please check regularly for updates)

- Infection prevention and control – health topic *(332)*.

Clostridioides difficile infection (CDI)

Intra-abdominal infection

Definition

Infection of the colon caused by the bacterium *C. difficile* that occurs mostly in patients with current/recent antibiotic use and with regular exposure to healthcare settings

Diagnosis

Clinical Presentation

Usually diarrhea (≥3 unformed/liquid stools in 24 hrs or more than normal for individual) with no other plausible cause +/- abdominal pain, cramping and fever

Severe cases (e.g. pseudomembranous colitis):
- Severe abdominal pain, high fever, organ dysfunction
- Toxic megacolon presents with signs of acute surgical abdomen and/or sepsis (diarrhea is often absent)

Microbiology Tests

- Consider testing symptomatic patients with no other plausible reason for diarrhea especially if recent or current exposure to antibiotics
- Currently no single test to diagnose CDI is completely reliable and the best approach remains controversial

Two commonly used approaches:

1. Start with highly sensitive test to detect *C. difficile*, if positive follow with a test to confirm toxin production
   - If toxin test negative: Consider *C. difficile* colonization
2. Perform two tests simultaneously, one to detect the presence of *C. difficile* and one to detect toxin production
   - Concordant results can reliably confirm (both tests positive) or exclude (both tests negative) infection
   - If results conflict and patient is symptomatic, treatment should be based on the pre-test probability of *C. difficile* infection

Important: in case of confirmed CDI, do not repeat testing during the same episode and do not test to confirm the resolution of the infection at the end of treatment

Other Laboratory Tests

Mild cases: Not usually needed

Severe cases:
- White blood cell count
- Creatinine and electrolytes

Imaging

Usually not needed unless a complication is suspected; in these cases, consider abdominal CT

Pathogen

C. difficile
- Gram-positive spore-forming bacterium widely present in the environment that can be acquired through ingestion of spores
- Infection can be caused by strains producing toxins when the intestinal mucosa of the colon is inflamed and disrupted

NAP1/027
- *C. difficile* toxigenic strain with a particular virulence that caused outbreaks in recent years especially in North America

Treatment

Clinical Considerations

- **Discontinue any other antibiotics except those treating *C. difficile* infection as soon as possible and adopt infection control measures to prevent transmission**
- Always recommend rehydration in patients with diarrhea; anti-diarrheal drugs not routinely necessary
- Diarrhea may resolve slowly over days, but clinical deterioration of a patient on appropriate treatment should precipitate escalation of treatment and a surgical referral

Antibiotic Treatment Duration

10 days

Antibiotic Treatment

Refers to a first episode, not recurrences (within 8 weeks of previous episode)

All dosages are for normal renal function

First Choice

ACCESS: Metronidazole 500 mg q8h **ORAL**

Second Choice

WATCH: Vancomycin 125 mg q6h **ORAL**

***In severe cases**: Oral vancomycin is preferred; vancomycin dose can be increased to 500 mg q6h and can be given in combination with IV metronidazole*

Global Antimicrobial Resistance and Use Surveillance System (GLASS) report

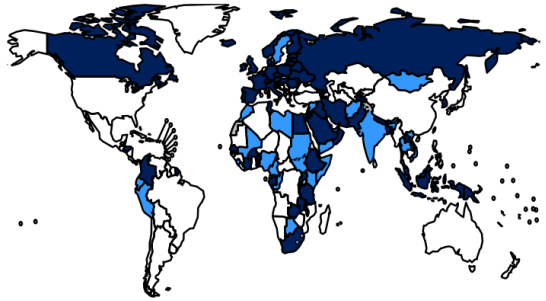
Antibiotic use data for 2022

World Health Organization

GLASS-AMU dashboard

Country participation and data contextual | Use by antimicrobial classes | Antibiotic use by AWaRe | Antibiotic use by ATC3

Antibiotic use by route of administration | Antimicrobial use by ATC4



Country	Type of data	Health [a,b]
Armenia	Import/Local manufacturing	**Level:** Tot **Sector:** Tot
Austria	Dispensing/Reimbursement	**Level:** Com, Hos **Sector:** Pub
Bahrain	Central drug store	

World Health Organization

Antimicrobial use data

National AMU aims to collect data for all registered antimicrobial products in the country

Product A Product B

List of products with all the information to uniquely identify the product and correctly apply the ATC/DDD methodology

- Product ID
- Number of units in each package
- Strength per unit of product
- Route of administration
- Substance
- ATC code and DDD

Use express in number of packages utilized—whether imported, manufactured, distributed, dispensed, or reimbursed—within the **population** in the specified **setting** over the course of the **year**

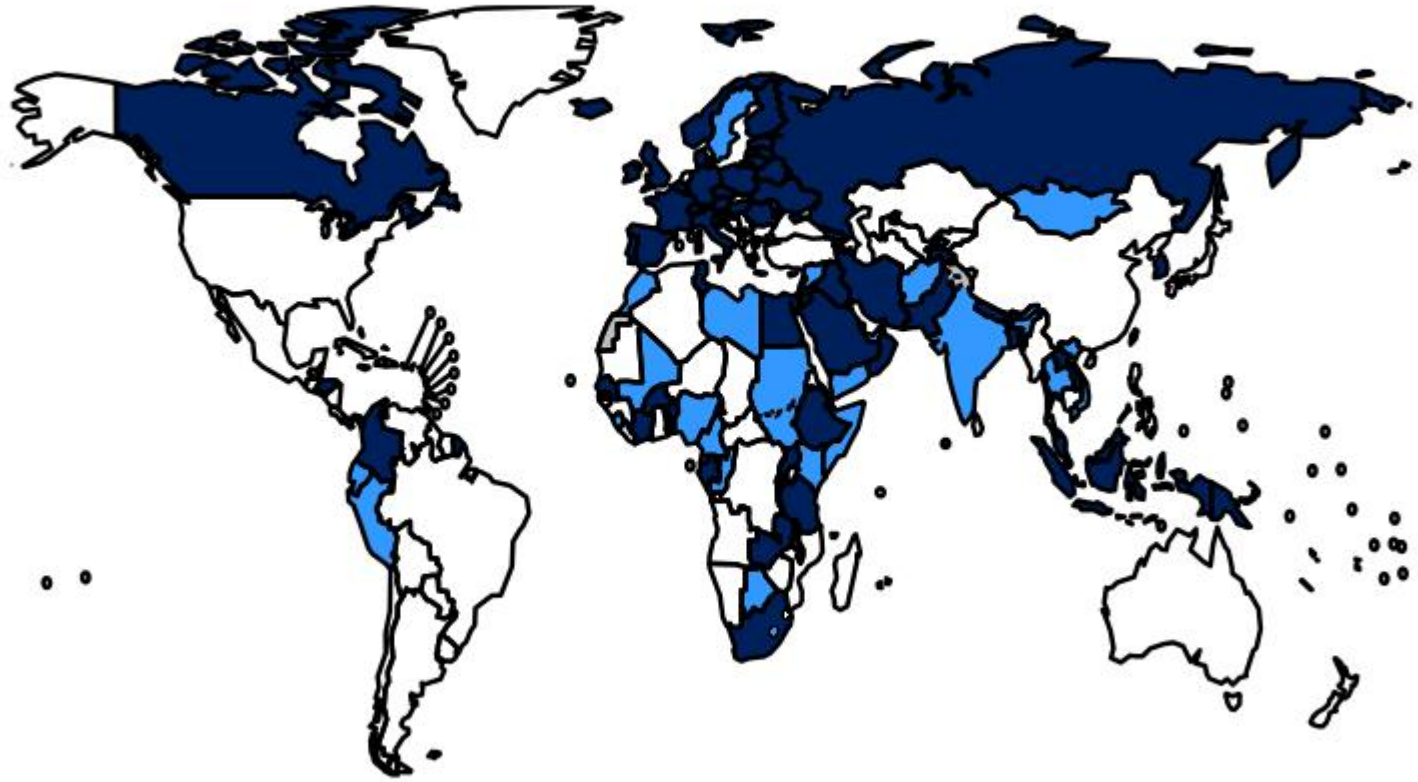
The **volume of each product used**, expressed in **DDDs**, is calculated by multiplying the amount of active substance per product by the number of packages used, and dividing the result by the corresponding DDD value

$$\text{Number of DDD}_{ATCi} = \frac{\textit{Total consumed quantities}_{ATCi}}{\textit{DDD}_{ATCi}}$$

Use by ATC substance: the consumption in DDDs for each product is aggregated and reported according to its ATC substance code

World Health Organization

Global AMU data



Enrolled and data provided
Enrolled but no data provided
Not applicable
Not enrolled

World Health Organization

GLASS-AMU data (2023) for possible CDI treatments

	CTAS with data	Oral fidaxomicin		Oral Vancomycin		Any of the two	
	n	n	%	n	%	n	%
Global	56	24	43%	24	43%	29	52%
African Region	6	0	0%	0	0%	0	0%
Eastern Mediterranean Region	7	2	29%	2	29%	2	29%
European Region	30	20	67%	16	53%	21	70%
Region of the Americas	3	1	33%	2	67%	2	67%
South-East Asia Region	3	0	0%	1	33%	1	33%
Western Pacific Region	7	1	14%	3	43%	3	43%
High Income	33	24	73%	22	67%	27	82%
Upper Middle Income	11	0	0%	1	9%	1	9%
Lower Middle Income	11	0	0%	1	9%	1	9%
Low Income	1	0	0%	0	0%	0	0%

What about the pipeline ?

AI-generated illustration created with Microsoft Copilot (2026)

World Health Organization

Among recent approvals we found three NTAs targeting *Clostridioides difficile* infections; they are the first NTAs ever approved

Non-traditional antibacterial agents that gained market authorization between 1 July 2017 and 15 February 2025

Name (trade name)	Marketing authorization holder(s)	Approved by (date)	Antibacterial class	Route of administration	Approved indication/s	Pathogen	Reference (product information)
SER-109 (VOWST (fecal microbiota spores, live-brpk)	Seres Therapeutics	US-FDA 04/2023	Live biotherapeutic product	PO	Recurrent/ refractory diarrhoea prevention [a]	*C. difficile*	Vowst
BB128 (Biomictra faecal microbiota)	BiomeBank	TGA (Aus) 11/2022	Live biotherapeutic product	Endoscopic delivery or enema	Recurrent/ refractory diarrhoea prevention [a]	*C. difficile*	Biomictra
RBX2660 (Rebyota (fecal microbiota, live-jslm)	Ferring Pharmaceuticals	US-FDA 11/2022	Live biotherapeutic product	Enema	Recurrent/ refractory diarrhoea prevention [a]	*C. difficile*	Rebyota
Ftortiazinon (fluorothyazinone) (to be administered with cefepime)	Gamaleya Research Institute of Epidemiology and Microbiology	Ministry of Health Russian Federation, 2024	Anti-virulence (thyazinone type III secretion system inhibitor)	PO	cUTI	*E. coli*, *K. pneumoniae* and *P. aeruginosa*	Ftortiazinon

TGA - Therapeutic Goods Administration

[a] Prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

World Health Organization

In clinical development we found 11 NTAs and 4 traditional (antibiotics) targeting CDIs

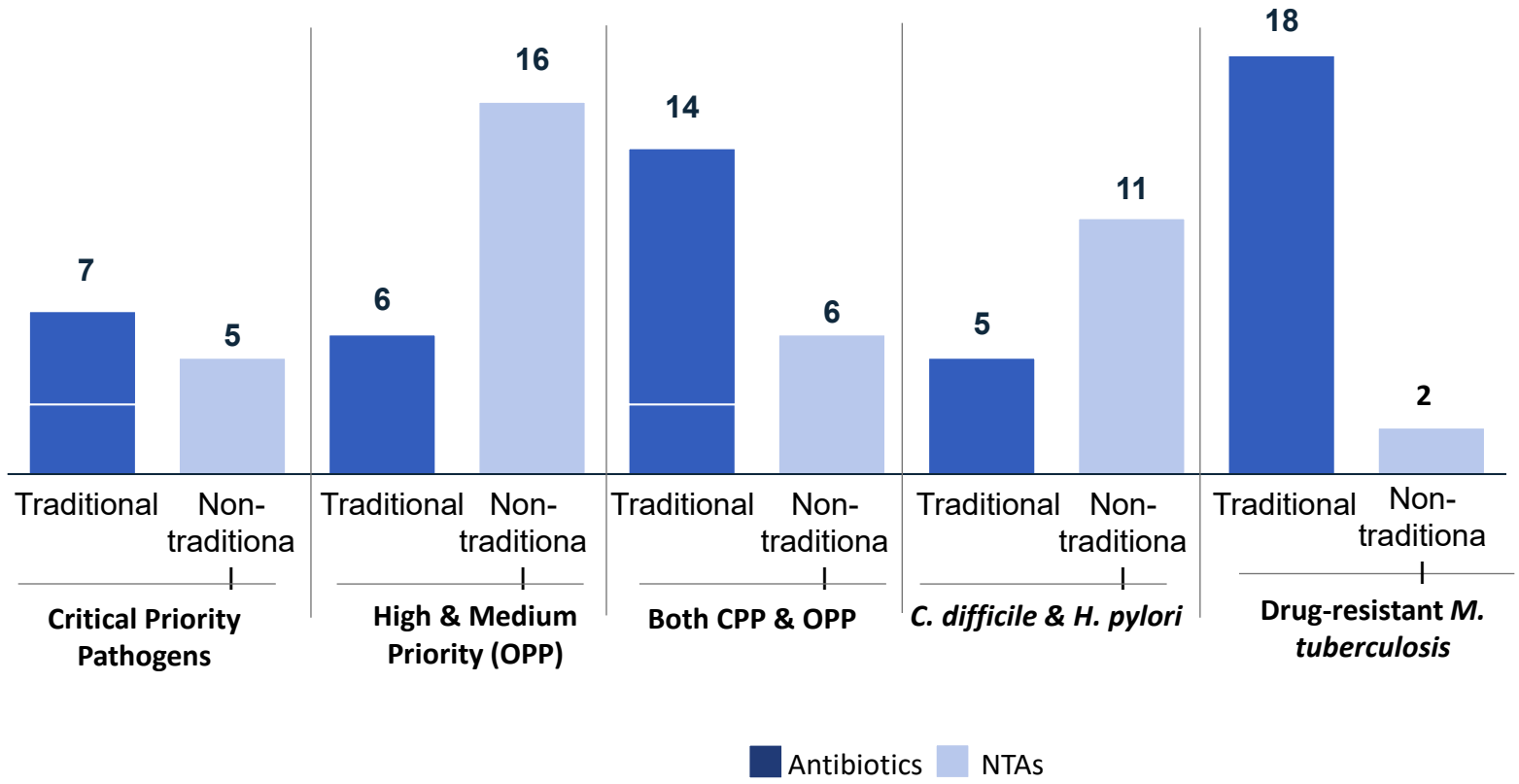
Activity of NTAs (40)

- 27 target BPPs *(except TB)*
- 11 target *C. difficile*
- 0 *target H. Pylori*
- 2 target TB

Activity of traditional products (50)

- **27** target BPPs *(except TB):* 17 active against at least 1 Gram-neg.
- **4** *C. difficile*
- **1** *H. Pylori*
- **18** (40%) target TB

Activity of antibacterial agents



World Health Organization

Source: 2025 Antibacterial agents in clinical and preclinical development: an overview and analysis

In the clinical pipeline, 4 antibiotics are being developed for the treatment of *C. difficile*

Name (synonym)	Phase	Antibiotic class	Route of administration	Developer	Pathogen	Innovation			
						NCR	CC	T	MoA
Ridinilazole	3[a]	Bis-benzimidazole	PO, not absorbed	Summit Therapeutics	*C. difficile*	✓	✓	✓	✓
CRS3123	2	Diaryldiamine	PO, not absorbed	Crestone/NIAID	*C. difficile*	✓	✓	✓	✓
Ibezapolstat (ACX-362E)	2	DNA polymerase IIIC inhibitor	PO, not absorbed	Acurx Pharmaceuticals	*C. difficile*	✓	✓	✓	✓
MGB-BP-3	2	Distamycin (DNA minor groove binder)	PO, not absorbed	MGB Biopharma	*C. difficile*	?	✓	✓	✓
Rifasutenizol (TNP-2198)	3	Rifamycin- nitroimidazole conjugate	PO, not absorbed	TenNor Therapeutics	*H. pylori*	-	-	-	-

Innovation assessment: ✓ criterion fulfilled; ? inconclusive data; - criterion not fulfilled.

CC: chemical class; CDIs: *C. difficile* infections; iv: intravenous; MoA: new mode of action; NCR: no cross-resistance; NIAID: National Institute of Allergy and Infectious Diseases; T: new target.

[a] Following negative results from the phase 3 study NCT04802837, the ongoing study in adolescents was terminated in alignment with corporate decision to pursue further development of drug candidate with a partner.

World Health Organization

In the clinical pipeline, we also identified 11 NTAs for the treatment of *C. difficile (1)*

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Pathogen
Antibodies	NCT06469151	AZD5148	1	mAb	IV	AstraZeneca	rCDI	*C. difficile*
	NCT04121169	IM-01	2	Chicken egg-derived anti-*C. difficile* polyclonal antibody	PO	ImmuniMed	CDI	*C. difficile*
Microbiome-modulating agents	NCT06306014	EXL01	1/2	Live biotherapeutic product	PO	Hospices Civils de Lyon, Exeliom Biosciences	rCDI	*C. difficile*
	NCT06237452	VE303	3	Live biotherapeutic product	PO	Vedanta Biosciences	rCDI	*C. difficile*
	NCT02865616	MET-2	1	Live biotherapeutic product	PO	NuBiyota/Takeda	rCDI	*C. difficile*
	NCT02981316	RBX7455	1	Live biotherapeutic product	PO	Ferring Pharmaceuticals (Rebiotix)	rCDI	*C. difficile*
	NCT04692181	SYN-004 (ribaxamase)	1b/2a	Antibiotic inactivator	PO	Theriva Biologics [a]	Prevention of CDI in allogeneic HCST	*C. difficile*
	NCT05911997	MTC01	1	Live biotherapeutic product	Endoscopic	Icahn School of Medicine at Mount Sinai	rCDI	*C. difficile*
	NCT04891965	ADS024 (formerly ART24)	1	Live biotherapeutic product	PO	Adiso Therapeutics [b]	rCDI	*C. difficile*
	NCT05201079	MBK-01	3	Live biotherapeutic product	PO	Mikrobiomik Healthcare Company	rCDI	*C. difficile*

Non-traditional antibacterials in clinical development for the treatment of *C. difficile (2)*

Category	Trial registration code	Name (synonym)	Phase	Antibacterial class	Route of administration	Developer	Clinical indication	Pathogen
Bacteriophages and phage-derived enzymes	NCT05330182	LMN-201	2/3	Phage endolysin and three toxin-binding proteins (5D, E3 and 7F)	PO	Lumen Bioscience	rCDI	*C. difficile*

Microbiome-modulating agents
Bacteriophages and phage-derived enzymes
Antibodies
Miscellaneous
Immune modulating agents

rCDI: recurrent Clostridium difficile infection.

[a]Formerly Synthetic Biologics.

[b]Formerly Artugen Therapeutics and Bacainn Therapeutics.

Clostridoides difficile infection and antimicrobial stewardship

Antibiotic exposure is the most important risk factor for CDI

World Health Organization

Antibiotics are among the most used medicines globally

Globally: estimated 34.3 billion DDD in 2023 for a population of 8.1 billion

- = about **4.2 DDD for every person in the world per year**

In some LMICs children **receive up to 25 antibiotic prescriptions** for respiratory tract infection or fever **during their first 5 years of life**

- Most of them inappropriate

World Health Organization

Klein et al. Proc Natl Acad Sci U S A. 2024 Dec 3;121(49):e2411919121.
Fink et al. Lancet Infect Dis. 2020 Feb;20(2):179-187.

There is large variation in overall antibiotic use among and within countries

The causes of the variation are incompletely understood

World Health Organization

AWaRe : Antibiotics are categorized into three groups

Essential Access, Watch and Reserve antibiotics need to be accessible and affordable for those who need them!

"Last-resort" options against MDRO

Higher "resistance potential"

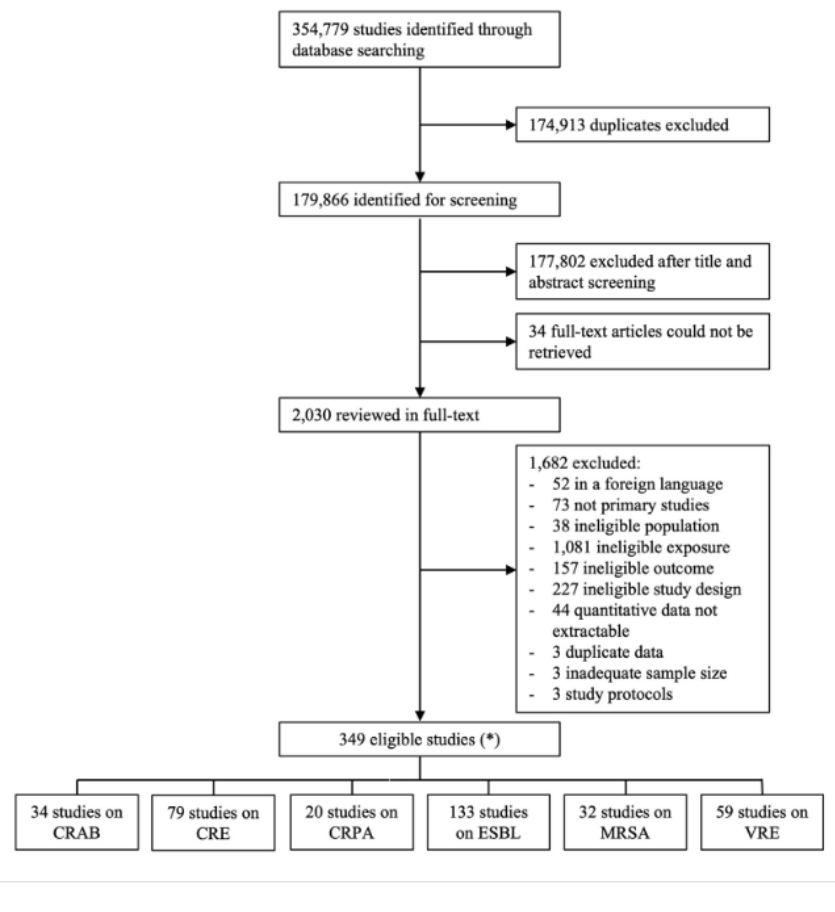
Often 1st or 2nd choice for common infectious syndromes

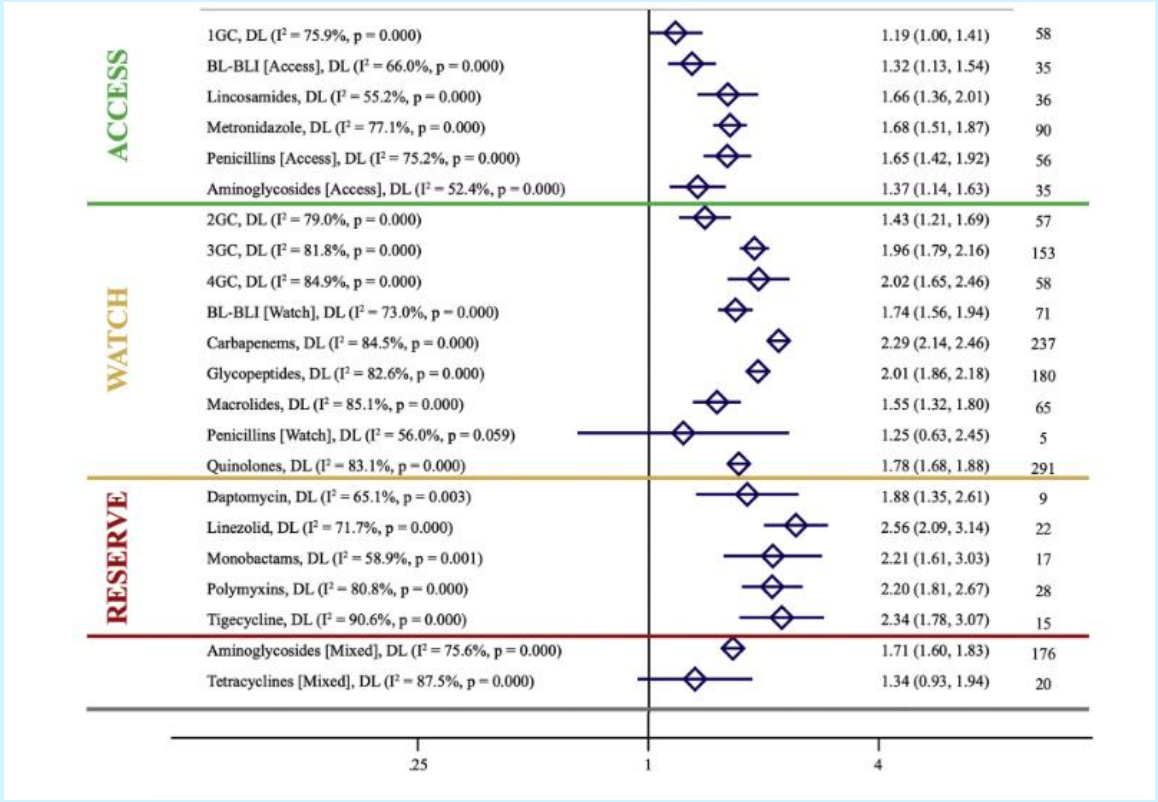
Lower "resistance potential"

https://www.who.int/publications/i/item/B09489

World Health Organization

Risk of resistance by AWaRe category: results from a systematic review





Sulis et al. Clin Microbiol Infect. 2022 Mar 23;S1198-743X(22)00153-7.

World Health Organization

Antibiotics and CDI risk

Almost all antibiotics have been associated with increased risk of CDI

Highest risk in meta-analyses usually associated with

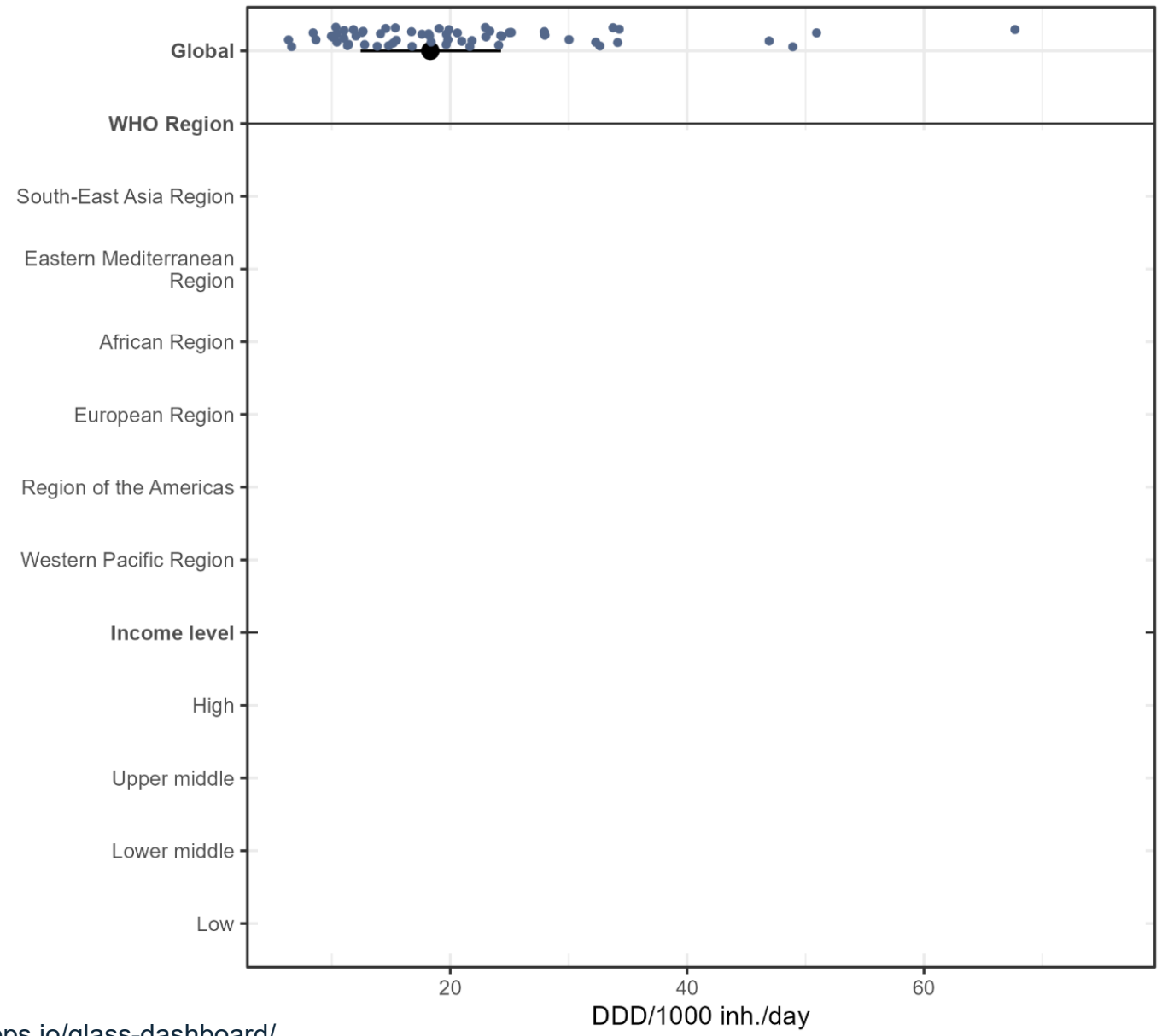
- **Clindamycin (Access)**
- **Cephalosporins (mostly Watch)**
- **Fluoroquinolones (Mostly Watch)**

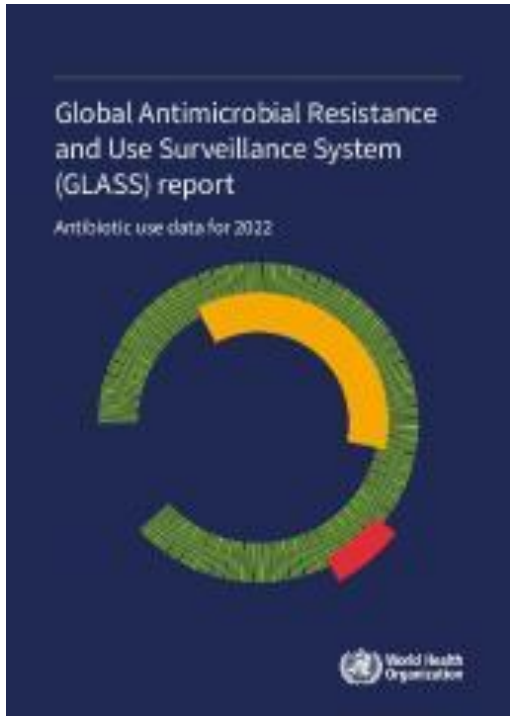
Clostridium difficile infection: risk with broad-spectrum antibiotics (NICE evidence summary 2015)

https://www.nice.org.uk/advice/esmpb1/chapter/full-evidence-summary-medicines-and-prescribing-briefing#evidence-review-2

World Health Organization

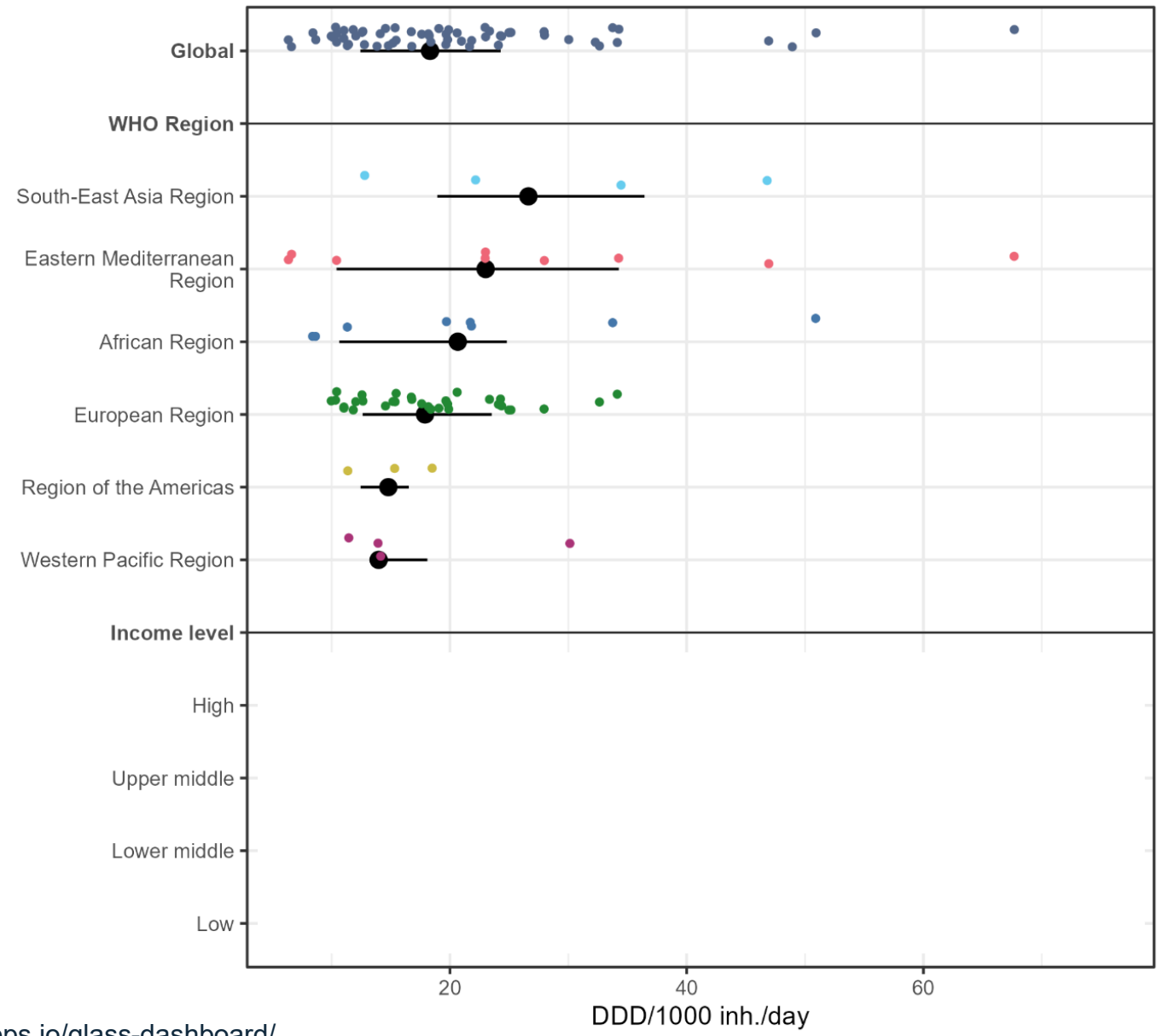
Total antibiotic use expressed as DDD per 1000 inhabitants per day in 60 CTAs in 2022, globally and by WHO Regions and World Bank income group classification

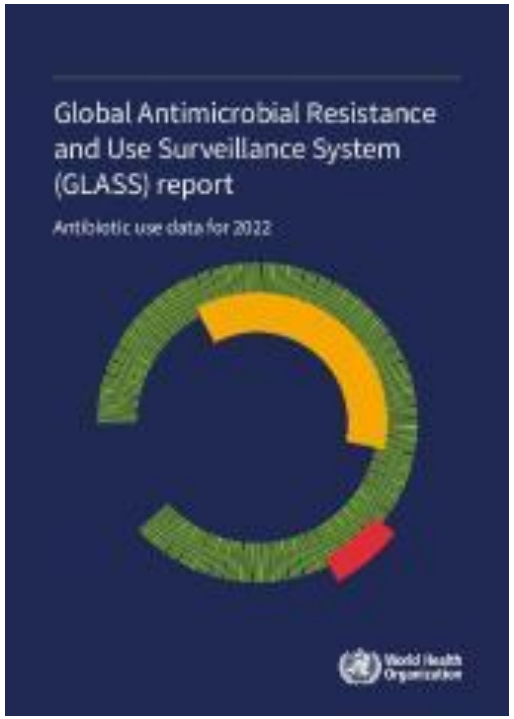




https://worldhealthorg.shinyapps.io/glass-dashboard/_

Total antibiotic use expressed as DDD per 1000 inhabitants per day in 60 CTAs in 2022, globally and by WHO Regions and World Bank income group classification





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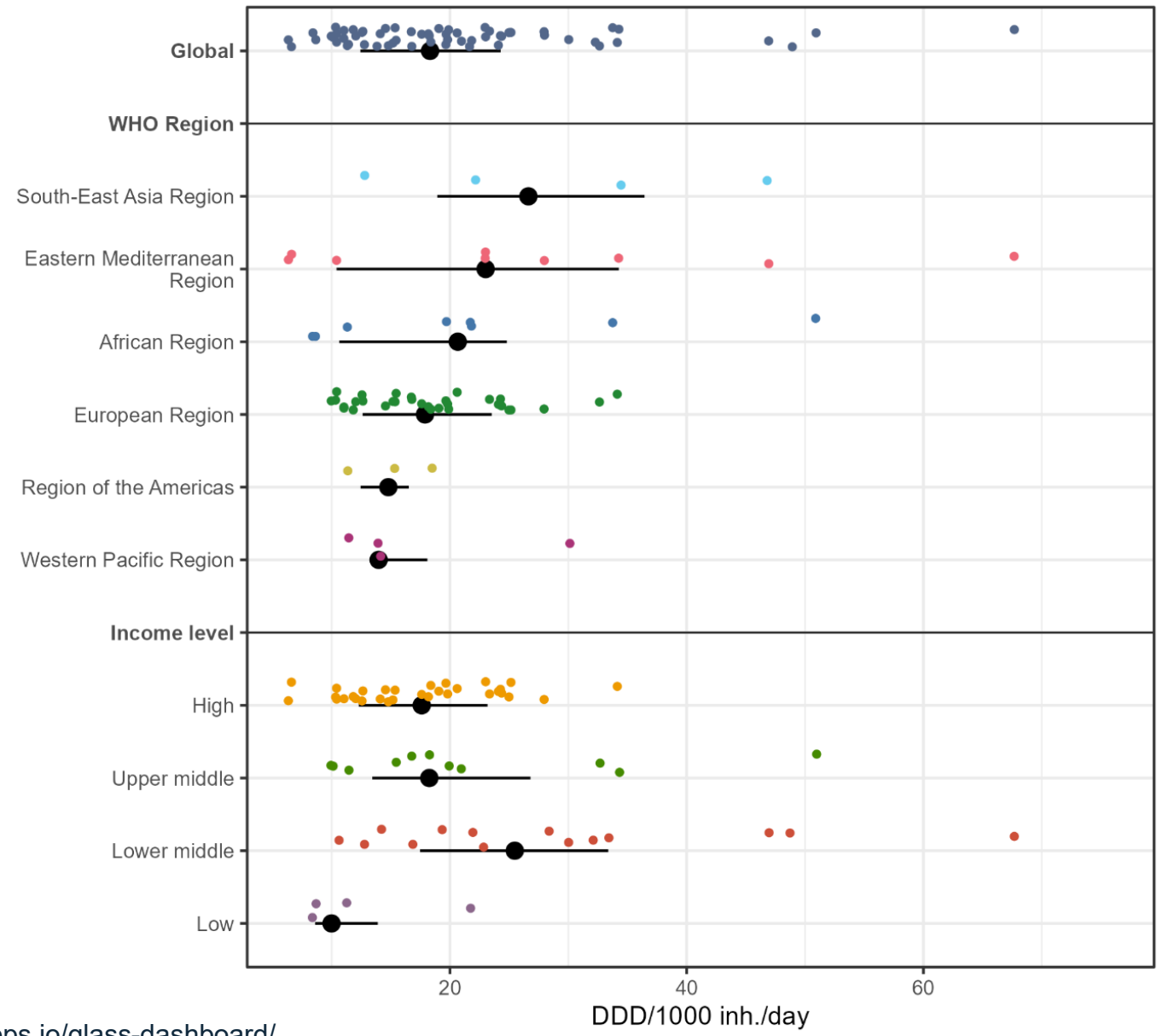
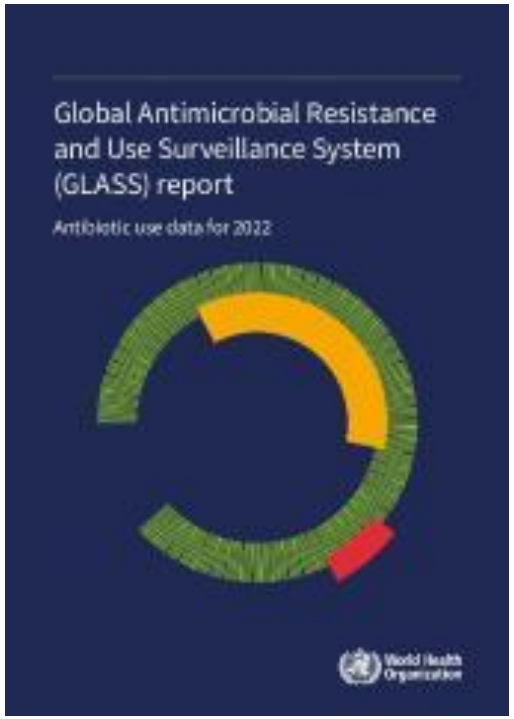
Total antibiotic use expressed as DDD per 1000 inhabitants per day in 60 CTAs in 2022, globally and by WHO Regions and World Bank income group classification

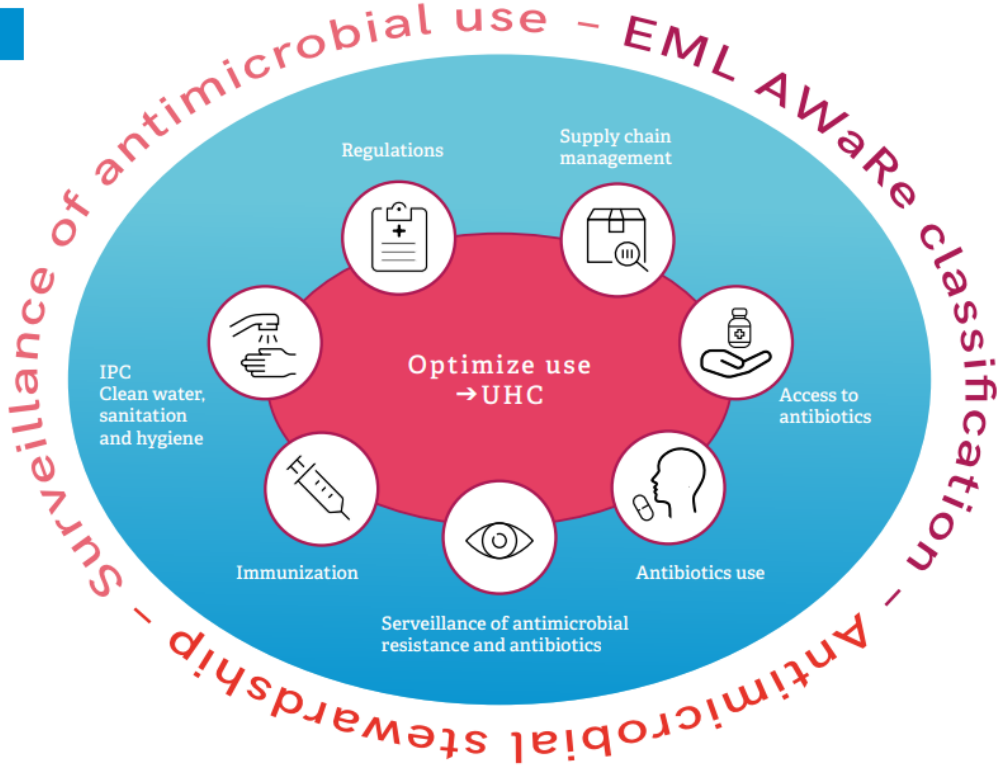




https://worldhealthorg.shinyapps.io/glass-dashboard/_

FIGURE 1

Integrated approach to optimizing use of antimicrobials towards universal health coverage



https://www.who.int/publications/i/item/9789241515481

World Health Organization

Most of the antibiotic use globally occurs in the outpatient setting

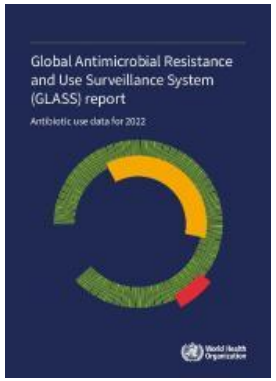
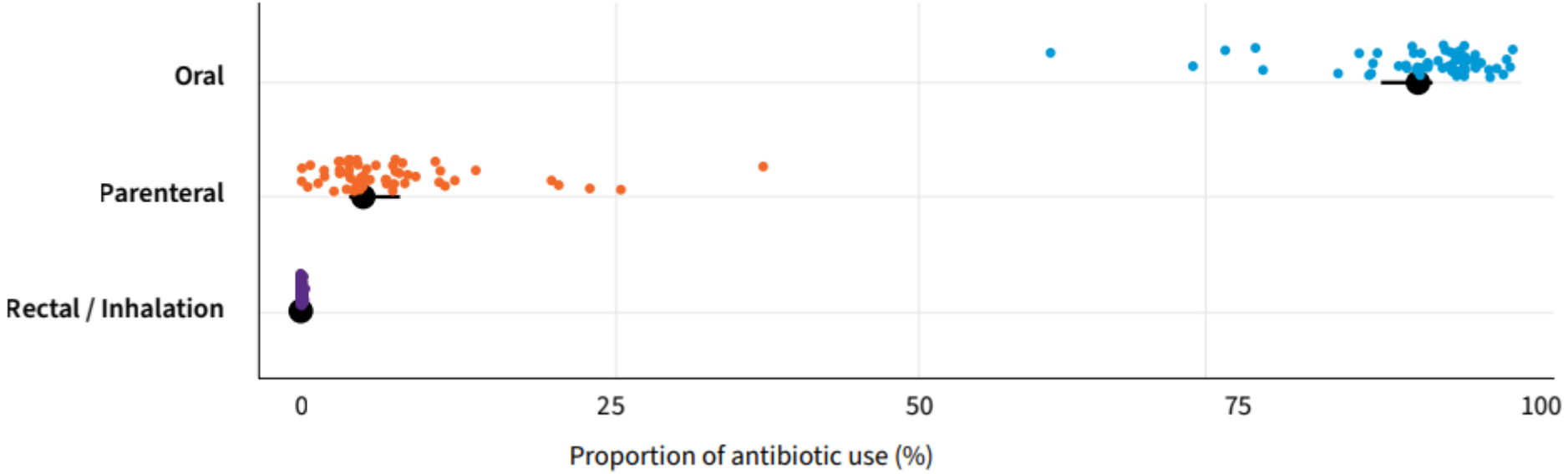


Fig. 10. Proportional distribution of antibiotic use by route of administration in 60 CTAs in 2022



World Health Organization

Antibiotic treatment guidelines are not available in many LMICs

Review of official websites for published standardized treatment guidelines in the 55 African Union countries

Complemented by contact with focal points from African CDC and WHO

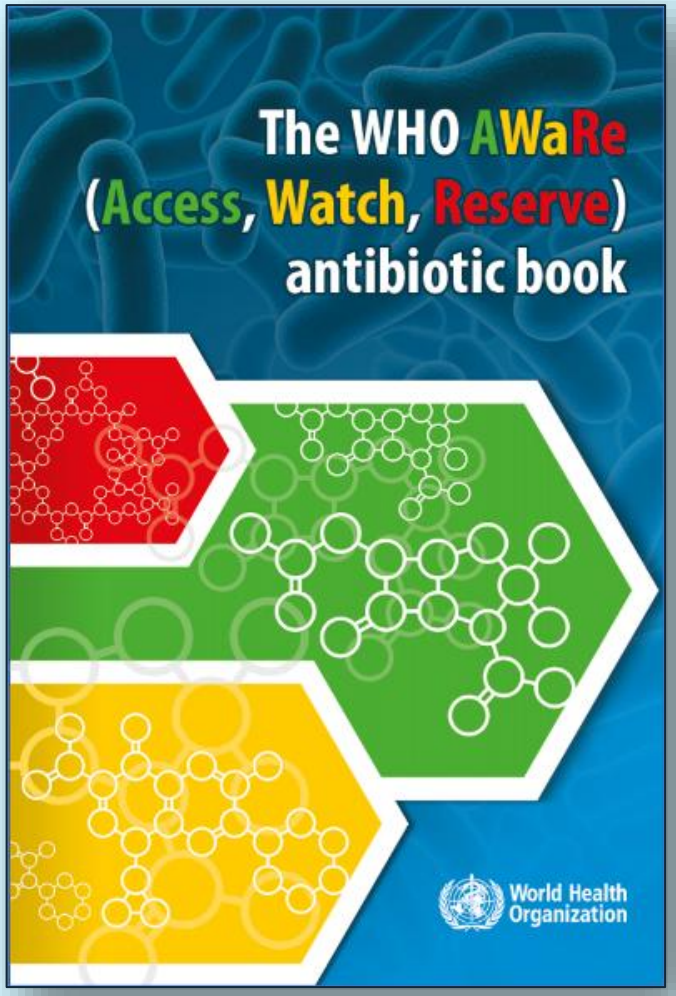
31 standardized treatment guidelines from 20 countries identified (2001-2018)

35 countries no guidelines identified	None developed according to GRADE methodology	Important variation in antimicrobial selection and dosage and duration of recommended therapies	None stated that antibiotic selection was based on local epidemiology of antibiotic resistance

Craig et al. Bull World Health Organ. 2022 Jan 1;100(1):50-59.

World Health Organization

WHO AWaRe antibiotic book



To provide simple guidance on **“HOW TO USE”** the antibiotics on the EML to manage common infections

Guidance for 34 common infections, surgical prophylaxis and use of Reserve antibiotics; **primary care** and **facility / hospital setting**, in **children and adults**.

Recommendations on empiric antibiotic treatment

(i.e., presumptive diagnosis not requiring any laboratory diagnostic)

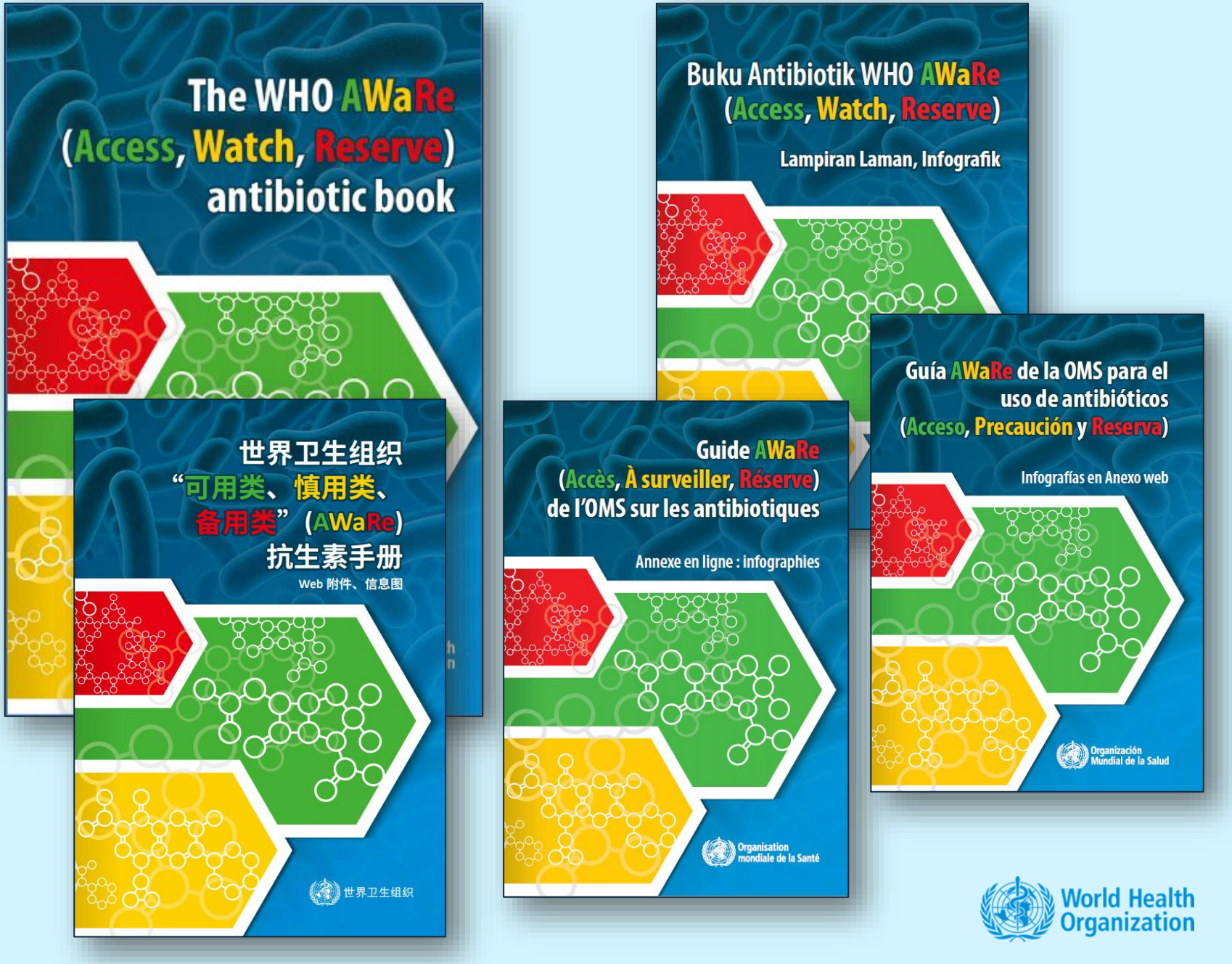
Includes guidance on making the clinical **Diagnosis**, the **Decision** if antibiotic needed, the choice of **Drug, Dose, Duration**

Short summaries of key features of microbiology, epidemiology, clinical presentation, diagnostics (in collaboration with EDL) and prevention

Target audience: **all health professionals giving antibiotics**

World Health Organization

The WHO AWaRe Antibiotic Book



World Health Organization

"Ensure, by 2030, that the use of WHO Access group antibiotics is expanded from the 2023 global target, and in that regard, taking into account national contexts, aim to achieve at least 70 per cent overall human antibiotic use globally, through investing in and strengthening stewardship programmes"

Political Declaration of the High-level Meeting on Antimicrobial Resistance (September 2024)

Improving diagnostics, surveillance, stewardship, and treatment access is crucial for CDI

Major data gaps about burden in LMICs due to underdiagnosis and lack of surveillance

***C. difficile* not (yet) included in GLASS-AMR; EDL inclusion hopefully will improve lab capacity and detection in the long term**

***C. difficile* not included in the BPPL because right now limited to antibiotic-resistant pathogens**

WHO EML lists metronidazole (Access) and oral vancomycin (Watch)

- **access to oral vancomycin and fidaxomicin (not on the EML) mainly limited to high-income countries**

Pipeline: 3 newly approved non-traditional agents, plus 11 NTAs and 4 antibiotics in development for CDI

Antibiotic exposure is the strongest predictor of CDI; global use remains high and highly variable with frequent inappropriate use and overuse of Watch antibiotics

- **Strengthening AMS and expanding AWaRe-informed prescribing is essential**

Thank you for your attention

Special thanks to:

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Valeria Gigante

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bhuttner@who.int

Paul Feuerstadt

Paul Feuerstadt is a board-certified gastroenterologist and Associate Clinical Professor of Medicine at Yale University School of Medicine, USA.

He specializes in gastrointestinal (GI) disorders with a focus on Clostridioides difficile infection, microbiome-based therapeutics, and eosinophilic esophagitis. Paul is an internationally recognized speaker, educator, and researcher, with numerous peer-reviewed publications and contributions to leading GI textbooks. He serves as Managing Partner at PACT-Gastroenterology Center and actively collaborates with pharmaceutical and biotech companies to advance patient care.

“Add On Therapies”

Paul Feuerstadt, MD, FACG, AGAF, FRCPE
Associate Clinical Professor of Medicine
Yale School of Medicine
PACT-Gastroenterology Center
Hamden, CT

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

General

- Merck and Co: Speakers Bureau
- Ferring/Rebiotix Pharmaceutical: Consultant, Advisory Board, Speakers Bureau
- SERES Therapeutics: Advisory Board
- Takeda Pharmaceuticals: Advisory Board
- Probiotech: Advisory Board
- Sanofi/Regeneron: Consulting/Advisory Board

Research Support

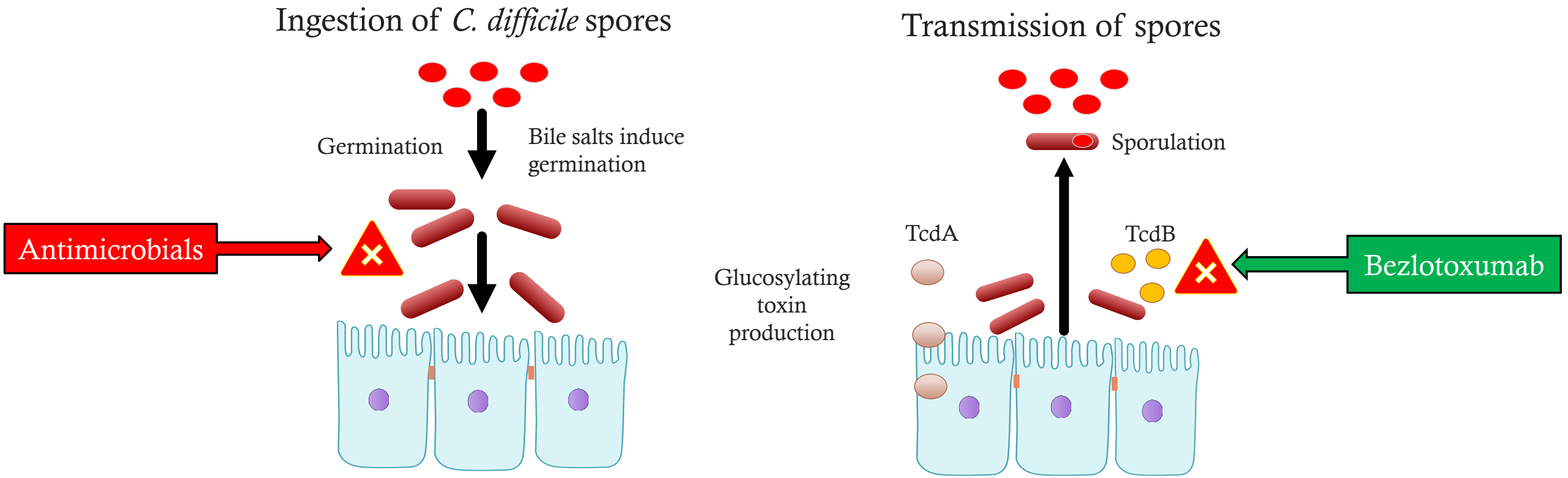
- Ferring Pharmaceuticals
- SERES Therapeutics
- Finch Therapeutics

All relevant financial relationships have been mitigated.

Treatment: What are we doing?

Attack the Vegetative Phase

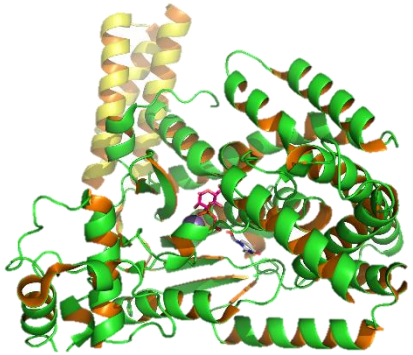
Boost Immune Response



Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

Multimodal Approach to Therapy

Bezlotoxumab



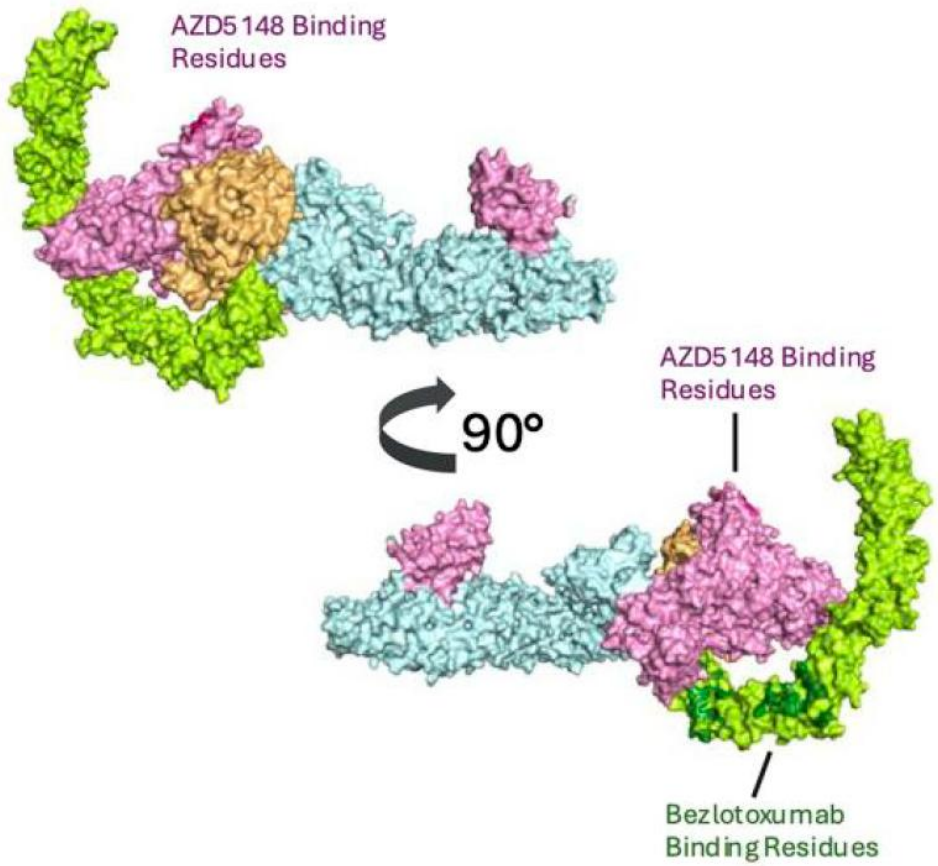
Merck to discontinue drug for bacterial infection

By **Reuters**

December 23, 2024 6:42 PM EST · Updated 2 months ago

Signage is seen at the Merck & Co. headquarters in Kenilworth, New Jersey, U.S., November 13, 2021. REUTERS/Andrew Kelly/File Photo

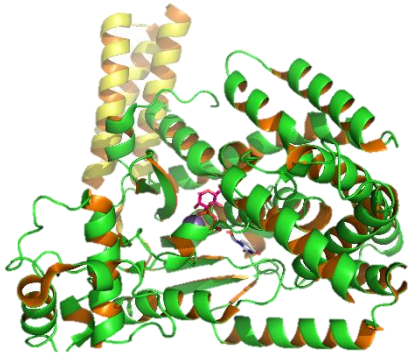
AZD-5148



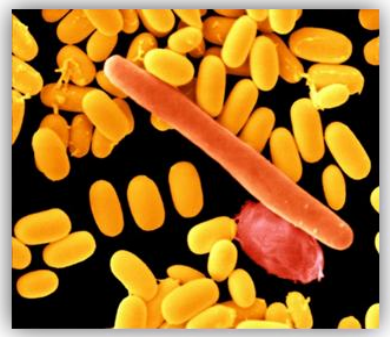
Mahool et al. J Inf Dis 2025 epub. Ahead of print

Multimodal Approach to Therapy

Bezlotoxumab



Fecal Microbiota Transplantation



GOALS OF TREATMENT FOR *C. DIFFICILE* INFECTION

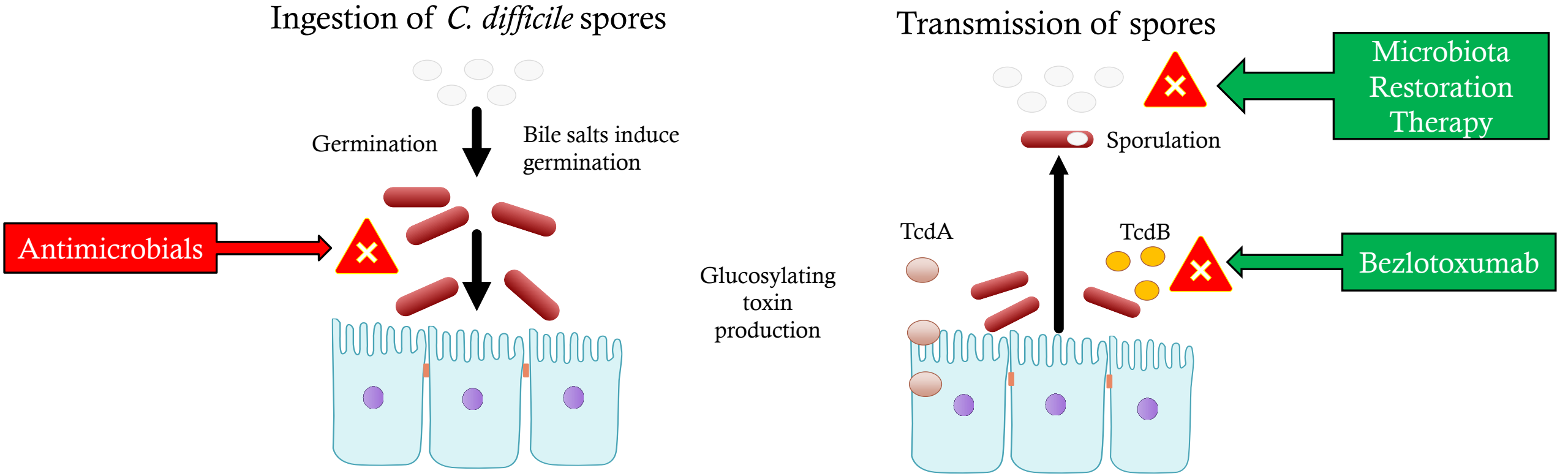
Fidaxomicin
Vancomycin

Healthy
Diverse
Microbiota

Treatment: What are we doing?

Attack the Bacteria

Boost Immune Response



AGA Microbiota Transplant Guideline

Recurrent *C. difficile* Infection

Is the patient at high risk for recurrence?

Immunocompetent adults

Recommend use of fecal microbiota-based therapies upon completion of SOC ABX

⊕⊕◯◯

Immunocompromised adults

Mild-Moderate Immunocompromise

Recommend use of conventional FMT upon completion of SOC ABX

⊕◯◯◯

Severe Immunocompromise

Recommend against use of fecal microbiota-based therapies upon completion of SOC ABX

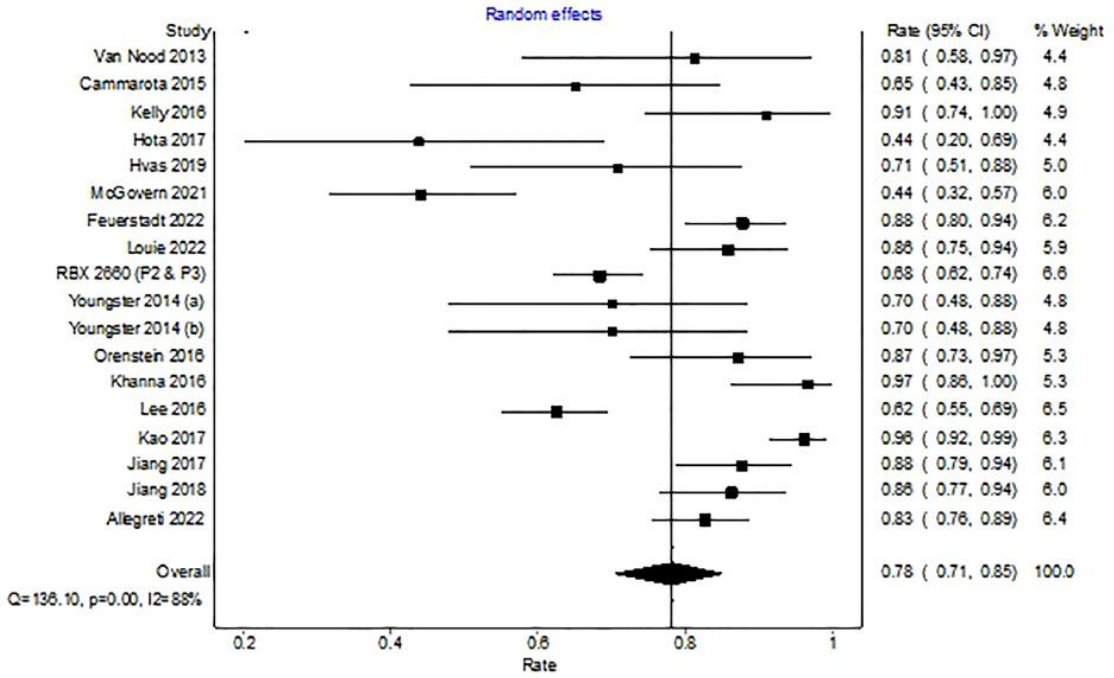
⊕◯◯◯

Peery et al. Gastroenterology 2024;166:409–434

Resolution of rCDI with FMT/MRT

All Clinical Trials

(n=19 trials, 18 studies)

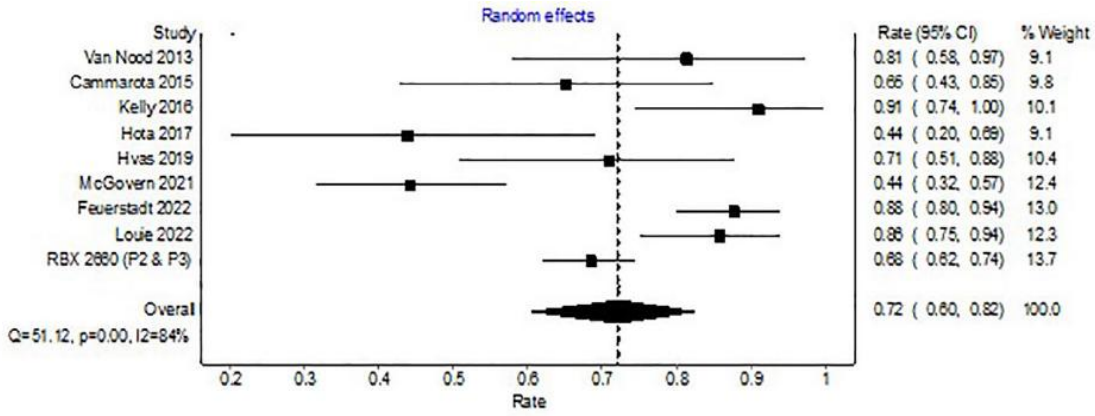


1,176 patients

Efficacy: 78% (95% CI: 71-85%)

Trials with a Control Arm

(n=10 trials, 9 studies)



523 patients

Efficacy: 72% (95% CI: 60-82%)

Tariq et al. Ther Adv Gastro 2023 Vol 16:1-9

Fecal Microbiota Transplant vs. FDA + MRT

	FMT	FDA + MRT
Donor Screening		
Sample Screening		
Good Manufacturing Procedure		
Clinical Trial Data		
Safety Data		
Ease of access		

Identification of a Donor

Fecal Microbiota Transplant vs. FDA + MRT

	FMT	FDA + MRT
Donor Screening	💩 💩	💩 💩 💩
Sample Screening	?	💩 💩 💩
Good Manufacturing Procedure		
Clinical Trial Data		
Safety Data		
Ease of access		

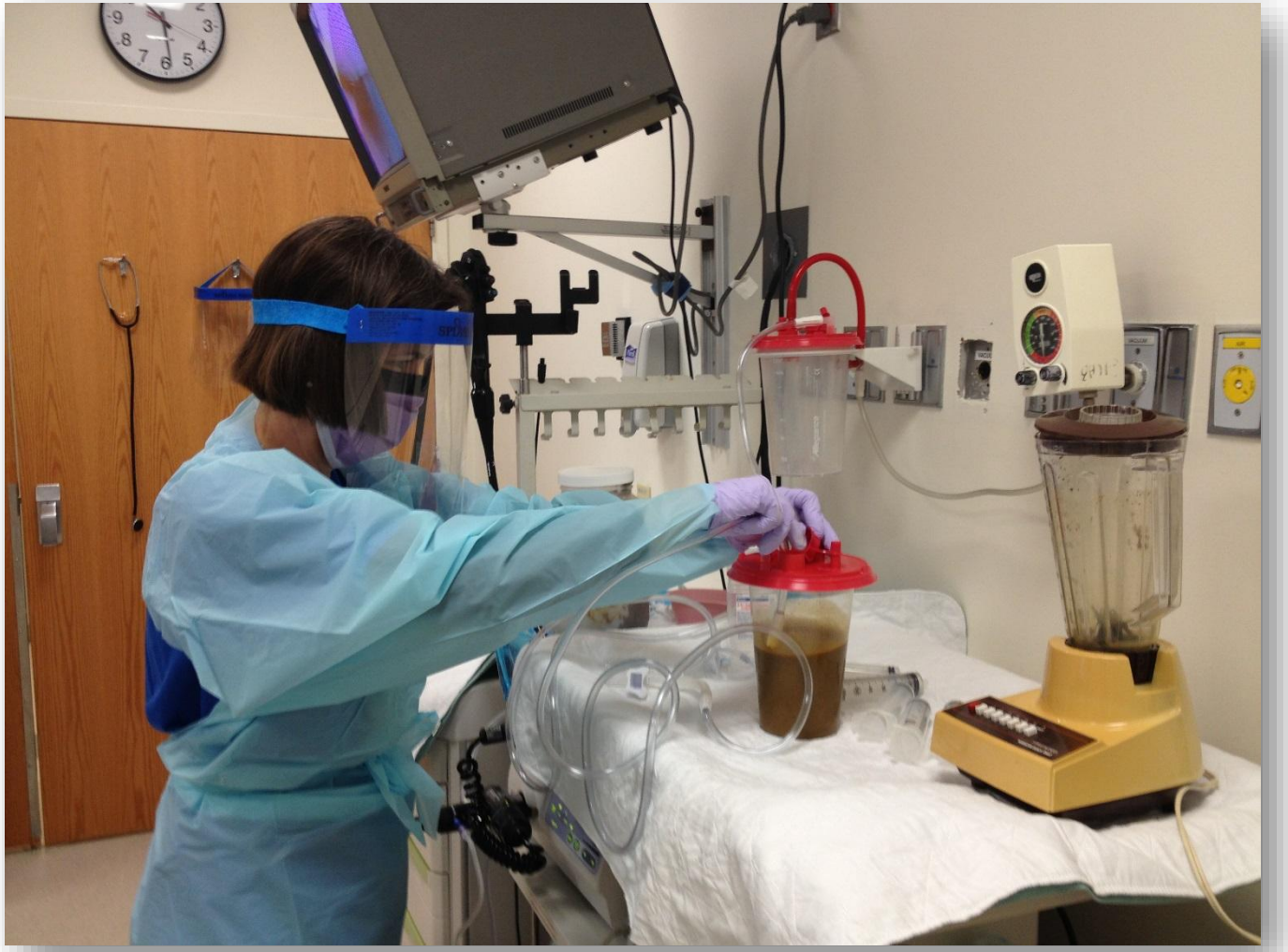
Fecal Microbiota Transplant vs. FDA + MRT

	FMT	FDA + MRT
Donor Screening	💩 💩	💩 💩 💩
Sample Screening	?	💩 💩 💩
Good Manufacturing Procedure	?	💩 💩 💩
Clinical Trial Data		
Safety Data		
Ease of access		

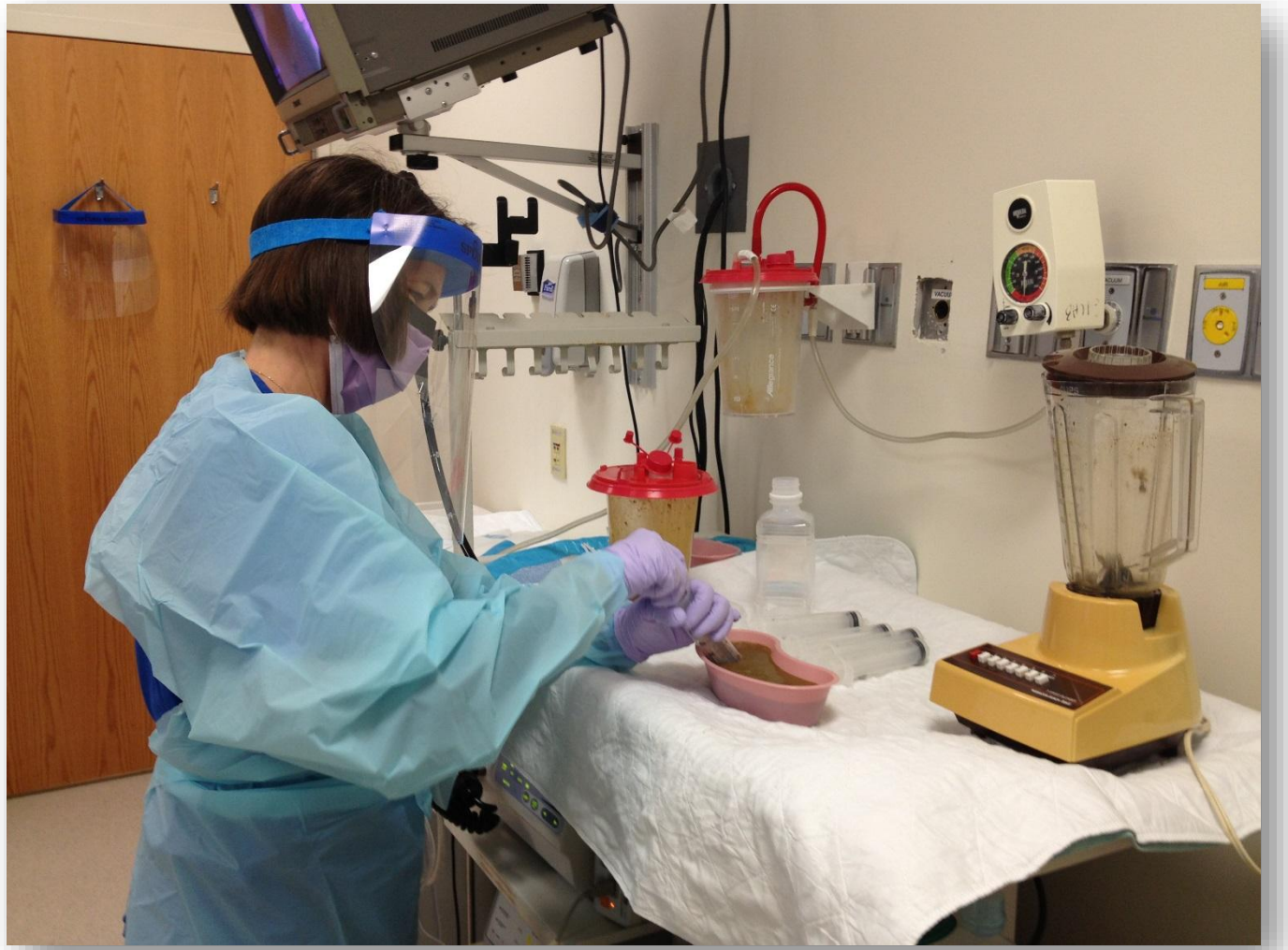
Fecal Microbiota Transplantation

Fecal Microbiota Transplantation

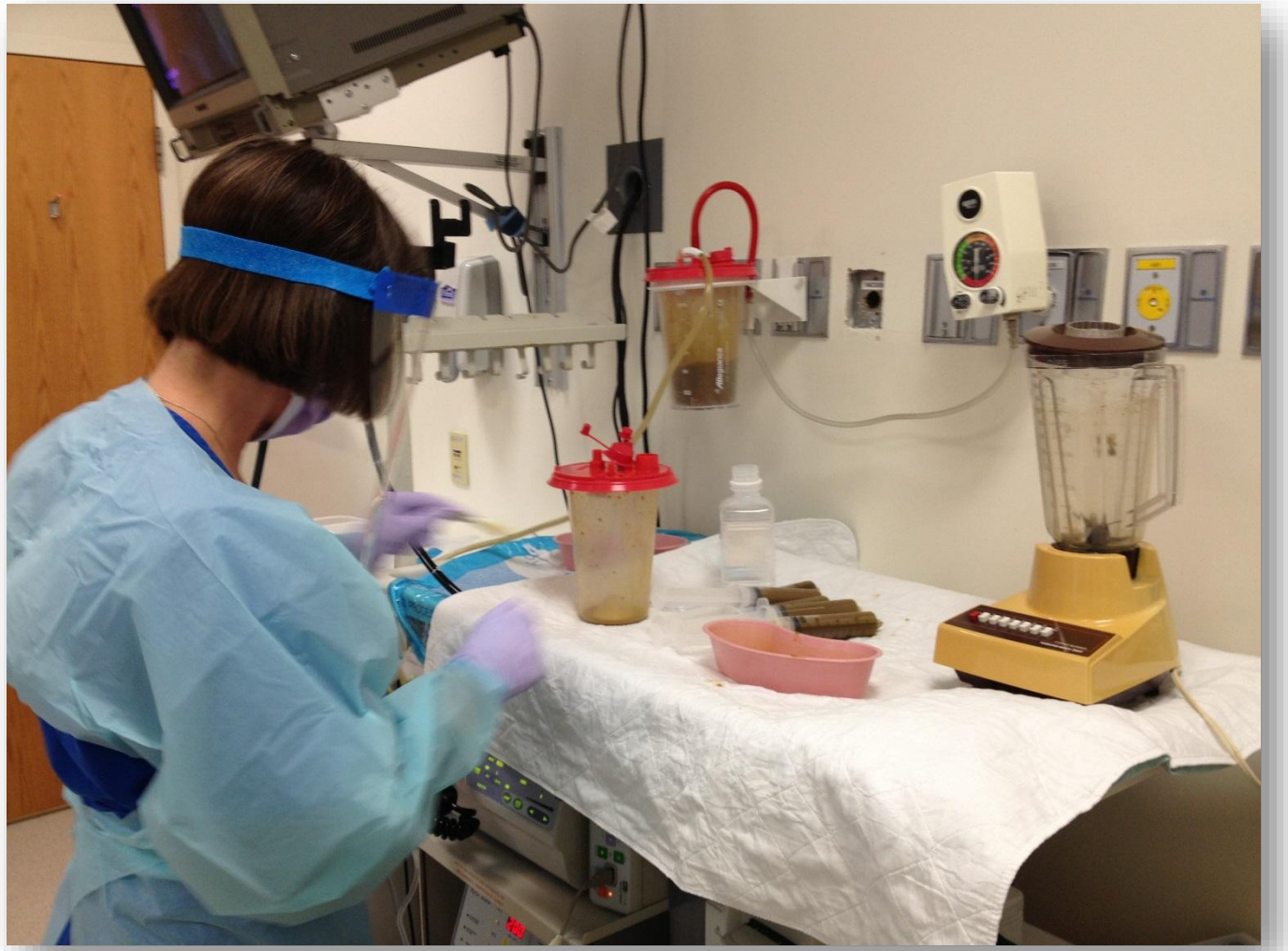
Fecal Microbiota Transplantation



Fecal Microbiota Transplantation



Fecal Microbiota Transplantation



Fecal Microbiota Transplant vs. FDA + MRT

	FMT	FDA + MRT
Donor Screening	💩 💩	💩 💩 💩
Sample Screening	?	💩 💩 💩
Good Manufacturing Procedure	?	💩 💩 💩
Clinical Trial Data	💩	💩 💩 💩
Safety Data		
Ease of access		

Fecal Microbiota Transplant vs. FDA + MRT

	FMT	FDA + MRT
Donor Screening	💩 💩	💩 💩 💩
Sample Screening	?	💩 💩 💩
Good Manufacturing Procedure	?	💩 💩 💩
Clinical Trial Data	💩	💩 💩 💩
Safety Data	💩 / 💩	💩 💩 💩
Ease of access		

Fecal Microbiota Transplant vs. FDA + MRT

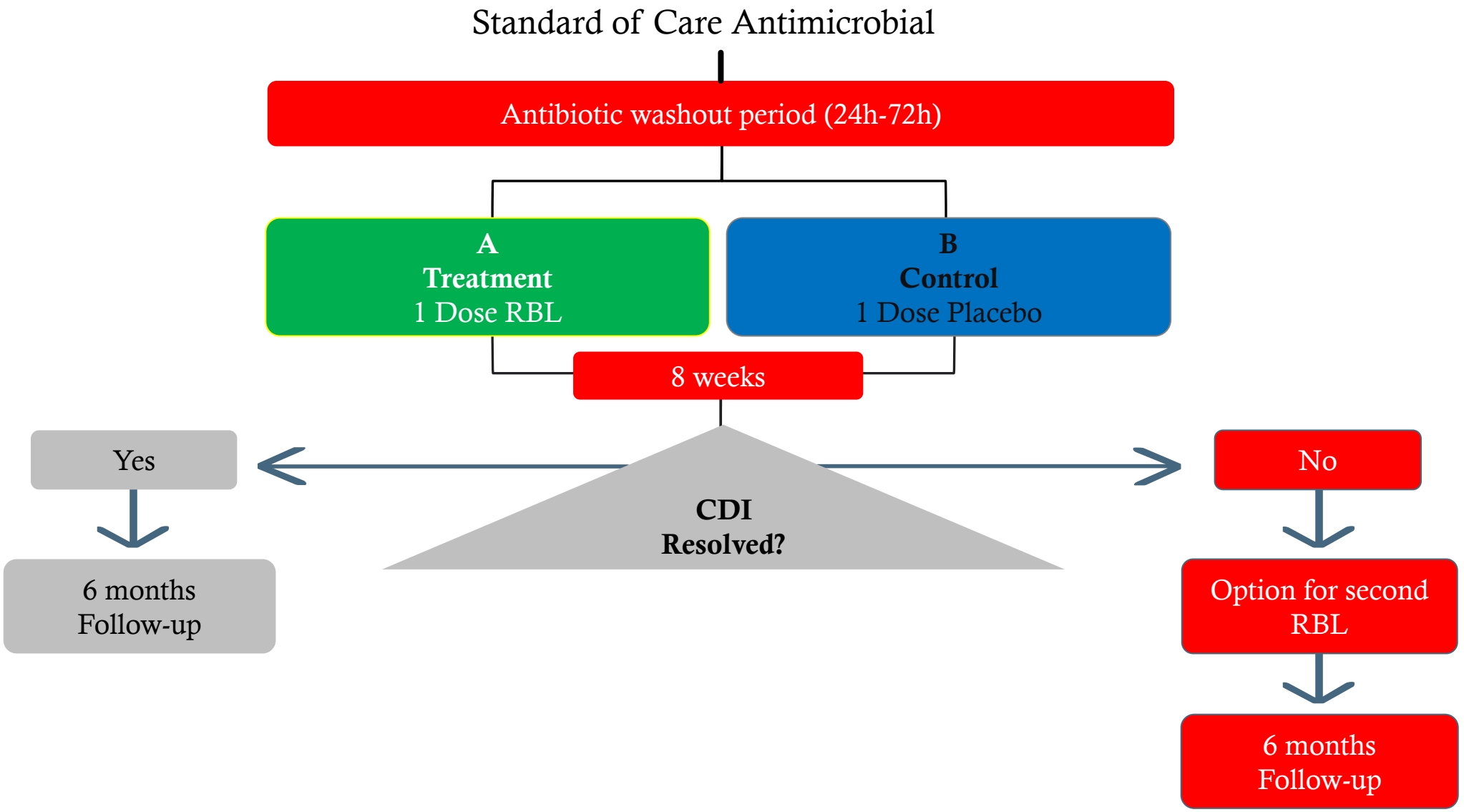
	FMT	FDA + MRT
Donor Screening	💩 💩	💩 💩 💩
Sample Screening	?	💩 💩 💩
Good Manufacturing Procedure	?	💩 💩 💩
Clinical Trial Data	💩	💩 💩 💩
Safety Data	💩 / 💩	💩 💩 💩
Ease of access	?	💩

Fecal Microbiota Live-JSLM (Rebyota™, RBL)

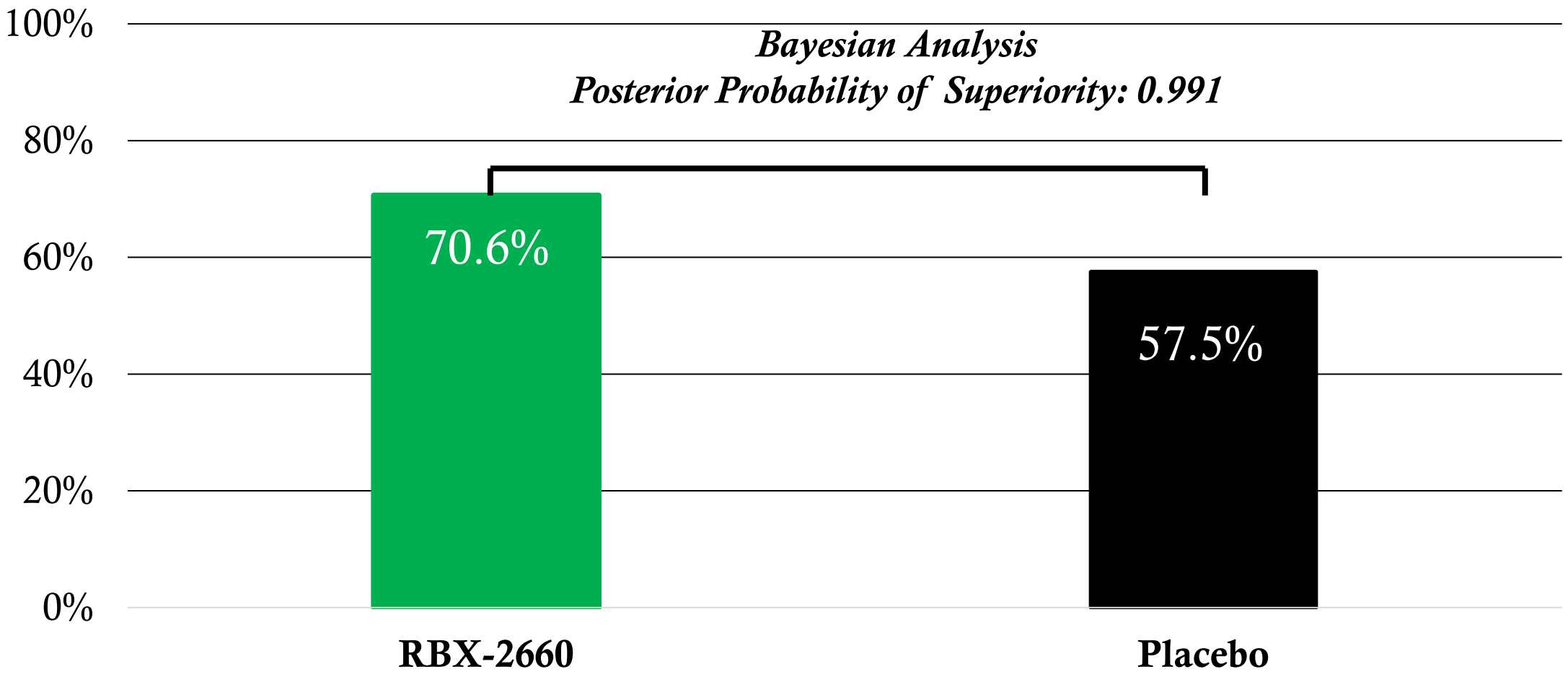
- Single-dose, microbiota-based live biotherapeutic agent
- Rectally administered
- 150 mL of therapeutic material
- 10^7 microbes per mL or 15 x 10^8 microbes per treatment
- Broad consortium
- A proprietary manufacturing process preserves diverse spore-forming and non–spore-forming bacteria, including *Bacteroides*

Orenstein R et al. *Clin Infect Dis*. 2016;62:596-602.
Blount KF et al. *Open Forum Infect Dis*. 2019;6:ofz095
Ray A, Jones C. *Future Microbiol*. 2016;11:611-616.

PUNCH-CD3: Phase 3 Trial Design

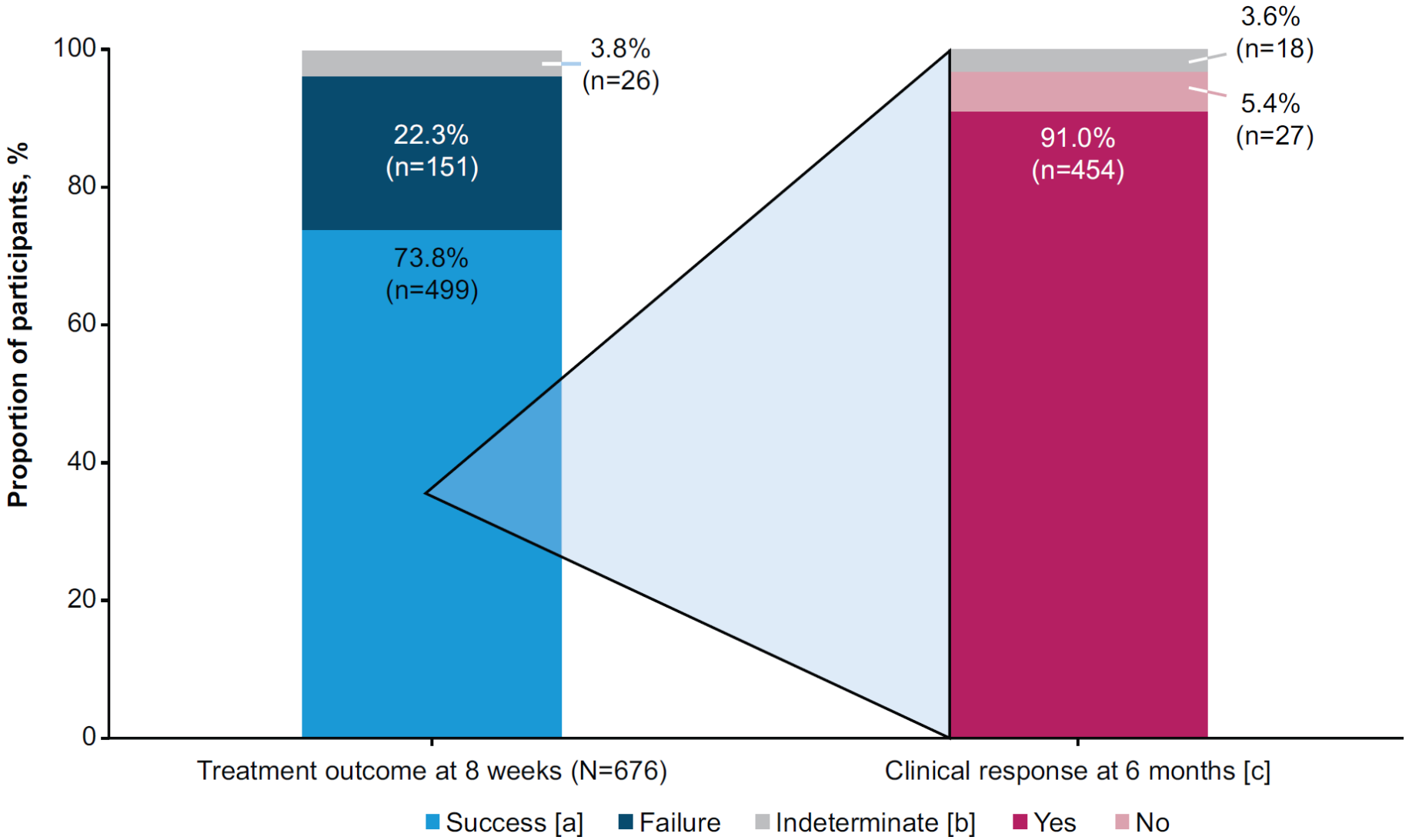


PUNCH-CD3: Phase 3
RBL Superior to Placebo



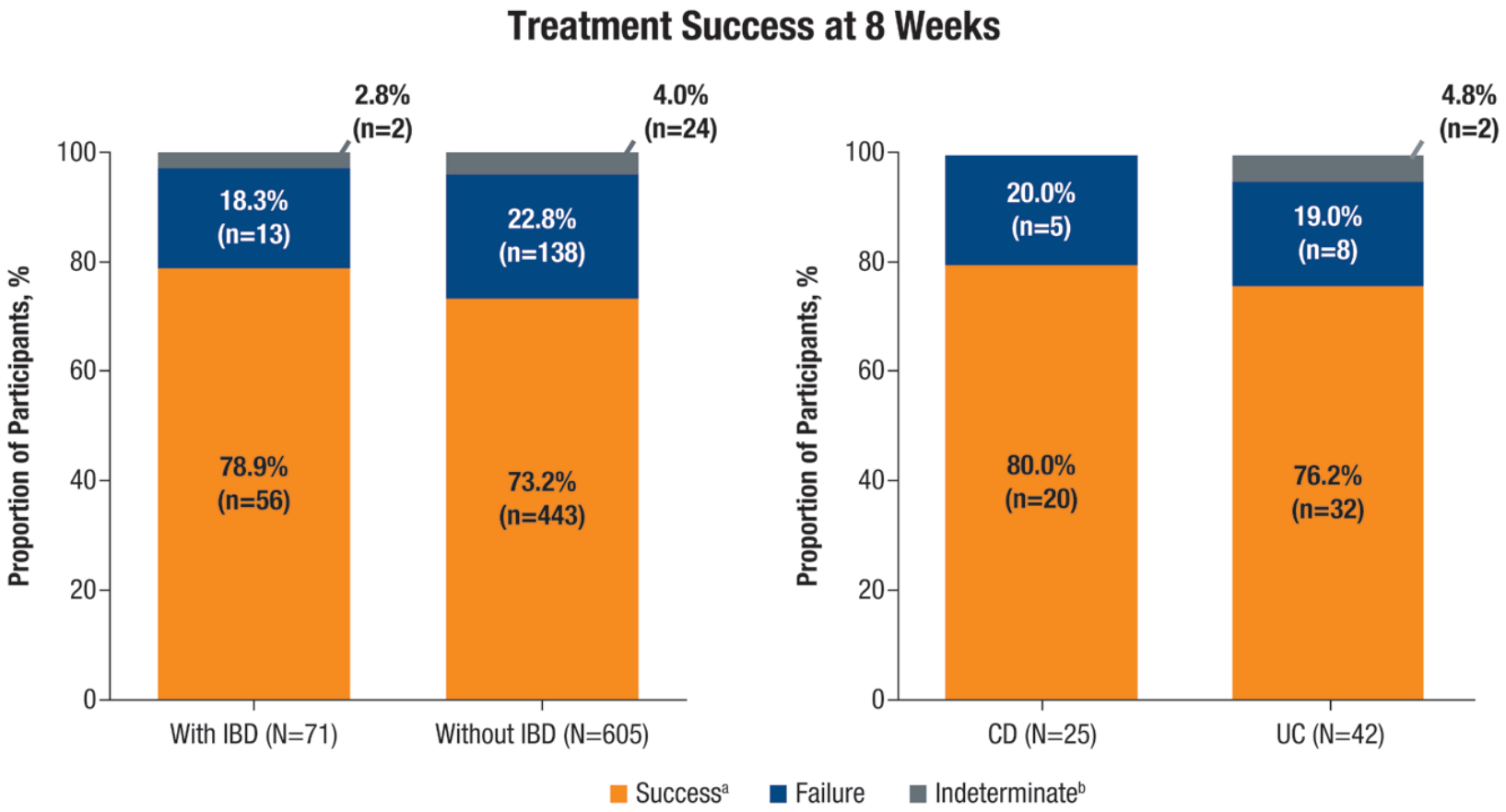
Khanna et al. Drugs. 2022 Oct;82(15):1527-1538

RBL Open Label Study



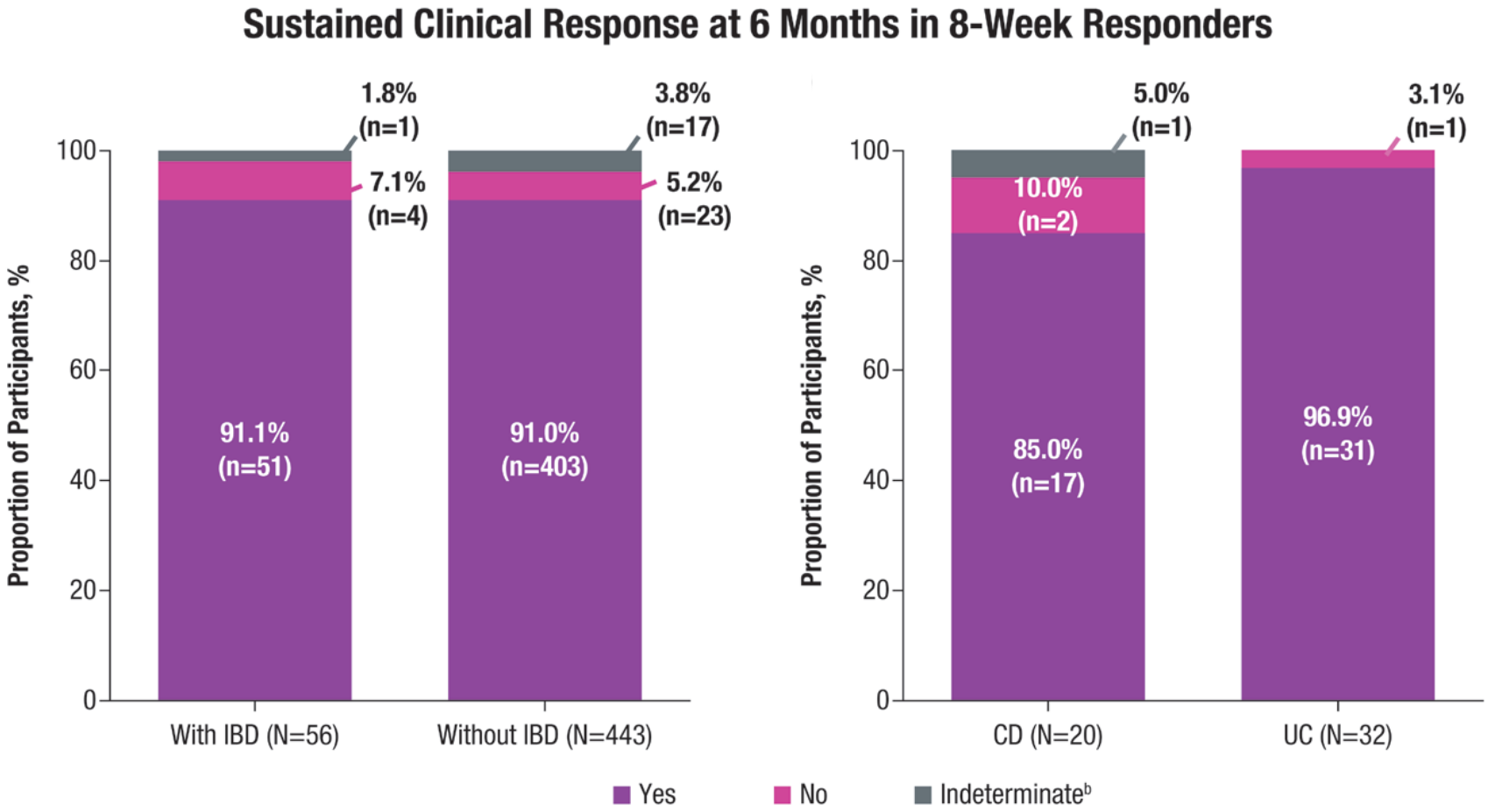
Feuerstadt et al. *Clin Infect Dis.* 2025 Feb 5;80(1):43-51

OLS Sub-Group: Inflammatory Bowel Disease



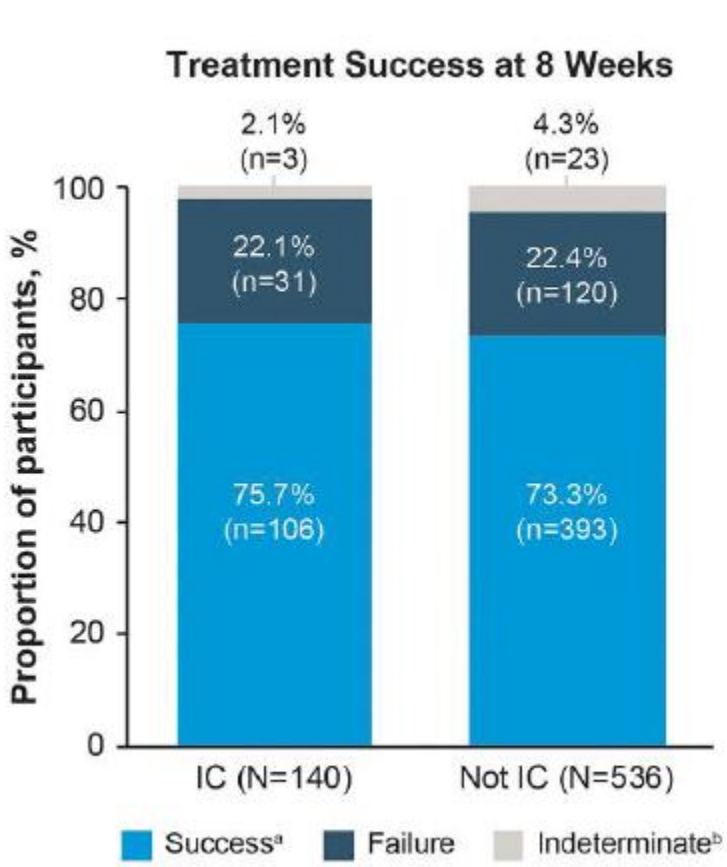
Allegretti et al. *Infl Bow Dis*. 2025 epub

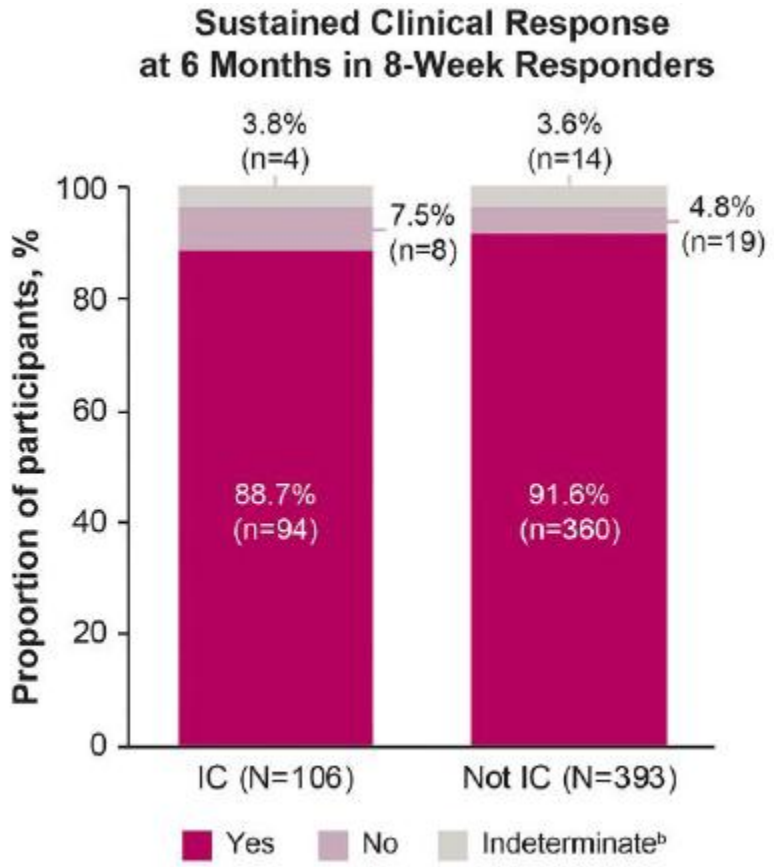
OLS Sub-Group: Inflammatory Bowel Disease



Allegretti et al. *Infl Bow Dis*. 2025 epub

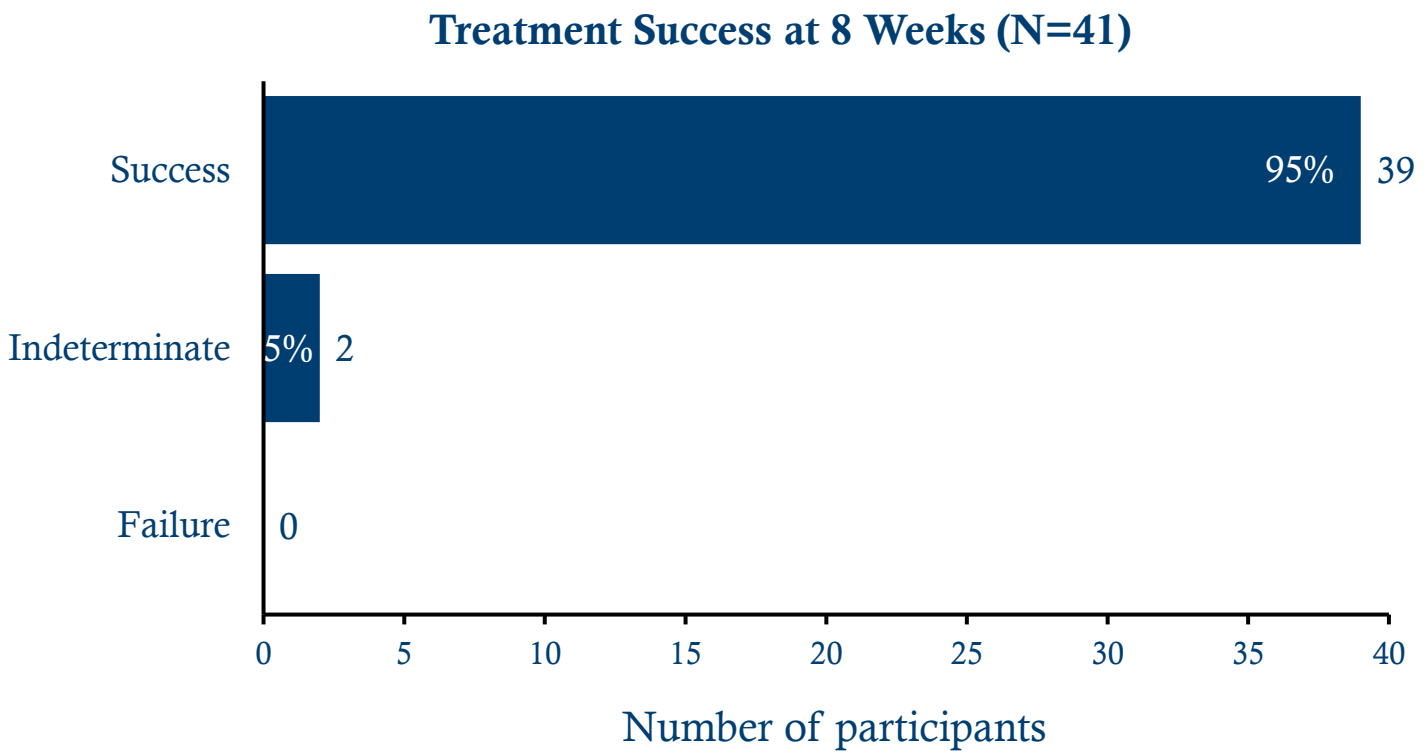
OLS Sub-Group: Immunocompromised





Alonso et al. *OFID*. 2025 epub Mar

CDI-Scope Study (Prospective)



- **Treatment success[a] at 8 weeks occurred in 39/41 participants (95%)**
- Two participants had indeterminate outcomes due to withdrawing consent prior to the 8-week follow-up assessment:
  - One due to an unrelated SAE (brain neoplasm)
  - One due to scheduling conflicts
  - Neither reported any CDI symptoms up to the time of withdrawal

CDI, *Clostridioides difficile* infection; SAE, serious adverse event.
[a]Defined as the absence of CDI recurrence through 8 weeks
Data on file. REB064. Ferring Pharmaceuticals Inc.

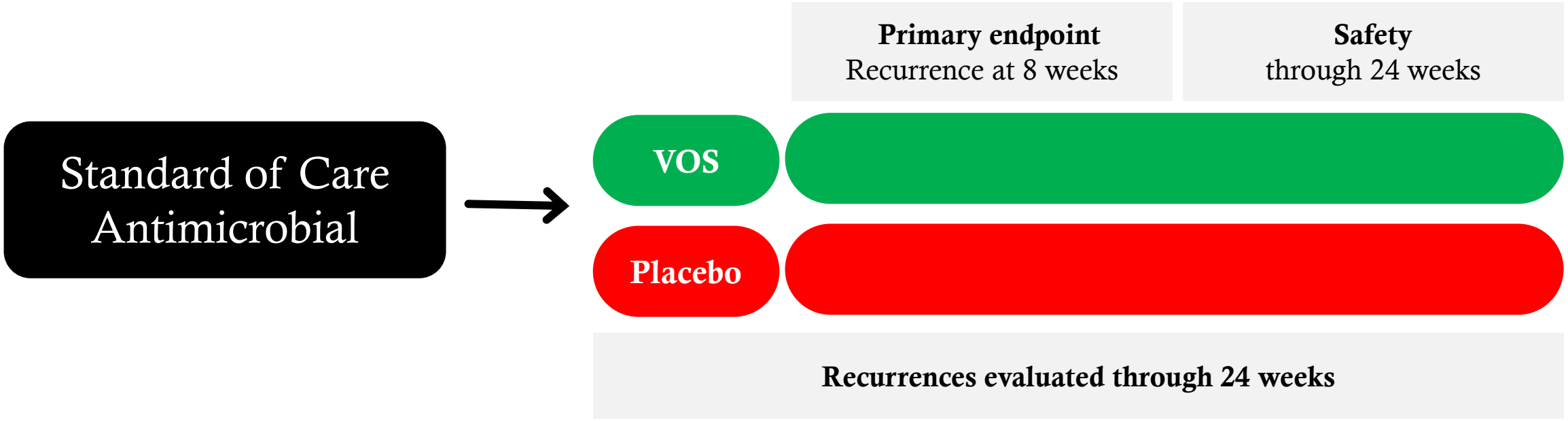
Khanna et al. DDW 2025

Fecal Microbiota Spores, Live-BRPK (Vowst™, VOS)

- Microbiota-based live biotherapeutic agent administered with 4 capsules daily over 3 days
- Orally administered
- 3 x 10^7 CFU per full treatment
- Narrow consortium
- A proprietary manufacturing process removes most fungi, parasites, viruses and non-spore forming bacteria resulting in predominantly Firmicutes spores

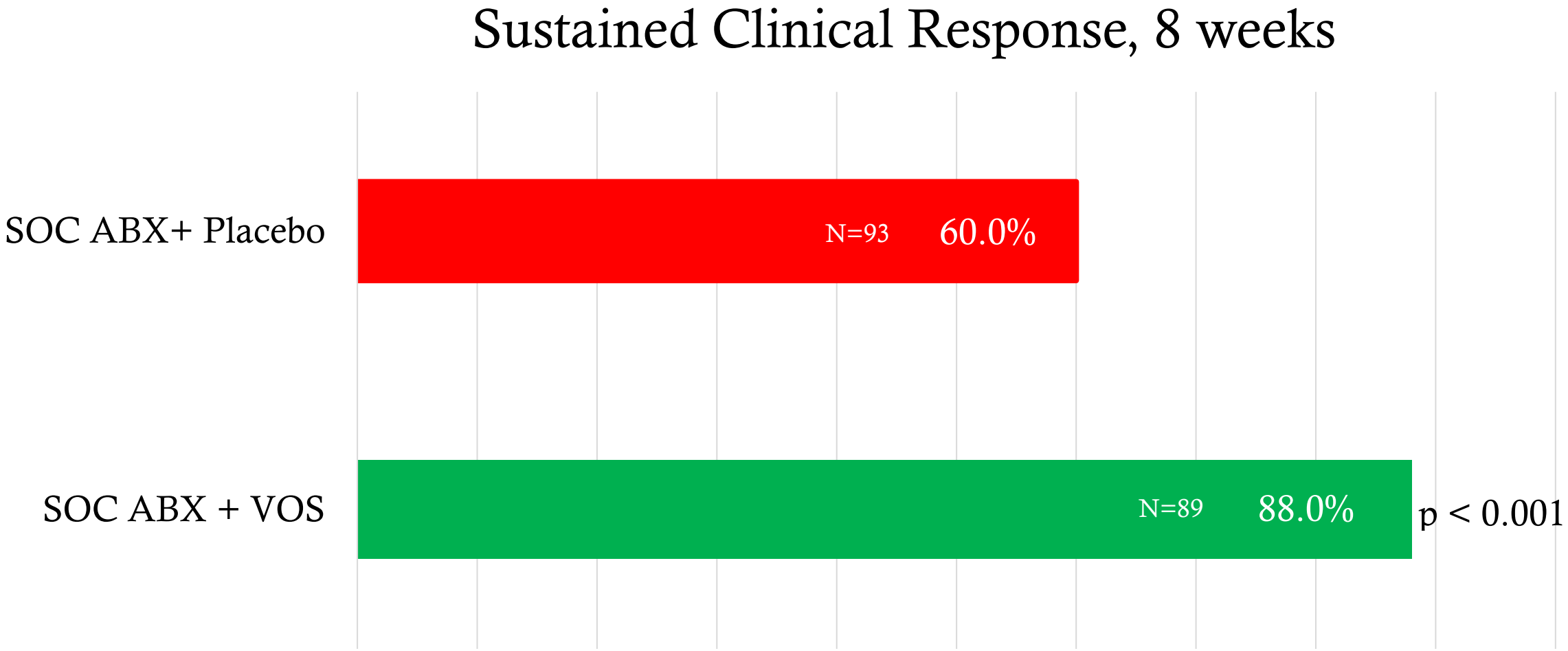
Korman L et al. *Gastroenterology* 2021;6:S-368.
Feuerstadt et al. *N Engl J Med.* 2022 Jan 20;386(3):220-229c

ECOSPOR-III: Phase 3 Trial Design



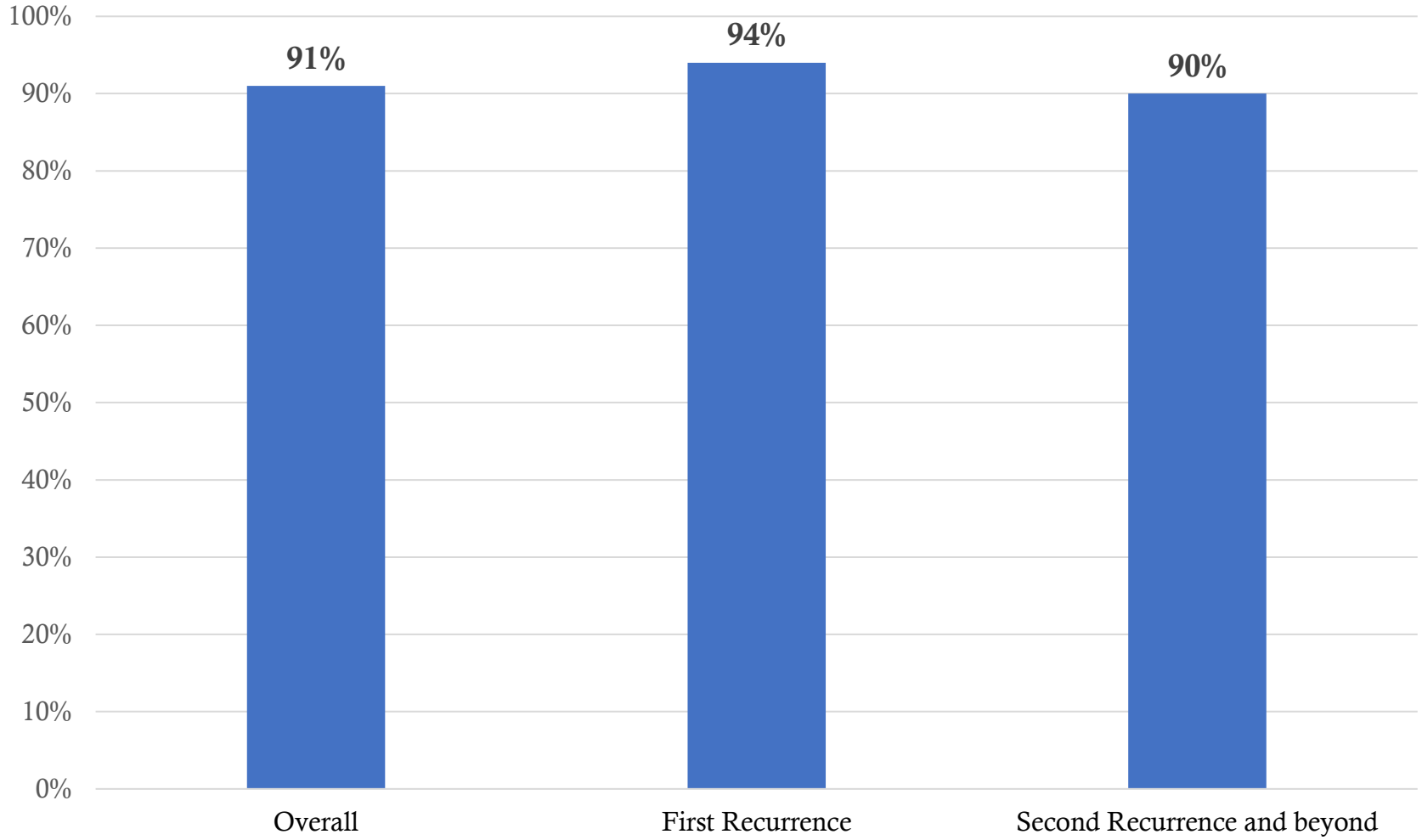
Feuerstadt et al. N Engl J Med. 2022 Jan 20;386(3):220-229

ECOSPOR-III: Phase 3
VOS superior to Placebo



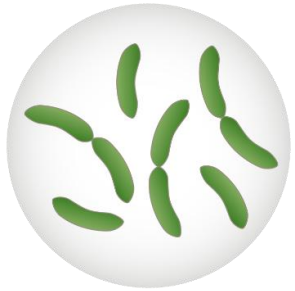
Feuerstadt et al. N Engl J Med. 2022 Jan 20;386(3):220-229

ECOSPOR-IV: Open Label Study

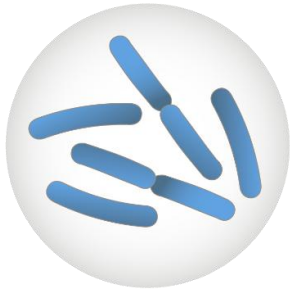


Simms et al. JAMA Netw Open. 2023 Feb 1;6(2)

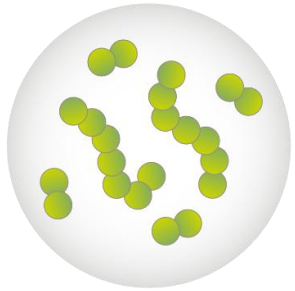
VE303 (Vedanta Biosciences)



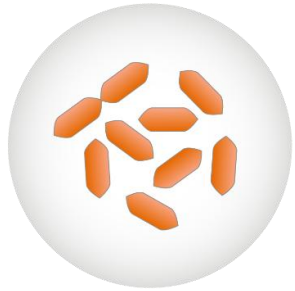
STRAIN #1
Enterocloster bolteae



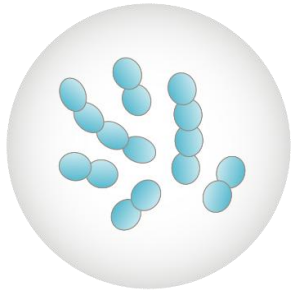
STRAIN #2
Anaerotruncus colihominis



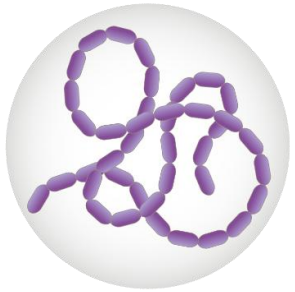
STRAIN #3
Sellimonas intestinalis



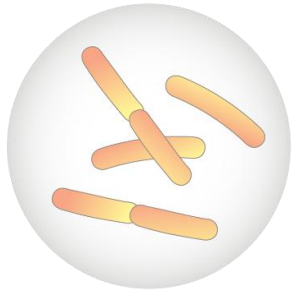
STRAIN #4
Otoolea symbiosa



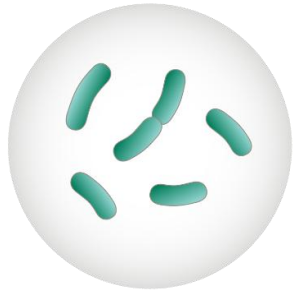
STRAIN #5
Blautia celeris



STRAIN #6
Dorea_A longicatena

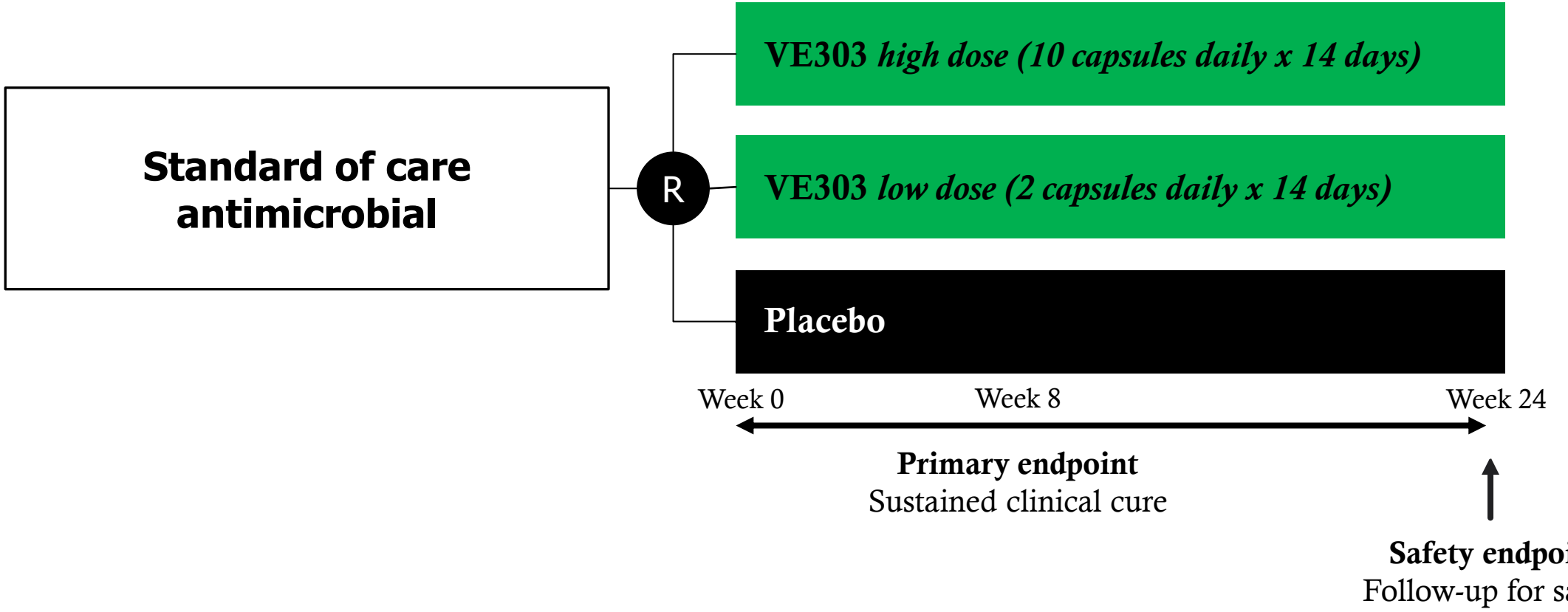


STRAIN #7
Clostridium AQ innocuum



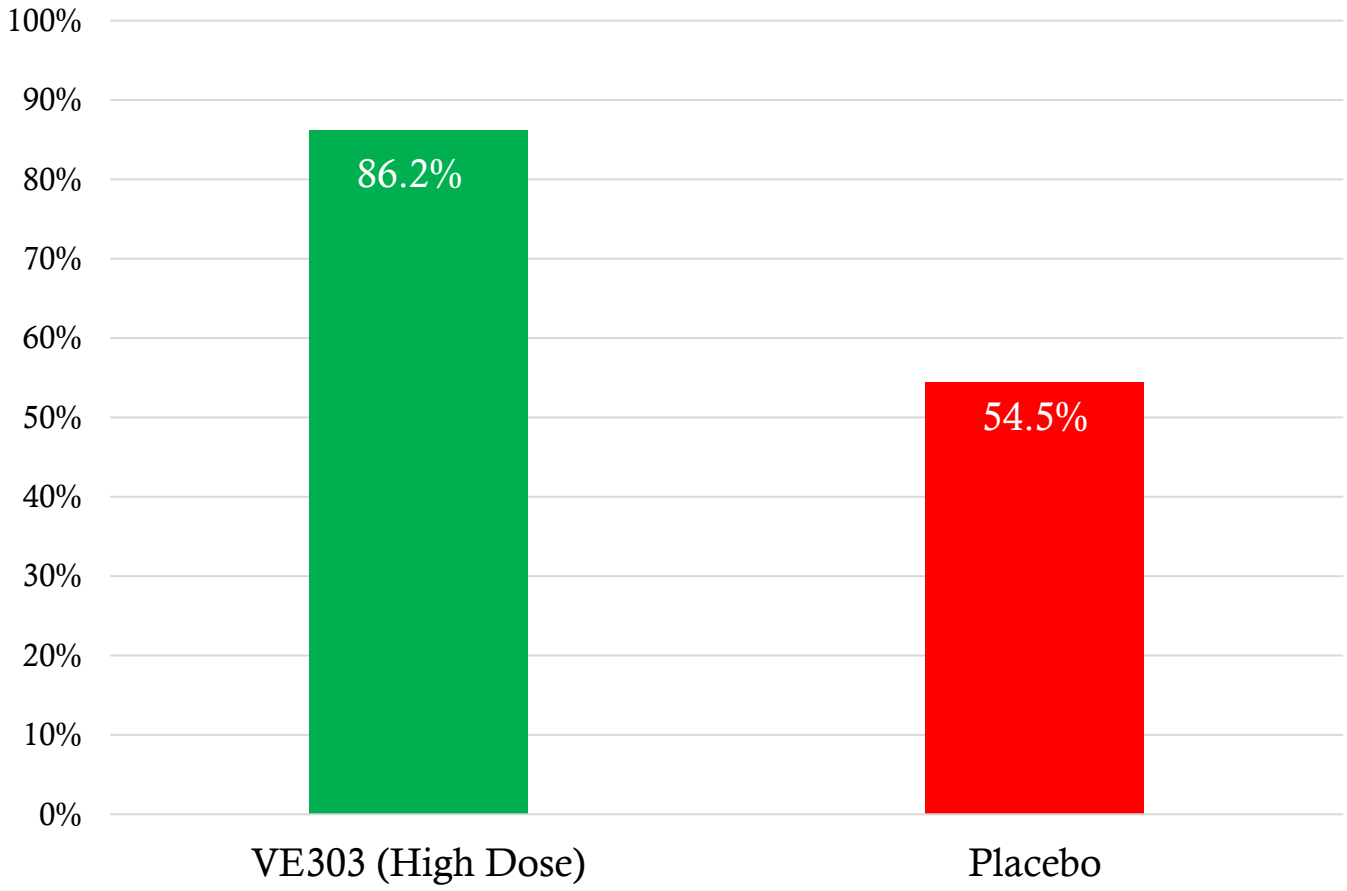
STRAIN #8
Flavonifractor plautii

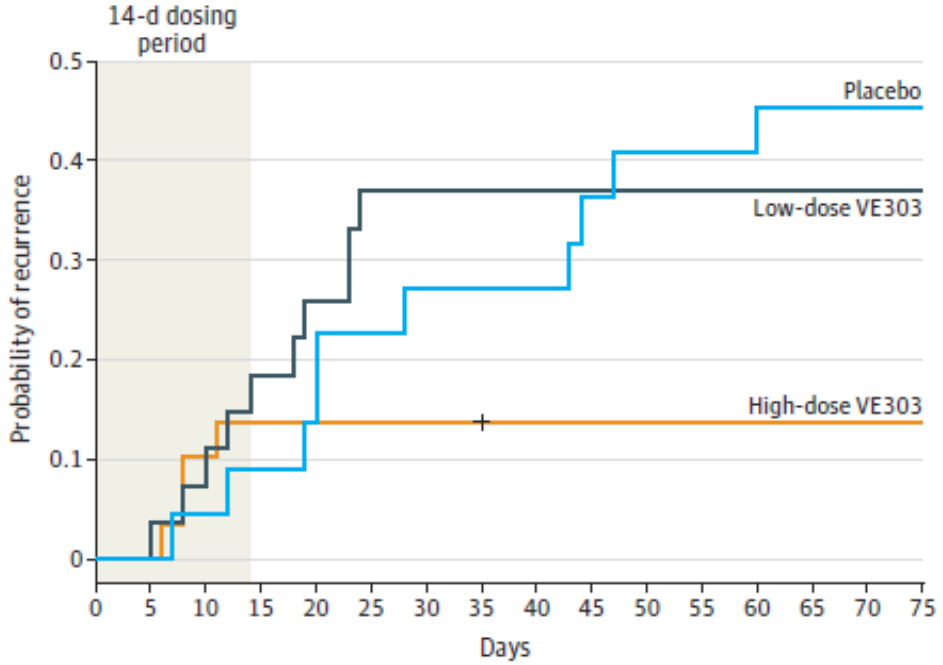
CONSORTIUM TRIAL:
Phase 2 Trial Design VE303



Louie et al. JAMA epub 2023 Apr 15

Consortium Trial: VE303
Phase 2 Trial
High Dose VE303 vs. Placebo, 8 weeks





Louie et al. JAMA epub 2023 Apr 15

Conclusions

- Recurrence is a major problem for CDI
- Antimicrobials largely treat half of the infection
- “Add on” therapies can significantly boost efficacy
- Bezlotoxumab is unfortunately no longer available
  - AZD-5148 might be the next generation
- MRT is safe and effective
  - Openbiome is no longer available
  - RBL and VOS are safe and effective
  - Keep your eyes out for VE303

Kerrie Davies

Kerrie Davies is a Consultant Clinical Scientist and Head of the HCAI research Group Laboratory. She is currently Co-lead for the Early Diagnosis and Personalised Care theme of the HealthTech Research Centre as well as Deputy theme lead of the Infection and AMR theme of the NIHR Leeds Biomedical Research Centre (BRC) at Leeds Teaching Hospitals NHS Trust. Kerrie is also Honorary Associate Professor of diagnostics for infectious disease at University of Leeds; Co-chair Empower Leeds Women, and Chair for the European Society of Clinical Microbiology and Infectious Disease study group committee for *C. Difficile*.

Kerrie has been researching *in vitro* diagnostics for over 20 years and defined the optimal C. difficile testing algorithm which was adopted in the UK and recommended in European, American, and Australasian testing guidelines. She has a passion for the impact of research on patients and healthcare, and in particular, supporting healthcare scientists in research careers. She was awarded CSO Healthcare Scientist of the year in 2021 for her work on COVID-19 diagnostics and an MBE for services to Healthcare Science in 2025.

Updates on Diagnosis

Dr Kerrie Davies

Consultant Clinical Scientist/Honorary Associate Professor of Diagnostics for Infectious Diseases
Deputy Lead AMR and Infection Theme, NIHR Leeds BRC
Co-Lead Early diagnosis and prevention Theme, NIHR Leeds HealthTech Research Centre
Co-chair Empower Leeds Women
Healthcare Associated Infections Research Group
Leeds Teaching Hospitals NHS Trust/University of Leeds

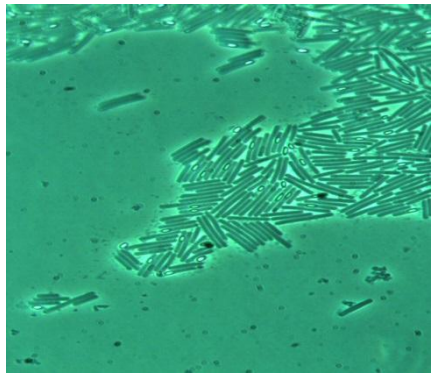
Chair, European Society of Clinical Microbiology and Infectious Disease study group committee for *C. difficile*

Chair C. Diff Trust

Disclosures

- Received research funding to the institute:
  - Astellas Pharma Europe Ltd (EUCLID)
  - bioMérieux
  - Pfizer
  - Techlab Inc
  - Sanofi Pasteur
  - Cepheid
  - Merck
  - A&J BioSciences
- Combacte-CDI:
  - Consortium of 7 academic and 6 EFPIA partners
    - BioMerieux, GSK, Pfizer, Astra-Zeneca, Sanofi-Pasteur, DaVolterra
- Received honorarium from:
  - Astellas Pharma Europe Ltd
  - Summit
  - Cepheid
  - Becton Dickinson
  - Tillotts Pharma UK

Diagnosis…it's complicated



Bug

- Grow the organism (culture)
- Cell surface protein (GDH)

More sensitive
***C. difficile* carriage**

Its Toxins

- Toxin activity
- Toxin protein

More specific
Lack of sensitivity

Its DNA

- Toxin genes (NAAT)

More sensitive
***C. difficile* carriage**

Information courtesy of Dr Kerrie Davies

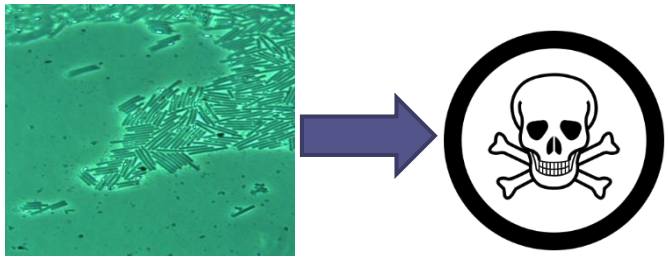
Not all toxin EIA tests are the same

Test	Sensitivity %
1	93
2	93
3	79
4	69
5	92
6	93
7	80
8	86
9	80

Eastwood et al J Clin Microbiol. 2009 Oct;47(10):3211-7

What about reference assays?

There are two reference methods



Cytotoxigenic culture

- Detects the presence of the bug (by culture) with the ability to produce toxin
- Good to assess performance of GDH/NAAT assays

Cell cytotoxicity neutralisation assay (CCNA)

- Detects the presence of toxin in the sample
- Good to assess performance of toxin detection assays

Fang et al 2017 Journal of Clinical Microbiology 55(3): 670-680.
Planche and Wilcox 2015 Infectious Disease Clinics of North America 29(1): 63-82

Which reference assay is more clinically reflective?

Stool status	Outcome		Total number of inpatients	% of inpatients that died (95% CI)
	Survived	Died		
1-Cytotoxin positive	392	78	470	16.6 (13.3-20.3)
2-Cytotoxin negative/cytotoxigenic culture positive	217	25	242	10.3 (6.8-14.9)
3-Both reference tests negative	5,836	539	6,375	8.5 (7.8-9.2)
Total	6,445	642	7,087	9.1 (8.4-9.8)

1 vs 2 Odds ratio 1.73 (1.-7-2.79) P = 0.026
1 vs 3 OR 2.15 (1.66-2.79) P <0.001
2 vs 3 OR 1.25 (0.82-1.91) P = 0.306

Planche T, et al. *Lancet Infectious Diseases* 2013; **13:** 936-945.

So what is the optimal diagnostic method?

So what is the optimal method?

- Large multicentre study compared single tests and algorithms with both reference methods
- Most sensitive algorithm = GDH/NAAT
- Most specific algorithm = Toxin EIA/NAAT
- Outcome analyses showed that a positive cytotoxin test correlates significantly with mortality (severity of disease)
- But, there is a third way…the Optimal method

Bug

Toxin

EIA: enzyme immunoassay, **GDH:** glutamate dehydrogenase, **NAAT:** nucleic acid amplification test, **PCR:** polymerase chain reaction

Planche T, et al. *Lancet Infectious Diseases* 2013; **13:** 936-945.

The optimal method

- GDH/Toxin EIA
  - Very similar performance to the algorithm optimised for specificity but detects clinically important toxin
  - High sensitivity of GDH as first line indicates possible presence of *C. difficile*
    - GDH +/Toxin EIA +ve = CDI likely present
    - GDH +/Toxin EIA –ve = *C. difficile* present
    - GDH –ve = No CDI or *C. difficile* present

(Potential C. diff excretor)

EIA: enzyme immunoassay, **GDH:** glutamate dehydrogenase, **NAAT:** nucleic acid amplification test, **PCR:** polymerase chain reaction

Planche T, et al. *Lancet Infectious Diseases* 2013; **13:** 936-945.

Diagnostic guidelines

- European Society of Clinical Microbiology and Infectious Diseases (ESCMID):
  - Detection of organism (GDH or NAAT), with reflex testing for *C. difficile* toxins
- IDSA/SHEA (USA):
  - Detection of organism (GDH or NAAT), with reflex testing for *C. difficile* toxins
  - Standalone NAAT with appropriate diagnostic stewardship
- ASID (Australasian)
  - Laboratories should use a screening test that is of adequate sensitivity (>90%) and adopt a testing algorithm that ensures specificity of the final result

Crobach MJ, et al. *Clinical Microbiology Infection* 2016; **12:** 1053-66.
McDonald et al, Clinical Infectious Disease.2018 66(7) 987-994.
Trubiano et al, Intern Med J. 2016 Apr;46(4):479-93.

What about standalone NAAT tests?

NAAT standalone tests

Advantages

- Rapid
- Simple
- Detects only toxigenic strains

Rates of asymptomatic carriage in hospitalised patients can vary from ~4.4-21%

Dependant on method of detection

NAAT cannot distinguish between colonisation/carriage and disease (CDI)

Overdiagnosis

Rates will be higher if you use NAAT testing

Disadvantages

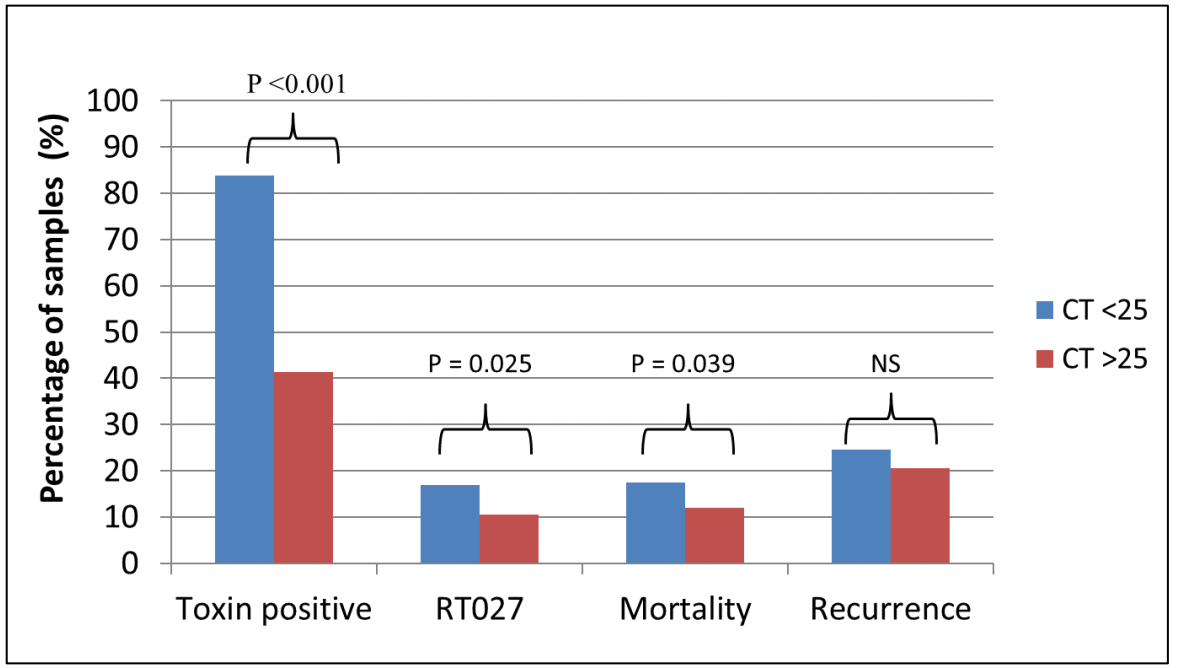
- Does not only detect 'true' CDI (no free toxin)
- NAAT+ve/Tox+ve significantly associated with;
  - higher bacterial load, greater Abx exposure, inflammation of the gut, presence of diarrhoea (all $p<0.001$) and longer duration of diarrhoea ($p= 0.03$), compared with NAAT+ve/Tox-ve patients
- CDI attributable mortality significantly higher in NAAT+ve/Tox+ve vs NAAT+ve/Tox-ve (8.4% vs 0.6% $p = 0.001$)

Polage et al :JAMA internal medicine 2015 175(11):1792-1801,
Truong et al. Diagnostic Microbiology and Infectious Disease 2017

NAAT: nucleic acid amplification test
Abx: antibiotic

Possible added value from diagnostic tests

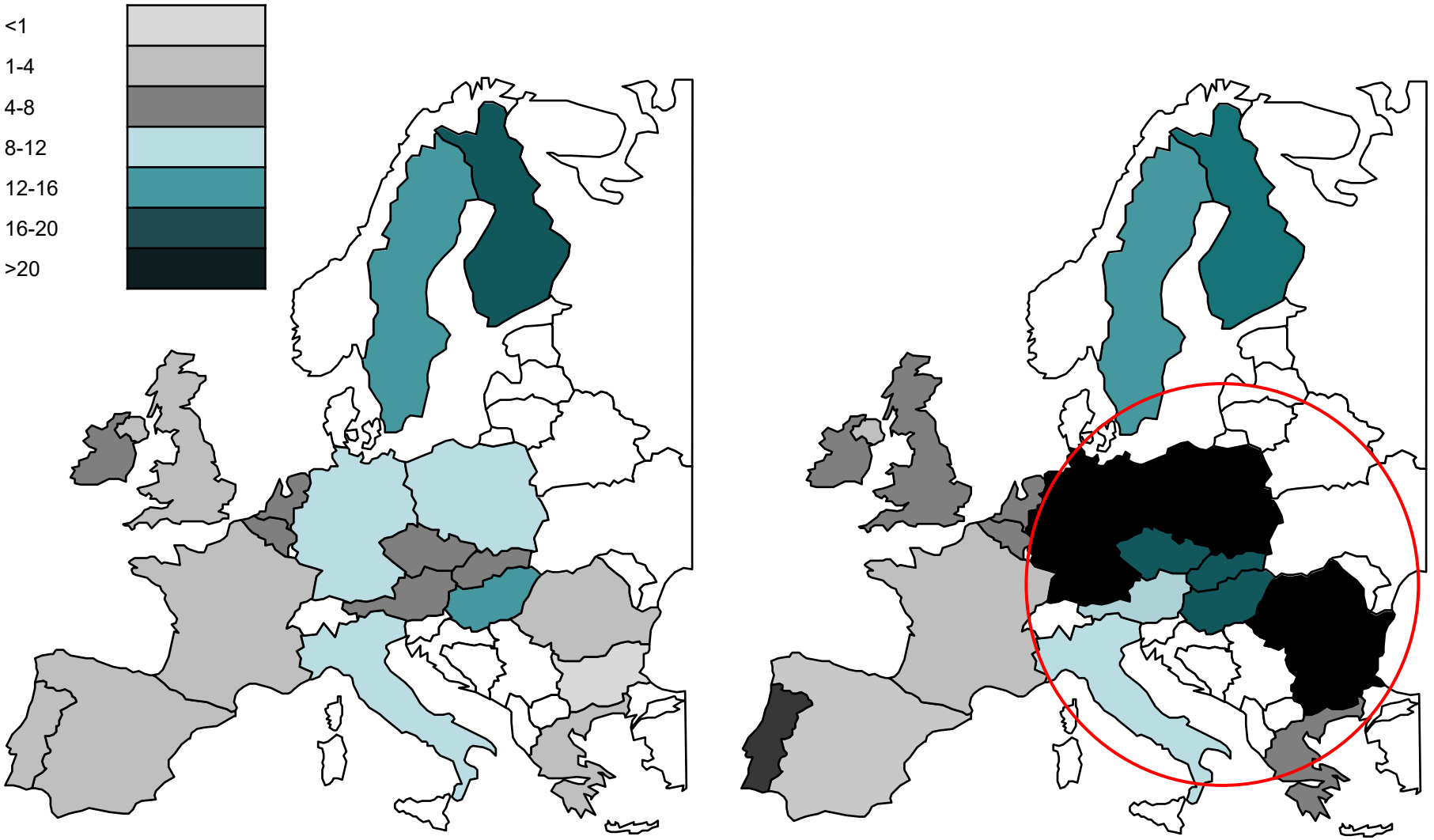
- Appears to be a correlation between burden of disease and severity
- NAAT tests can provide some information on bioload within the sample (CT value)
  - Correlates with toxin positivity, severity, length of stay and mortality
  - May guide treatment options
    - Bezlotoxumab



Davies et al. PLoS One. 2018 Dec 5;13(12)
Reigadas et al Journal of Antimicrobial Chemotherapy 2016 71(5): 1380-1385

What about who and when you test?

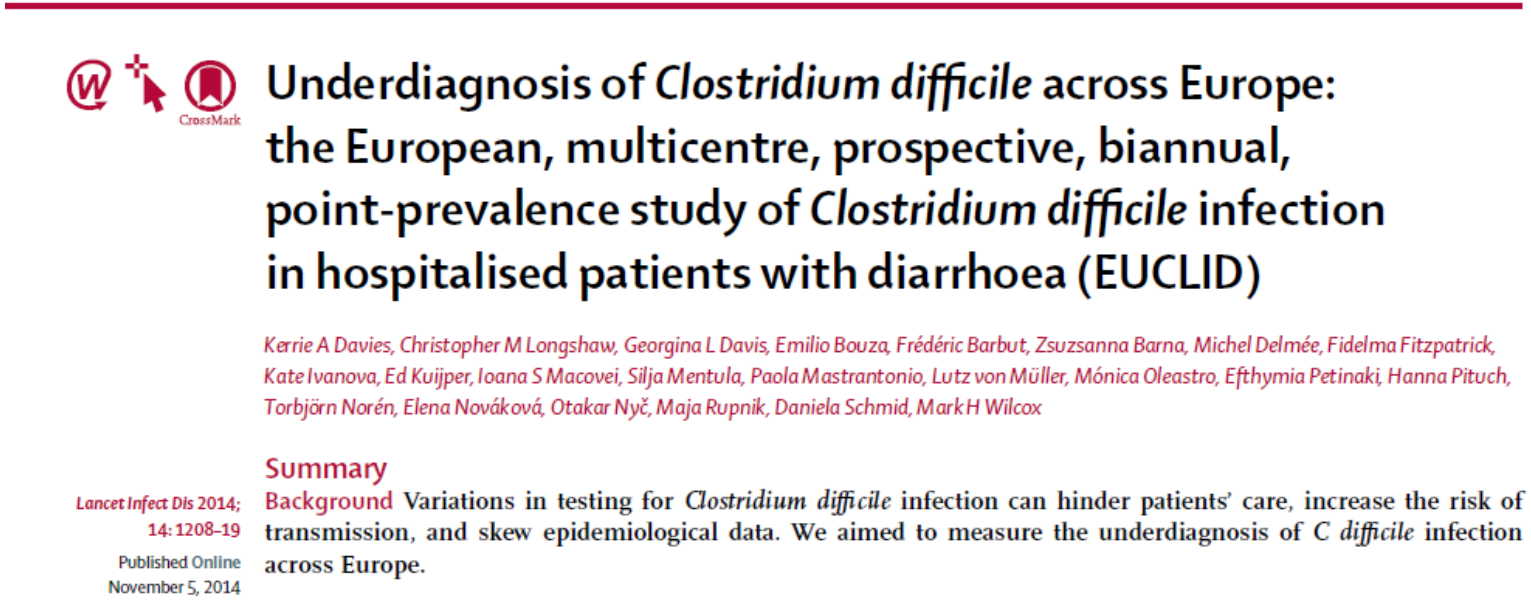
There are more cases of CDI than are reported



Reported

Measured

Underdiagnosis of cases



Underdiagnosis of *Clostridium difficile* across Europe: the European, multicentre, prospective, biannual, point-prevalence study of *Clostridium difficile* infection in hospitalised patients with diarrhoea (EUCLID)

Kerrie A Davies, Christopher M Longshaw, Georgina L Davis, Emilio Bouza, Frédéric Barbut, Zsuzsanna Barna, Michel Delmée, Fidelma Fitzpatrick, Kate Ivanova, Ed Kuijper, Ioana S Macovei, Silja Mentula, Paola Mastrantonio, Lutz von Müller, Mónica Oleastro, Efthymia Petinaki, Hanna Pituch, Torbjörn Norén, Elena Nováková, Otakar Nyč, Maja Rupnik, Daniela Schmid, Mark H Wilcox

Lancet Infect Dis 2014; 14: 1208–19

Published Online November 5, 2014

Summary

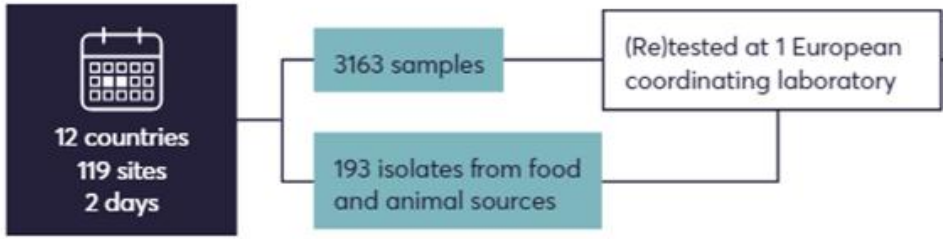
Background Variations in testing for *Clostridium difficile* infection can hinder patients' care, increase the risk of transmission, and skew epidemiological data. We aimed to measure the underdiagnosis of *C difficile* infection across Europe.

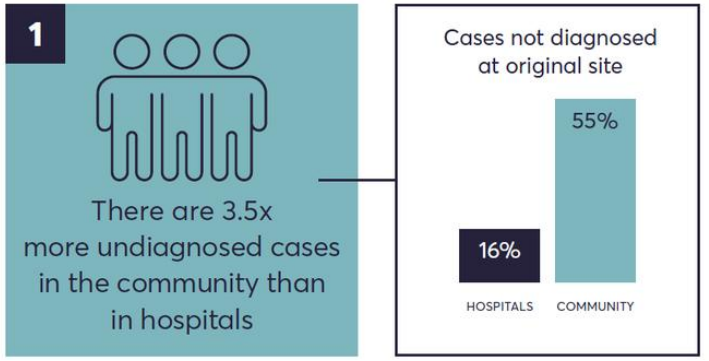
This study estimated the under-ascertainment of CDI in hospitals across Europe to be

23%

There are more missed cases in the community

- Testing ALL samples submitted enabled detection of missed cases
- There were a higher proportion of undiagnosed cases in the community than in the hospital
  - **55% community cases missed**
  - **16% hospital cases missed**
- Lack of clinical suspicion led to lack of testing

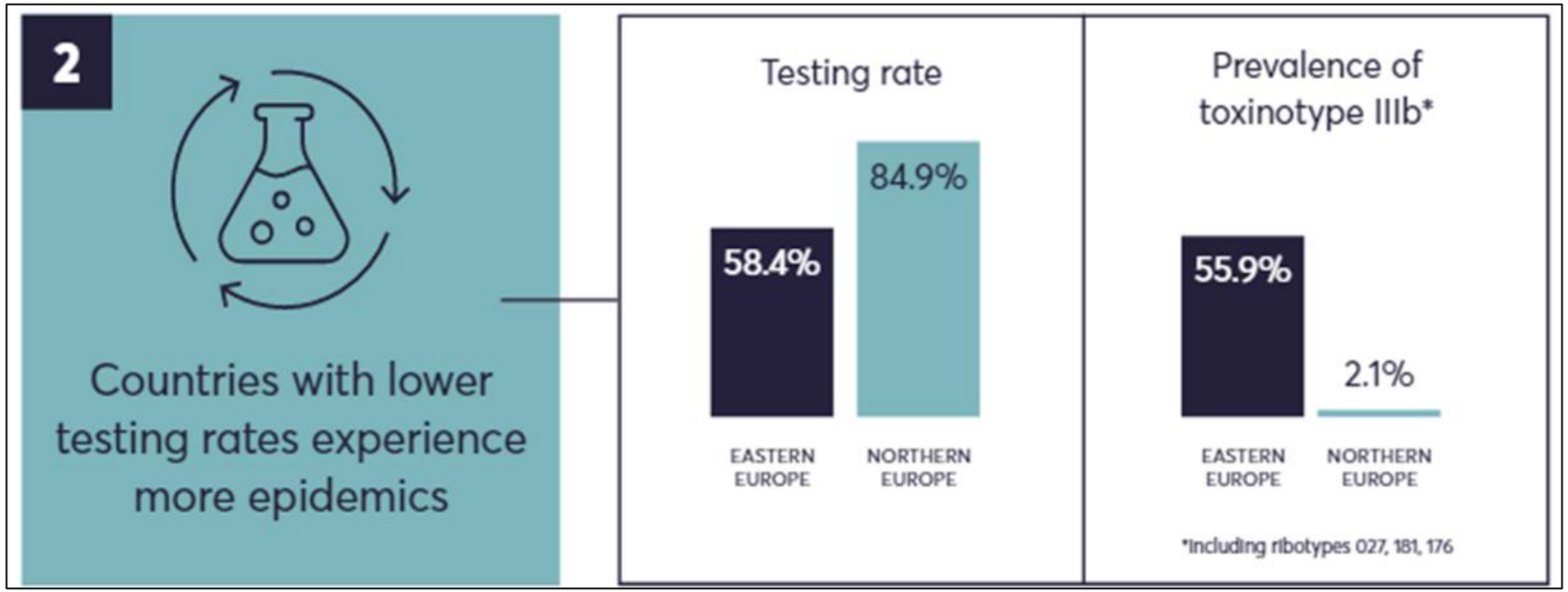




3x more undiagnosed community CDI cases compared to hospital
(~111000 vs. 37000 cases/year in Europe)

Viprey et al Eurosurveillance 2022 Jun;27(26):2100704.

Increased awareness reduces outbreaks



- This suggests that lack of suspicion and testing leads to
  - Under-diagnosis
  - Outbreaks of infection
  - Suggests possible spread from hospitals to community or vice versa

Viprey et al Eurosurveillance 2022 Jun;27(26):2100704.

Adverse outcomes for missed cases of CDI -EUCLID

- 80% of missed cases had no documented reason for failure to test for CDI
- Missed CDI cases were:
  - Younger
  - Associated with significantly increased length of diarrhoea
  - They were not less sick
    - All cause mortality and white cell counts were similar in both groups, although 'missed' cases had a higher temperature
- There is potential for adverse outcomes if CDI diagnoses are missed
  - For the patient
  - For onward transmission

Mini-oral eposter Davies et al ECCMID 2016

Adverse outcomes for missed cases of CDI-COMBACTE-CDI

- Of hospital missed cases
  - Two were re-admitted to hospital twice (after initial non-treatment for CDI); one died within 4 months; the other received a diagnosis of CDI after 40 days

- Of community missed cases
  - Most were under 65 years old (88%)
  - Two thirds of those reported a history of potential risk factors for CDI;
    - antibiotic use, previous CDI or contact with a healthcare facility
  - None of these cases were treated for CDI
  - One obtained a delayed CDI diagnosis (25 days after the original sample) and required three hospital admissions

Viprey et al Eurosurveillance 2022 Jun;27(26):2100704.

Who should we test? - Diagnostic stewardship

Should consider:

- Symptomatic
  - Diarrhoea
  - Faecal sample takes the shape of the container
- Not on laxatives

Should not exclude by:

- Age
  - Missed patients are younger
- Hospital contact
  - Some community cases do not have healthcare contact

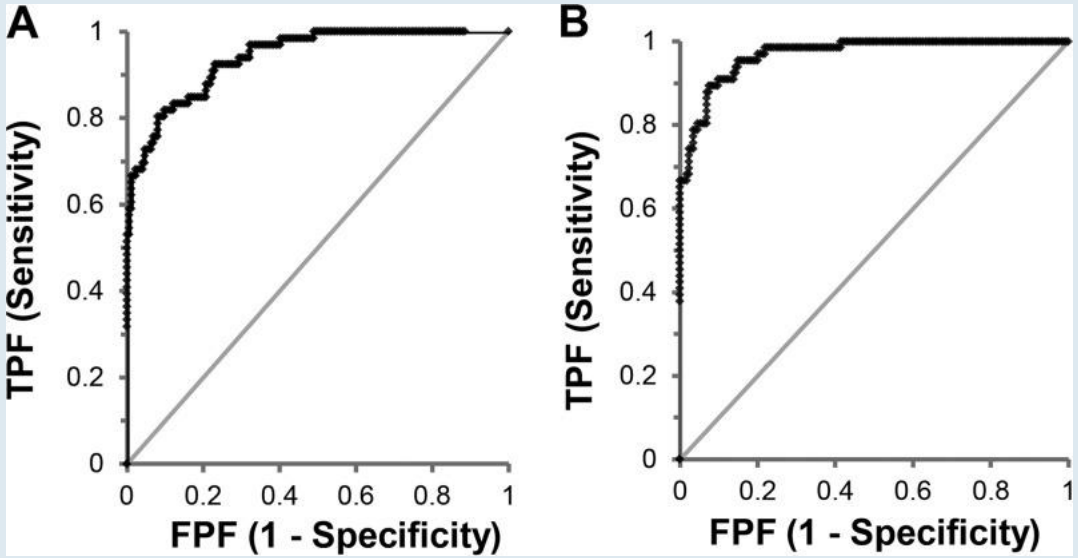
Ultimately this impacts patients lives, so let’s get this right!

The future

Novel technologies

- Ultrasensitive *C. difficile* toxin detection assays
  - Potential to detect lower levels of toxin
  - Potential to differentiate CDI cases and carriage

- Unfortunately, none currently on the market



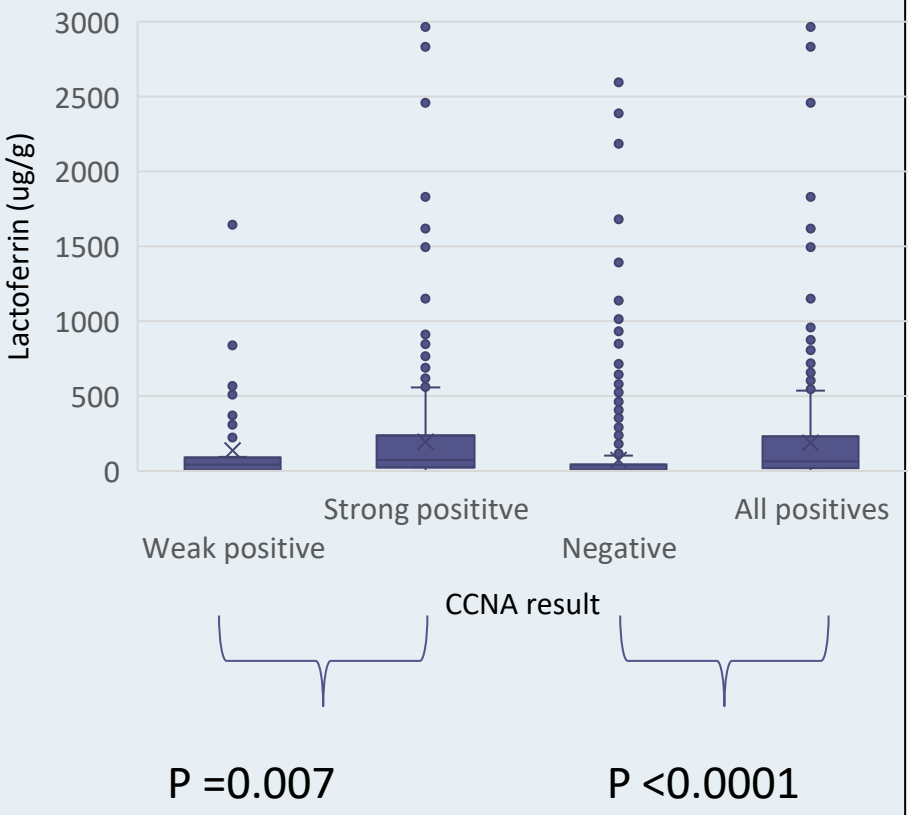
Receiver operating characteristic (ROC) curves obtained for SIMOA toxin A (A) and toxin B (B) assays. The ROC curves of SIMOA toxin A and toxin B assays are created by plotting the true-positive rate against the false-positive rate at various threshold settings, using the concentration obtained for each pretreated sample and the CDI status of the patient (n = 240).

Pollock N. Journal of Clinical Microbiology 2016 54(2): 259-264
Banz et al Journal of Clinical Microbiology 2018 56(8) pii: e00452-18
Pollock et al. Clinical Infectious Disease 2019 68(1): 78-86
Viprey et al Eurosurveillance 2022 Jun;27(26):2100704

Additional laboratory assays

- Gut inflammatory markers
  - Lactoferrin
  - Calprotectin
- Higher levels of both in patients with CDI vs controls
- May be a marker of severity of CDI
- Adding lactoferrin to GDH pos/Toxin neg EIA results increased sensitivity
  - Useful added value for clinicians when uncertain about validity of EIA result
  - Reduces overall specificity if used on ALL samples

Lactoferrin results for different categories of CCNA



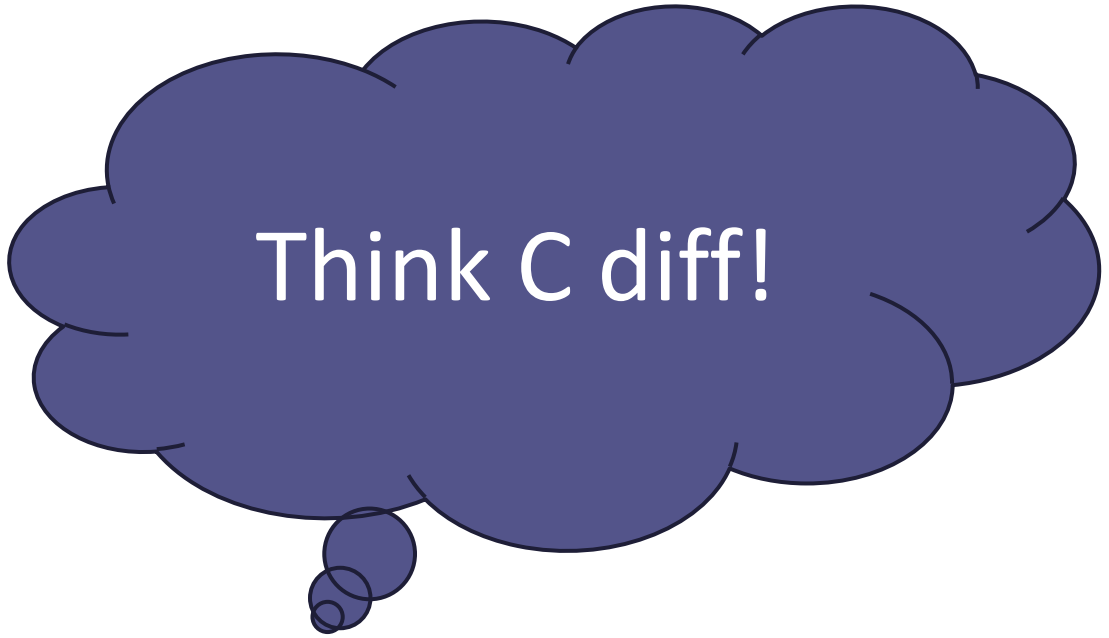
Increasing algorithm sensitivity

		CCNA
		Pos
GDH/Toxin/ Lactoferrin	Pos	363
	Neg	25
		388

Previous sensitivity	82.6%
New sensitivity	93.6%

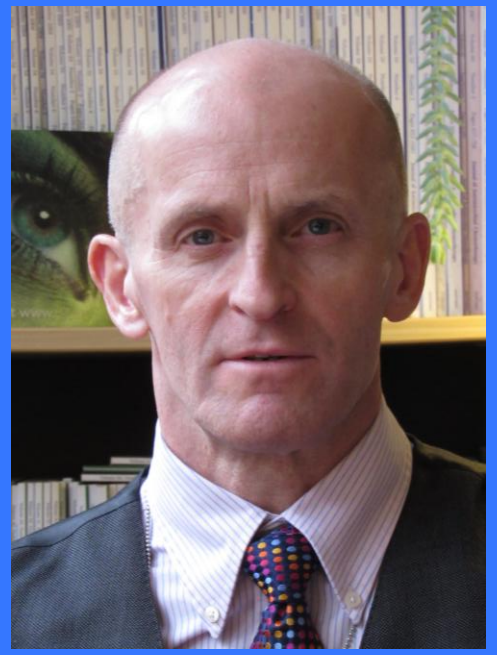
Specificity will ↓

Barbut et al European Journal of Clinical Microbiology and Infectious Disease 2017 36(12): 2432-2430
Kim et al Annals of Laboratory Medicine 2017 37(1): 53-57
Davies. Poster at ESCMID Global 2023


Think C diff!


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos

Mark Wilcox



Mark Wilcox is Professor of Medical Microbiology at the University of Leeds, UK and a Consultant Microbiologist. He is also Head of Microbiology Research & Development at Leeds Teaching Hospitals NHS Trust (LTHT) and Expert on C. difficile infection for UK Health Security Agency and National Clinical Director of Antimicrobial Resistance Diagnostics & Infection Prevention and Control for NHS England.

Mark has formerly been the Director of Infection Prevention and an Infection Control Doctor, Clinical Director of Pathology and Head of Microbiology at LTHT. He leads a Healthcare-Associated Infection Research Group at the University of Leeds. In 2024, he was awarded an OBE in the King's New Year's Honours for services to healthcare, and especially Infection Prevention & Control.

C. difficile infection prevention & therapy

Current developments

Professor Mark Wilcox

University of Leeds & Leeds Teaching Hospitals, UK

NHS England (National Clinical Director for IPC & AMR)

UK Health Security Agency (Expert on *C. difficile*)

CDI therapeutic pipeline

Phase 2

- Ibezapolstat (Efficacy, safety, pharmacokinetics, and associated microbiome changes of ibezapolstat compared with vancomycin in adults with Clostridioides difficile infection: a phase 2b, randomised, double-blind, active-controlled, multicentre study - PubMed) **16 + 14**
- CRS3123 (Safety and efficacy of CRS3123 in adults with a primary episode or first recurrence of Clostridioides difficile infection: a phase 2, randomised, double-blind, multicentre, vancomycin-controlled study - The Lancet Infectious Diseases) **29 + 14**
- LMN-201
- AZD 5148
- REC-3964
- EXL01
- NCTD-M3
- ORAL-LYO-FMT

Phase 3

- Ridinilazole appears to have been discontinued
- VE303

VE303 (Vedanta)

Study Overview

Brief Summary

The overall objective of the RESTORATiVE303 study is to evaluate the safety and the Clostridioides difficile infection (CDI) recurrence rate at Week 8 in participants who receive a 14-day course of VE303 or matching placebo. The objectives and endpoints are identical for Stage 1 (recurrent CDI) and Stage 2 (high-risk primary CDI).

Official Title

A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of **VE303** for Prevention of Recurrent Clostridioides **Difficile** Infection

Conditions

Clostridium Difficile | Clostridium Difficile Infections | Clostridium Difficile Infection Recurrence | Clostridioides Difficile Infection | Clostridioides Difficile Infection Recurrence | CDI | C. Diff Infection | Recurrent Clostridium Difficile Infection | C.Difficile Diarrhea | Diarrhea Infectious

Intervention / Treatment

- Biological: **VE303**
- Biological: Placebo

Other Study ID Numbers

- VE303-003

Study Start (Actual)

2024-05-20

Primary Completion (Estimated)

2027-06

Study Completion (Estimated)

2027-10

Enrollment (Estimated)

852

Study Type

Interventional

Phase

Phase 3

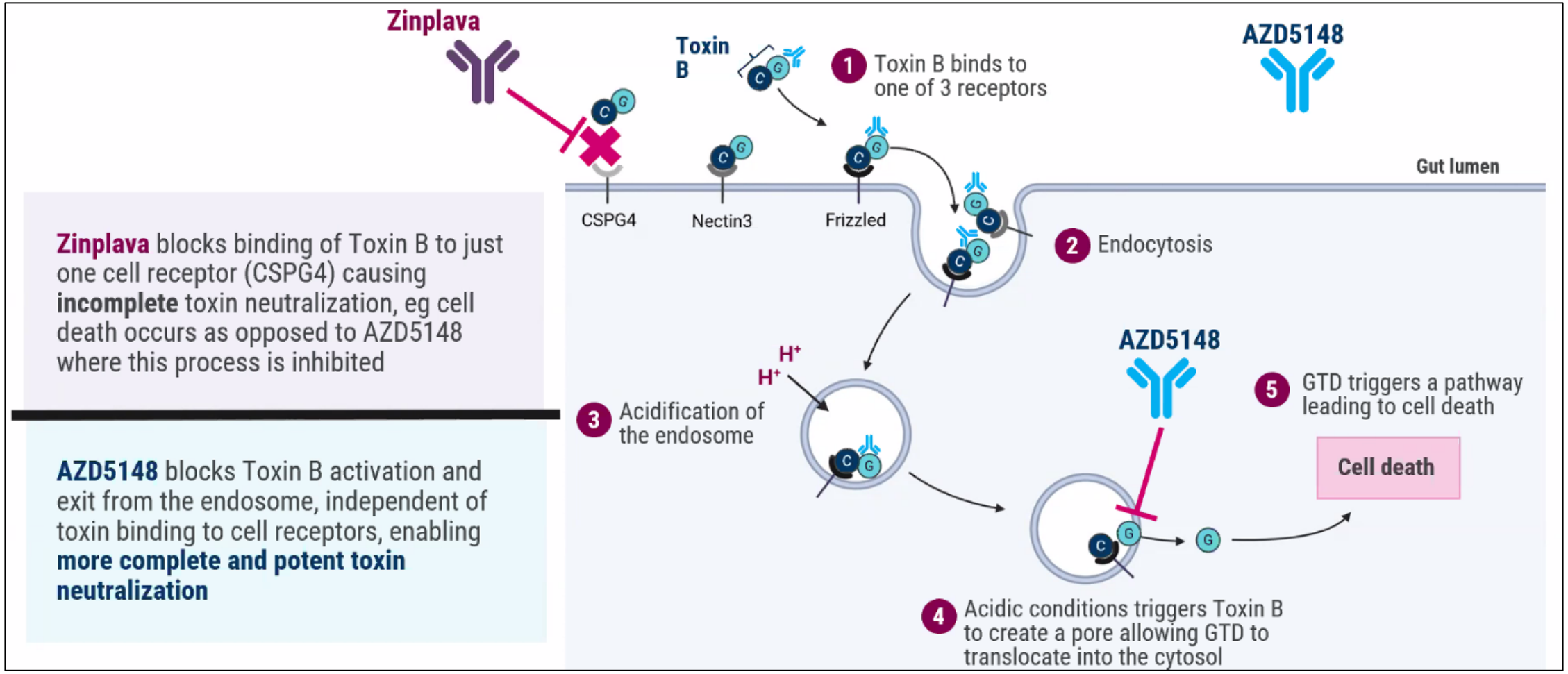
https://clinicaltrials.gov/study/NCT06237452?cond=Difficile&intr=VE303&rank=2

LMN-201 (Lumen Bioscience)

- LMN-201 consists of orally delivered whole, dried, non-viable biomass of spirulina (*Arthrospira platensis*) grown from 4 separate strains, each of which has been engineered to express one of the following therapeutic proteins:
  - 3 toxin-binding proteins that bind and inhibit *C. difficile* toxin B
  - 1 lysozyme-like enzyme that selectively degrades the C. difficile cell wall (- rapid destruction)
- NCT05330182 is a phase 2, randomized, double-blind, placebo-controlled study of LMN-201 for prevention of CDI recurrence
- Started Aug 2024 ??? - estimated completion Dec 2027; aiming to enrol 375 subjects
- 21 patients completed 7 days of LMN-201 plus standard of care (SoC) antibiotics (metronidazole, vancomycin, or fidaxomicin). All patients (21/21; 95% confidence interval (CI) 85%-100%) achieved initial clinical resolution, significantly outperforming ($p<<0.001$) the 80% initial clinical cure rate (625/781; 95% CI 77-83%) observed in the active arm of the large MODIFYI and II studies.

https://clinicaltrials.gov/study/NCT05330182?cond=Difficile&intr=LMN-201&rank=1

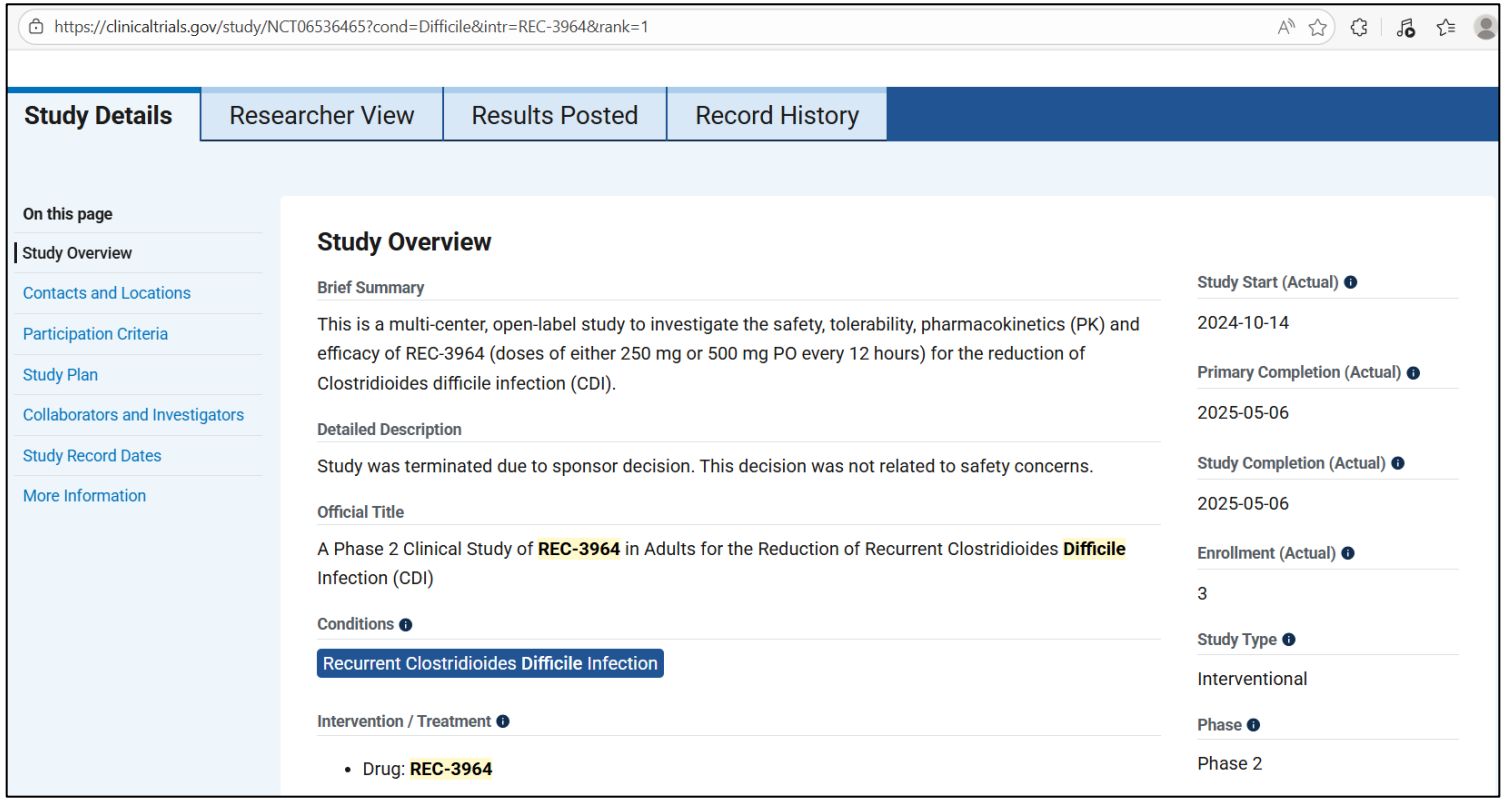
Toxin B neutralistion – bezlotoxumab vs AZD 5148



https://clinicaltrials.gov/study/NCT07285213?intr=AZD5148&rank=3

REC-3964 (Recursion)

- REC-3964 is an oral, novel, diazepinedione-class chemical entity identified from Recursion's high-content phenotypic imaging platform. REC-3964 inhibits toxins associated with CDI



https://clinicaltrials.gov/study/NCT06536465?cond=Difficile&intr=REC-3964&rank=1

EXL01

- *Faecalibacterium prausnitzii* constitutes a specific therapeutic target; it is a commensal bacterium of the human gut, making up nearly 5% of the fecal microbiota - associated with an individual's state of health
- Evaluation of EXL01, a new live biotherapeutic to prevent recurrence of CDI in high-risk patients (LIVEDIFF). Phase I/II trial to assess the efficacy and safety of oral administration of EXL01, a single isolated unmodified strain of *F. prausnitzii*, in preventing CDI recurrence in high-risk patients (Sponsor = Hospices Civils de Lyon)
- The study will be conducted in 2 parts. The phase I (Part A) is planned to include 6 patients. The phase II (Part B) will include 50 patients in two arms (25 patients each arm)
- Up to 9 sites in France; target 56 subjects; estimated trial end - 2027

https://clinicaltrials.gov/study/NCT06306014?cond=Difficile&intr=EXL01&rank=1

NCTD-M3

- NTCD-M3 has also been awarded Fast Track status by the FDA. Destiny Pharma acquired global rights to the NTCD-M3 program in November 2020
- Exclusive collaboration and co-development agreement for NTCD-M3 with Sebela Pharmaceuticals® worth up to $570m plus royalties
- Destiny Pharma became insolvent in 2024
- AMR-Bio

Clinical Infectious Diseases
MAJOR ARTICLE

A Randomized Controlled Trial of Efficacy and Safety of Fecal Microbiota Transplant for Preventing Recurrent *Clostridioides difficile* Infection

Dimitri M. Drekonja,[1,a] Aasma Shaukat,[2,a] Yuan Huang,[3,4] Jane H. Zhang,[3] Andrew R. Reinink,[1] Sean Nugent,[1] Jason A. Dominitz,[5] Anne Davis-Karim,[6] Dale N. Gerding,[7] and Tassos C. Kyriakides[3,4]

[1]Division of Infectious Diseases, Department of Medicine, Minneapolis Veterans Affairs Health Care System, Minnesota, USA; [2]Division of Gastroenterology, Department of Medicine, New York Harbor Veterans Affairs Healthcare System, New York, USA; [3]Veterans Affair Cooperative Studies Program Coordinating Center-West Haven, West Haven, Connecticut, USA; [4]Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut, USA; [5]Division of Gastroenterology, Department of Medicine, Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA; [6]Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico, USA; and [7]Division of Infectious Diseases, Department of Medicine, Edward Hines Jr Veterans Affairs Hospital, Hines, Illinois, USA

Background. *Clostridioides difficile* infection (CDI) is the most common cause of healthcare–associated infections in US hospitals, with 15%–30% of patients experiencing recurrence. The aim of our randomized, double-blind clinical trial was to assess the efficacy of capsule-delivered fecal microbiota transplant (FMT) versus placebo in reducing recurrent diarrhea and CDI recurrence. The secondary aim was FMT safety assessment.

Methods. Between 2018 and 2022, Veterans across the Veterans Health Administration system with recurrent CDI who responded to antibiotic treatment were randomized in a 1:1 ratio to oral FMT or placebo capsules. Randomization was stratified by number of prior CDI recurrences (1 or ≥2). The primary endpoint was clinical recurrence by day 56, defined as >3 unformed stools daily for ≥2 days with or without laboratory confirmation of *C. difficile*, or death within 56 days.

Results. The study was stopped due to futility after meeting prespecified criteria. Of 153 participants (76 FMT, 77 placebo) with an average age of 66.5 years, 25 participants (32.9%) in the FMT arm and 23 (29.9%) in the placebo arm experienced the primary endpoint of diarrhea and possible or definite CDI recurrence or death within 56 days of capsule administration (absolute difference, 3.0% [95% confidence interval, −11.7% to 17.7%]). Stratification by number of recurrences revealed no statistically significant differences. There were no clinically important differences in adverse events.

Conclusions. FMT therapy versus placebo did not reduce CDI recurrence or death at 56 days. There were no meaningful differences in adverse events between treatment groups.

Clinical Trials Registration. NCT03005379.

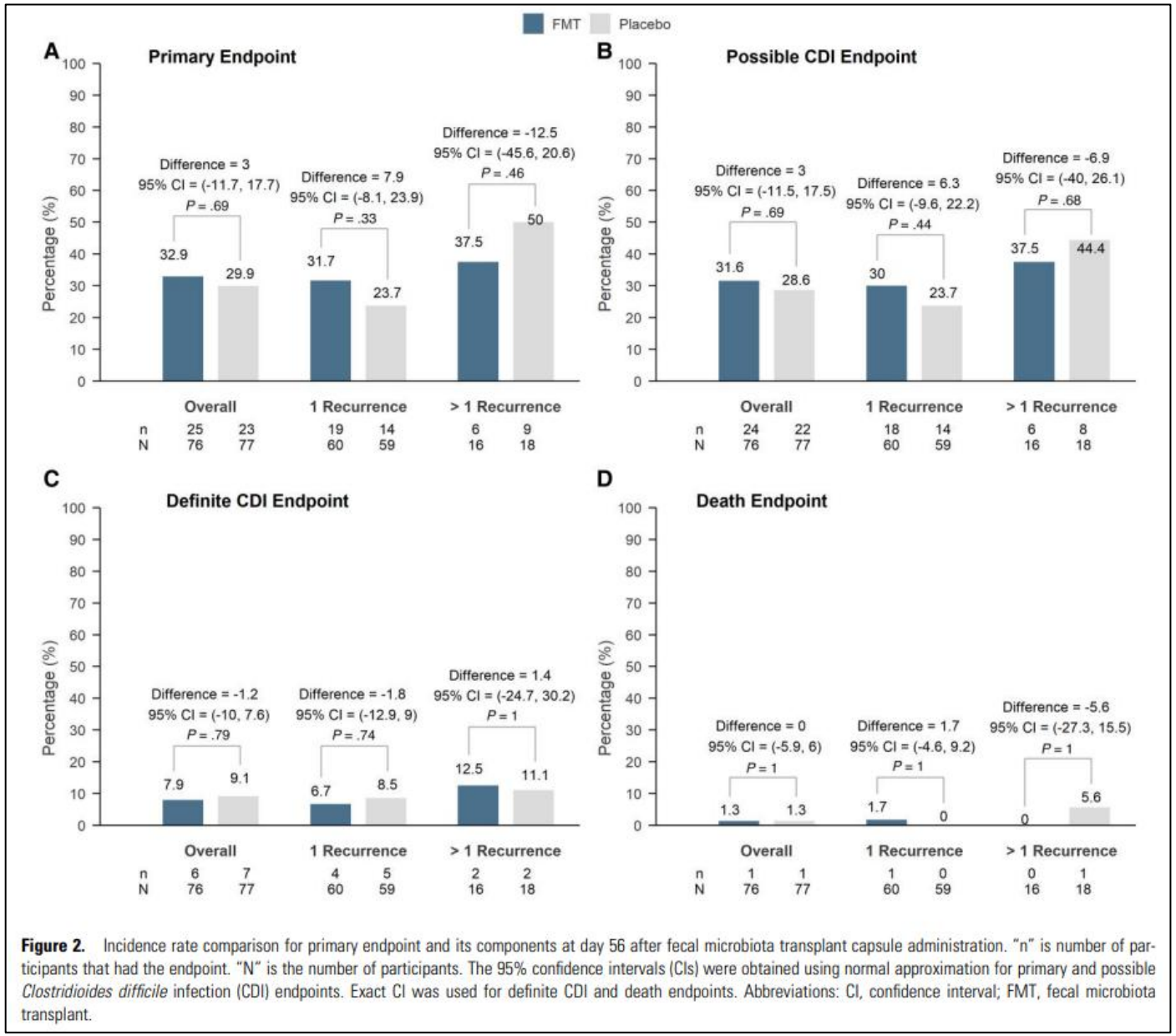
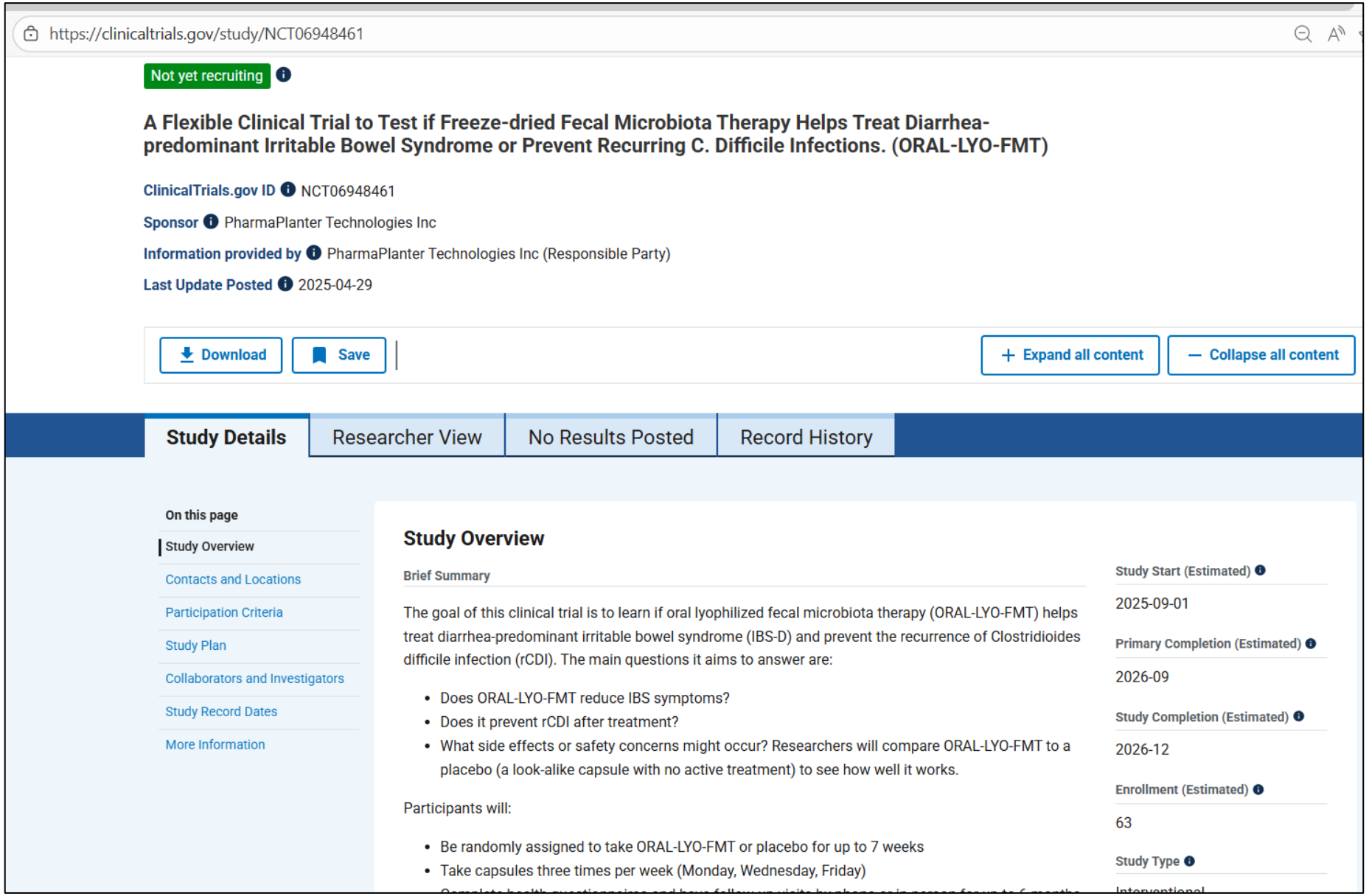


Figure 2. Incidence rate comparison for primary endpoint and its components at day 56 after fecal microbiota transplant capsule administration. "n" is number of participants that had the endpoint. "N" is the number of participants. The 95% confidence intervals (CIs) were obtained using normal approximation for primary and possible *Clostridioides difficile* infection (CDI) endpoints. Exact CI was used for definite CDI and death endpoints. Abbreviations: CI, confidence interval; FMT, fecal microbiota transplant.

Drekonja DM et al. Clin Infect Dis 2024:ciae467. doi: 10.1093/cid/ciae467.

ORAL-LYO-FMT


https://clinicaltrials.gov/study/NCT06948461
Not yet recruiting
A Flexible Clinical Trial to Test if Freeze-dried Fecal Microbiota Therapy Helps Treat Diarrhea-predominant Irritable Bowel Syndrome or Prevent Recurring C. Difficile Infections. (ORAL-LYO-FMT)
ClinicalTrials.gov ID NCT06948461
Sponsor PharmaPlanter Technologies Inc
Information provided by PharmaPlanter Technologies Inc (Responsible Party)
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On this page
Study Overview
Contacts and Locations
Participation Criteria
Study Plan
Collaborators and Investigators
Study Record Dates
More Information
Study Overview
Brief Summary
The goal of this clinical trial is to learn if oral lyophilized fecal microbiota therapy (ORAL-LYO-FMT) helps treat diarrhea-predominant irritable bowel syndrome (IBS-D) and prevent the recurrence of Clostridioides difficile infection (rCDI). The main questions it aims to answer are:
Does ORAL-LYO-FMT reduce IBS symptoms?
Does it prevent rCDI after treatment?
What side effects or safety concerns might occur? Researchers will compare ORAL-LYO-FMT to a placebo (a look-alike capsule with no active treatment) to see how well it works.
Participants will:
Be randomly assigned to take ORAL-LYO-FMT or placebo for up to 7 weeks
Take capsules three times per week (Monday, Wednesday, Friday)
Study Start (Estimated)
2025-09-01
Primary Completion (Estimated)
2026-09
Study Completion (Estimated)
2026-12
Enrollment (Estimated)
63
Study Type
Interventional

Other contenders (?) and failures

- **ridinilazole, surotomycin, cadazolid**, **tolevamer,** ramoplanin, LFF571, SynsorbCD, *SYN-004 (ribaxamase)*

All failed

- MBK-01
- ART24 / ADSO24
- RBX7455, a Non-frozen, Orally Administered Investigational Live Biotherapeutic, Is Safe, Effective, and Shifts Patients' Microbiomes in a Phase 1 Study for Recurrent Clostridioides difficile Infections
- MET-2 appears to be safe, efficacious, and well tolerated among patients with recurrent C difficile infection. Results must be validated in controlled studies

CDI therapeutic pipeline

Phase 2

- Ibezapolstat (Efficacy, safety, pharmacokinetics, and associated microbiome changes of ibezapolstat compared with vancomycin in adults with Clostridioides difficile infection: a phase 2b, randomised, double-blind, active-controlled, multicentre study - PubMed) **16 + 14**
- CRS3123 (Safety and efficacy of CRS3123 in adults with a primary episode or first recurrence of Clostridioides difficile infection: a phase 2, randomised, double-blind, multicentre, vancomycin-controlled study - The Lancet Infectious Diseases) **29 + 14**
- LMN-201
- AZD 5148
- REC-3964
- EXL01
- NCTD-M3
- ORAL-LYO-FMT

Phase 3

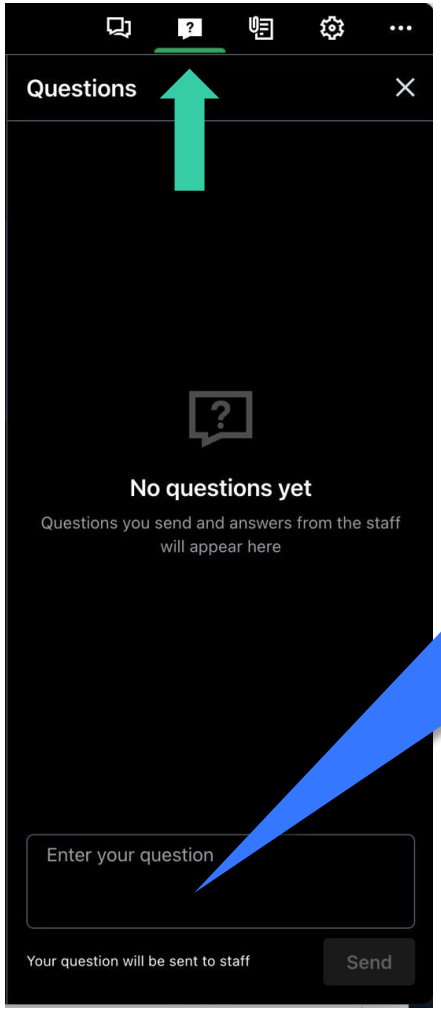
- Ridinilazole appears to have been discontinued
- VE303

$$$$$$ needed

How to submit your questions

REVIVE by GARDP

If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

Today's speakers

REVIVE by GARDP

Current developments in *Clostridioides difficile* prevention, therapy and R&D

Moderator:
Christian John Lillis
Peggy Lillis Foundation, USA

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WHO, Switzerland

Paul Feuerstadt
Yale School of Medicine, USA

Kerrie Davies
University of Leeds, UK

Mark Wilcox
University of Leeds, UK

Upcoming webinars

REVIVE by GARDP

Journal Club: Key findings from recent publications in antimicrobial R&D

- With Melis Anahtar, Nicole Scarangella-Oman, David Paterson & Nazgul Sakenova
- 26 March 2026, 17:00-18:30 CET

Natural Product-inspired antibiotics: Successes and future prospects

- With Mark Butler & Christine Beemelmanns
- 28 April 2026, 09:30-11:00 CEST

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And more coming up!

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