Clostridioides difficile infection

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Clostridium difficile and *Clostridioides difficile*: Two validly published and correct names (Oren and Rupnik , 2018)

Why is C. difficile called that?

The species name difficile is a form of the Latin adjective difficilis because when first identified (by Hall and O'Toole in 1935), the organism was difficult to isolate and grew slowly in pure culture.

Based on 16S rRNA gene sequence analysis, the closest relative of *Clostridium difficile* is *Clostridium mangenotii* with a 94.7% similarity value and both are located within the family *Peptostreptococcaceae* that is phylogenetically far removed from *C. butyricum* and other members of *Clostridium* sensu stricto.

Based on phenotypic, chemotaxonomic and phylogenetic analyses, novel genus *Clostridioides* gen. nov. is proposed for *Clostridium difficile*. Lawson et al., 2016.

Dormant spore vs metabolically active cell

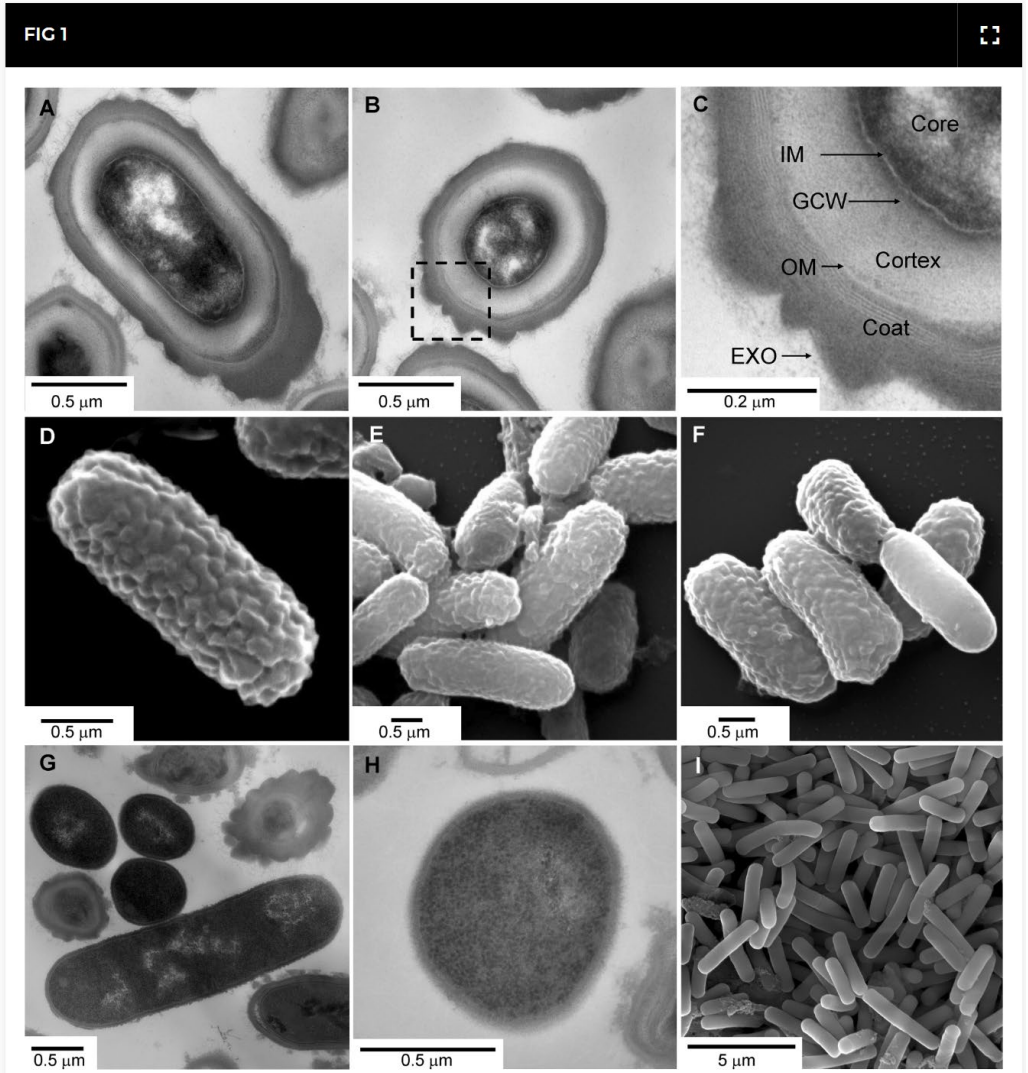
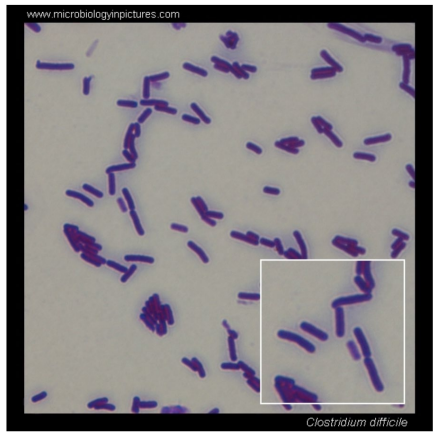
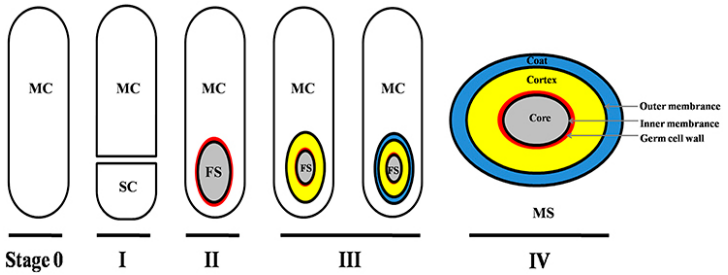


FIG 1 *C. difficile* spore structure and cell morphology visualized by TEM and SEM. Spores (A to F) and vegetative cells (G to I) derived from the *C. difficile* R20291 strain were embedded in epoxy resin, sectioned, and imaged by TEM (A, B, C, G, and H) or were chemically dried, sputter coated, and imaged by SEM (D, E, F, and I). IM, inner membrane; GCW, germ cell wall; OM, outer membrane; EXO, exosporium.



Gram-positive
Obligate anaerobe
Can produce toxins (A, B some strains Binary)
Spore-forming

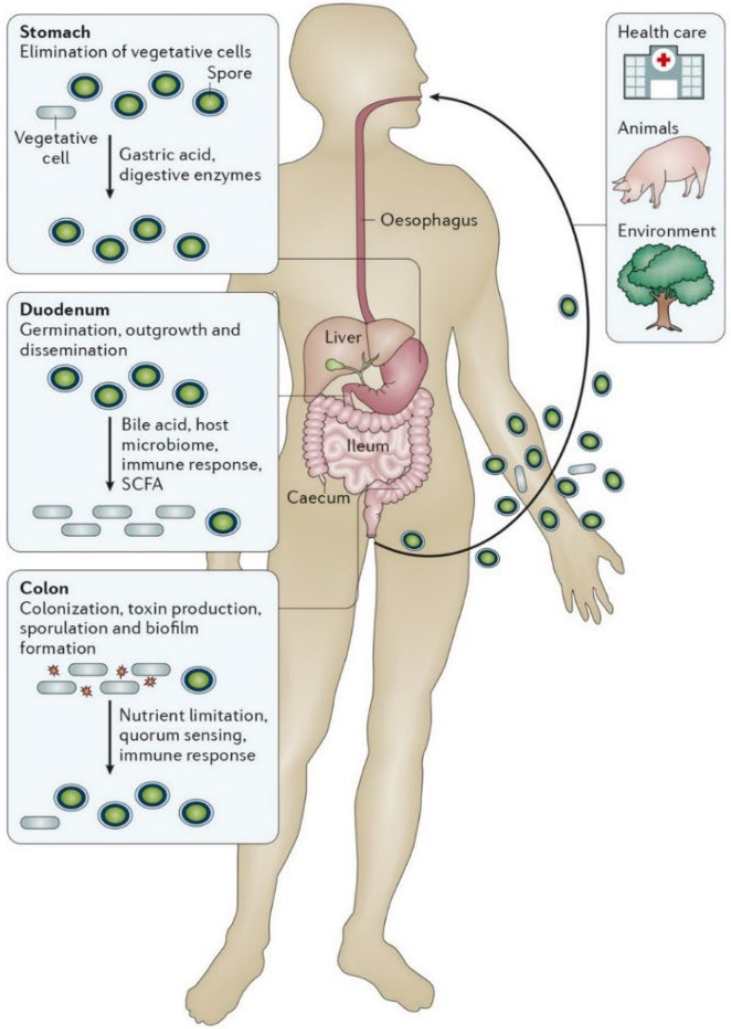


Spore formation by *C. difficile* is crucial for the survival and dissemination of the bacterium in the environment.

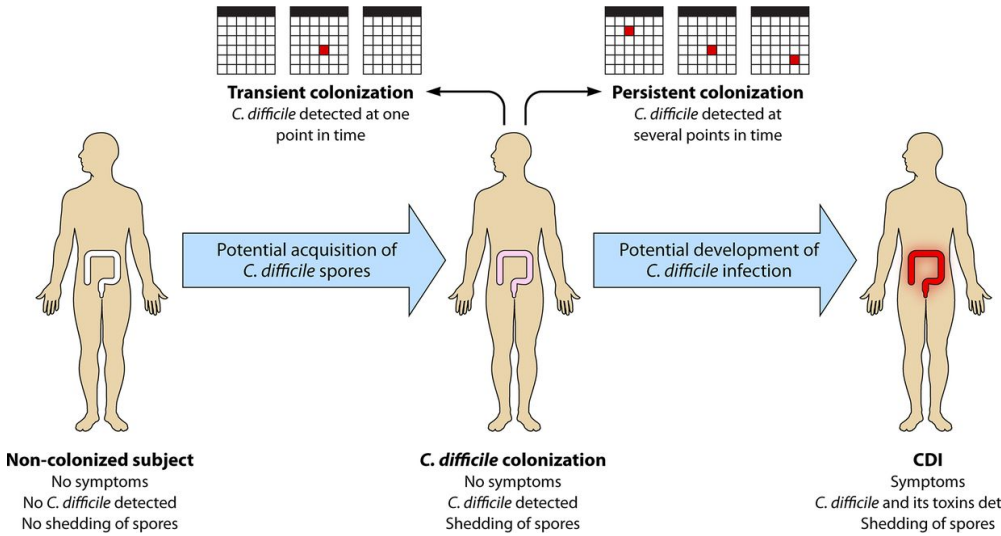
The dormant aerotolerant and highly resistant spore facilitates efficient transmission and persistence in the host.

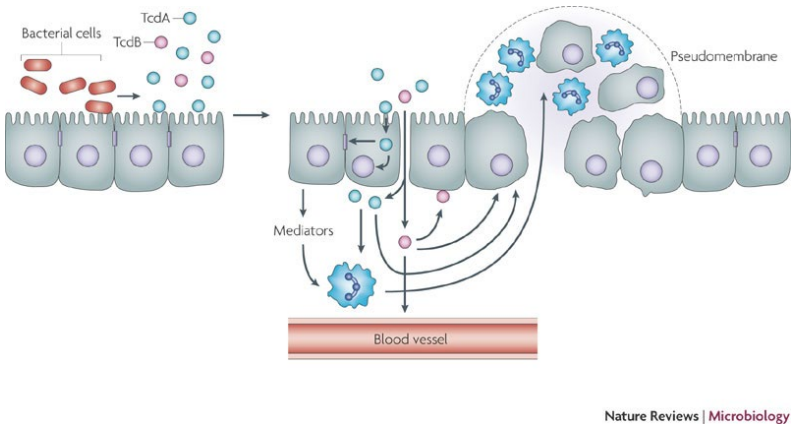
Spores are resistant to different environmental conditions, antibiotics, and some disinfectants (usage of sporicidal ones).

Clostridioides difficile infection (CDI)



Fecal-oral route of transmission
Asymptomatic colonization or infection
Recurrence of CDI (25%, 50%)
Symptoms: watery diarrhea, fever, loss of appetite, nausea, and abdominal pain/tenderness, **pseudomembranous colitis, toxic megacolon**.

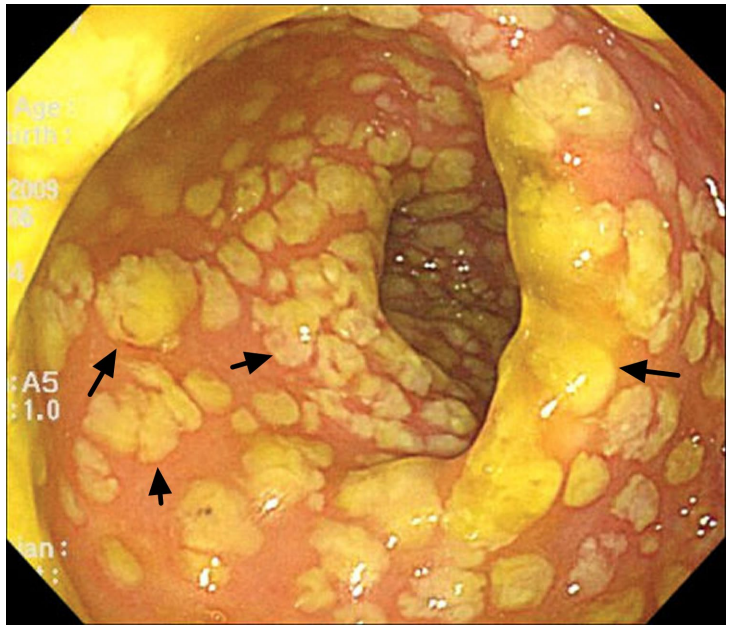




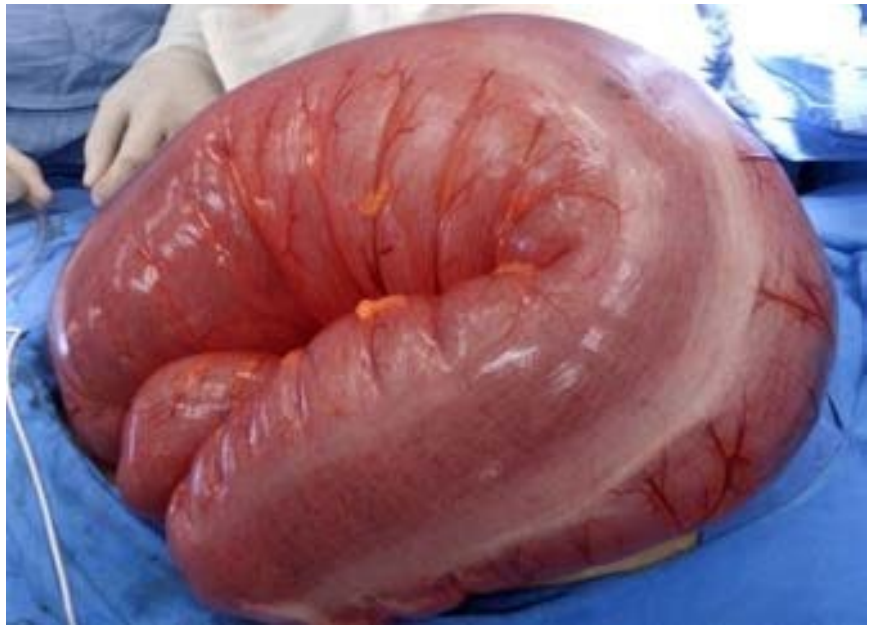
Toxins=disruption of cytoskeletal structure and tight junctions with subsequent cell rounding, detachment and cell death.

Smits et al., 2016; Crobach et al., 2018; Chilton et al., 2018

Severe forms of CDI

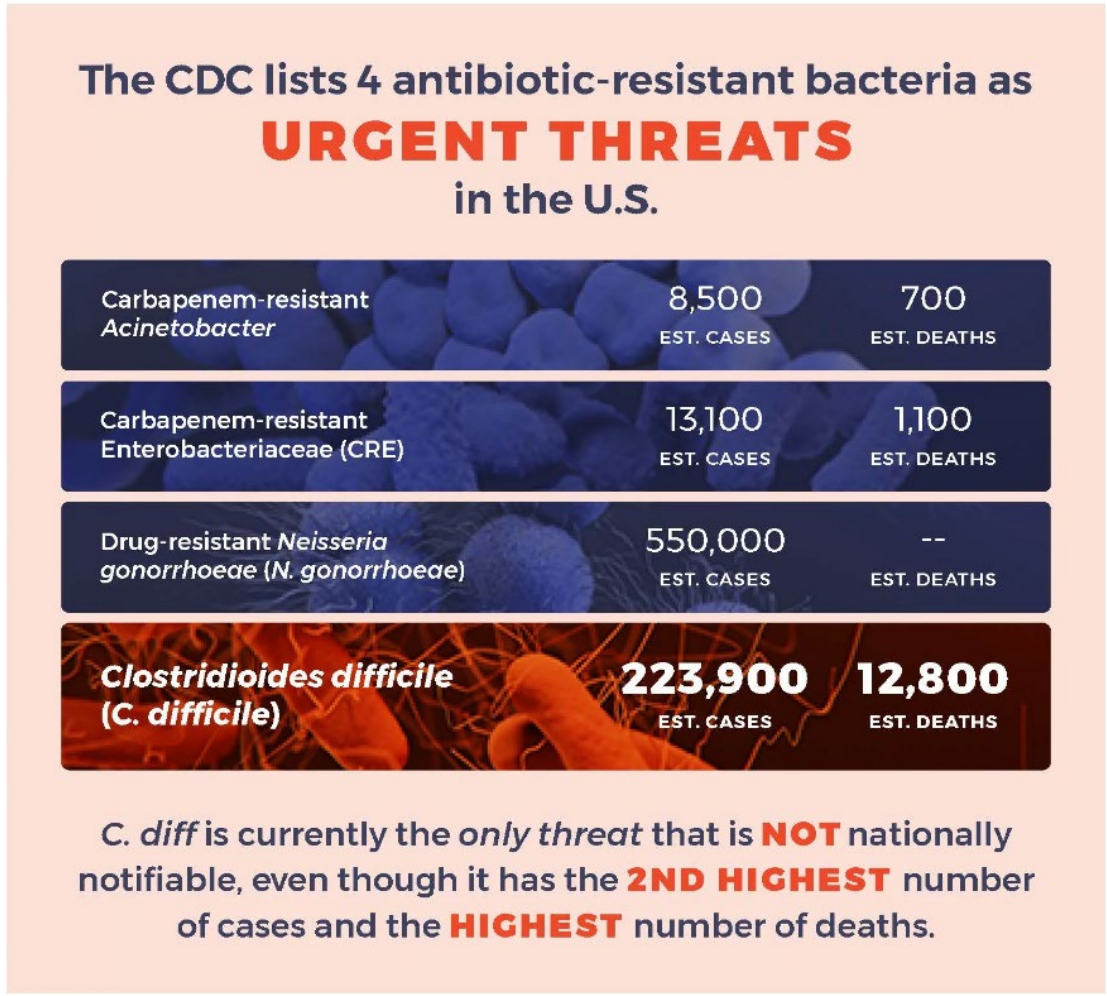


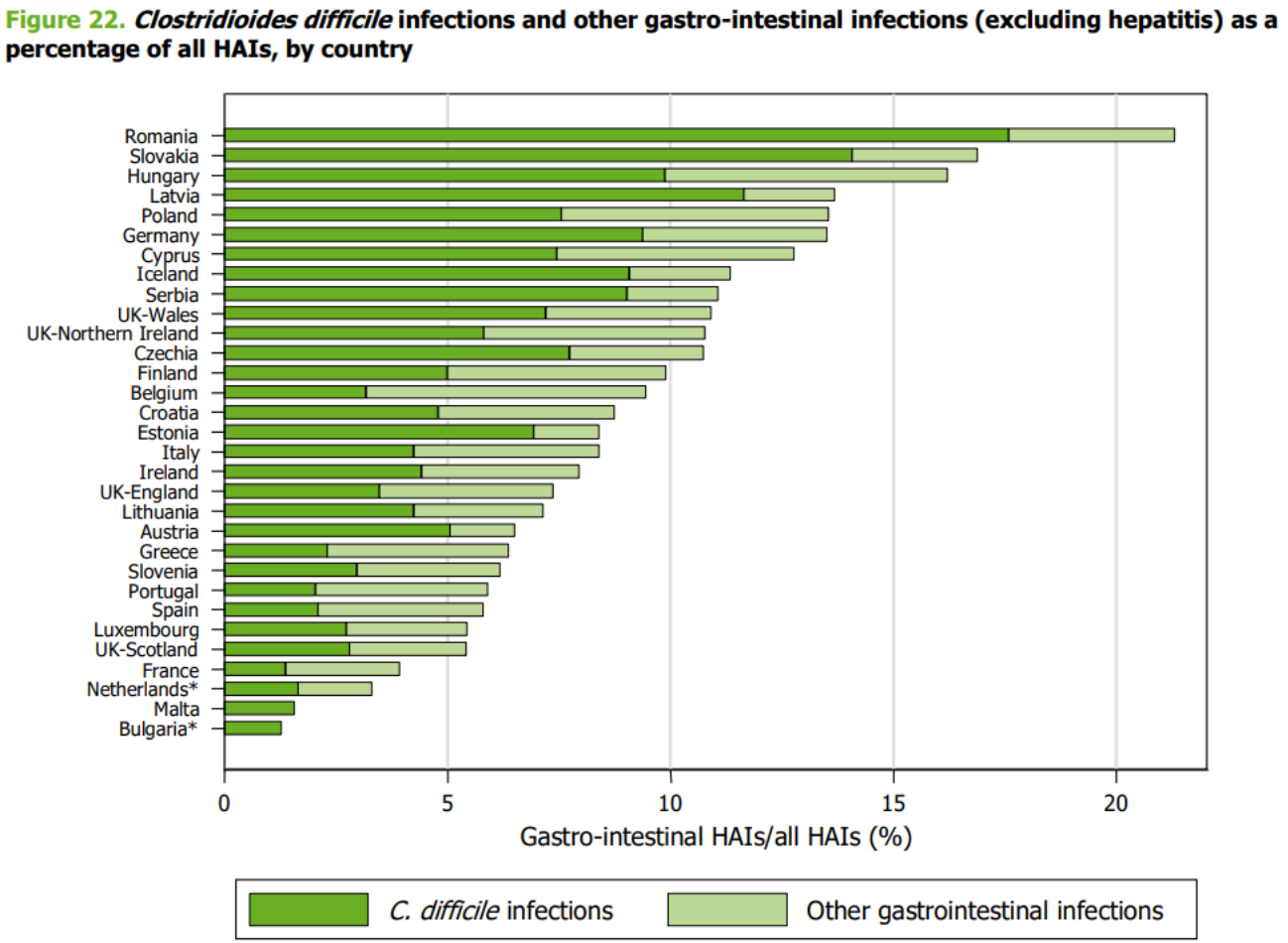
Pseudomembranous colitis



Paralytic ileus = toxic megacolon, surgical intervention, high mortality

How common is CDI?





124 000 CDI cases a year
Approx. 17% die. 4% in relation to CDI

European mean: 5 cases per 10,000 bed-days

What does a patient at risk of CDI look like?

RISK factors for CDI

Advanced age ≥ 65 years
Comorbidity conditions
Exposure to acid-suppressing agents (PPIs)
Exposure to antibiotics
Exposure to the healthcare system
Immunosuppressive conditions and agents (cancer, chemotherapy, organ transplant, HIV)
Manipulation of GI system (feeding tubes, surgery)

EVERYTHING WHICH AFFECTS MICROBIOTA

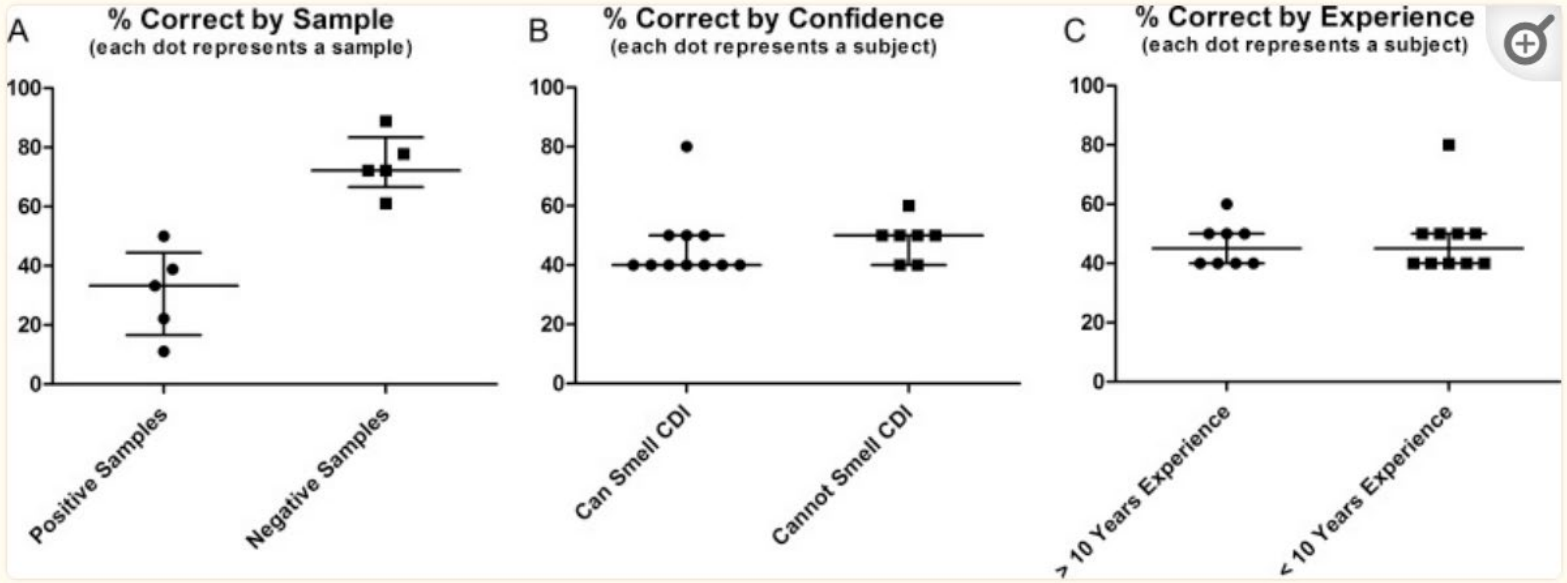
Laboratory diagnostics–odor?

Clin Infect Dis. 2013 Feb 15; 56(4): 615–616.
doi: 10.1093/cid/cis974

PMCID: PMC3571629
PMID: 23166192

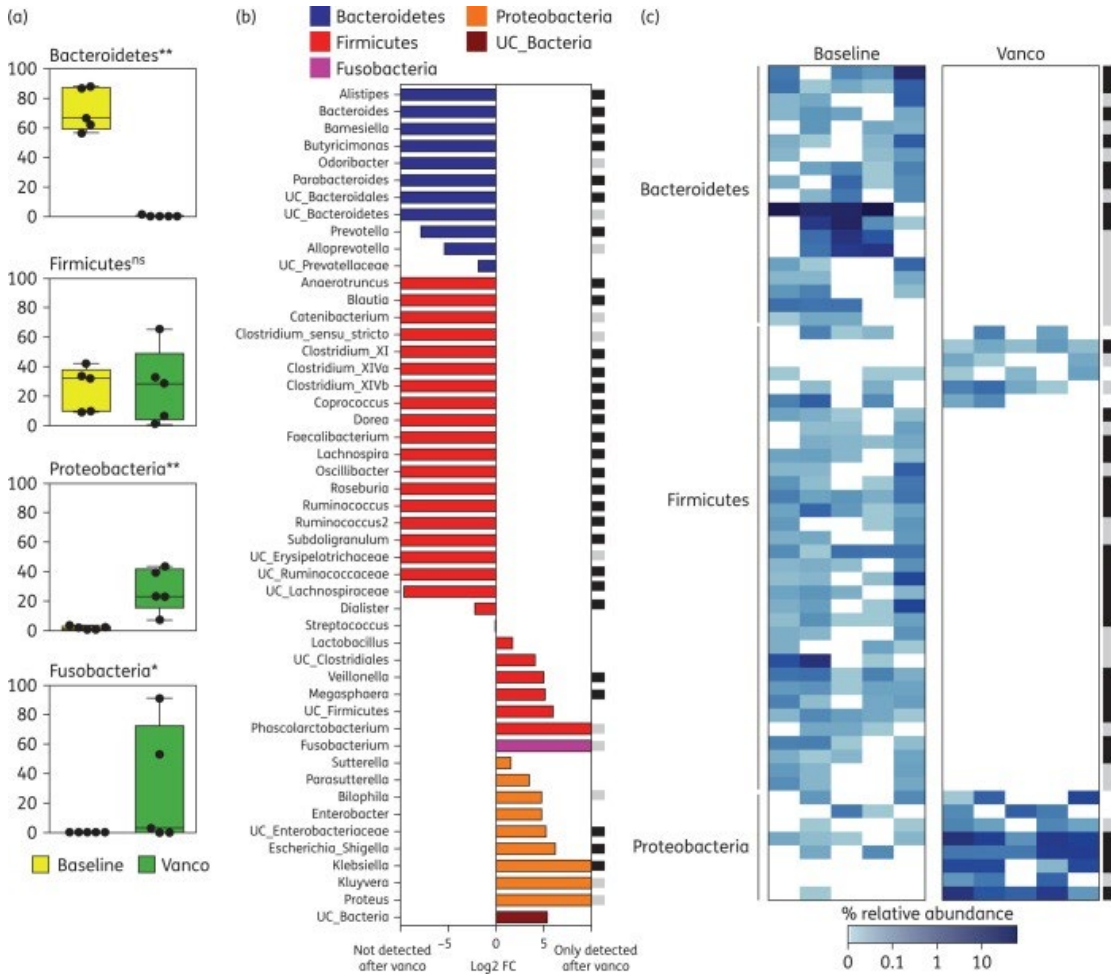
The Nose Knows Not: Poor Predictive Value of Stool Sample Odor for Detection of *Clostridium difficile*

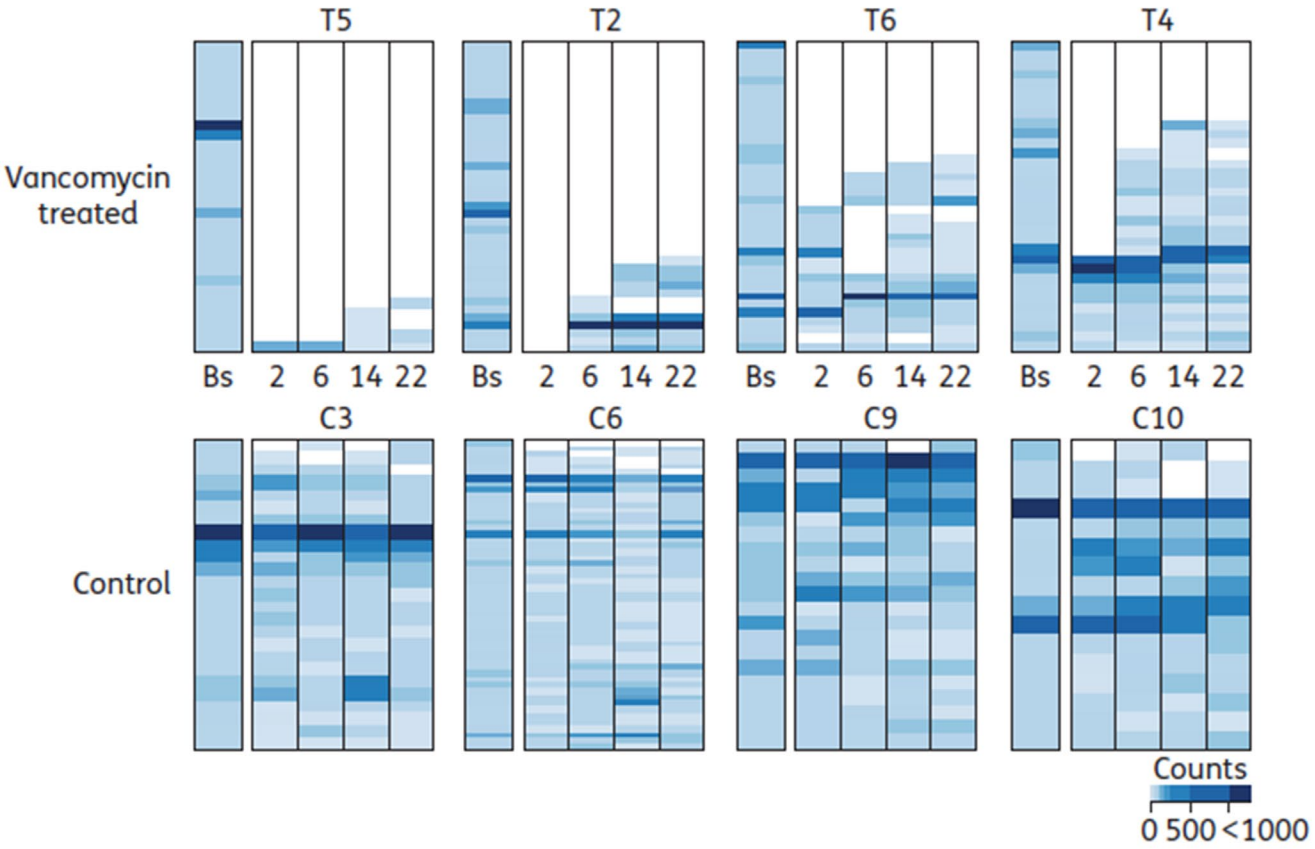
Krishna Rao,[1,2] Daniel Berland,[1,3] Carol Young,[4,5] Seth T. Walk,[1,2,6] and Duane W. Newton[4,5]



The dog correctly identified 25 of the 30 cases (sensitivity 83%, 65% to 94%) and 265 of the 270 controls (specificity 98%, 95% to 99%).

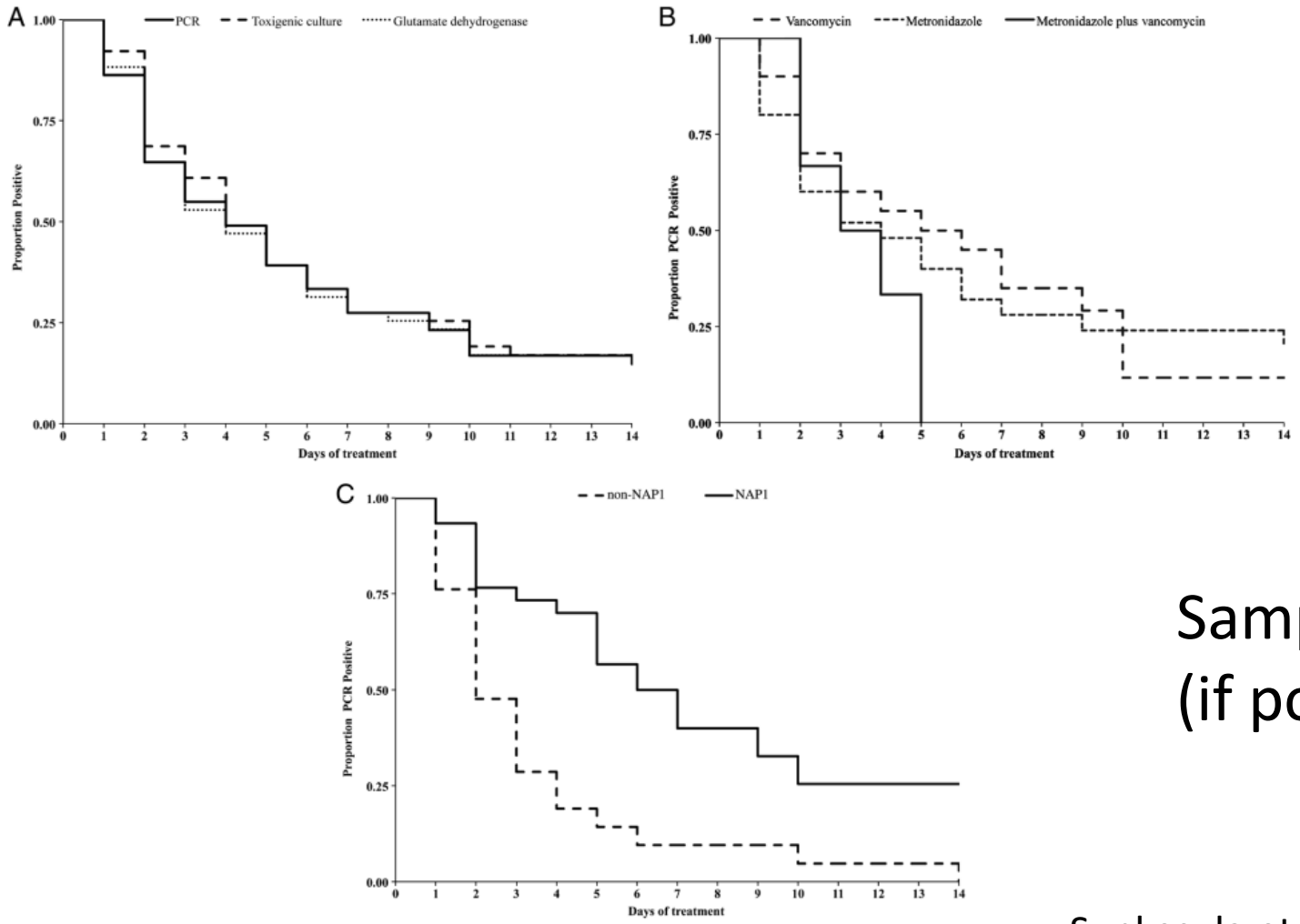
Vancomycin and its effect on the gut microbiota





Isaac, JAC, 2017

Empirical *Clostridium difficile* Infection (CDI) Therapy Result in False-Negative CDI Diagnostic Test Results



Sampling before treatment (if possible)!

Sunkesula et al., 2013

Who should be tested?

In inpatient care, all hospitalised patients aged **≥2 years** who have had three or more unformed stools within 24 hours
*40 000 inpatients are undiagnosed a year because lack of clinical suspicion (Davies et al., 2014)

Children under 2 years should be tested on a **case-by-case basis** after consultation with a paediatrician and clinical microbiologist.
(NO age restriction in Motol hospital)

In children, if CDI laboratory testing is indicated, the likelihood of *C. difficile* **colonisation and coinfection with other intestinal pathogens should be considered.**

Crobach et al., 2016; Krutova et al., CMI, 2022

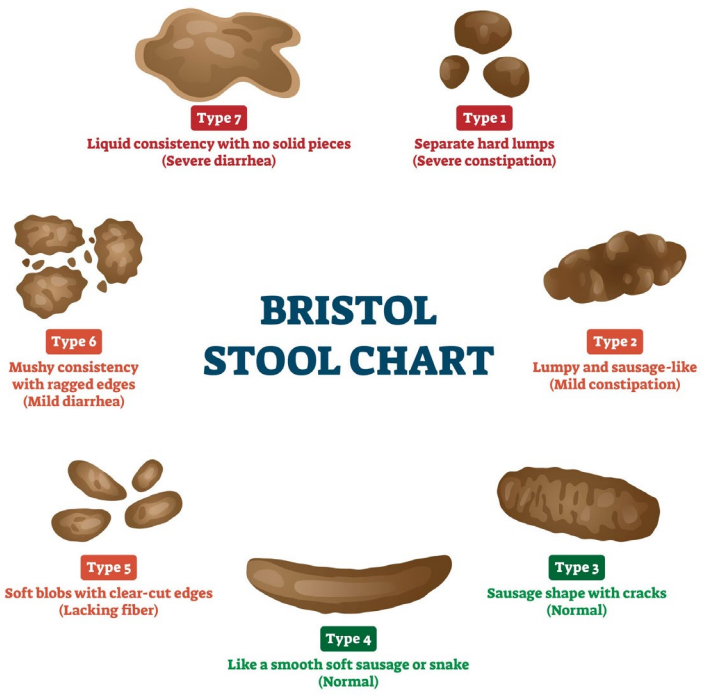
Who should be tested?

In the community, people who are unresponsive to the oral rehydration and specific treatment is considered → (hospitalisation)

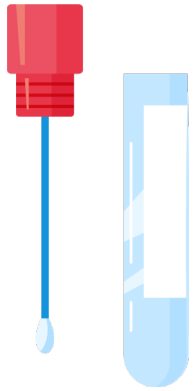
In children, if **CDI** laboratory testing is indicated, the likelihood of *C. difficile* **colonisation and coinfection with other intestinal pathogens should be considered**.

Krutova et al., CMI, 2022

Sampling for stool testing: gastrointestinal infection



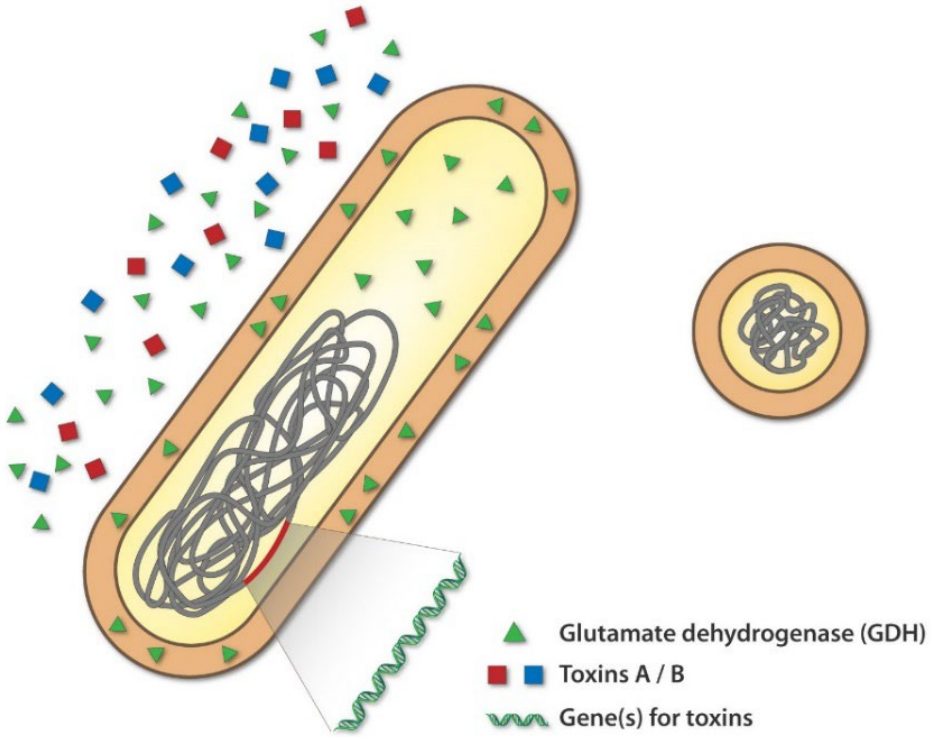
Unformed stool sample
(taking the shape of a container)



Rectal swab:
Paralytic ileus only

Bacterial culture: stool is not available

What can we test?



Glutamate dehydrogenase (GDH)
(enzyme produced by all *C. difficile*), **EIA**

Toxins A/B
(virulence factor(s)), **EIA**

Gene (s) fragment(s) for toxins, **PCR**
(do not report toxins!)

C. difficile culture
(spores)

What test(s) should be used?

PPV and NPV for different categories of index tests at hypothetical CDI prevalences of 5, 10, 20 and 50%

Test type	CDI prevalence 5%		CDI prevalence 10%		CDI prevalence 20%		CDI prevalence 50%	
	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Well-type EIA GDH	38	100	54	99	72	98	91	94
Membrane-type EIA GDH	34	100	52	100	71	99	91	98
Well-type EIA toxins A/B	69	99	83	98	91	96	98	87
Membrane-type EIA toxins A/B	81	99	90	98	95	95	99	83
NAAT	46	100	64	100	80	99	94	96

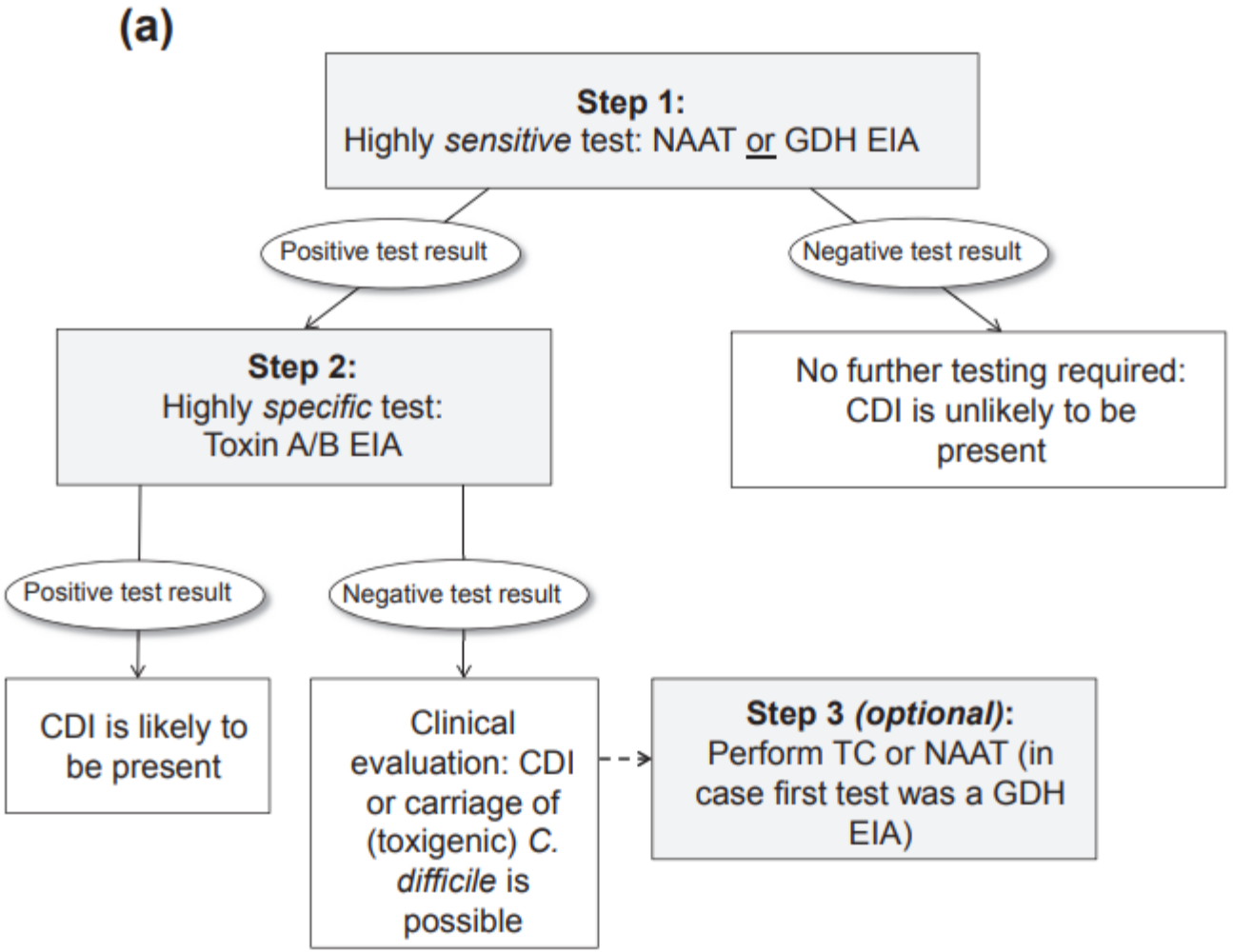
Pooled estimates of sensitivity and specificity compared to cell cytotoxicity neutralization assay were used to calculate the predictive values.
CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; NPV, negative predictive value; PPV, positive predictive value.

No single commercial test can be used as a stand-alone test for diagnosing CDI as a result of inadequate positive predictive values at low CDI prevalence.

✓ **Therefore, the use of a two-step algorithm is recommended**

Crobach et al., CMI, 2016

Laboratory diagnostics of CDI



Crobach et al., CMI, 2016

Children – co-infections

In children, the CDI test should not be the only test in case of diarrhoea!

de Graaf et al., 2015

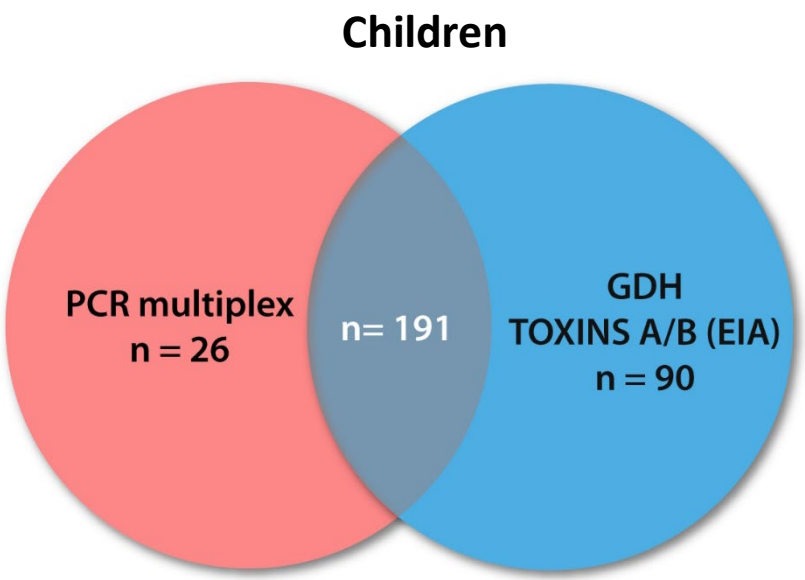
Table 2 Number of reported gastrointestinal co-infections in *C. difficile*-positive patients by pathogen

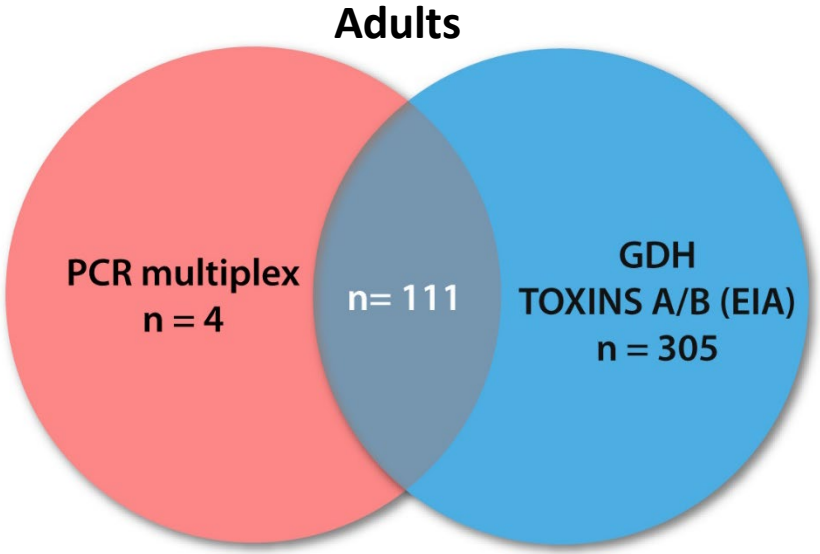
Pathogen	Number of co-infection reports (%)
Viruses	164 (73.9)
Rotavirus	97 (43.7)
Adenovirus	32 (14.4)
Norovirus	17 (7.7)
Astrovirus	9 (4.1)
Sapovirus	5 (2.3)
Others[a]	4 (1.8)
Bacteria	53 (23.9)
E. coli	17 (7.7)
Enteropathogenic	8 (47.1)
Enterotoxigenic	3 (17.6)
Verocytotoxin-producing	4 (23.5)
O18	1 (5.9)
Not specified	1 (5.9)
Salmonella spp.	11 (5.0)
Campylobacter spp.	11 (5.0)
Yersinia spp.	6 (2.7)
Others[b]	8 (3.6)
Parasites	5 (2.3)
Blastocystis hominis	1 (0.45)
Entamoeba histolytica	2 (0.9)
Giardia spp.	2 (0.9)

[a] Calicivirus (n=2), coxsackievirus (n=1), enterovirus (n=1)

[b] *Bacillus cereus* (n=3), *Aeromonas* spp. (n=2), *Shigella* spp. (n=2), *Vibrio cholerae* (n=1)

Stool testing: ÚLM FNM





May-August 2022

- **Multiplex PCR** (daily)
- bacteria, viruses, parasites
- AusDiagnostics (panel M)
- 20 targets (AusDiagnostics (panel M)

CDI (2 hod) - EIA

ArcDia - mariPOC CDI

- Glutamate dehydrogenase (GDH)
- *C. difficile* toxiny A/B

Internal evaluation: Krutova et al., JCM, 2019

C. difficile (PCR positive)

n=21/115 (18.3%)

GDH negative
toxin A/B negative

n=2/21 (9.5 %)

Shigella (n=1)
Adenovirus (n=1)

n=2/2 (100%)

No patient was treated

C. difficile (PCR positive)

n=65/191 (34.0%)

GDH negative
toxin A/B negative

n=6/65 (9.2 %)

mNAAT negative

n=6/6 (100%)

No patient was treated

C. difficile (PCR positive)

n=21/115 (18.3%)

GDH positive
toxin A/B positive

n=14/21 (66.7%)

Aeromonas (n=2)
Rotavirus + Adenovirus (n=1)

n=3/14 (21.4%)

All patients were treated for CDI

Rotavirus a Norovirus co-infecti-on – 96 years old patient

C. difficile (PCR positive)

n=65/191 (34.0%)

GDH positive
toxin A/B positive

n=29/65 (44.6%)

Aeromonas (n=2)
Rotavirus (n=4)
Adenovirus (n=3)
Norovirus + Adenovirus (n=1)

n=10/29 (34.5%)

Four patients (40%) were treated from co-infection group.
Nine patients (47.4%) were treated from *C. difficile* „only" group.
Frequent diarrhea significant dehydration, weight loss

C. difficile (PCR positive)

n=21/115 (18.3%)

GDH positive
toxin A/B negative

n=5/21 (23.8%)

Campylobacter (n=1)
Rotavirus (n=1)
Norovirus GII (n=1)

n=3/5 (60.0%)

One adult patient– abdomen pain, diarrhoea, palliative care, treated by vancomycin, RT012

C. difficile (PCR positive)

n=65/191 (34.0%)

GDH positive
toxin A/B negative

n=30/65 (46.2%)

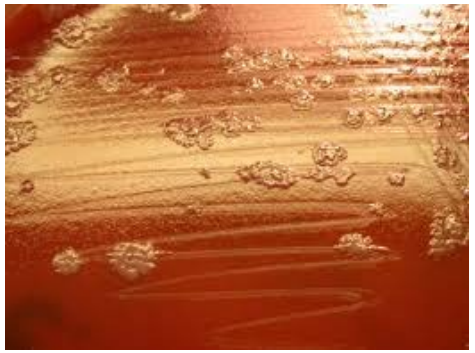
Sapovirus (n=1)
Rotavirus (n=3)
Norovirus GII (n=3)
Adenovirus (n=2)
Astrovirus (n=2)
Rotavirus a Norovirus (n=1)
Norovirus a Adenovirus (n=1)

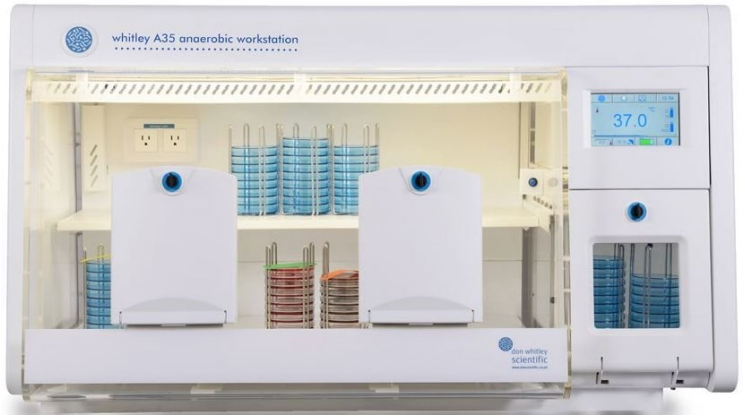
n=6/6 (100%)

One patient treated (after 2nd cycle of chemotherapy, diarrhoea, increasing CRP, 9 month)

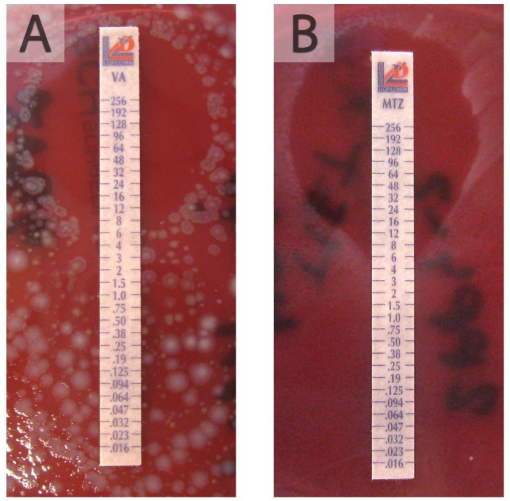
RT033 (del *tcdA* gene, *tcdB* gene – not present, binary toxin genes)

Culture of *C. difficile*-why?

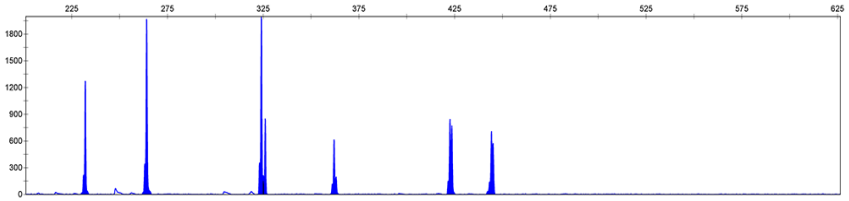




Stool sample and alcohol 1:1, 30 minutes. Suppressing of other bacteria in sample, germination of spores. Culture on selective media, anaerobic atmosphere 24-48 hrs.



Antimicrobial susceptibility testing and characterisation of strain for epidemiologic purposes



Guidance documents USA/Europe

Clin Infect Dis. 2018 Mar 19;66(7):987-994. doi: 10.1093/cid/ciy149.

Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L Clifford McDonald [1], Dale N Gerding [2], Stuart Johnson [2 3], Johan S Bakken [4], Karen C Carroll [5], Susan E Coffin [6], Erik R Dubberke [7], Kevin W Garey [8], Carolyn V Gould [1], Ciaran Kelly [9], Vivian Loo [10], Julia Shaklee Sammons [6], Thomas J Sandora [11], Mark H Wilcox [12]

Practice Guideline · Clin Infect Dis. 2021 Sep 7;73(5):755-757. doi: 10.1093/cid/ciab718.

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults

Stuart Johnson [1 2], Valéry Lavergne [3 4], Andrew M Skinner [1 2], Anne J Gonzales-Luna [5], Kevin W Garey [5], Ciaran P Kelly [6], Mark H Wilcox [7]

Clinical Microbiology and Infection 28 (2022) 1085–1090

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

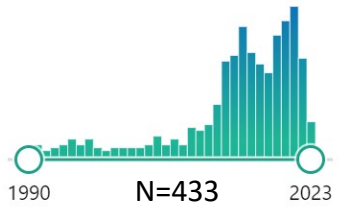
How to: *Clostridioides difficile* infection in children

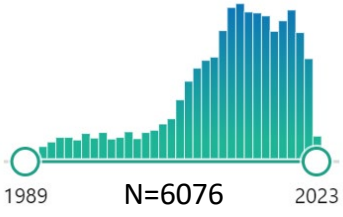
Marcela Krutova [1, 7, 8, *], Tim G.J. de Meij [2], Fidelma Fitzpatrick [3, 7, 8], Richard J. Drew [4, 7], Mark H. Wilcox [5, 7], Ed J. Kuijper [6, 7, 8]

Clin Microbiol Infect. 2021 Dec;27 Suppl 2:S1-S21. doi: 10.1016/j.cmi.2021.09.038. Epub 2021 Oct 20.

European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults

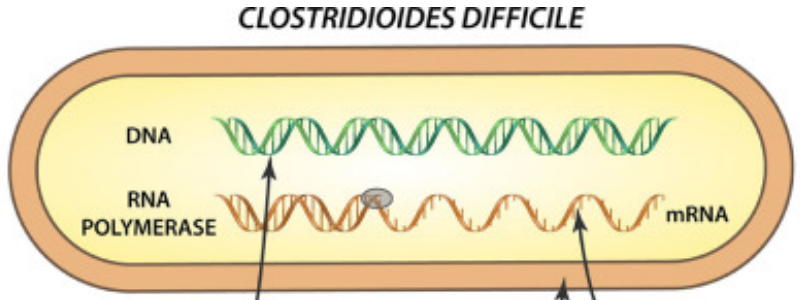
Joffrey van Prehn [1], Elena Reigadas [2], Erik H Vogelzang [3], Emilio Bouza [2], Adriana Hristea [4], Benoit Guery [5], Marcela Krutova [6], Torbjorn Norén [7], Franz Allerberger [8], John E Coia [9], Abraham Goorhuis [10], Tessel M van Rossen [3], Rogier E Ooijevaar [11], Karen Burns [12], Bente R Scharvik Olesen [13], Sarah Tschudin-Sutter [14], Mark H Wilcox [15], Maria J G T Vehreschild [16], Fidelma Fitzpatrick [17], Ed J Kuijper [18];
Guideline Committee of the European Study Group on Clostridioides difficile





European guidance documents do not include children, a separate document (expert opinion).

Antimicrobials approved for CDI treatment



	METRONIDAZOLE	VANCOMYCIN	FIDAXOMICIN
SYSTEMIC ABSORPTION	HIGH	LOW	LOW
STOOL CONCENTRATION	LOW	HIGH	HIGH
REDUCTION OF BIOACTIVITY BY FAECES	HIGHEST	LOWER	LOWER
EFFECT ON DIVERSITY OF MICROBIOTA	REDUCTION	REDUCTION	PRESERVATION
STOOL SHEDDING DECLINE	SLOW	RAPID	RAPID
ENVIRONMENTAL CONTAMINATION	HIGHEST	LOWER	LOWER (STEEPER)
SPOROCIDAL EFFECT	—	NO	YES
INHIBITION OF SPORULATION	NO	NO	YES

SUPPORTIVE · LESS-SUPPORTIVE · NON-SUPPORTIVE · — NO DATA

Overview of pharmacodynamic, pharmacokinetic and microbiological properties for oral administration of metronidazole, vancomycin and fidaxomicin.

Pharmacokinetic differences of metronidazole, vancomycin and fidaxomicin.

Krůtová et al., 2022

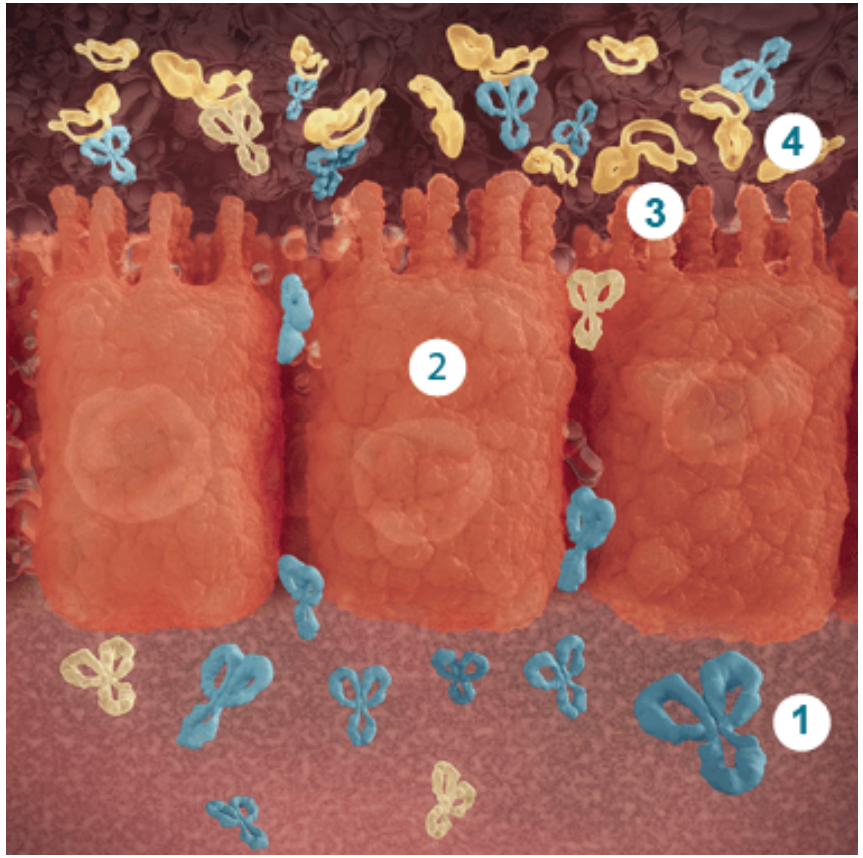
Passive immunisation

Bezlotoxumab (ZINPLAVA™) is a human monoclonal antibody that binds to *Clostridioides difficile* toxin B indicated to reduce the recurrence of CDI.

Should only be used in conjunction with antibacterial drug treatment of CDI!

Clinical Trial › N Engl J Med. 2017 Jan 26;376(4):305-317. doi: 10.1056/NEJMoa1602615.

The rate of recurrent C. difficile infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, **-10.1** percentage points; 95% confidence interval [CI], -15.9 to -4.3; P<0.001; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, -**9.9** percentage points; 95% CI, -15.5 to -4.3; P<0.001)



1.ZINPLAVA
2.Damaged gut epithelial cells
3.Toxin B
4.ZINPLAVA binding to toxin B

FMT: Feacal microbiota transplant

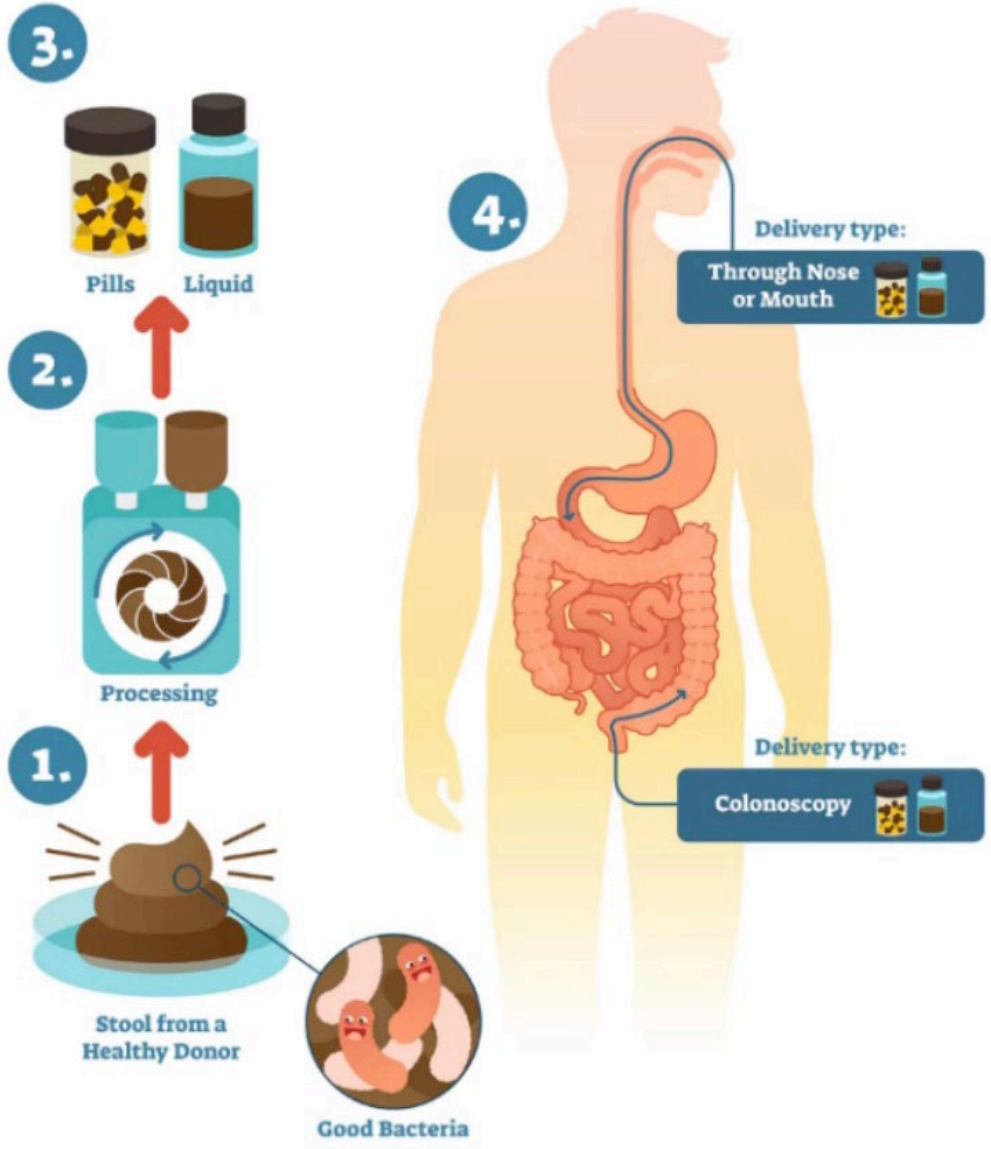


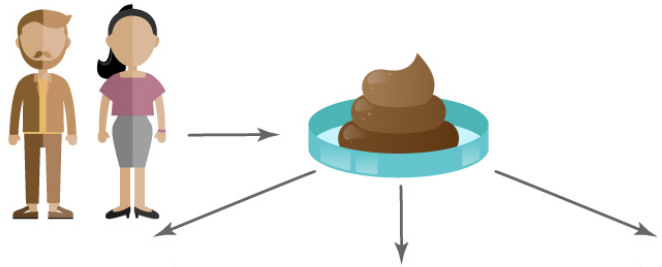
Table 2
Donor screening by laboratory screening of faeces and serum

Laboratory screening serum	Laboratory screening faeces
• Hepatitis A (IgM + IgG) • Hepatitis B (HBsAg + anti-Hbcore) • Hepatitis C (anti-HCV) • Hepatitis E (IgM + IgG) • HIV (anti-HIV, type 1 and 2) • Lues; *Treponema pallidum* (Ig) • Cytomegalovirus (IgM + IgG) • Epstein Barr Virus (IgM + IgG) • *Strongyloïdes* (IgG1/IgG4)[a]	• *Clostridium difficile* (PCR) • *Helicobacter pylori* (antigen test) • Bacterial gastroenteritis: (PCR, followed by culture) *Salmonella* spp. *Campylobacter* spp., *Campylobacter jejuni*, *C. coli*, *Shigella* spp., *Yersinia enterocolitica* and *Y. pseudotuberculosis*, *Aeromonas* spp., *Plesiomonas shigelloides*, and Shiga Toxin-producing *E. coli* • Antibiotic-resistant bacteria (culture); ESBL and/or carbapenemase-producing bacteria, vancomycin-resistant enterococci, and methicillin-resistant *Staphylococcus aureus* • Viral pathogens (PCR): Norovirus serotype I+II, Astrovirus, Sapovirus, Rotavirus, Adenovirus 40/41, Adenovirus non-40/41, Enterovirus, Parechovirus, Hepatitis E • Parasites (PCR): *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium parvum* and *C. hominis*, *Microsporidium* spp, *Strongyloïdes*[a] • Microscopy for ova, cysts, and larvae [69]: e.g. *Blastocystis hominis*

Questionnaire: 1 day before donation of faeces
Stool frequency/pattern, general health, use of antibiotics, travel history, sexual behaviour

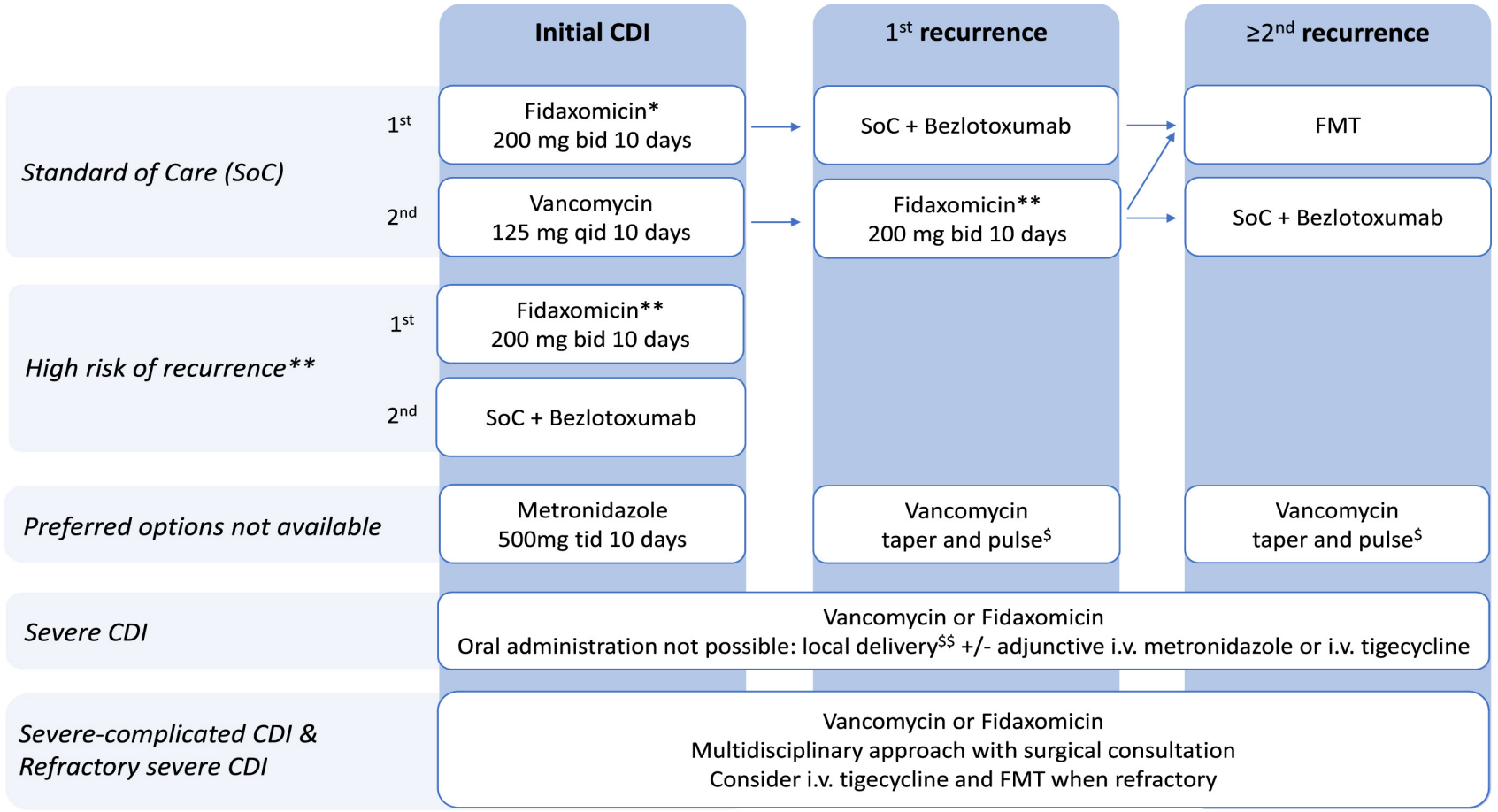
Terveer et al., 2017

Future FMT? Live biotherapeutics



PRODUCT NAME	RBX2660	SER-109	VE303
PRODUCT TYPE	FMT-DERIVED		BACTERIAL CONSORTIA
STOOL PROCESSING	Dilution (0.9% saline/polyethylene glycol)	Spore enrichment (50 – 70% v/v EtOH 2-hrs treatment)	Bacterial culture (8 strains of Clostridiales)
FORM OF DELIVERY	Liquid enema	4x Oral capsules	2x / 10x Oral capsules Low dose / High dose
REDUCTION OF rCDI	13.1%	28.0%	8.5% / 31.7%
BATCH-TO-BATCH VARIATION	YES	YES	NO
CHARACTERIZATION OF COMPOSITION	NO	NO	YES
RISK OF PATHOGEN (AMR) TRANSMISSION	POSSIBLE	POSSIBLE	LIMITED

Currently valid guidance document for CDI treatment



* Risk stratification for risk of recurrence may be applied for selective use of fidaxomicin in case of limited access or resources.

** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65-70 years. Additional risk factor(s) to consider are healthcare-associated CDI, prior hospitalization ≤ 3 months, prior CDI episode, continued non-CDI antibiotic use, and PPI therapy started during/after CDI diagnosis. The risk of recurrence is assumed higher with more risk factors present.

$ Vancomycin taper and pulse: 2 weeks 125 mg qid, followed by 1 week 125 mg bid, then 1 week 125 mg qd, then 1 week 125 mg q48h, and finally 125 mg q72h for 1 week.

$$ Rectal or nasoduodenal delivery

van Prehn et al., 2021

Prevention of CDI

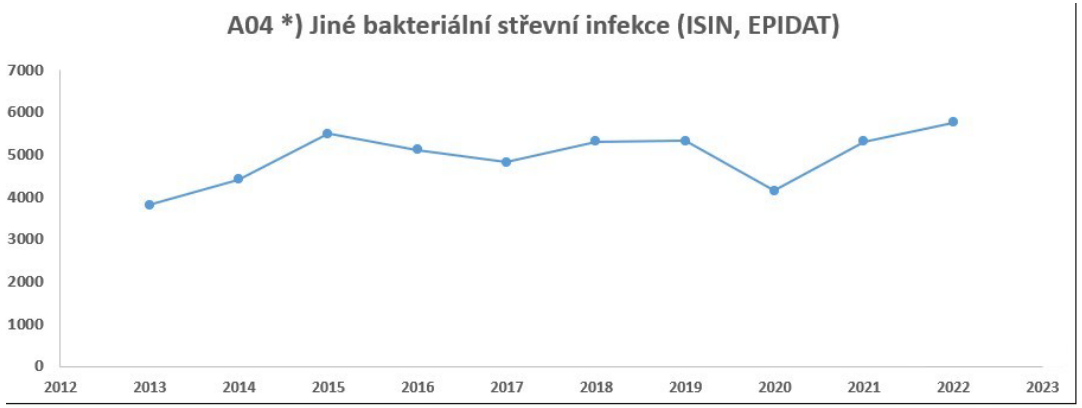
Review > Clin Microbiol Infect. 2018 Oct;24(10):1051-1054. doi: 10.1016/j.cmi.2018.02.020.
Epub 2018 Mar 2.

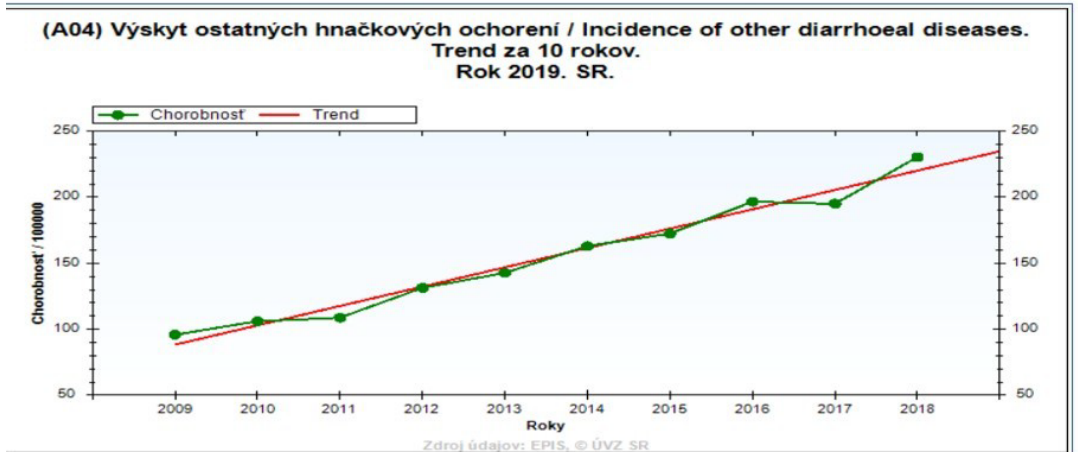
Guidance document for prevention of Clostridium difficile infection in acute healthcare settings

- ✓ Hand hygiene – water and soap (instead of alcohol-based hand rub), but combination?
- ✓ Use of personal protective equipment (PPE): gloves and gowns/disposable aprons
- ✓ Use contact precautions
- ✓ Introduce daily environmental sporicidal disinfection and terminal disinfection of rooms of patients with CDI
- ✓ Restriction of antibiotic agents/classes is effective
- ✓ Reducing the duration of antibiotic therapy
- ✓ Educate healthcare workers on prevention of CDI to enhance their knowledge and skills
- ✓ Educate CDI patients and visitors on prevention measures for CDI

Surveillance CDI!

National *C. difficile* surveillance





FN MOTOL

ISIN (Informační systém infekčních nemocí)
-dříve EPIDAT

EPIS (Epidemiologický informační systém)

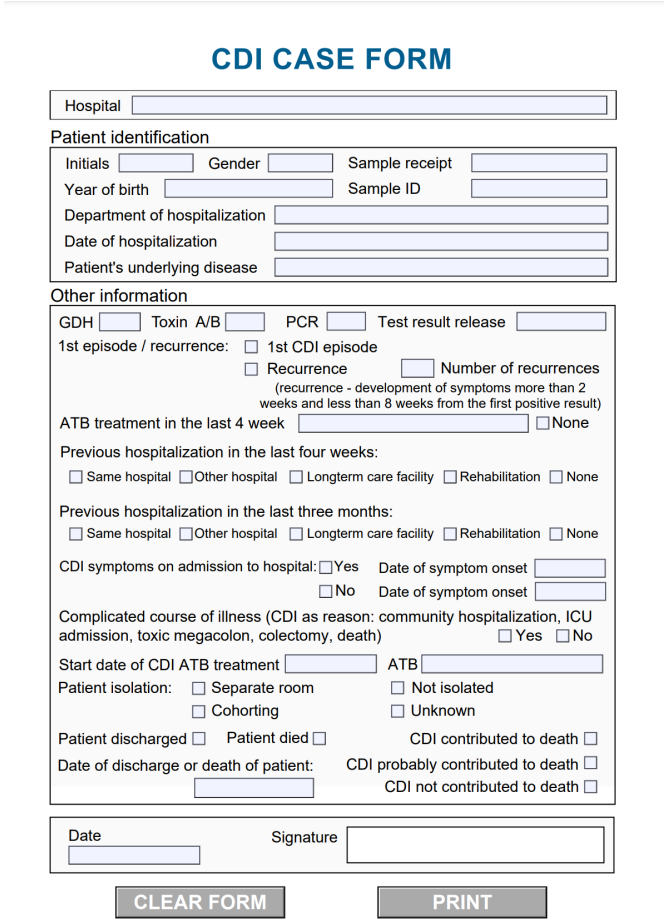
Czech and Slovak system for infectious diseases reporting.
Code A04: Other bacterial Intestinal infections

C. difficile surveillance

Table 1. Information collected for different CDI surveillance options

	Minimal surveillance	Light surveillance	Enhanced surveillance	Form
Collected information	• **Minimum CDI surveillance for each hospital** (aggregated numerator data) • **Hospital data for each hospital** (aggregated denominator data)	• **Minimum CDI surveillance for each hospital** (aggregated numerator data) • **Hospital data for each hospital** (aggregated denominator data)	• **Minimum CDI surveillance for each hospital** (aggregated numerator data) • **Hospital data for each hospital** (aggregated denominator data)	• **Form H** (aggregated numerator and denominator data)
		• **Information on each CDI case** (case-based numerator data)	• **Information on each CDI case** (case-based numerator data)	• **Form C** (case-based numerator data)
			• **Microbiological data** (for the first 5 consecutively detected cases in each participating healthcare facility: characterisation, susceptibility testing and typing of each *C. difficile* isolate)	• **Form M** (one form for each *C. difficile* isolate)
Surveillance period	**Recommended:** continuous surveillance for 12 months, starting on the first* day of the month. The **recommended minimum** surveillance period is three consecutive months, preferably from 1 October to 31 December, or from 1 January to 31 March. The absolute minimum surveillance period is one month, starting on the first day of the month. *The pilot study demonstrated that completion of Form H is made much easier by starting surveillance on the first day of a month.			

ECDC, CDI surveillance protocol v2.4, 32 pages



CDI CASE FORM

Hospital

Patient identification

Initials | Gender | Sample receipt

Year of birth | Sample ID

Department of hospitalization

Date of hospitalization

Patient's underlying disease

Other information

GDH | Toxin A/B | PCR | Test result release

1st episode / recurrence: ☐ 1st CDI episode

☐ Recurrence ☐ Number of recurrences

(recurrence - development of symptoms more than 2 weeks and less than 8 weeks from the first positive result)

ATB treatment in the last 4 week ☐ None

Previous hospitalization in the last four weeks:

☐ Same hospital ☐ Other hospital ☐ Longterm care facility ☐ Rehabilitation ☐ None

Previous hospitalization in the last three months:

☐ Same hospital ☐ Other hospital ☐ Longterm care facility ☐ Rehabilitation ☐ None

CDI symptoms on admission to hospital: ☐ Yes Date of symptom onset

☐ No Date of symptom onset

Complicated course of illness (CDI as reason: community hospitalization, ICU admission, toxic megacolon, colectomy, death) ☐ Yes ☐ No

Start date of CDI ATB treatment | ATB

Patient isolation: ☐ Separate room ☐ Not isolated ☐ Cohorting ☐ Unknown

Patient discharged ☐ Patient died ☐ CDI contributed to death ☐

Date of discharge or death of patient: CDI probably contributed to death ☐

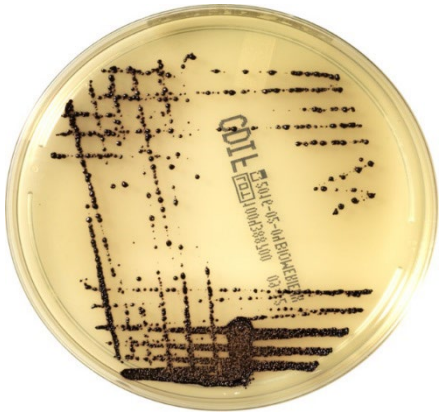
CDI not contributed to death ☐

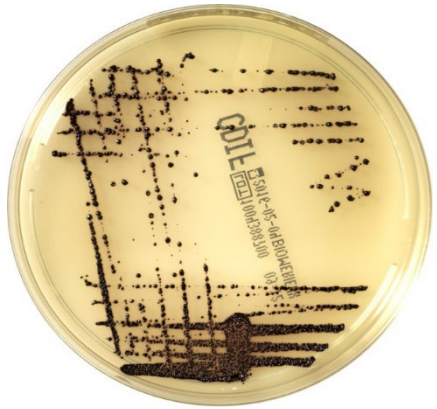
Date | Signature

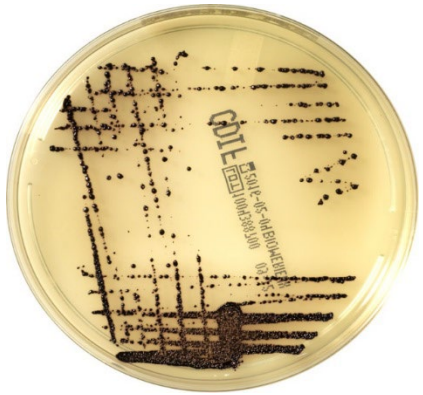
CLEAR FORM PRINT

Krutova M. - Faculty Hospital Motol

Why should we characterize *C. difficile* isolates (CDI cases)? Name the CDI case!

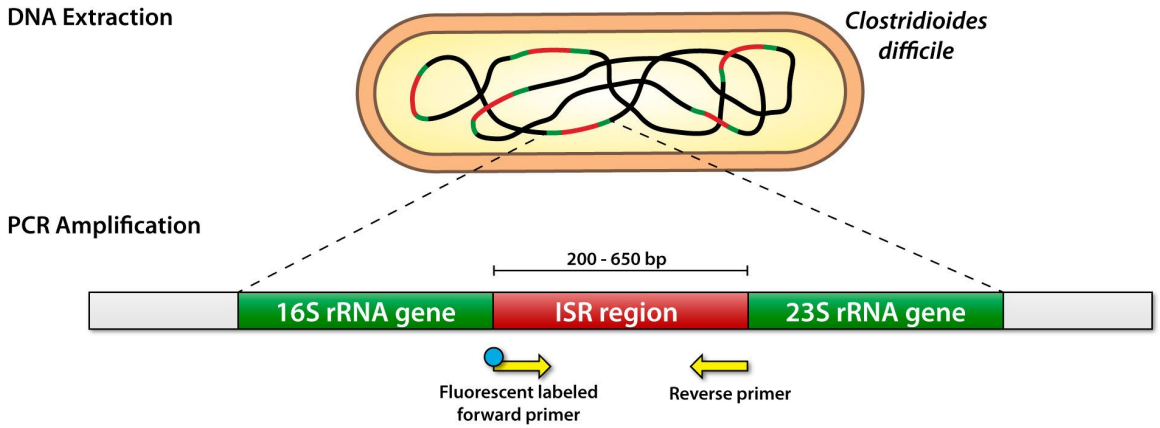



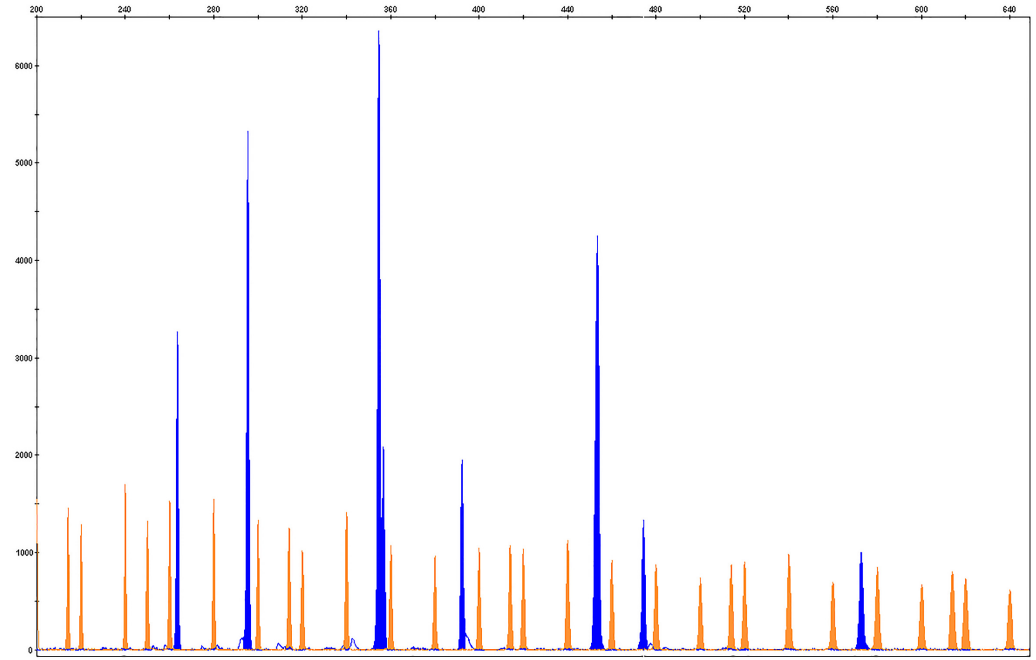




Monitoring of the occurrence and spread within healthcare facility

C. difficile PCR ribotyping





AGES
Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH

WEBRIBO

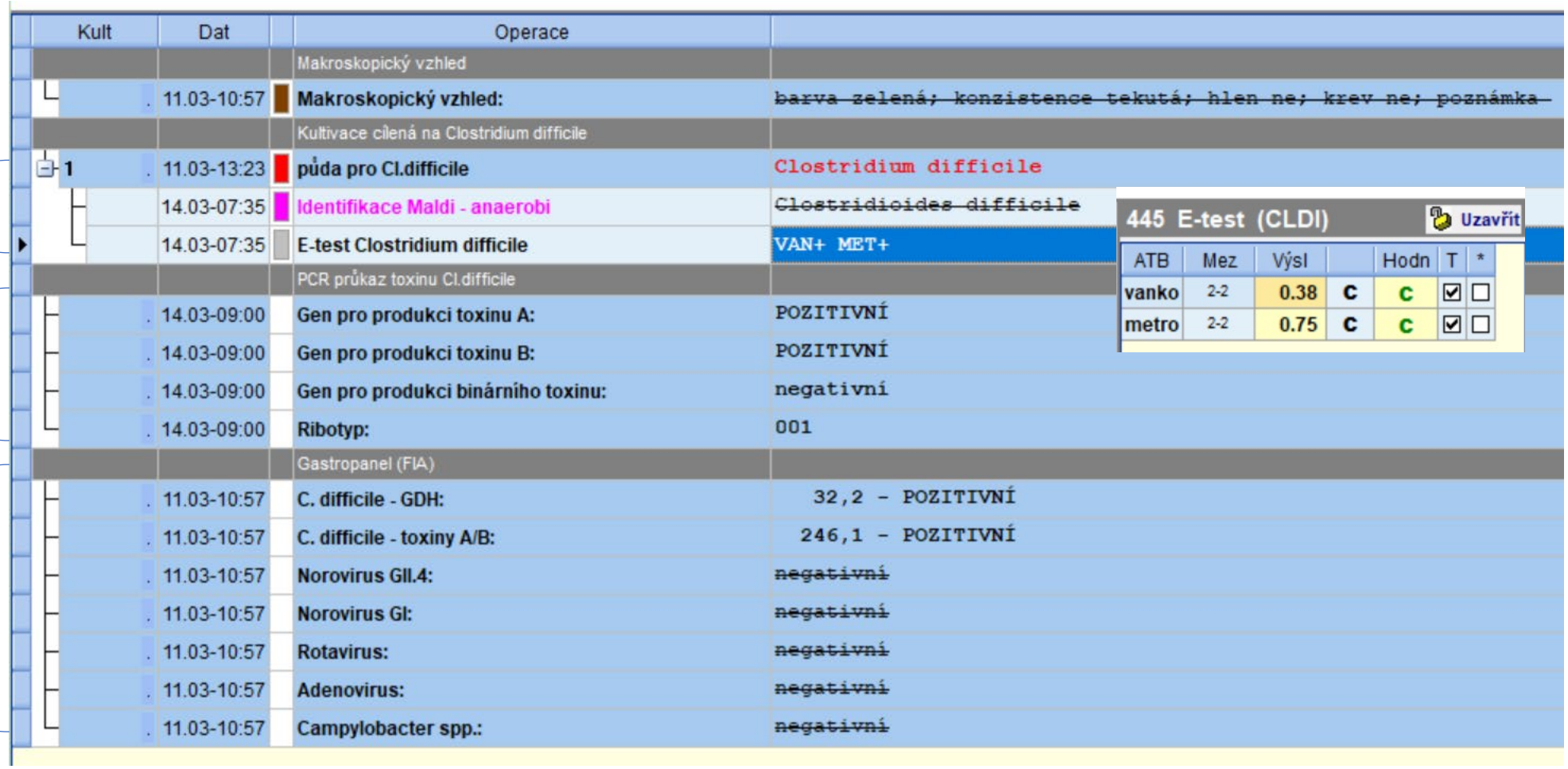
Implementation of ribotyping data into routine microbiology

Macroscopy

Culture

Isolate characterisation

Stool testing



Kult	Dat	Operace	
		Makroskopický vzhled	
	11.03-10:57	Makroskopický vzhled:	~~barva zelená; konzistence tekutá; hlen ne; krev ne; poznámka~~
		Kultivace cílená na Clostridium difficile	
1	11.03-13:23	půda pro Cl.difficile	Clostridium difficile
	14.03-07:35	Identifikace Maldi - anaerobi	~~Clostridioides difficile~~
	14.03-07:35	E-test Clostridium difficile	VAN+ MET+
		PCR průkaz toxinu Cl.difficile	
	14.03-09:00	Gen pro produkci toxinu A:	POZITIVNÍ
	14.03-09:00	Gen pro produkci toxinu B:	POZITIVNÍ
	14.03-09:00	Gen pro produkci binárního toxinu:	negativní
	14.03-09:00	Ribotyp:	001
		Gastropanel (FIA)	
	11.03-10:57	C. difficile - GDH:	32,2 - POZITIVNÍ
	11.03-10:57	C. difficile - toxiny A/B:	246,1 - POZITIVNÍ
	11.03-10:57	Norovirus GII.4:	~~negativní~~
	11.03-10:57	Norovirus GI:	~~negativní~~
	11.03-10:57	Rotavirus:	~~negativní~~
	11.03-10:57	Adenovirus:	~~negativní~~
	11.03-10:57	Campylobacter spp.:	~~negativní~~

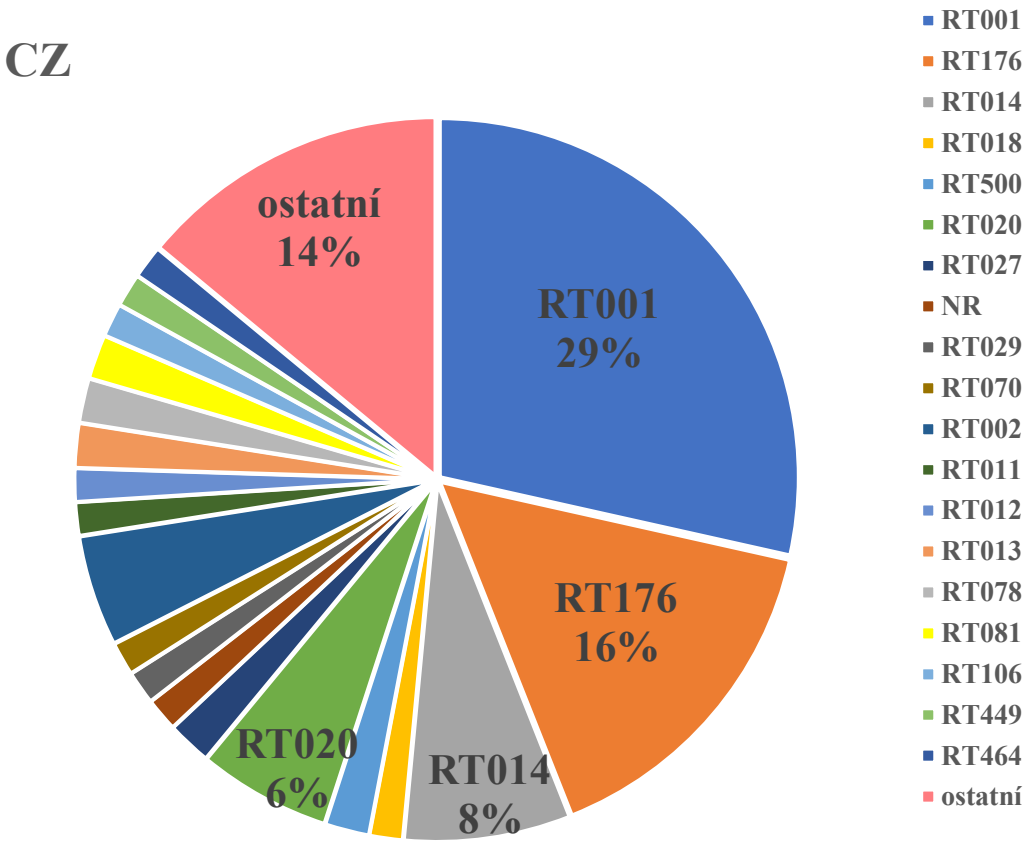
445 E-test (CLDI) Uzavřít

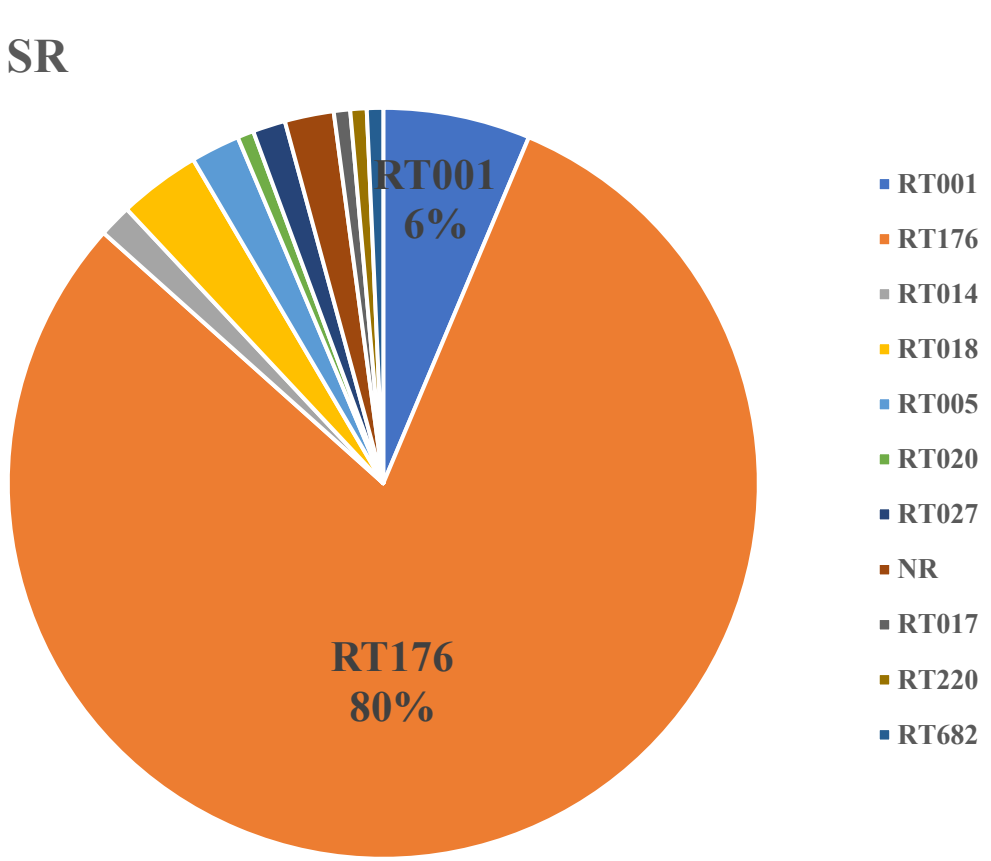
ATB	Mez	Výsl		Hodn	T	*
vanko	2-2	0.38	C	C	☑	☐
metro	2-2	0.75	C	C	☑	☐

FN MOTOL

Microbiology, laboratory information system

PCR ribotyping national data



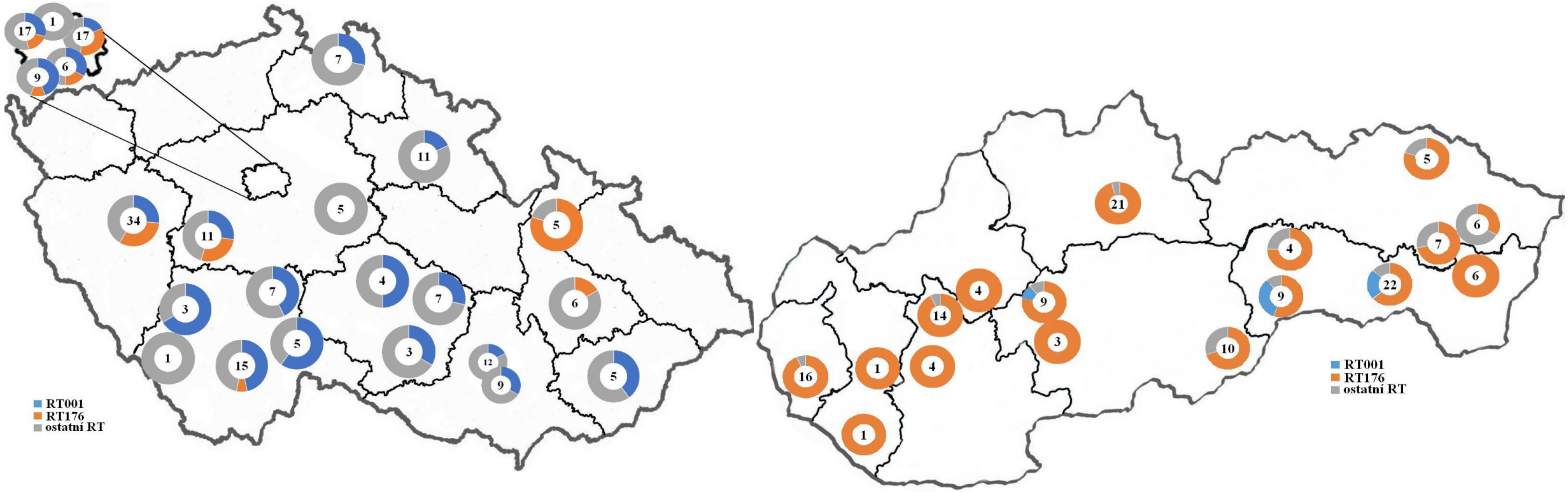


52 ribotyping profiles

Zíková J., diploma thesis

RT=ribotype, NR=new ribotype

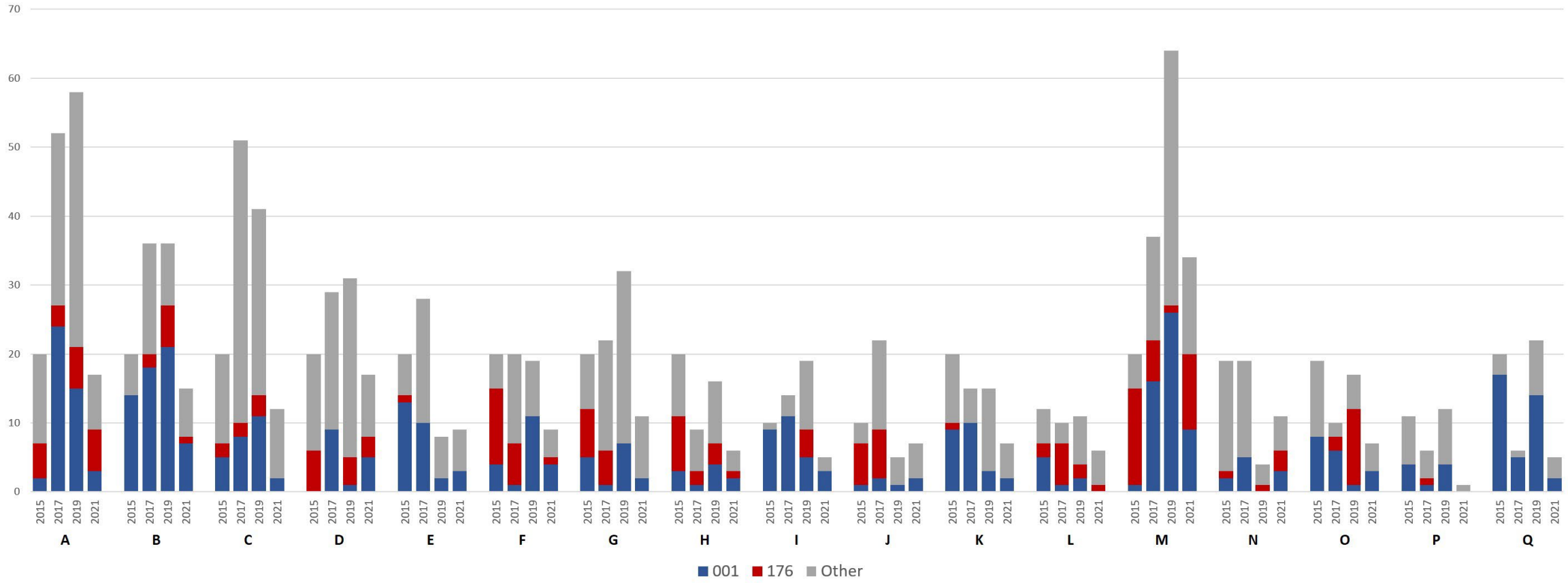
Geographical distribution of participating hospitals



Zíková J., diplomová práce

Zíková J., diploma thesis

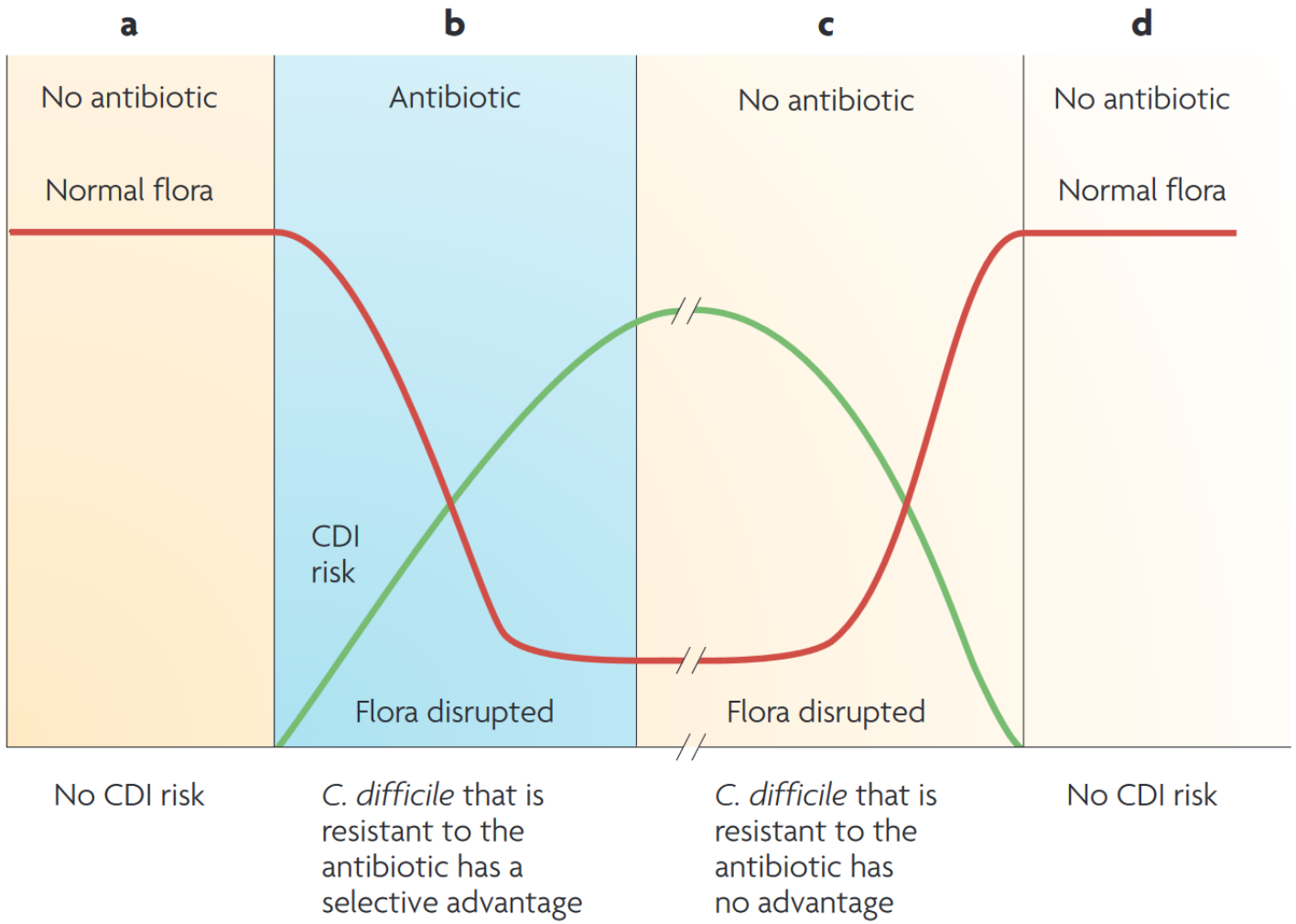
Czech Republic 2015-2021



2015 - RT001 33% RT176 25%
2017- RT001 33% RT176 11%

2019 – RT001 33% RT176 10%
2021 - RT001 29% RT176 16%

Safe Antibiotics for Patients at Risk of CDI – *C. difficile* Colonization



Rupnik et al., 2009

Safe antibiotics for patients at risk of CDI?
The effect of antibiotics on the composition of the gut microbiota

Table 1a
Changes in the abundance of aerobic bacteria in the intestinal microbiota associated with adminstration of antibiotics (reported on genus level).

Increased abundance | Decreased abundance | Inconsisted findings
Increased abuandance or no change | Decreased abundance or no change | No change in aubundance
White boxes depict that no finfings were reported for the respective bacteria

	AEROBIC BACTERIA																	
	Total number	*ACINETOBACTER*	*BACILLUS*	*CITROBACTER*	*CORYNEBACTERIUM*	*ENTEROBACTERIACEAE**	*ENTEROBACTER*	*ENTEROCOCCUS*	*ESCHERICHIA*	*KLEBSIELLA*	*MORGANELLA*	*MICROCOCCUS*	*PROTEUS*	*PSEUDOMONAS*	*SALMONELLA*	*STAPHYLOCOCCUS*	*STREPTOCOCCUS*	Other bacteria	Normalisation (after antibiotic treatment)
PENICILLINS																		
Penicillin[22-25]	na[22-25]		na[22]			na[24]		↓[25] na[22,24]	↑[22] na[25]	↑[22]							na[22,24]		d14[22,25]
Amoxicillin[26-33,149]	↑GN[30]		na[32]	↑[29]	↑[32]	↑[28,31,33]	↑[28,31,32]	↑[28,32,33] na[30,31,149]	↓[29,32] ↑[27]	↑[28-32,149]	↑[29]			↑[33]		↑[31] na[32,33]	↑[31,32] ↓[32] na[33]	↑*Shigella*[27]	d7-d21[30-32,149] not d28-55[27-29,33] not 12m[26]
Ampicillin[34]	na[25]							↑[25]	na[25]										d14[25]
Bacampicillin[43,34]						na[34]		na[34]									na[34]		
Pivmecillinam[35]			na[35]				↑[35]	na[35]	↓[35]	↑[35]									
Mezlocillin[25]	na[25]							na[25]	na[25]								↓[25]		d14[25]
Azlocillin[36]								↓[36]	↓[36]	↑[36]							↓[36]		d14[36]
Flucloxacillin[37]				↑[37]		↑[37]			↑[37]	↑[37]			↑[37]						
Amoxicillin/clavulanate[37-40,147]				↑[37]		↑[37,39,40]	↑[36]	↑[147]	↑[37-39,147]	↑[37] na[147]									d14-d28[36,147] not d14-d60[39,40]
Piperacillin[25]	na[25]							↑[25]	↑[25]										d14[25]
Ticarcillin[25]	na[25]							↑[25]	na[25]										d14[25]
Ticarcillin/clavulanate[41]			na[41]		na[41]	↓[41]		↑[41]				na[41]				na[41]	↑[41]		d14[41]
CEPHALOSPORINS																			
Cefadroxil[24]			na[24]					na[22]	na[25]							na[22]	↓[22]		d14[22]
Cephaloridine[25]	na[25]							na[25]	na[25]										
Cephazolin[25]																			
Cefaclor[33,42,43]				↑[43]		↑[33] na[42]	↑[43]	↑[33] na[42]		↑[43]						↑[43] ↓[33]	↓[33] na[42]		not d14-42[33,43]
Cefprozil[44]						↓[44]		↑[44]								↑[44]			d44[44]
Cefuroxime axetil[45,46,50,149]			na[45]	↑[46]		↓[46] d45	↑[46]	↑[45,50,149]	↓[46] na[149]	↑[46]					↑[50]	↓[45] ↑[46] na[50]	↑[45]		d14[46,50,149] not d14[45]
Cefuroxime[25]	na[25]							↑[25]	na[25]										d14[25]
Cefoxitin[23,25,47]	na[25]			↑[47]		↑[23]	↑[23]	↑[23] na[25]	na[25]				↑[47]	↑[23]		↑[47]	↑[47]		d14[23]
Cefotetan[25]	↓[25]							↑[25]	↓[25]										d14[25]
Latamoxef[25]	↑[25]							↑[25]	↓[25]										d14[25]
Loracarbef[30,48]	na[30,48]		na[48]		na[48]	na[48]		↑[30,48]		↑[30]		na[48]				na[48]	↑[48]		d7[48] not d21[30]
Cefixime[43,49,50]						↓[43,50]		↑[49,50]	↓[43,49]						↑[50]	↑[50] na[50]	↓[49]		d14[49] not d14[50]
Cefoperazone[51,52]			↓[51]		↑[52] ↓[51]	↓[52]		↑[51]		↑[51]				↑[52]		↑[52] ↓[51]	↓[51]	↑*Stenotrophomonas*[51]	
Cefotaxime[25]	na[25]							na[25]	na[25]										

(*continued on next page*)

P. Zimmermann and N. Curtis/Journal of Infection 79 (2019) 471–489

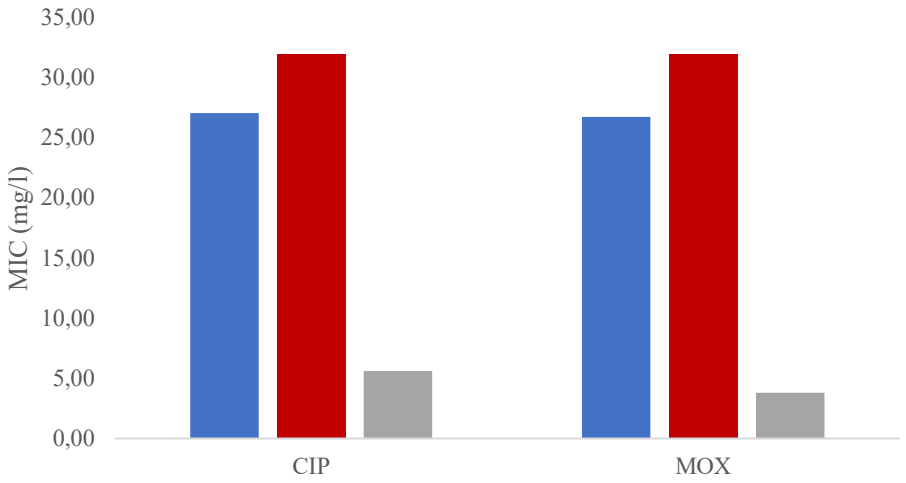
- ✓ Antibiotics cause significant changes in the intestinal microflora. These changes include a decrease in bacterial diversity,
- ✓ changes in the abundance of certain bacteria and an increase in antibiotic resistance.
- ✓ The longest duration of changes was observed after treatment with ciprofloxacin (one year), clindamycin (two years) and clarithromycin with metronidazole (four years). However, these findings are limited by the follow-up period.

(Zimmermann and Curtis, JI, 2019)

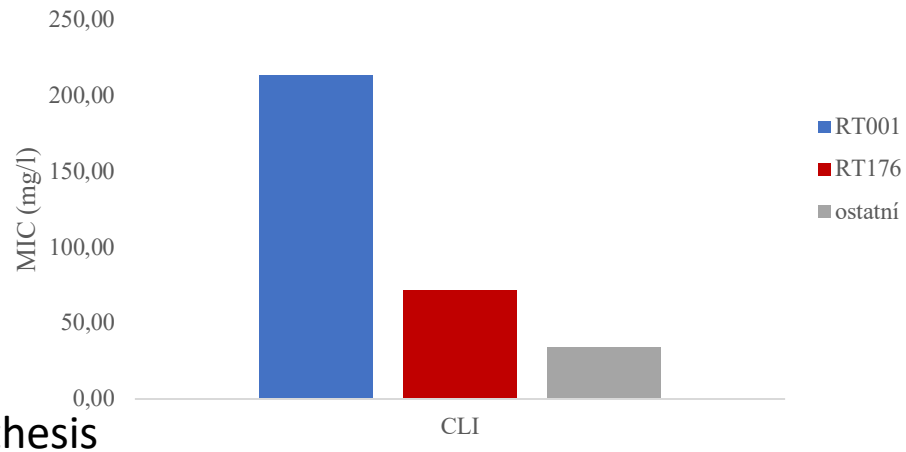
Risky ATB
fluoroquinolones and clindamycin

- CZ

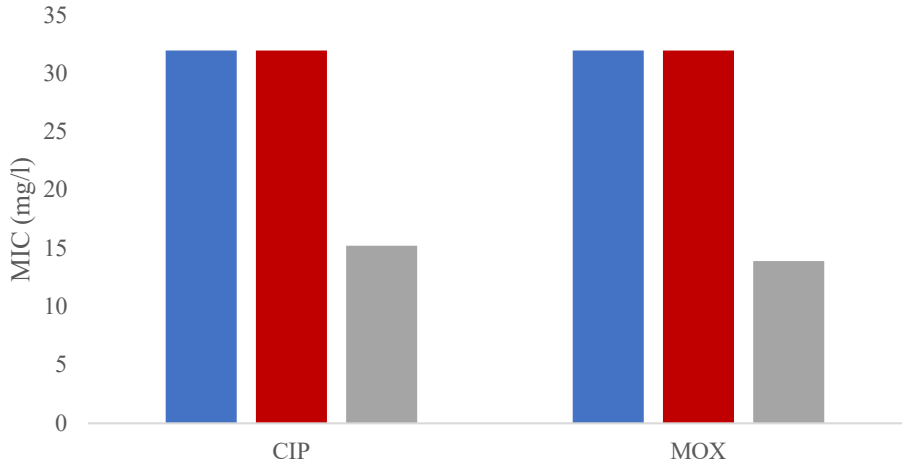
AK substitutions
T82I v GyrA

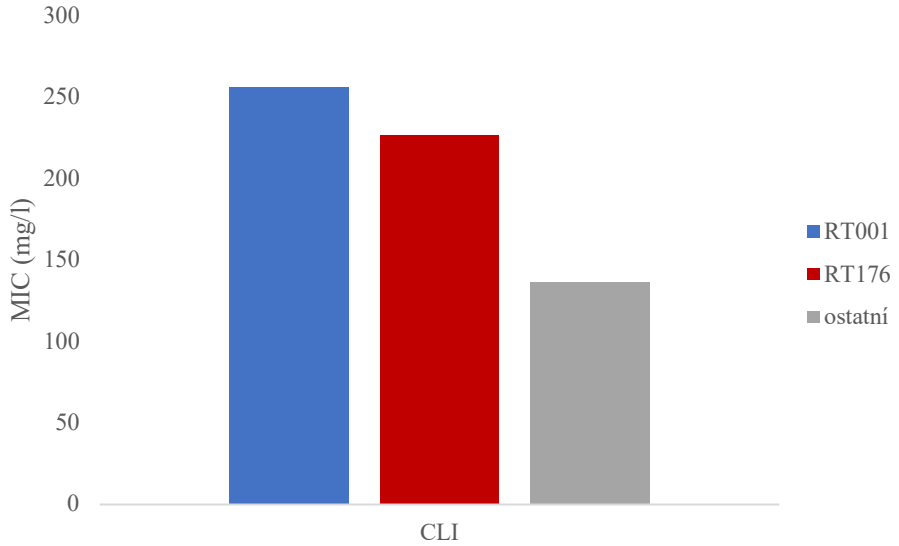


*erm*B, *cfr*B
Transmissibility!



- SR

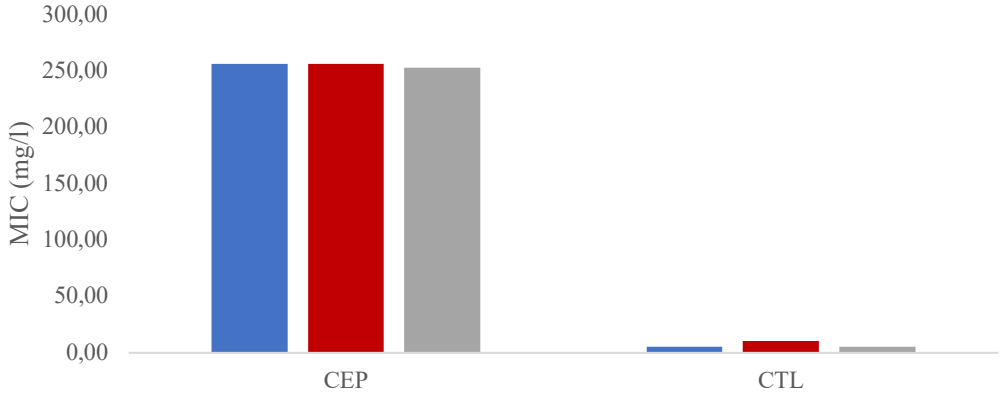


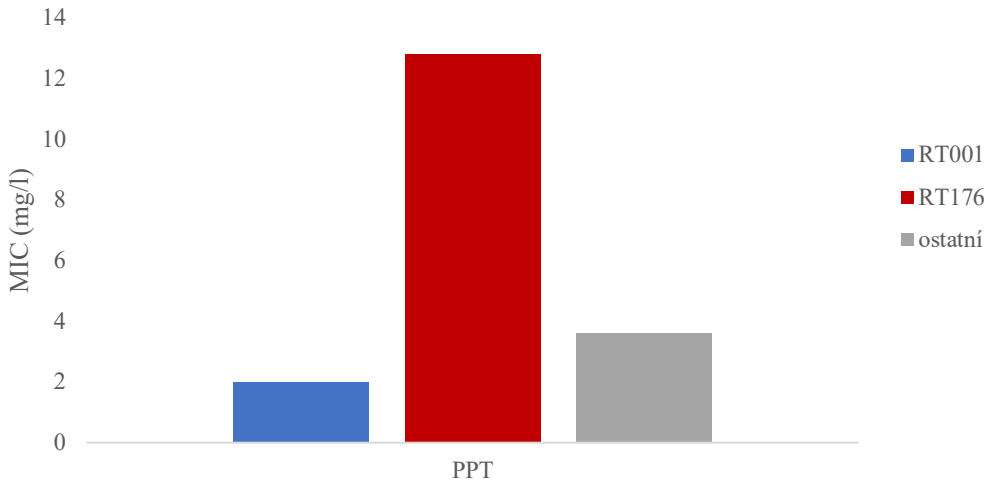


Zíková J., diploma thesis

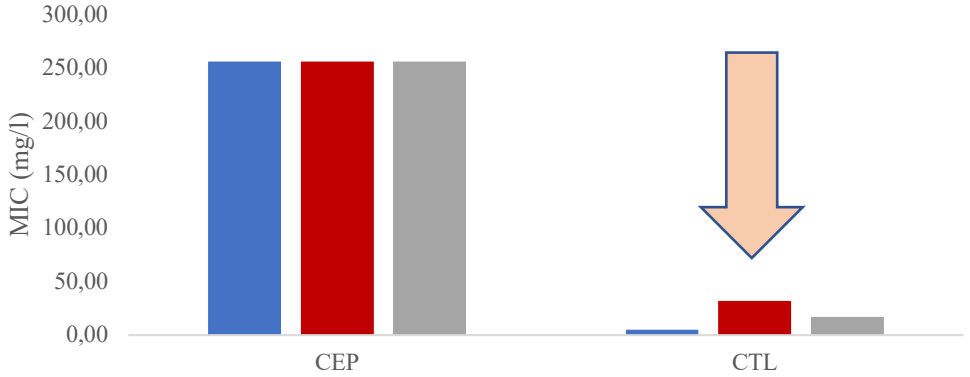
Frequently used ATB
Cephalosporins or piperacillin tazobactam?

- ČR





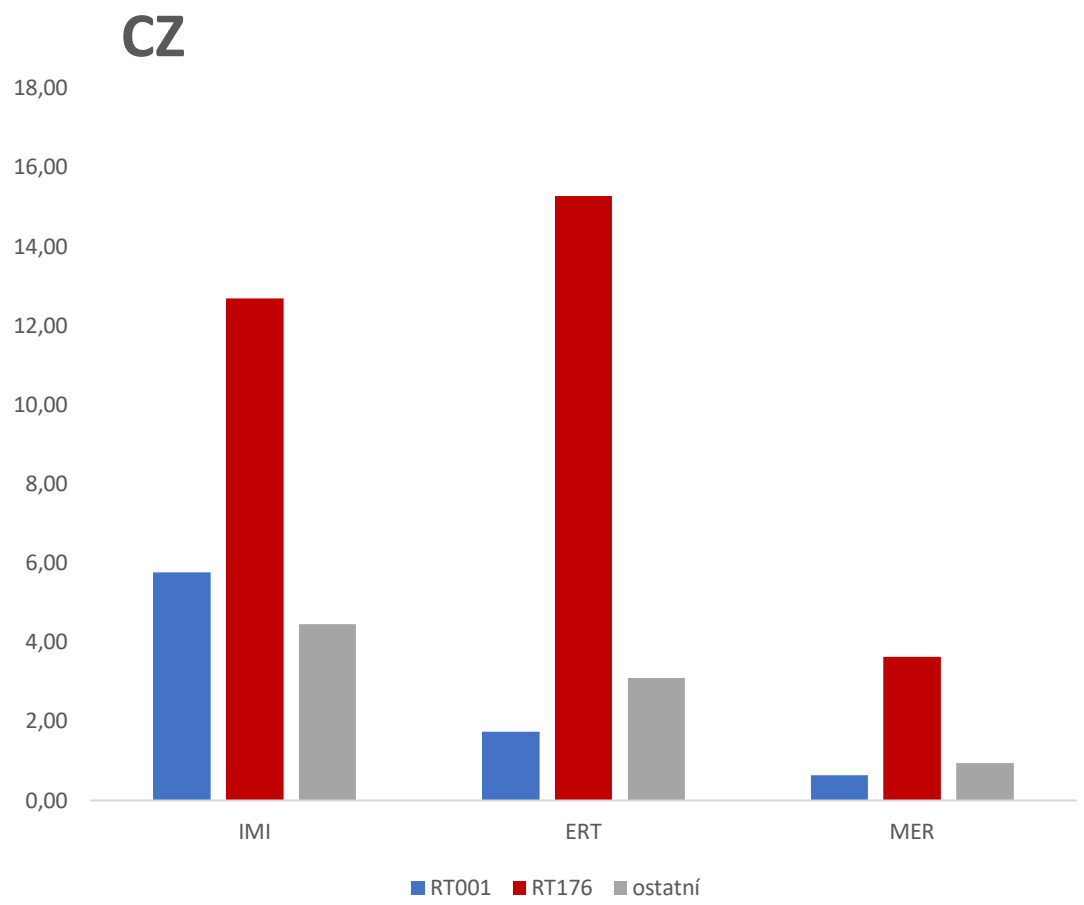
- SR

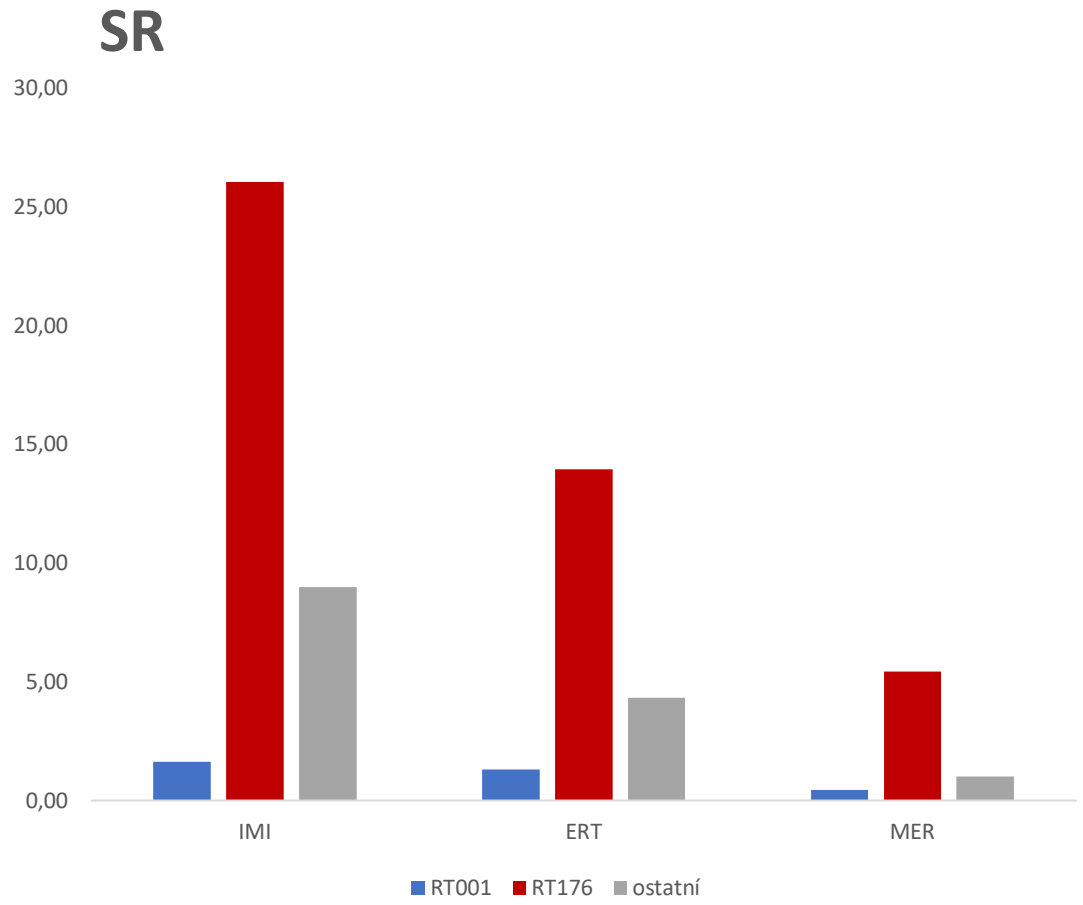


We don't know the mechanisms yet

Zíková J., diploma thesis

Carbapenems

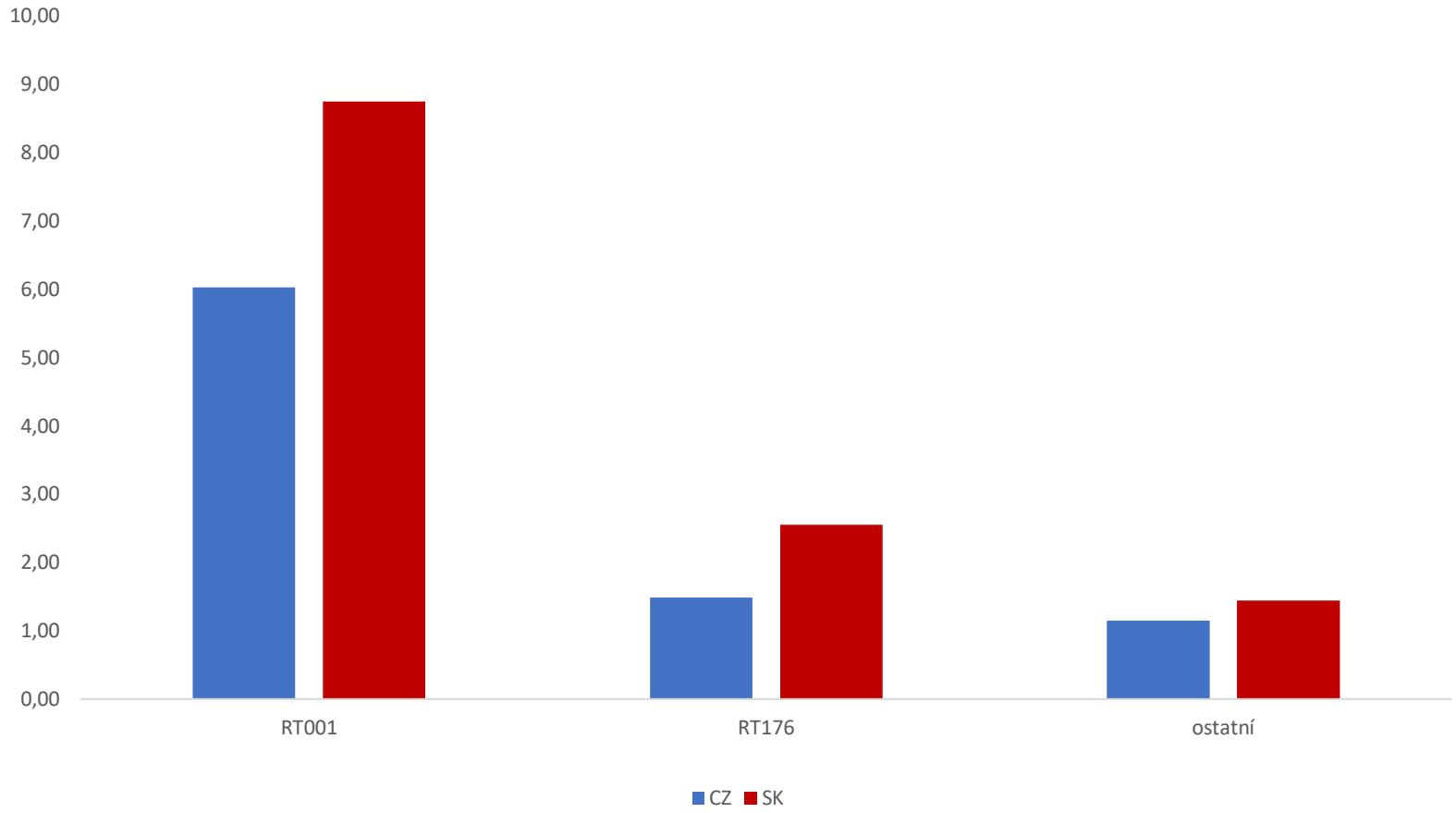




Zíková J., diploma thesis

We don't know the mechanism yet

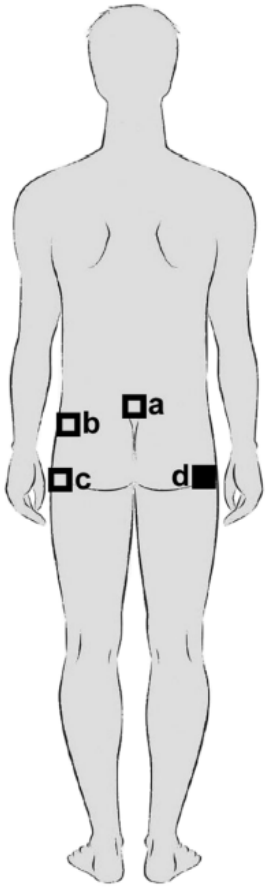
Linezolid at risk!!



Presence of *cfr*B gene, which also causes resistance to clindamycin and erythromycin!

Zíková J., diploma thesis

Extraintestinal *C. difficile* infections



MICROBIOLOGICAL FINDINGS AND TREATMENT

2nd day

Decubitus ***a-d***: polymicrobial findings: MRSA, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterococcus faecalis*, and *Alcaligenes faecalis*.

14th day

Decubitus ulcers ***a, b*** – plastic surgery

Antibiotic coverage: vancomycin and piperacillin/tazobactam

26th day

Change to cotrimoxazol

37th day

Decubitus ***d***: *Pseudomonas aeruginosa*, decubitus ***a-c***: normal microflora

Urine: *Klebsiella pneumoniae* (ESBL positive)

Change to piperacillin/tazobactam

41st day

Drain decubitus ***b***: ESBL-positive *E. coli*

Change to imipenem/cilastatin

43th day

Decubitus ulcers ***c, d*** – surgical intervention

Antibiotic coverage: imipenem/cilastatin was supplemented by vancomycin

54th day

Decubitus ***d***: *Pseudomonas aeruginosa* resistant to imipenem/cilastatin

Change to: cefoperazone/sulbactam and amikacin

71st day

Decubitus ***d***: *Clostridium difficile*

Change to: metronidazole (the first six days intravenously and then orally for the next eight days)

81st day

Decubitus ***d:*** surgical revision

Antibiotic coverage: piperacillin/tazobactam (20 days) and vancomycin (16 days)

Fig. 1 Localization of decubitus ulcers (a–d) and timeline of microbiological findings and antibiotic treatment

Nyč et al., 2015

Extraintestinal infections caused by *C. difficile* are rare.
Examples:

- Bacteraemia with or without plaque infection
- Intra-abdominal infections, extra-abdominal infections
- abscesses (spleen, brain)
- Reactive arthritis, osteomyelitis
- Infections of prosthetic shoulder and knee joint replacements

- Non-healing wounds
- In a spore-contaminated environment
- C. difficile is only pathogen

Think about ANAEROBES

Thank you for your attention!