Clostridioides difficile – ein Update

Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V.

Frühjahrstagung der PEG
ausgerichtet von der Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V.
28./29. April 2025

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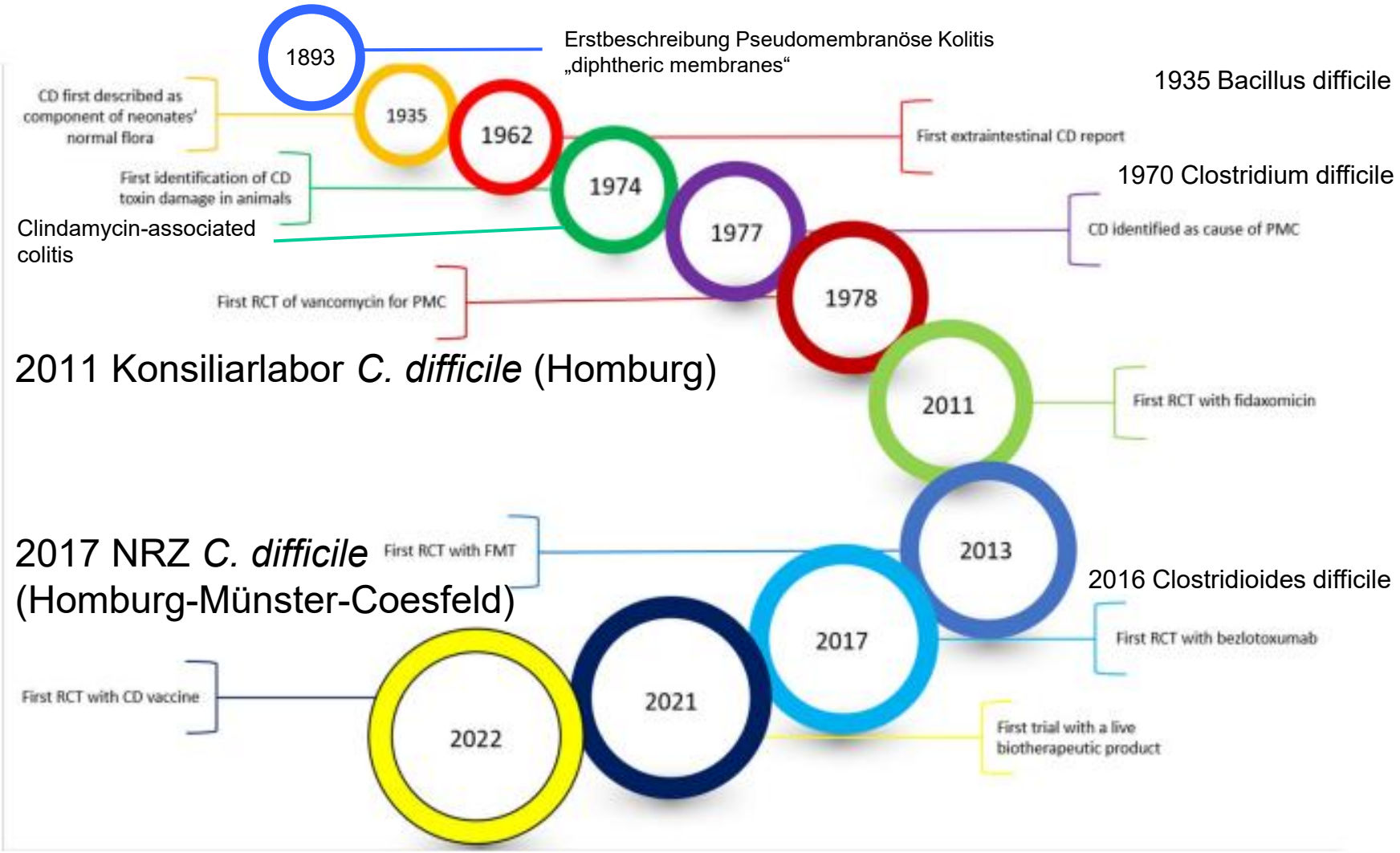
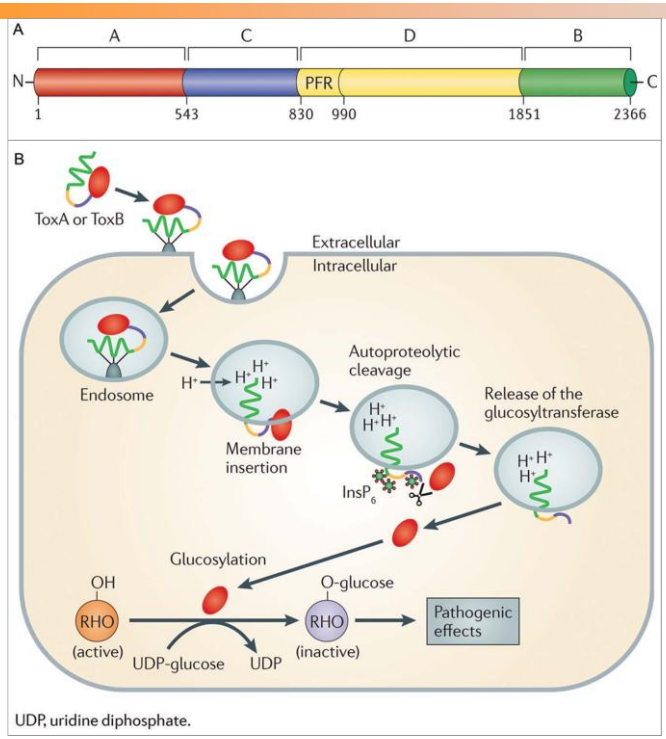
Nationales Referenzzentrum *Clostridium difficile*
Homburg | Münster | Coesfeld

Coesfeld, 18.06.2025

Historischer Überblick (*C. difficile*)



CMR di Bella et al 2024



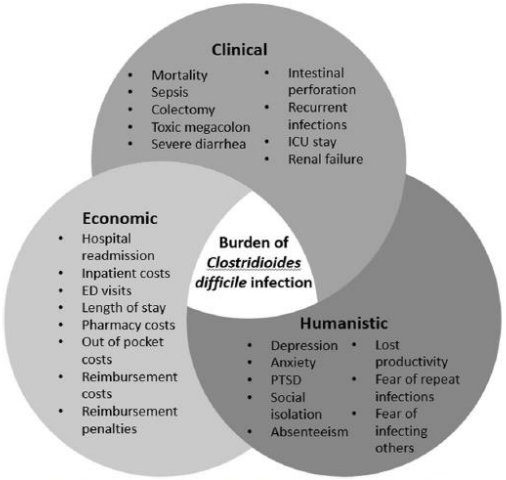
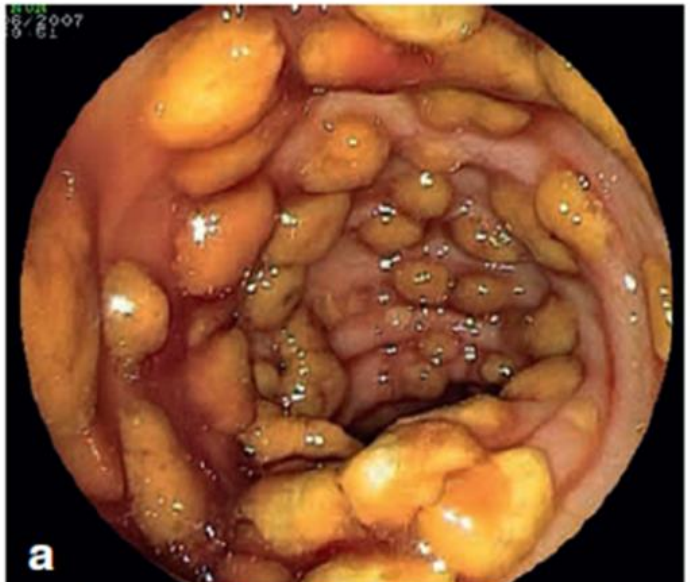
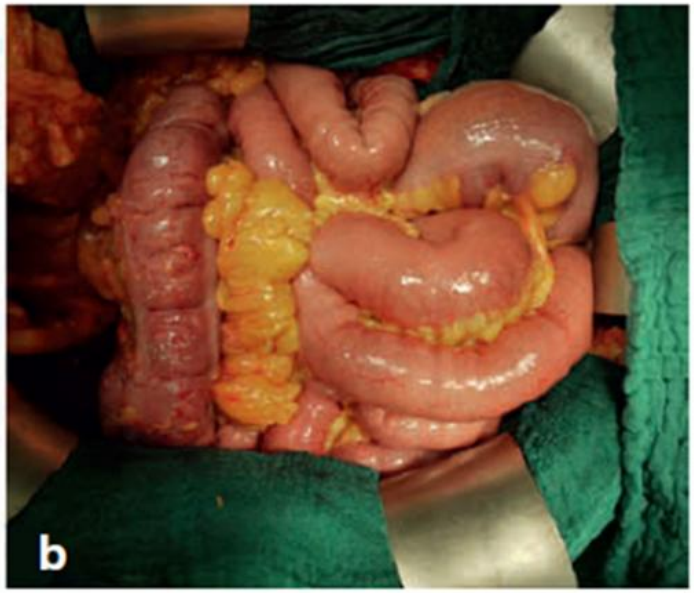


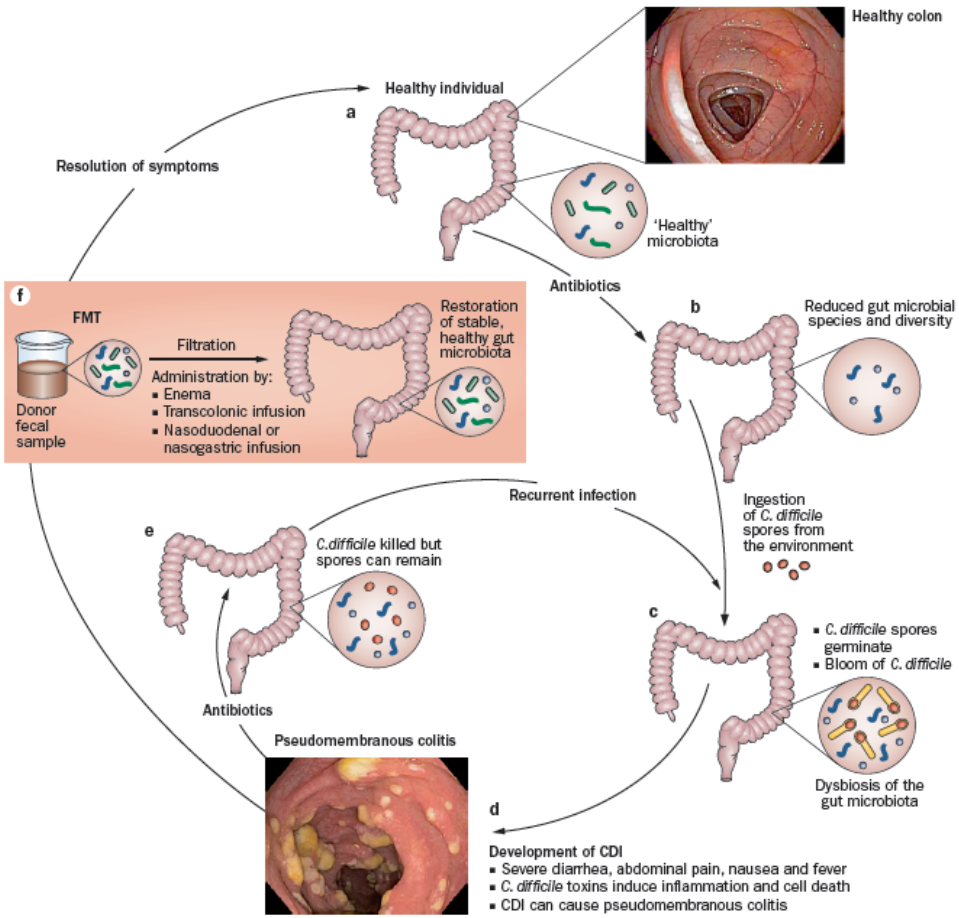
Fig. 1 Burden of *Clostridioides difficile* infection. *ED* emergency department; *ICU* intensive care unit; *PTSD* post-traumatic stress disorder

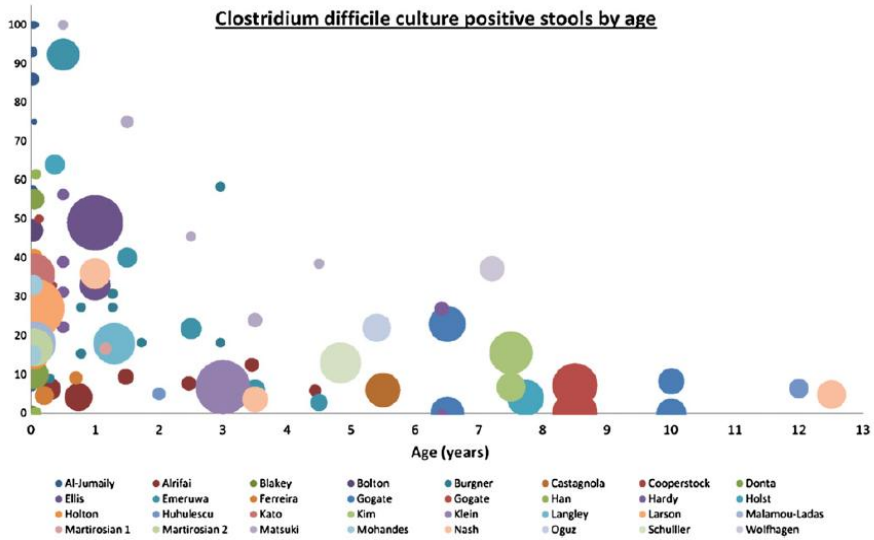


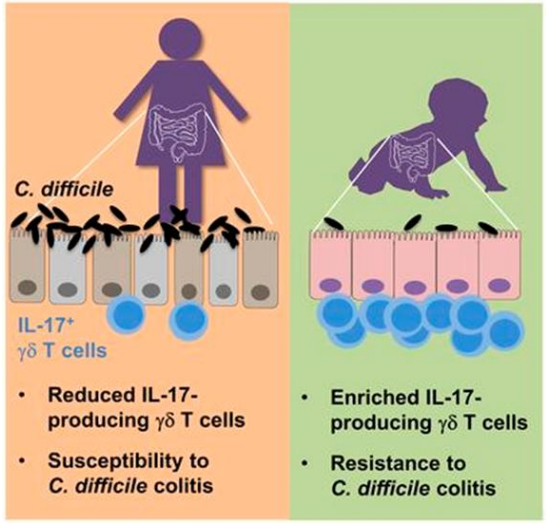


Awad et al, Gut Microbes 2014; Lübbert et al DÄ 2014, Feuerstadt *et al. BMC Infectious Diseases (2023) 23:132*

Pathogenese
(Microbiota/Immunität)





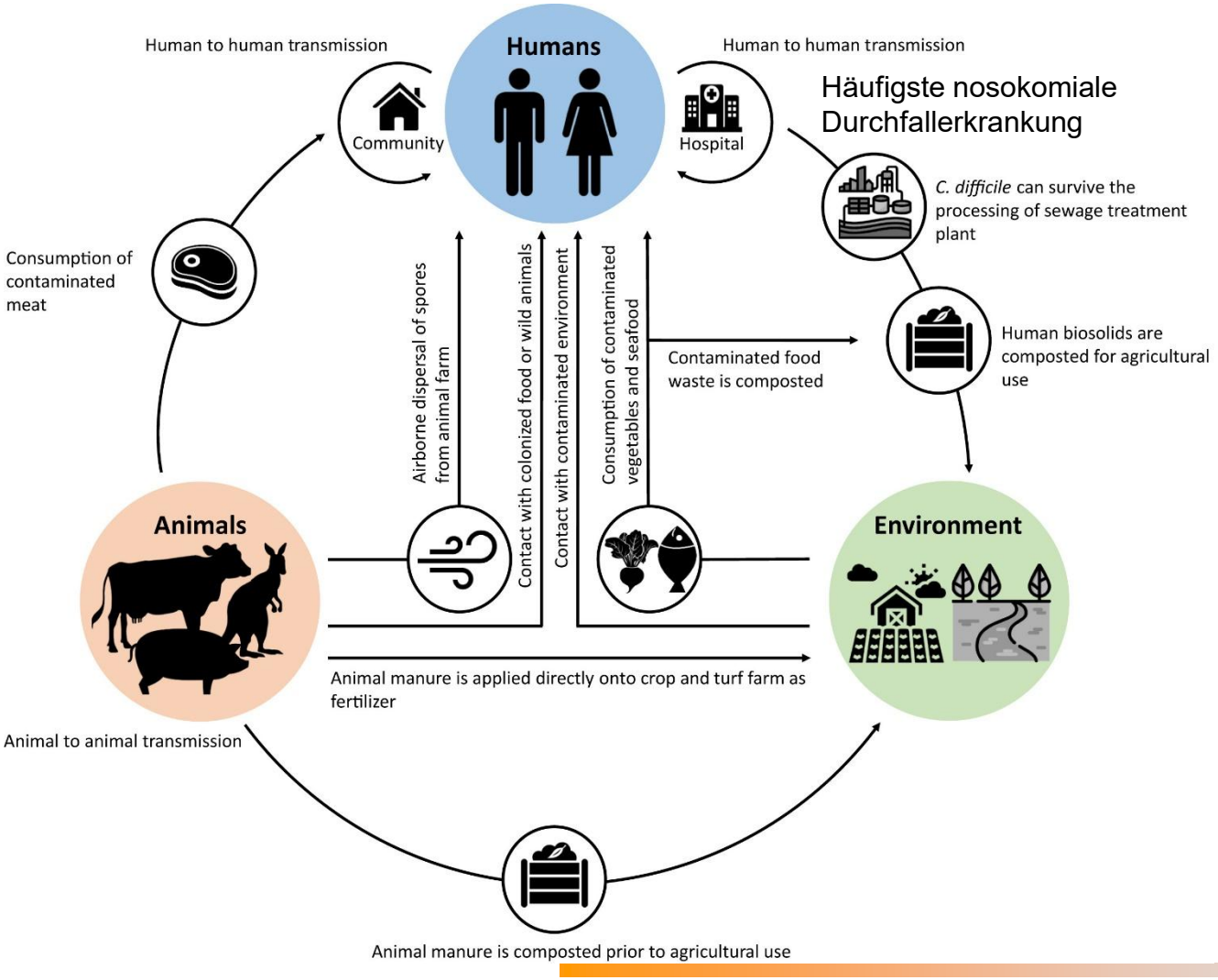


iLC2s: type 2 innate lymphoid cells

Kelly & LaMont, NEJM 2008, Chen et al JCI 2020, Feghaly et al Curr Opin Gastroenterol 2015, Naz&Petri Clinical Microbiology Reviews 2023

One health

C. difficile ein relevantes, globales Problem



Clinical Microbiology and Infection 2020 26857-863DOI: (10.1016/j.cmi.2019.10.023)

Hauptrisikofaktor: Antibiotika

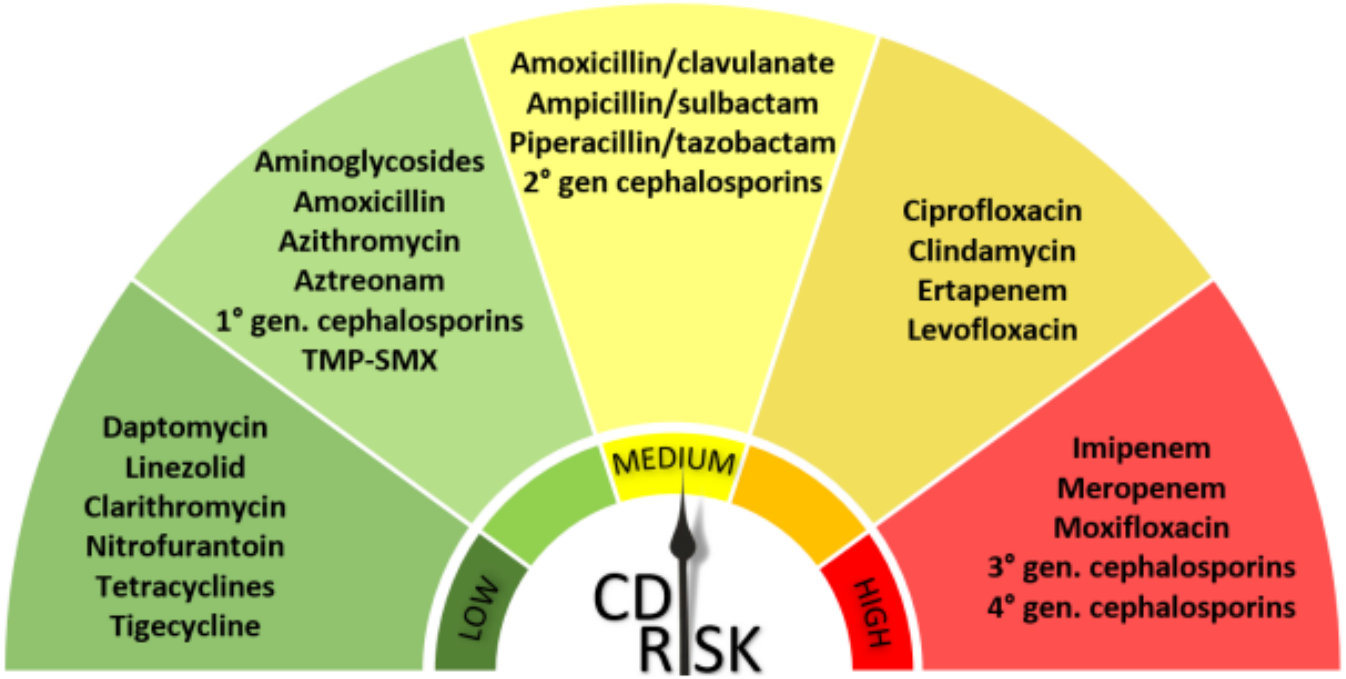


FIG 3 Approximate risk of CDI development according to different antimicrobials (65, 73–77).

- Lincosamides e.g., clindomycin[1,2] – the first antibiotic to be associated with CDI[3] — OR 16.8–20.43[1,2]
- Fluoroquinolones[1,2] — OR 5.5–5.65[1,2]
- Cephalosporins[1,2] — OR 4.47–5.68[1,2]
- Macrolides e.g., erythromycin[1,2] — OR 2.55–2.65[1,2]
- Penicillins[1,2] (widely used, in medicine and dentistry)[4] — OR 2.71–3.25[1,2]
- Sulphonamides/trimethoprim[1,2] — OR 1.81–1.84[1,2]

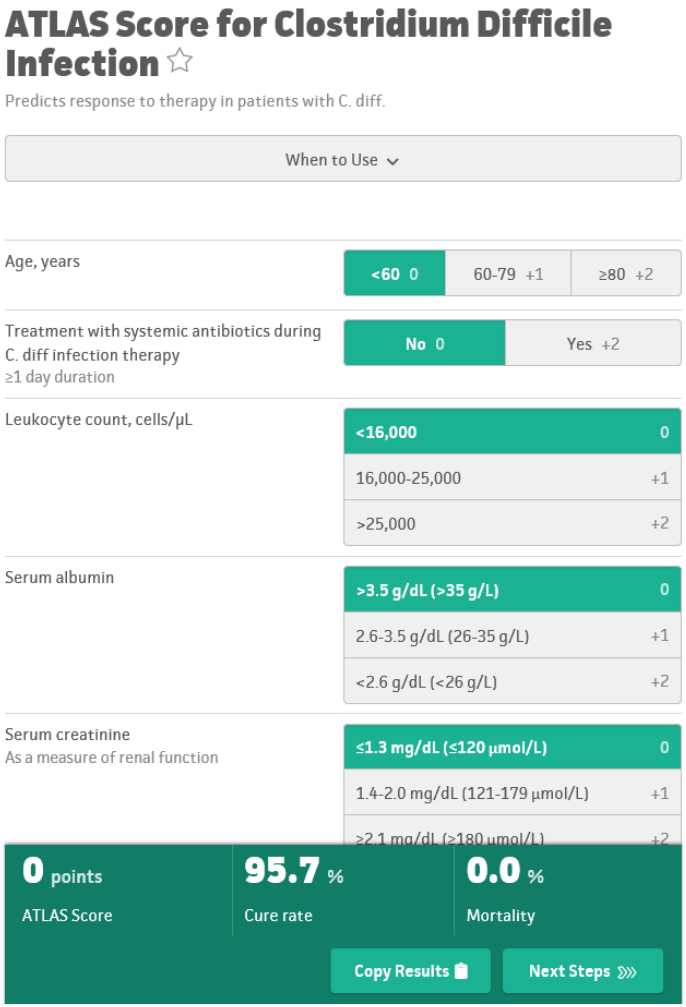
C. difficile, *Clostridioides difficile*; CDI, *Clostridioides difficile* infection; OR, odds ratio.

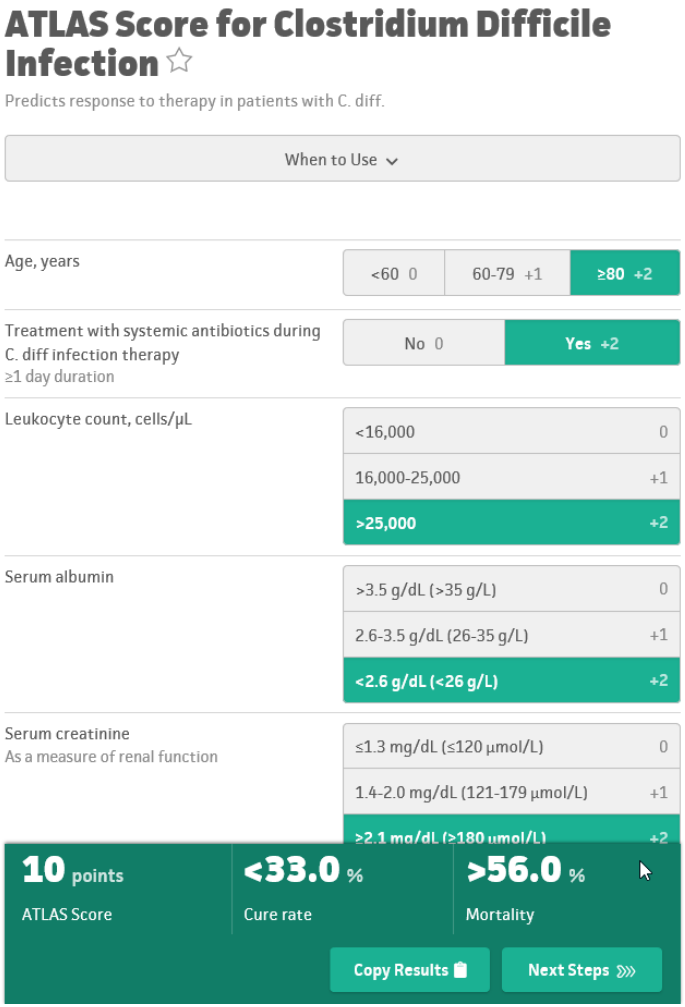
1. Brown KA, et al. Antimicrob Agents Chemother 2013;57:2326-32; 2. Deshpande A, et al. J Antimicrob Chemother 2013;68:1951-61.; 3. Barlett JG, et al. NEJM 1978;298:531-34; 4. Beacher N, et al. Br Dent J 2015;219:275-79.

Di Bella et al CMR 2024

Risikofaktoren/Schwere der CDI: ATLAS Score

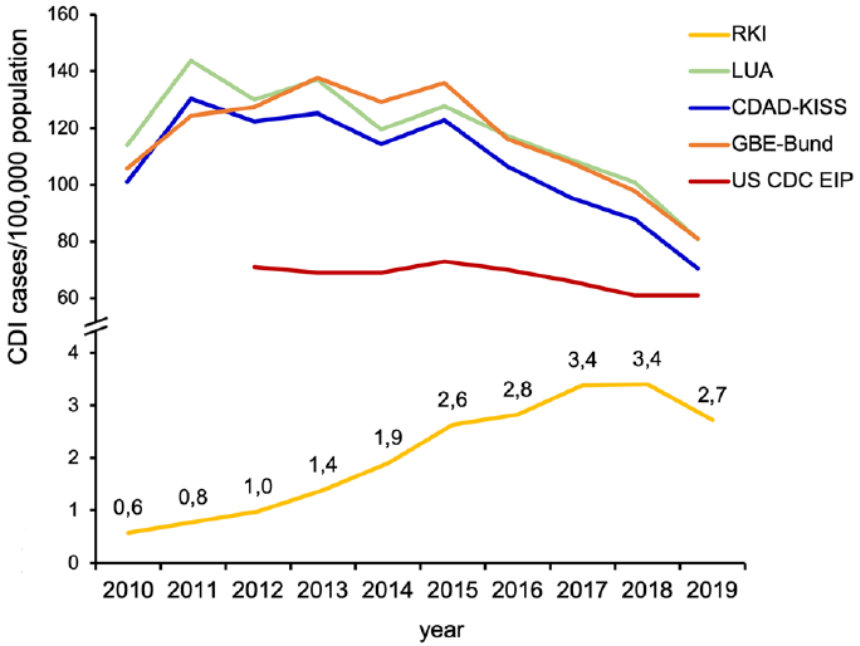
(age, treatment with systemic antibiotics, leukocyte count, albumin and serum creatinine)

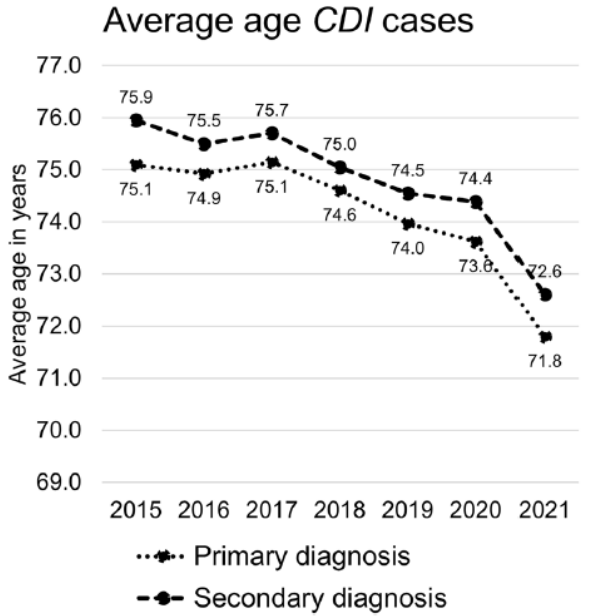




https://www.mdcalc.com/atlas-score-clostridium-difficile-infection

Epidemiologie





Definition der schweren CDI

Ein klinisch schwerer Verlauf der CDI liegt vor, wenn

1. der Erkrankte zur Behandlung einer ambulant erworbenen *Clostridioides (früher Clostridium) difficile*-Infektion in eine medizinische Einrichtung aufgenommen wird,
2. der Erkrankte zur Behandlung der *Clostridioides (früher Clostridium) difficile*-Infektion oder ihrer Komplikationen auf eine Intensivstation verlegt wird,
3. ein chirurgischer Eingriff, z.B. Kolektomie, aufgrund eines Megakolons, einer Perforation oder einer refraktären Kolitis erfolgt oder
4. der Erkrankte innerhalb von 30 Tagen nach der Feststellung der *Clostridioides (früher Clostridium) difficile*-Infektion verstirbt und die Infektion als direkte Todesursache oder als zum Tode beitragende Erkrankung gewertet wird.

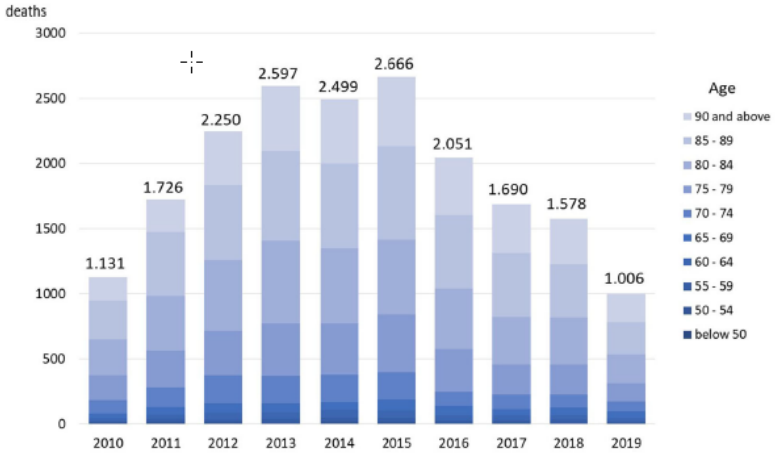
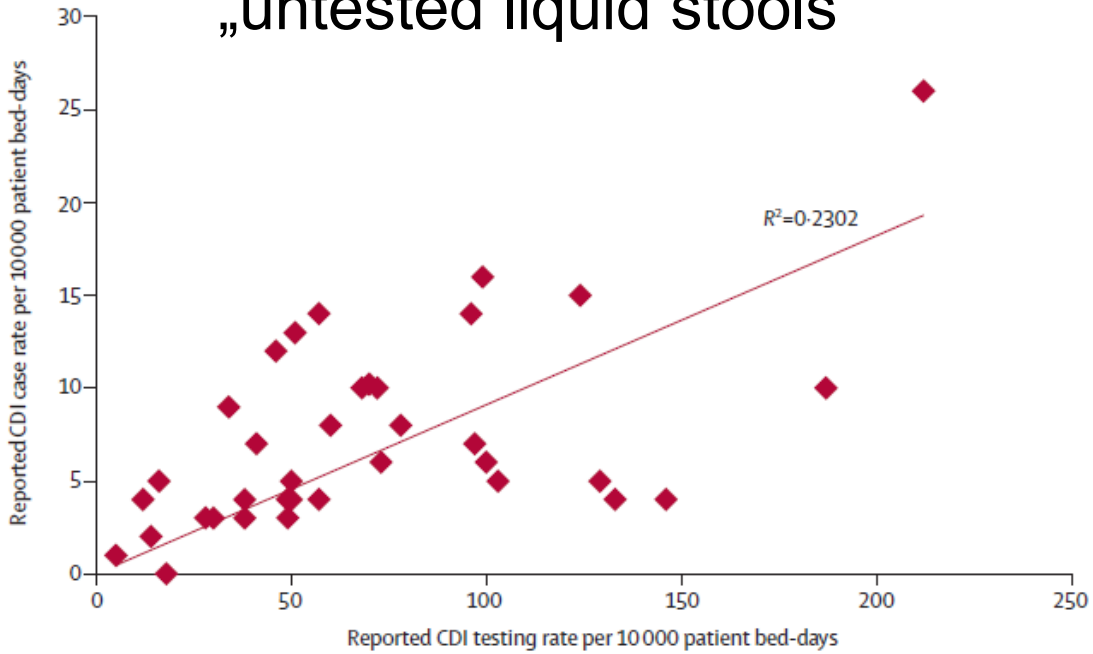


Fig. 2 Age-stratification of CDI-related deaths 2010–2019 including nosocomial and community-acquired CDI cases (source: GBE-Bund)

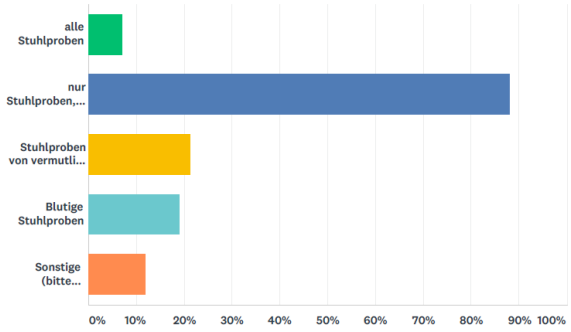
Brestrich et al. Infect Dis Ther https://doi.org/10.1007/s40121-023-00785-2
Vehreschild et al. Infection https://doi.org/10.1007/s15010-023-02044-5

Diagnostic stewardship: „Unterdiagnose“ „untested liquid stools“



Q3 Welche Stuhlproben werden bei Ihnen auf das Vorhandensein von C. difficile untersucht (Mehrfachnennungen möglich)?

Answered: 42 Skipped: 2



ANTWORTOPTIONEN	BEANTWORTUNGEN	
alle Stuhlproben	7,14%	3
nur Stuhlproben, bei denen der Einsender explizit die Diagnostik von C. difficile anfordert	88,10%	37
Stuhlproben von vermutlich nosokomialen Diarrhoefällen	21,43%	9
Blutige Stuhlproben	19,05%	8
Sonstige (bitte spezifizieren)	11,90%	5

Davis et al, Lancet 2014; NRZ C. difficile 2019

Hygienemanagement plus ABS

Übertragungen vermeiden / Ausbrüche erkennen

Stationen mit <20 Betten	Stationen mit ≥20 Betten
≥2 nosokom. CDI / Woche	≥3 nosokom. CDI / Woche
≥4 nosokom. CDI / Monat	≥5 nosokom. CDI / Monat

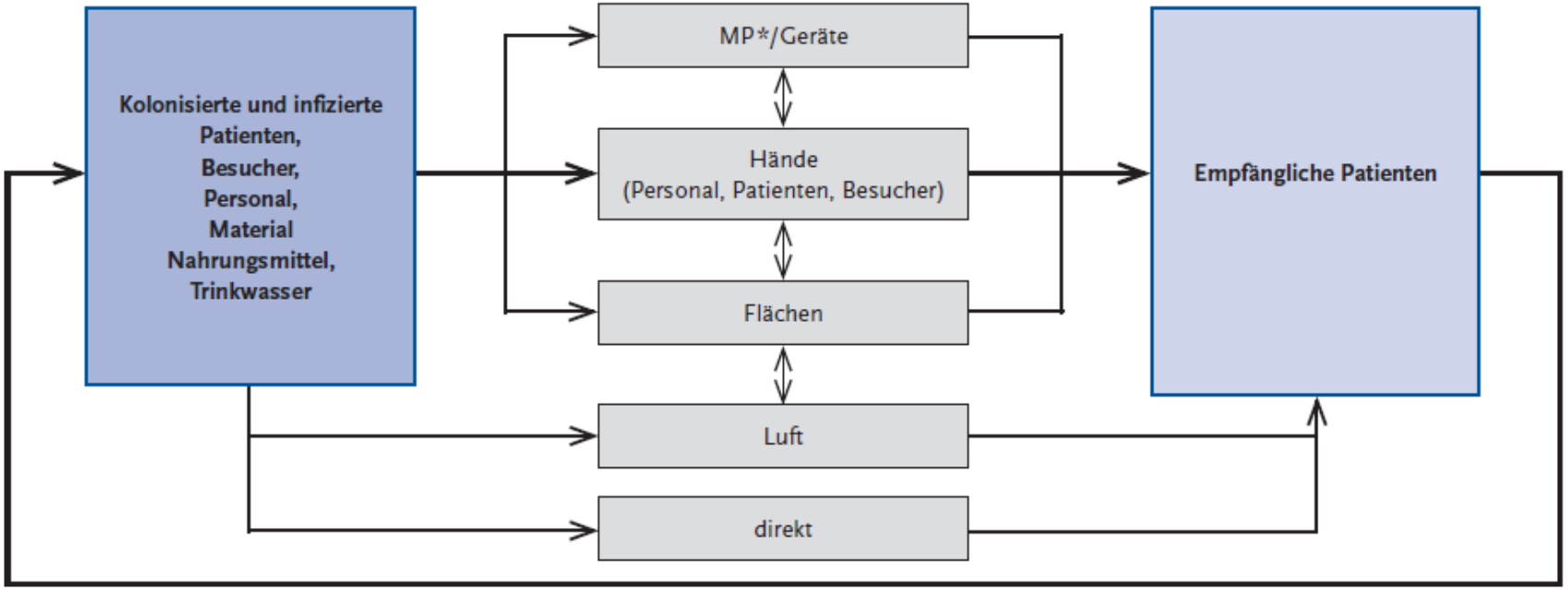
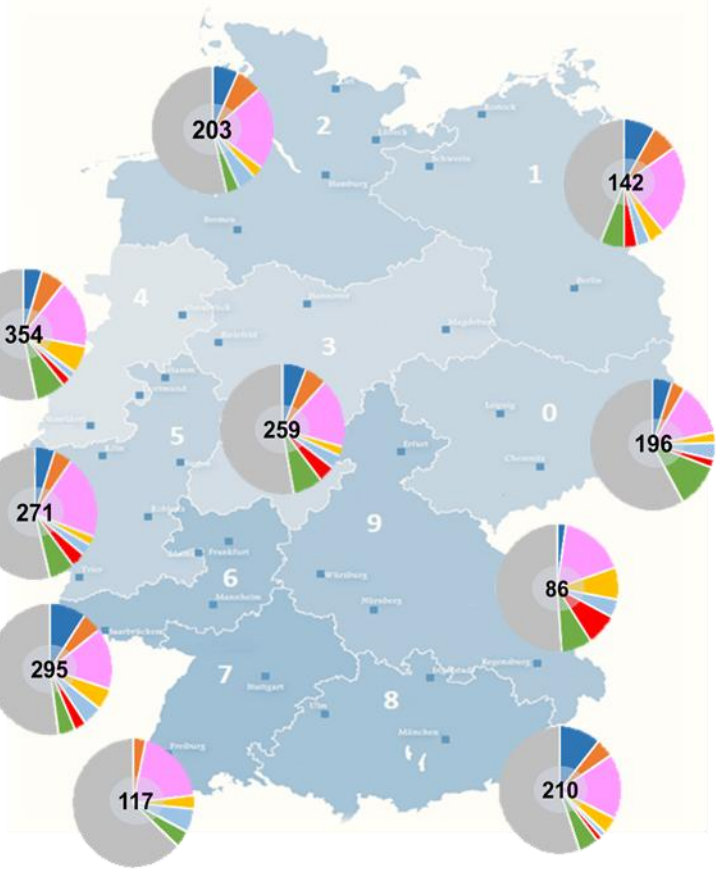
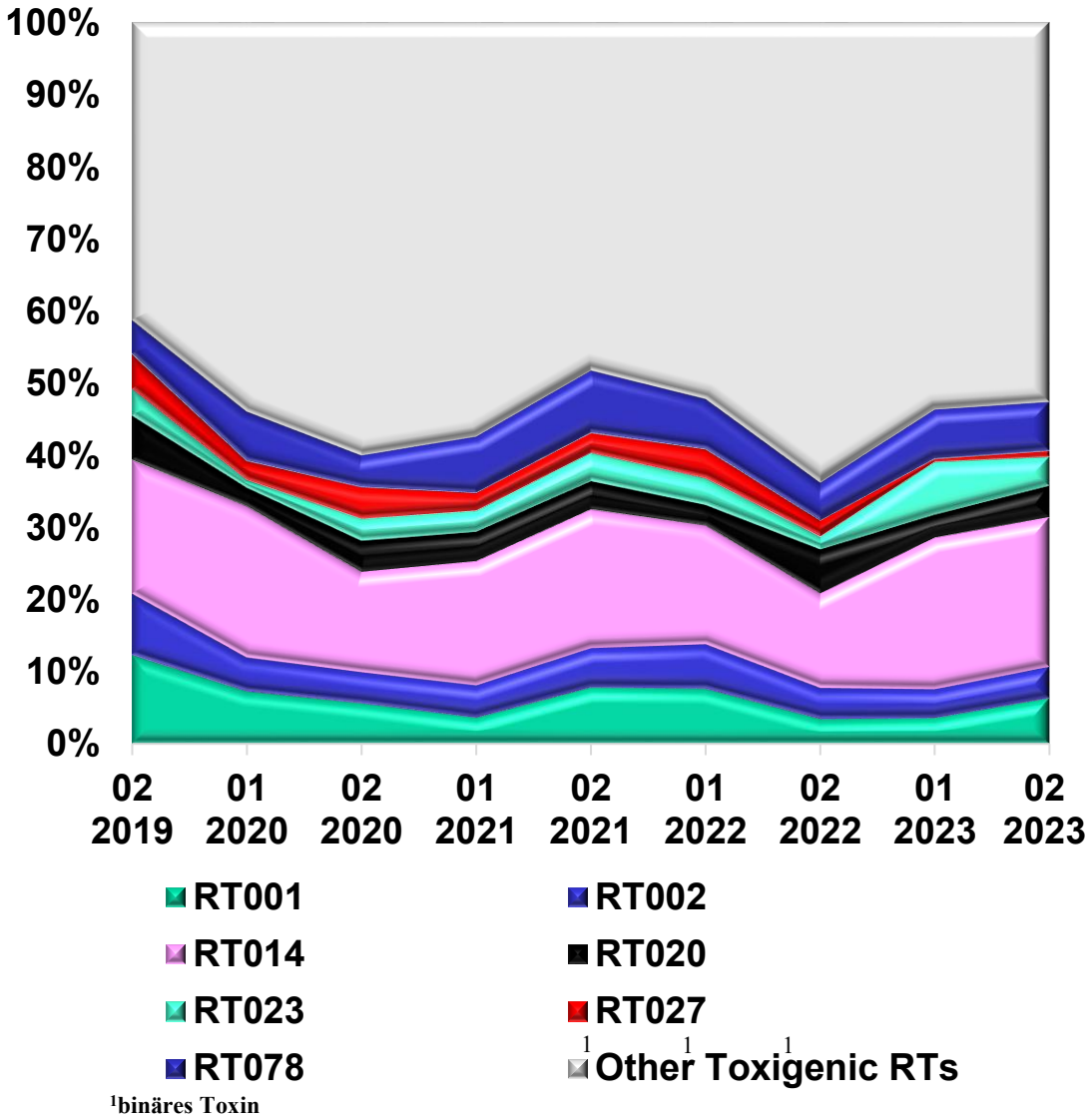


Abb. 1: Übertragungswege von Krankheitserregern verändert nach Hübner[2]. * MP = Medizinprodukte

Tschudin-Sutter et al. CMI 2018

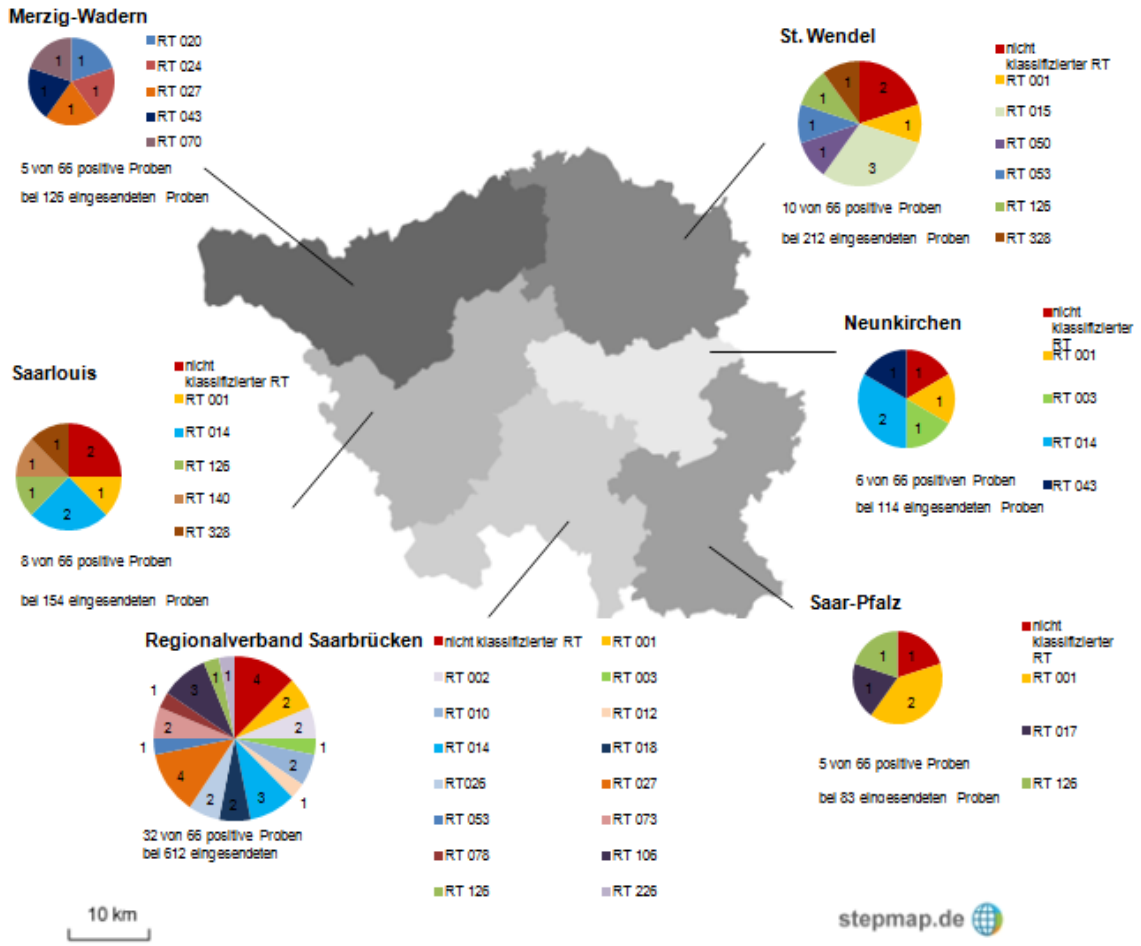
Punktprävalenzstudie (2x/Jahr)





[1]binäres Toxin

Asymptomatische Carrier in Altenheimen (hoher Diversität)

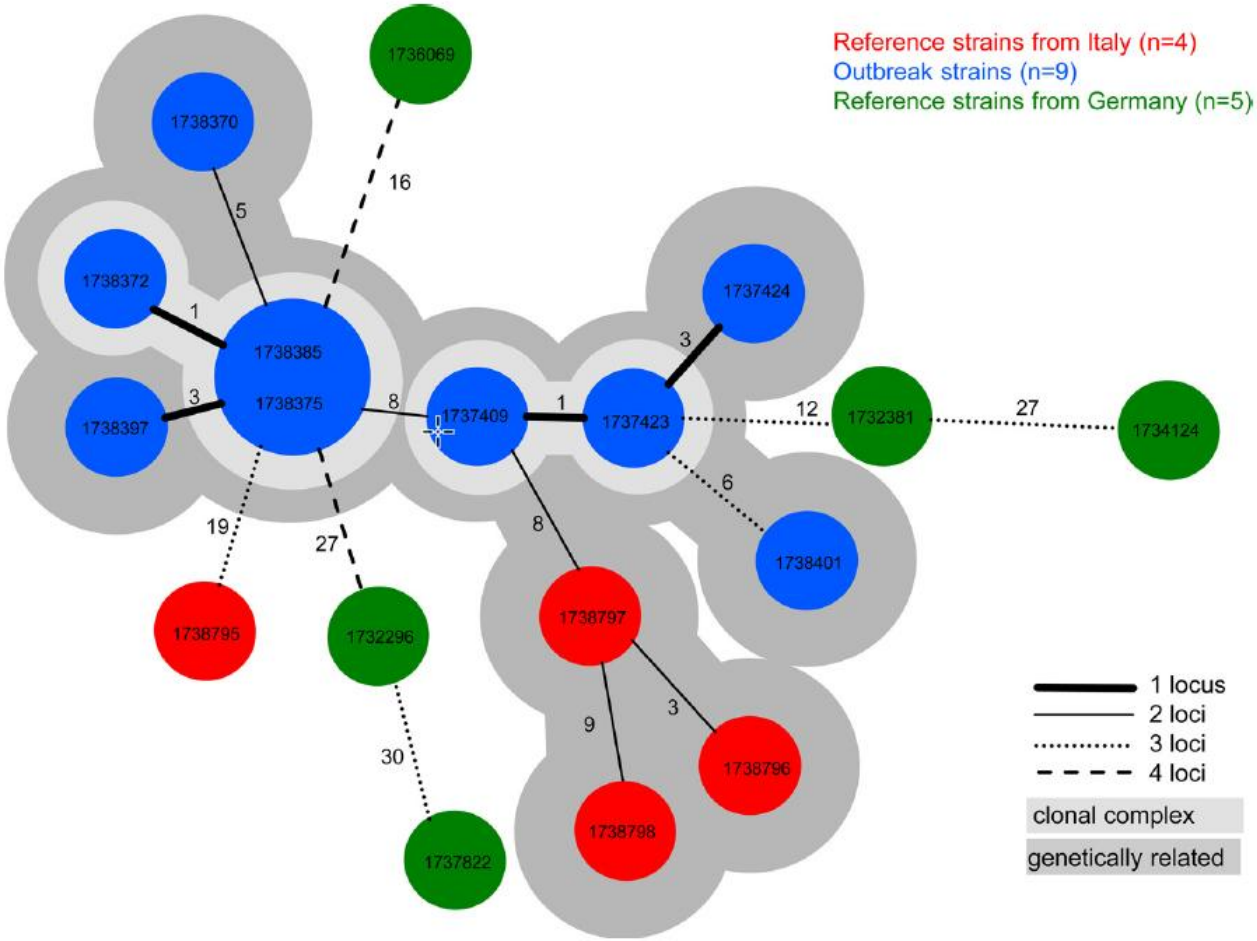


Meier et al. (unpublished)

Coesfeld, 18.06.2025

Molekulare Ausbruchsuntersuchungen (cgMLST)

RT018 in einem Krankenhaus in Süddeutschland



Molekulare Epidemiologie

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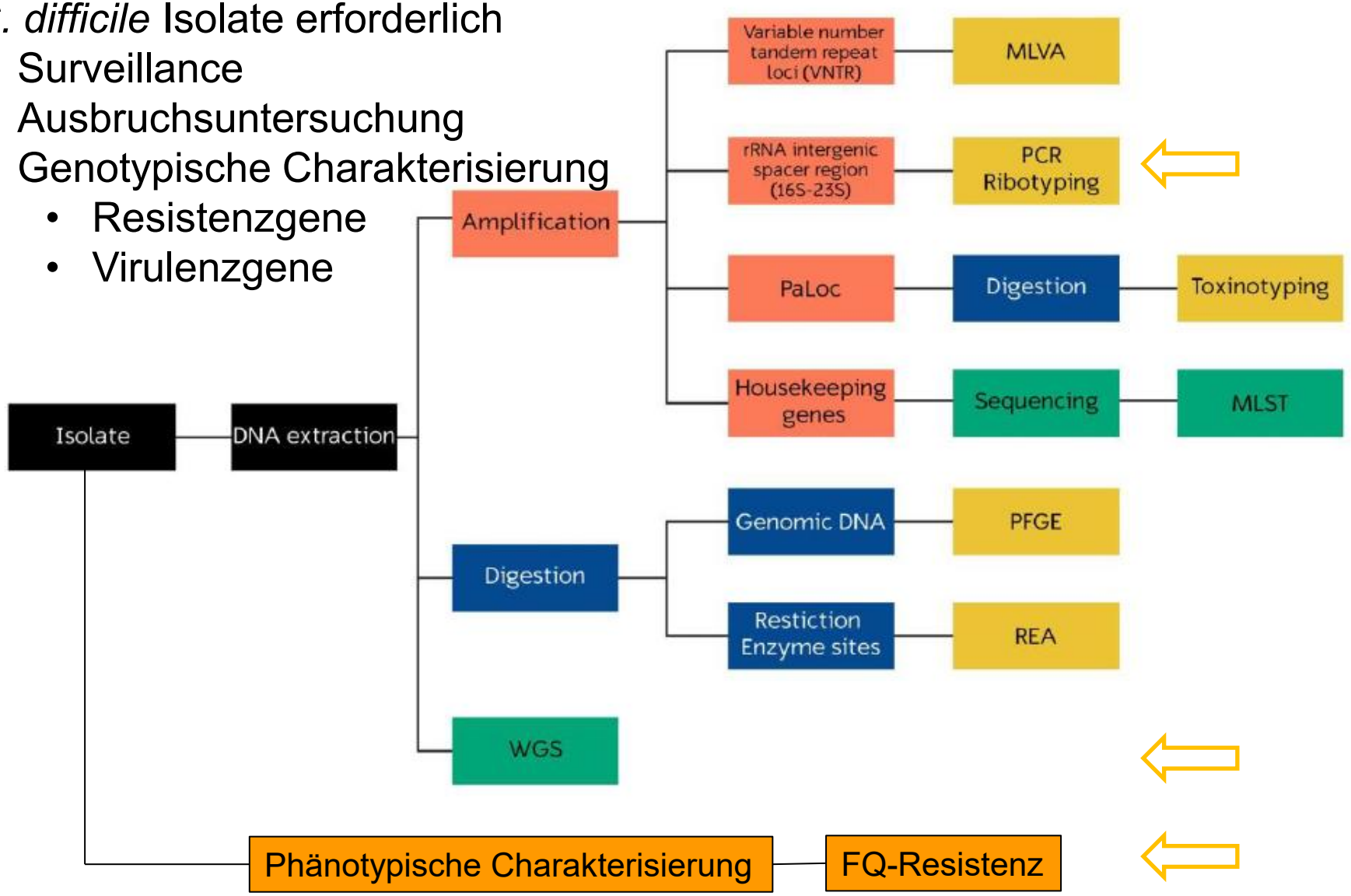
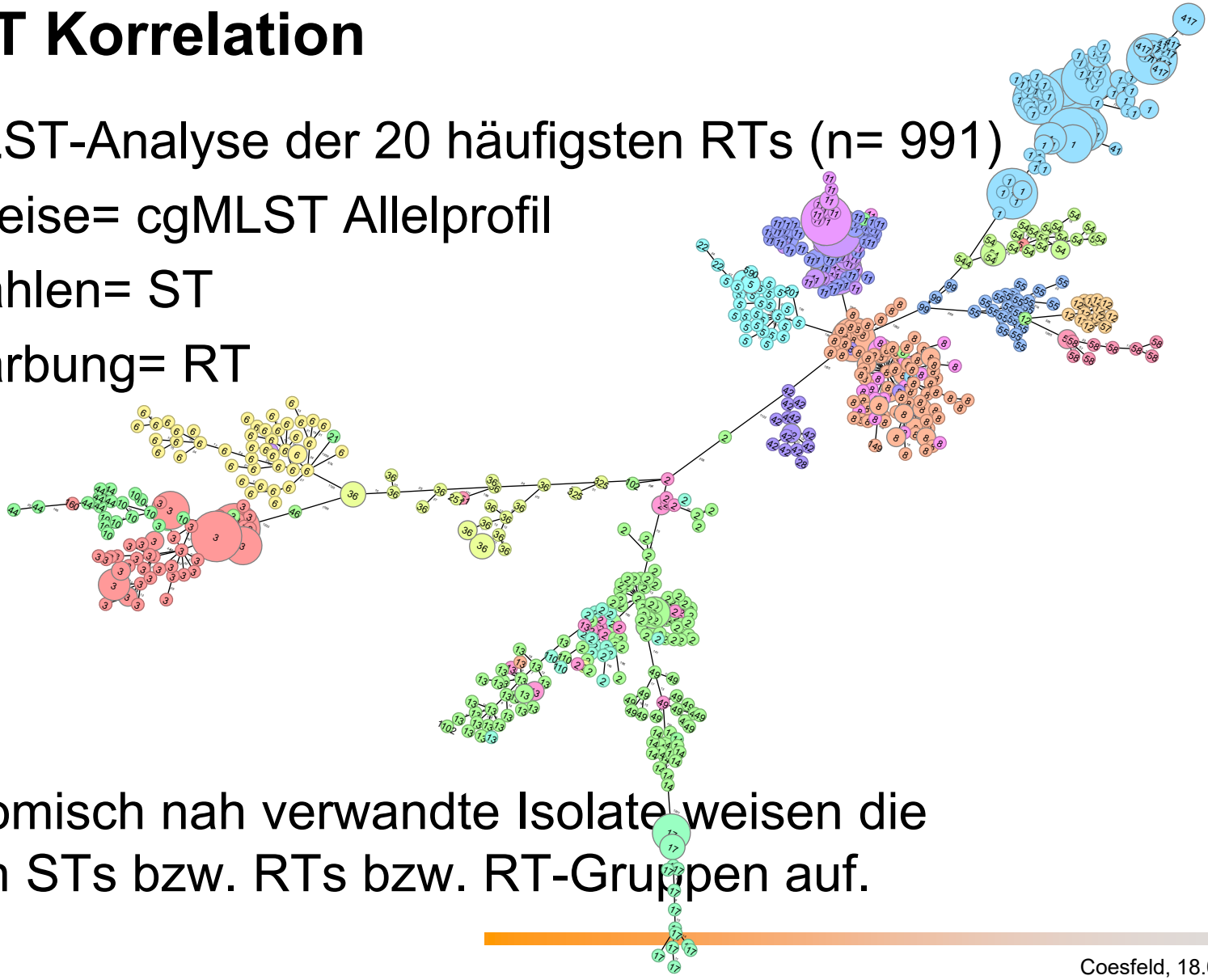
C. difficile Isolate erforderlich

- Surveillance
- Ausbruchsuntersuchung
- Genotypische Charakterisierung
  - Resistenzgene
  - Virulenzgene



ST/RT Korrelation

- cgMLST-Analyse der 20 häufigsten RTs (n= 991)
  - Kreise= cgMLST Allelprofil
  - Zahlen= ST
  - Färbung= RT



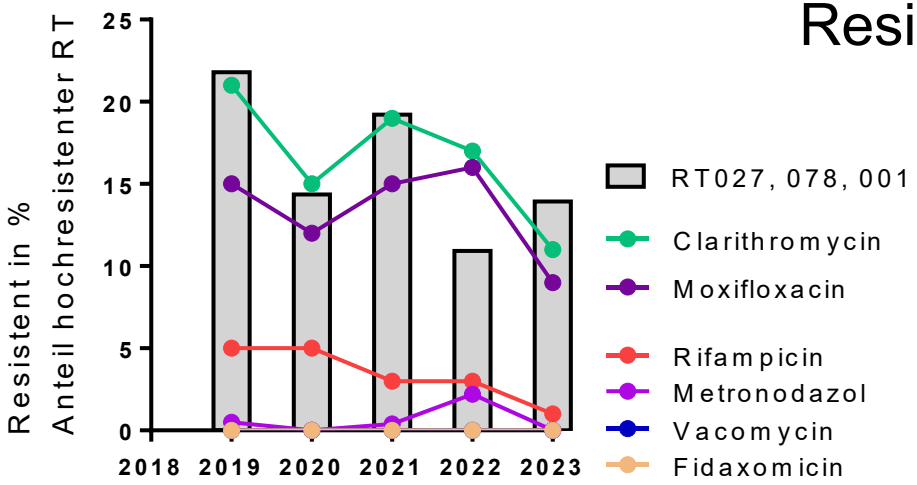
→ Genomisch nah verwandte Isolate weisen die gleichen STs bzw. RTs bzw. RT-Gruppen auf.

ST/RT Korrelation

- *C. difficile*-Sequenzdaten + RT
  - Literatur
  - EnteroBase-Datenbank
  - Eigene Stammsammlung
- n = 4384
- Darstellung von ST/RT-Paaren n > 20
- Sequenztypen (ST, innerer Ring)
- Ribotypen (RT, mittlerer Ring)
- Abgeleitete RTs/RT Gruppen (äußerer Ring)

Vorläufige, unveröffentlichte Daten: Mellmann, Schneider (2024)

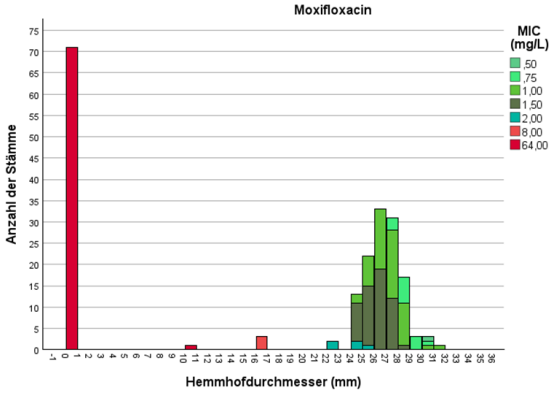
Resistenzenentwicklung (2019-2023)

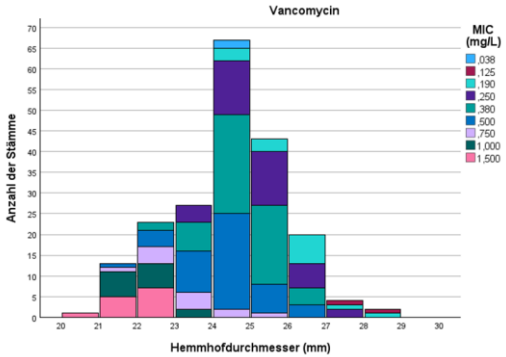


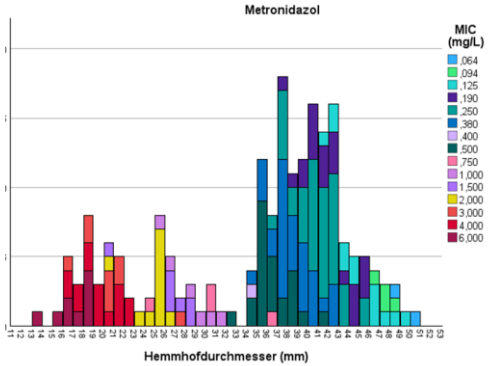
Ribotyp	Anzahl	Vancomycin	Metronidazol	Moxifloxacin	Clarithomcyin	Rifampicin
RT001	136	0%	0%	32%	35%	1%
RT002	110	0%	0%	3%	2%	1%
RT014	381	0%	0%	9%	5%	1%
RT020	89	0%	0%	6%	4%	1%
RT023[1]	75	0%	0%	5%	0%	1%
RT027[1]	56	0%	11%	91%	89%	68%
RT078[1]	139	0%	0%	35%	58%	1%
Andere	1143	0%	0%	9%	14%	2%
Total	2129	0%	0%	14%	17%	3%

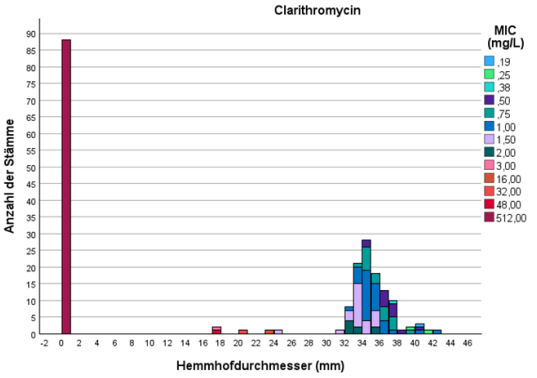
Orientierende phänotypische Resistenztestung von *C. difficile* (Agar-Diffusionstest)

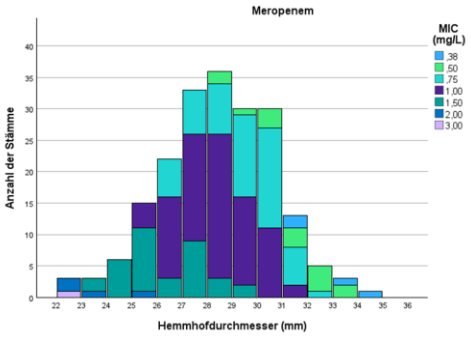
- Gruppe 1: Monophasisch (dosisabhängig)
- Gruppe 2: Polyphasisch (dosisabhängig)
- Gruppe 3: Binär (dosisabhängig)
- Gruppe 4: eingeschränkte Interpretation (<u>nicht</u> dosisabhängig)

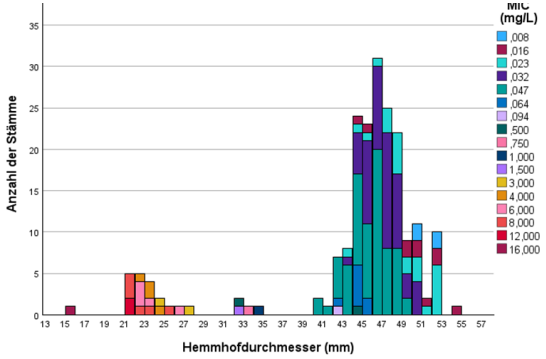


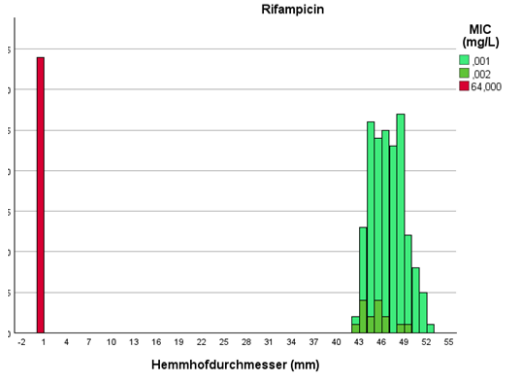












Phänotypische Charakterisierung von *C. difficile*

Orientierende Testung von Multiresistenz Profilen

	Regular substances EUCAST "C. difficile profile 1" (suggested zone diameters, NRZ)	**Additional substances "C. difficile profile 2"** (suggested zone diameters, NRZ)	Comparison **C. perfringens** (Zone diameter EUCAST)
Ampicillin-sulbactam	**X (na)**		**27**
Piperacillin-tazobactam	**X (na)**		**24**
Meropenem	**X (<23mm)**		**25**
Metronidazole	**X (<33 (<25)mm)**		**16**
Clindamycin	**X (na)**		**(25)**
Vancomycin	**X (<20mm)**		**12**
Moxifloxacin		**X (<20mm)**	
Clarithromycin		**X (<28mm)**	
Rifampicin		**X (<38mm)**	
Tetracycline		**X (<38 (<32)mm)**	
Tigecycline		**X (<33mm)**	
(Fidaxomicin*)		**X (<22mm?)**	

Klinische Bedeutung der Resistenztestung

- Orientierende Antibiotika Resistenztestung zur Stammcharakterisierung (Agar-Diffusion)
  - Wildtyp vs. multiresistente/nosokomiale Stämme
  - Phänotypische Unterscheidung von Ausbruchstämmen (ähnliche Resistenzprofile)
- Therapeutische Resistenztestung (MHK, E-Test/Agar-Dilution)

Ausblick

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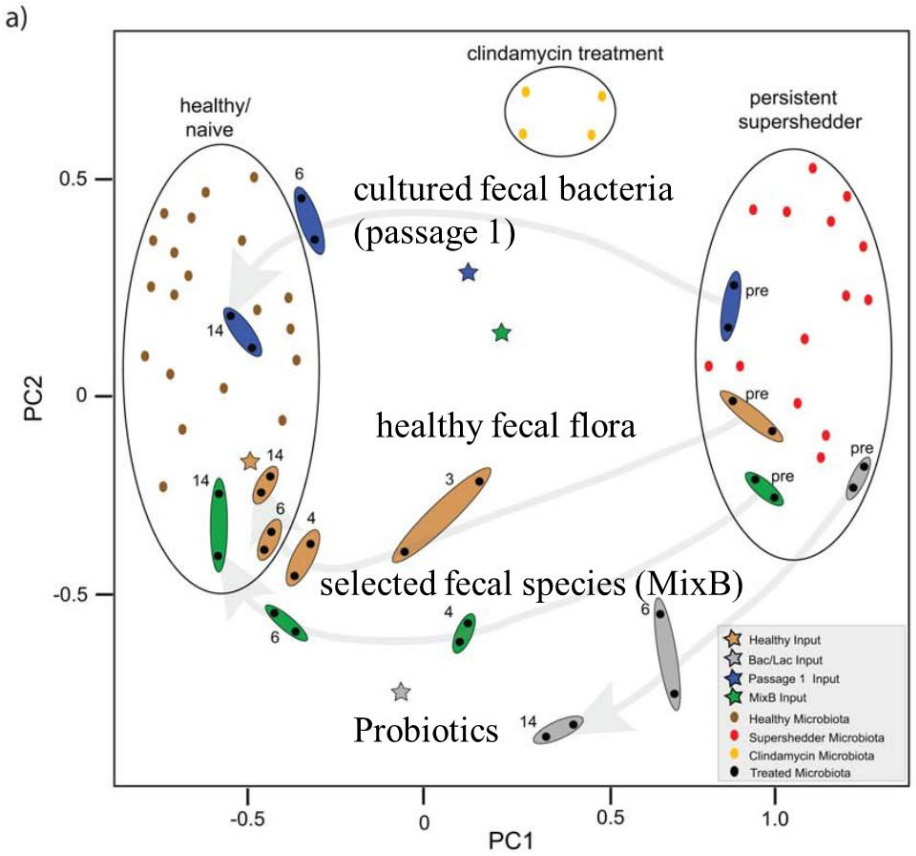
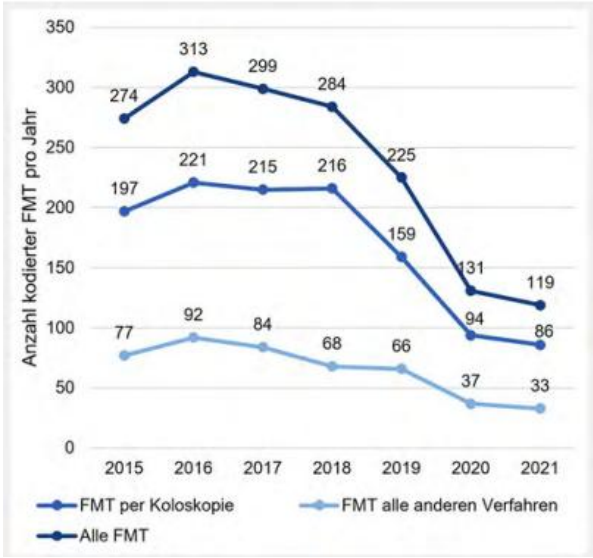
Fecal Microbiota Therapy (FMT) / Live Biotherapeutic Products / Next gen. Probiotika





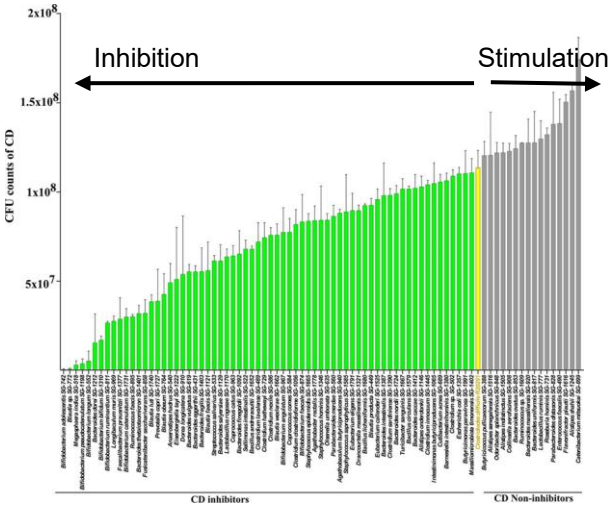


TABLE 3 FDA-approved and late-stage live biotherapeutic products for CDI

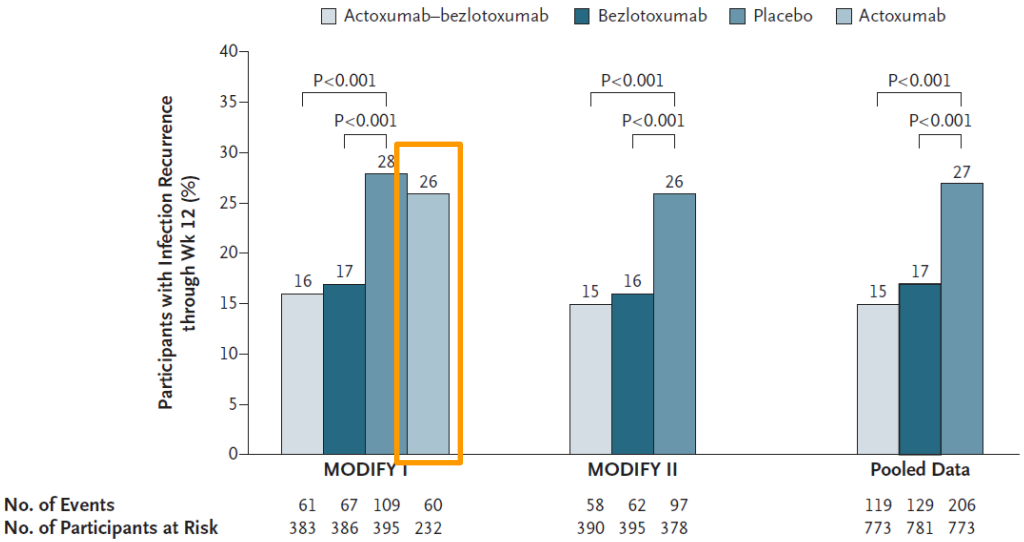
Product	Content	Phase	Route	Posology	Clinical cure (8 weeks)	Safety
RBX2660	Suspension of microbiota (from HD)	III	Enema	One enema once	71%–79%	Good
SER109	Pure Firmicutes bacterial spores (from HD)	III	Oral	4 cp Daily for 3 days	87%–91%	Good
VE303	Consortium of eight non-pathogenic Clostridia (from HD)	II	Oral	10 cp Daily for 14 days	>95%	Good

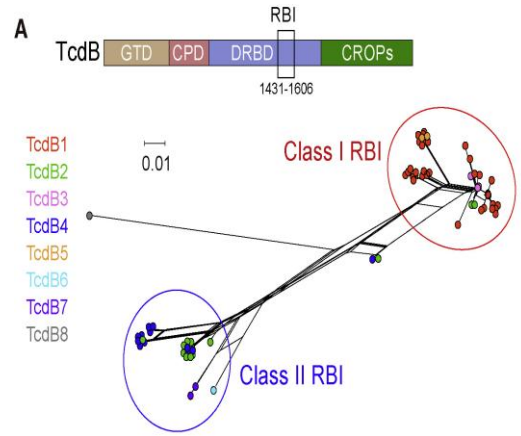
[a]cp, capsules; HD, healthy donors.

Lawley et al, 2012 PLOS Path

Coesfeld, 18.06.2025

Passive/aktive Impfung (Fokus: „Antitoxin B“)





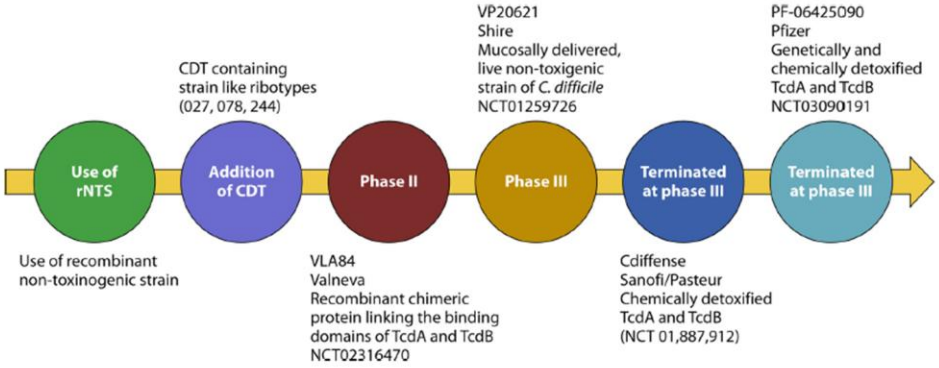
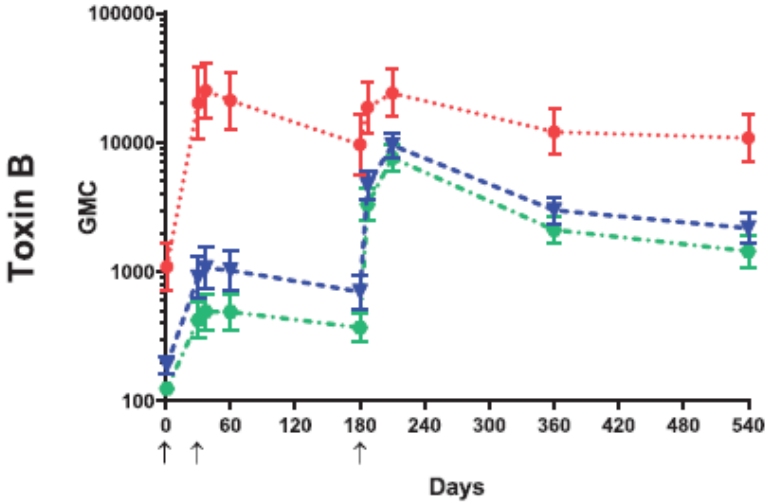


FIG 3 Past, present, and future of *C. difficile* vaccine in development. Two major phase III trials for *C. difficile* vaccines from Sanofi and Pfizer were determined futile and halted. The vaccines from Shire are in a phase III trial and one from Valneva was phase II terminated. Many vaccines have been tested at the murine model level by adding a third CDT toxin of *C. difficile*. Even nontoxinogenic strains with a recombinant vector containing domains of toxin A and toxin B were tested as potent vaccine candidates.

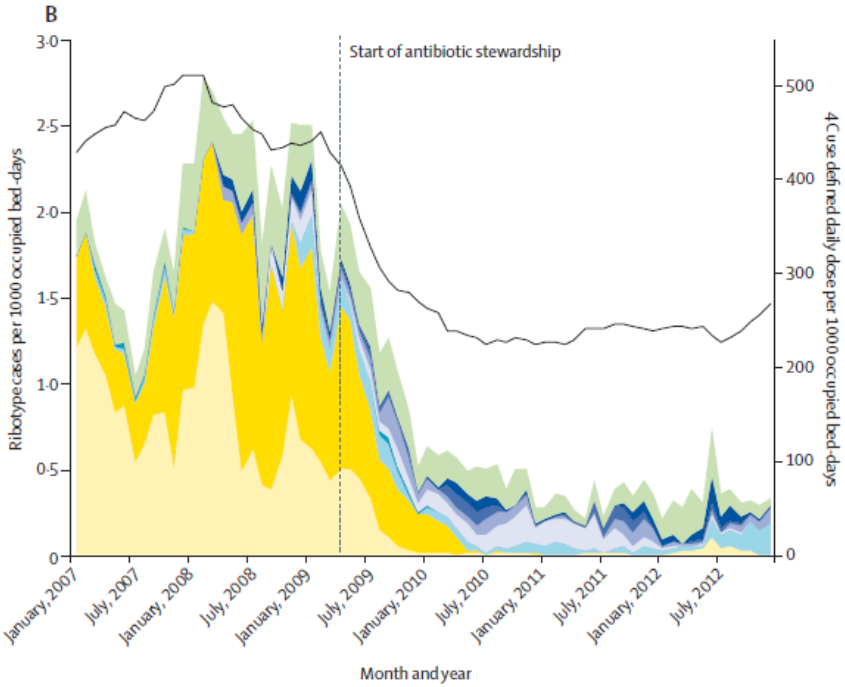


Coesfeld, 18.06.2025

Kitchin et al CID 2020, CMR June 2023 Volume 36 Issue 2 10.1128/cmr.00157-22, Luo et al Cell 2022 Mar 17;185(6):980-99

Zusammenfassung

C. difficile ist ein wichtiger Indikator für
- Antibiotic Stewardship (ABS)
- Diagnostic Stewardship
  - Untererfassung vermeiden
  - Mögliche Ausbrüche erkennen
    - Material asservieren (NRZ)
- Hygienemanagement



Aufgaben des NRZ
- Molekulare Epidemiologie
  - Typisierung im NRZ: Ribotyp/ST(cgMLST) Transformation
  - Ausbruchuntersuchungen/meldepflichtige Fälle
- Stärkung der Kultur im lokalen Labor
  - Einfache Phänotypiesierung (Agar-Diffusionstest)
- „neue Therapien“
  - FMT
  - Impfungen

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Vielen Dank an alle Einsender von Stämmen und interessanten Fällen
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Robert Koch-Instituts • Referenznetzwerk des