Clostridioides difficile infections: Preventive strategies

Jon Edman Wallér

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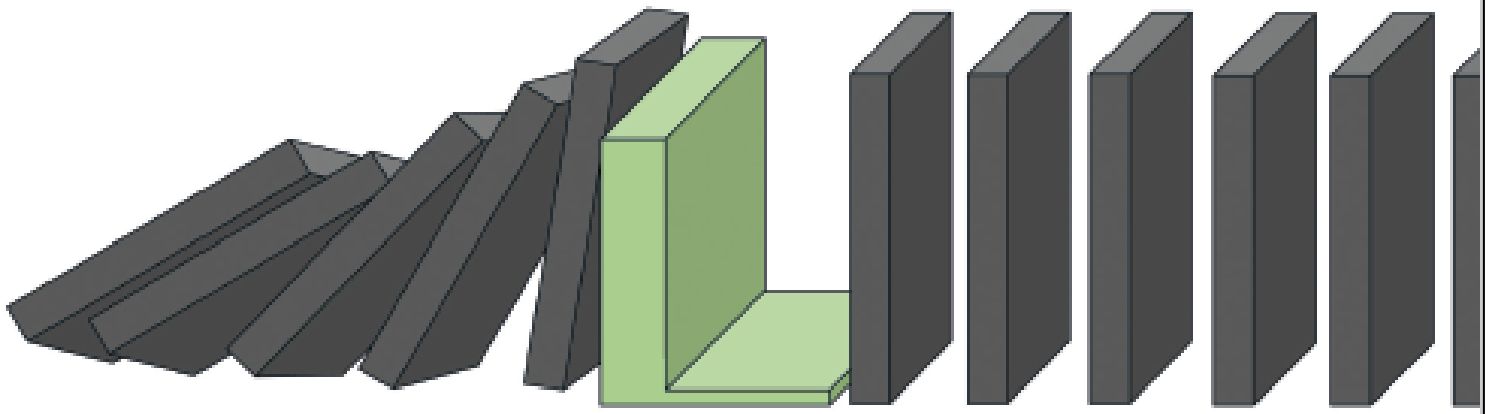


Clostridioides difficile: Preventive strategies

Jon Edman Wallér

LIST OF PAPERS

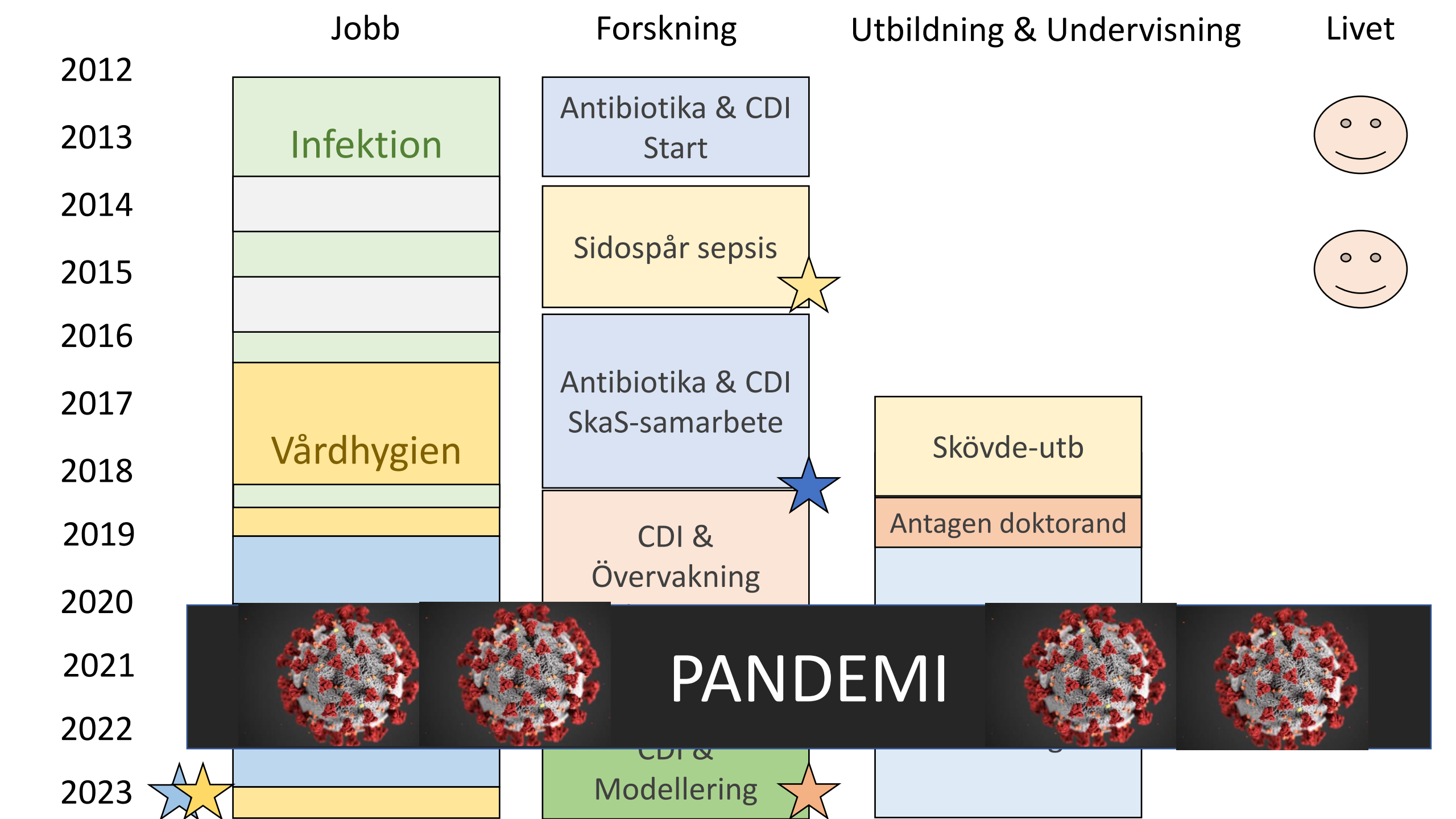
This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Karp J*, **Edman-Wallér J***, Toepfer M, Lundqvist A, Jacobsson G. *Clostridioides difficile* incidence related to in-hospital cephalosporin use: a tale of two highly comparable hospitals. *Journal of Antimicrobial Chemotherapy* 2019; 74(1):182-189. doi: 10.1093/jac/dky408.

II. **Edman-Wallér J**, Toepfer M, Karp J, Rizzardi K, Jacobsson G, Werner M. *Clostridioides difficile* outbreak detection: evaluation by ribotyping and whole genome sequencing of a surveillance algorithm based on ward-specific cut-offs. *Infection Control and Hospital Epidemiology* 2023; Jun 23;1-5, online ahead of print. doi: 10.1017/ice.2023.113

III. **Edman-Wallér J**, Rizzardi K, Jacobsson G, Gerlee P. *Clostridioides difficile* transmission: a compartmental model accounting for environmental spore persistence. Submitted manuscript.

* Shared first authorship.


Jobb
Forskning
Utbildning & Undervisning
Livet
2012
2013
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2023
Infektion
Vårdhygien
Antibiotika & CDI
Start
Sidospår sepsis
Antibiotika & CDI
SkaS-samarbete
CDI &
Övervakning
Modellering
Skövde-utb
Antagen doktorand
PANDEMI

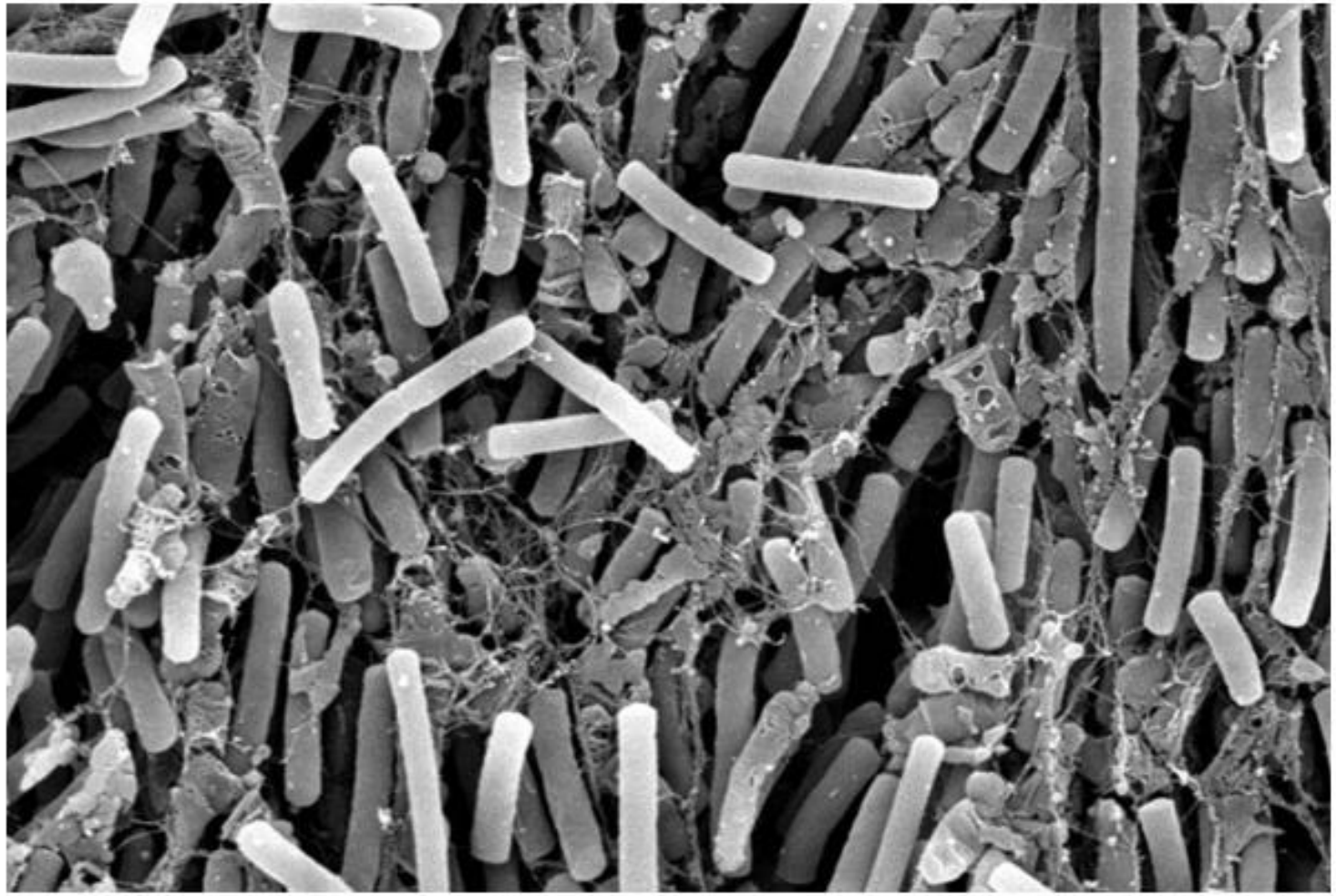


Figure 1. C. difficile *bacteria as viewed in a scanning electron microscope. The bacteria are in the early stages (three days) of forming a biofilm. Work available in the Creative Commons Public Domains, produced by Semenyuk et al. PLoS One, 2014. [4]*

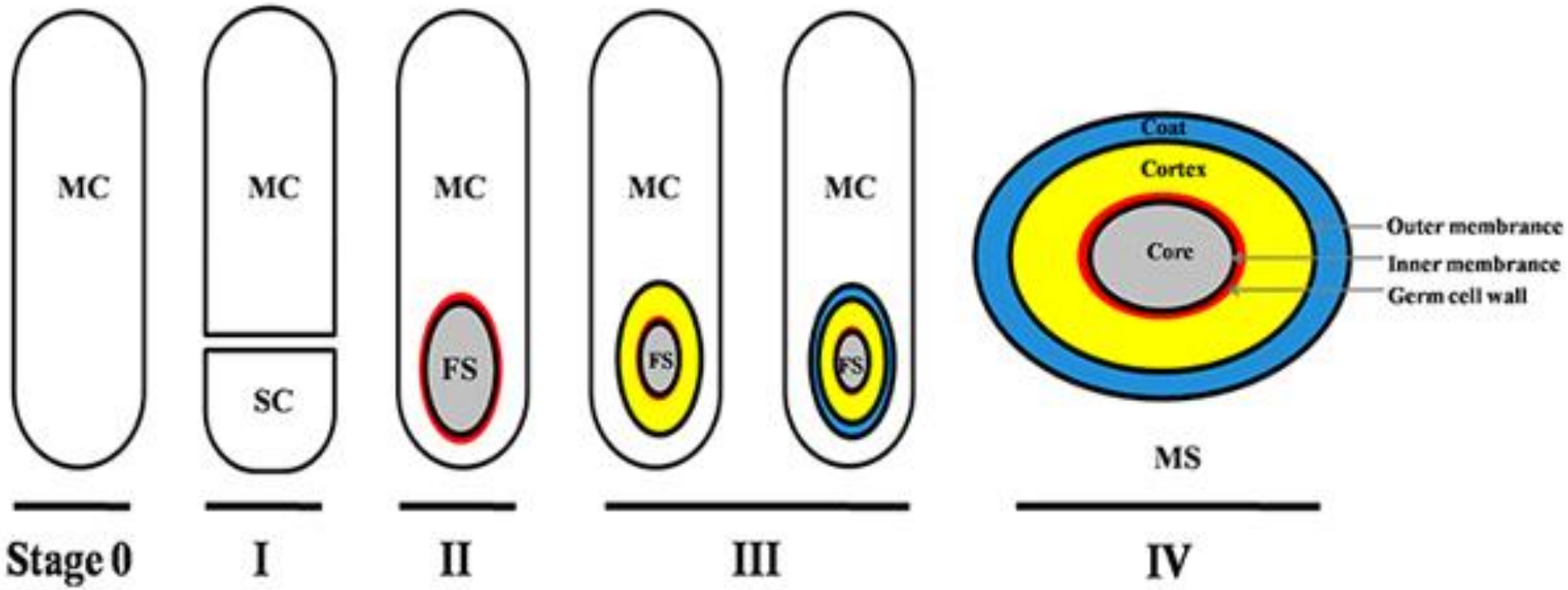
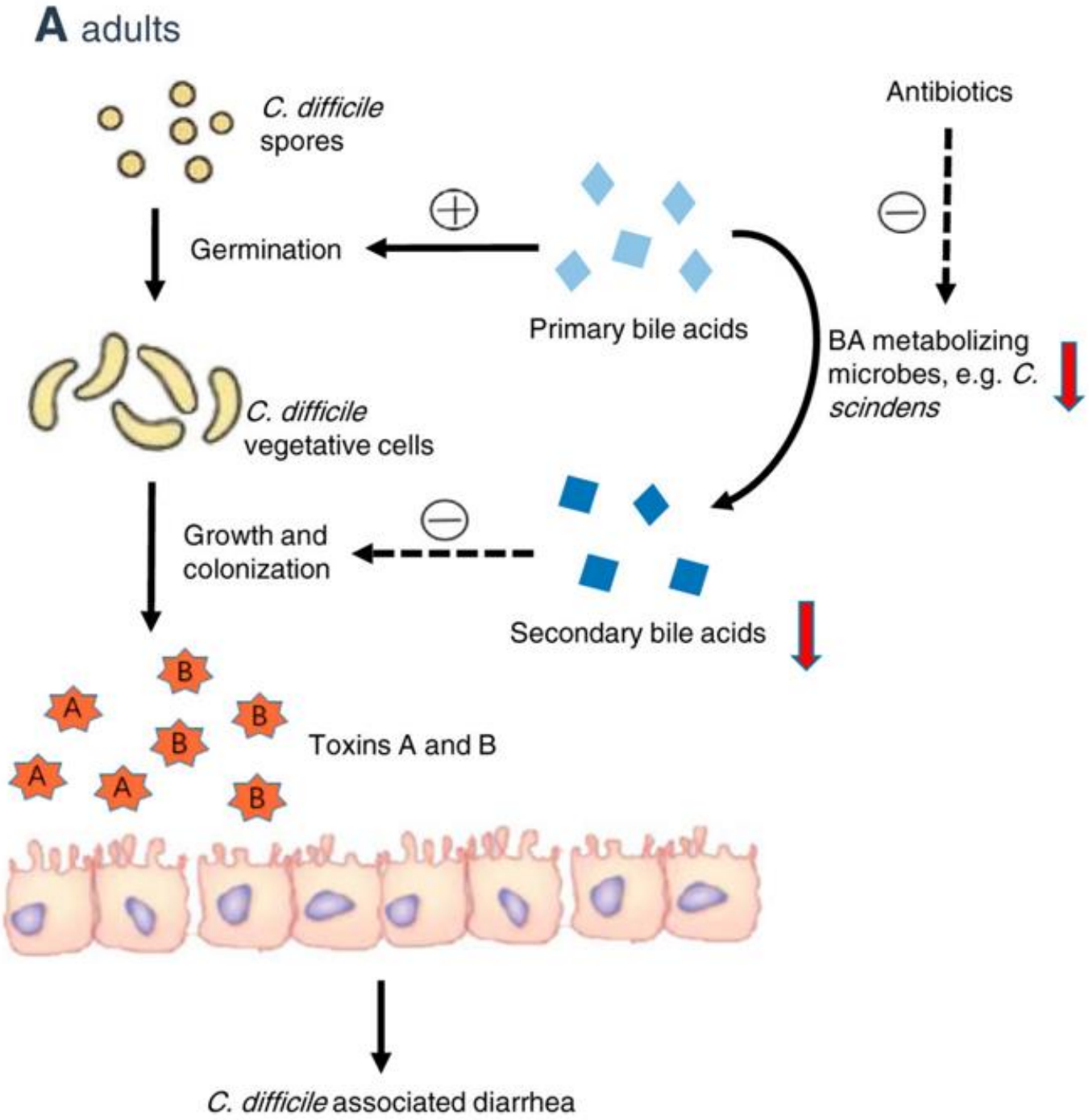
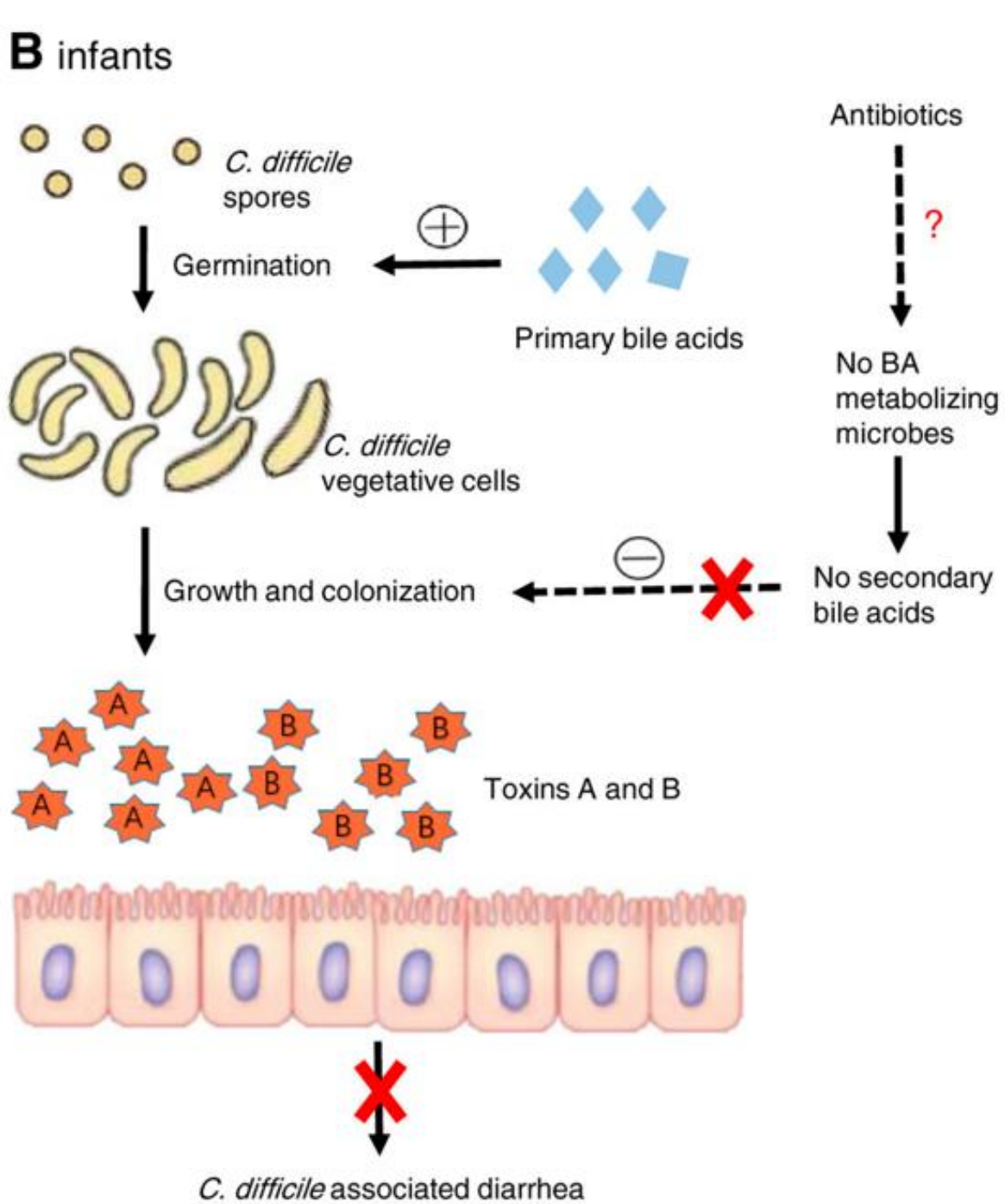


Figure 2. Different stages of sporulation and the final structure of the C. difficile *spore. MC, mother cell compartment; SC, smaller compartment; FS, forespore compartment; MS, mature spore. Reproduced with permission from Zhu et al., Front Cell Infect Microbiol, 2018, Copyright Zhu, Sorg & Sun.*


A adults
C. difficile spores
Germination
C. difficile vegetative cells
Growth and colonization
Antibiotics
Primary bile acids
BA metabolizing microbes, e.g. C. scindens
Secondary bile acids
Toxins A and B
C. difficile associated diarrhea


B infants
C. difficile spores
Germination
Primary bile acids
Antibiotics
?
No BA metabolizing microbes
C. difficile vegetative cells
Growth and colonization
No secondary bile acids
A
B
Toxins A and B
C. difficile associated diarrhea

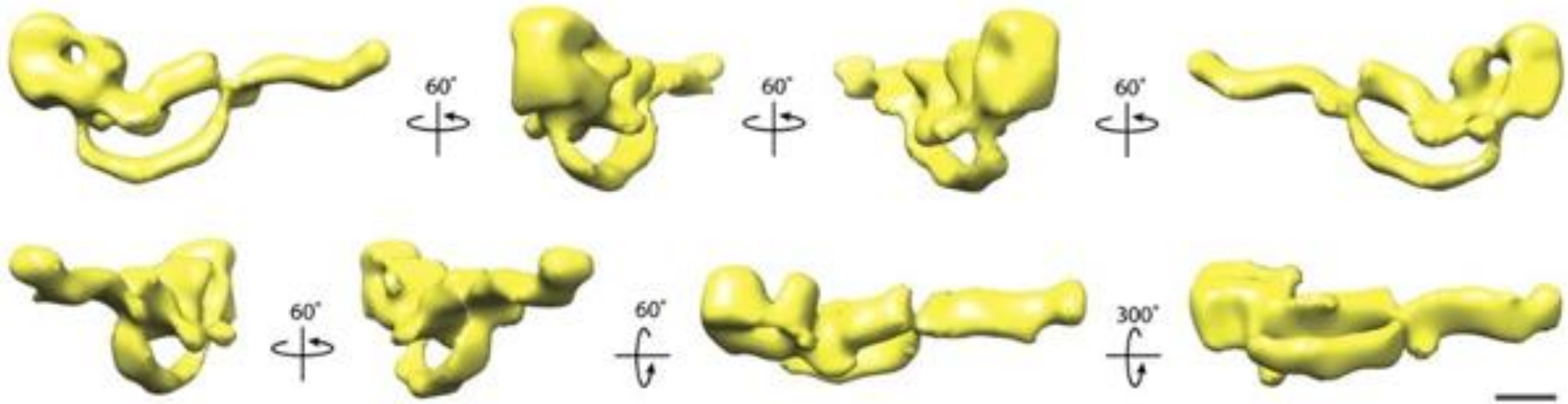


Figure 4. C. difficile *Toxin A as viewed from different angles. 3D reconstruction based on negative stain electron microscopy. Toxin B has a similar structure (not shown). The scale bar in the lower right represents 5 nanometers. Reproduced with permission from Pruitt et al., PNAS, 2010. [44]*

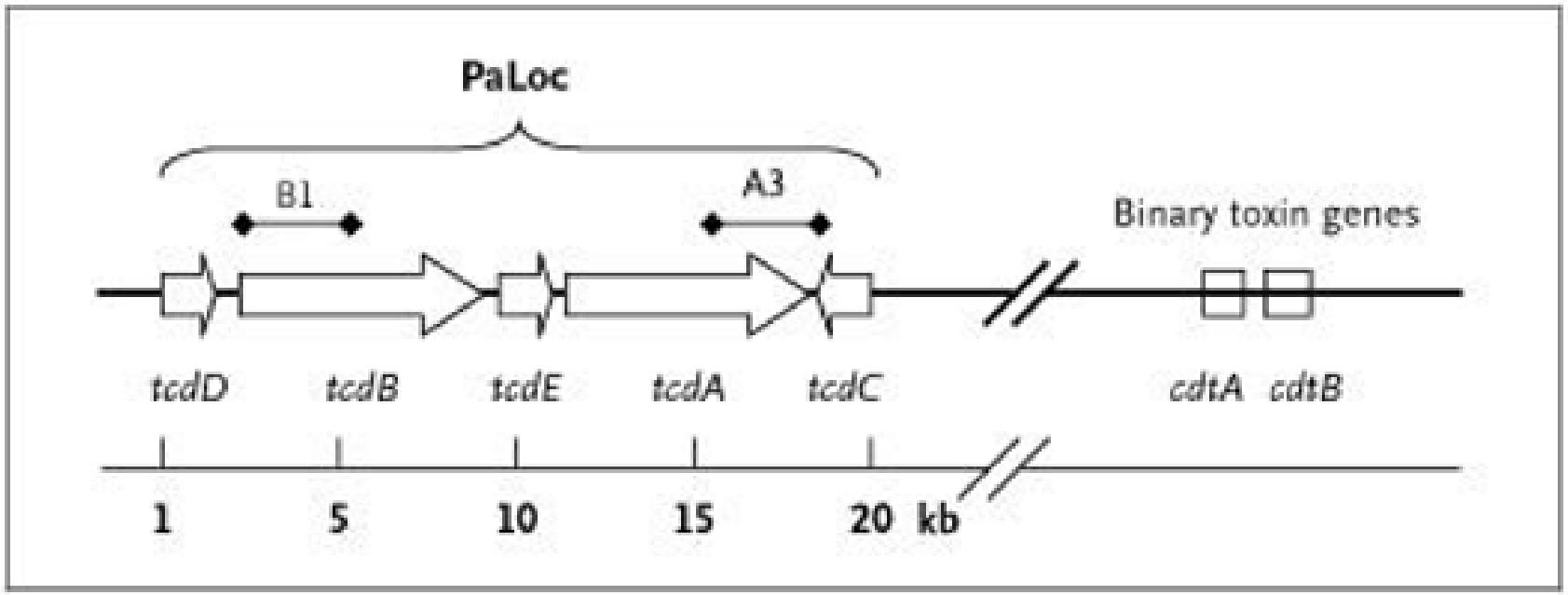


Figure 5. Genes within the Pathogenicity Locus (PaLoc) of the C. difficile *genome. The cdt genes are present in a different genomic location. Reproduced with permission from McDonald et al., N Engl J Med, 2005, [51] Copyright Massachusetts Medical Society.*

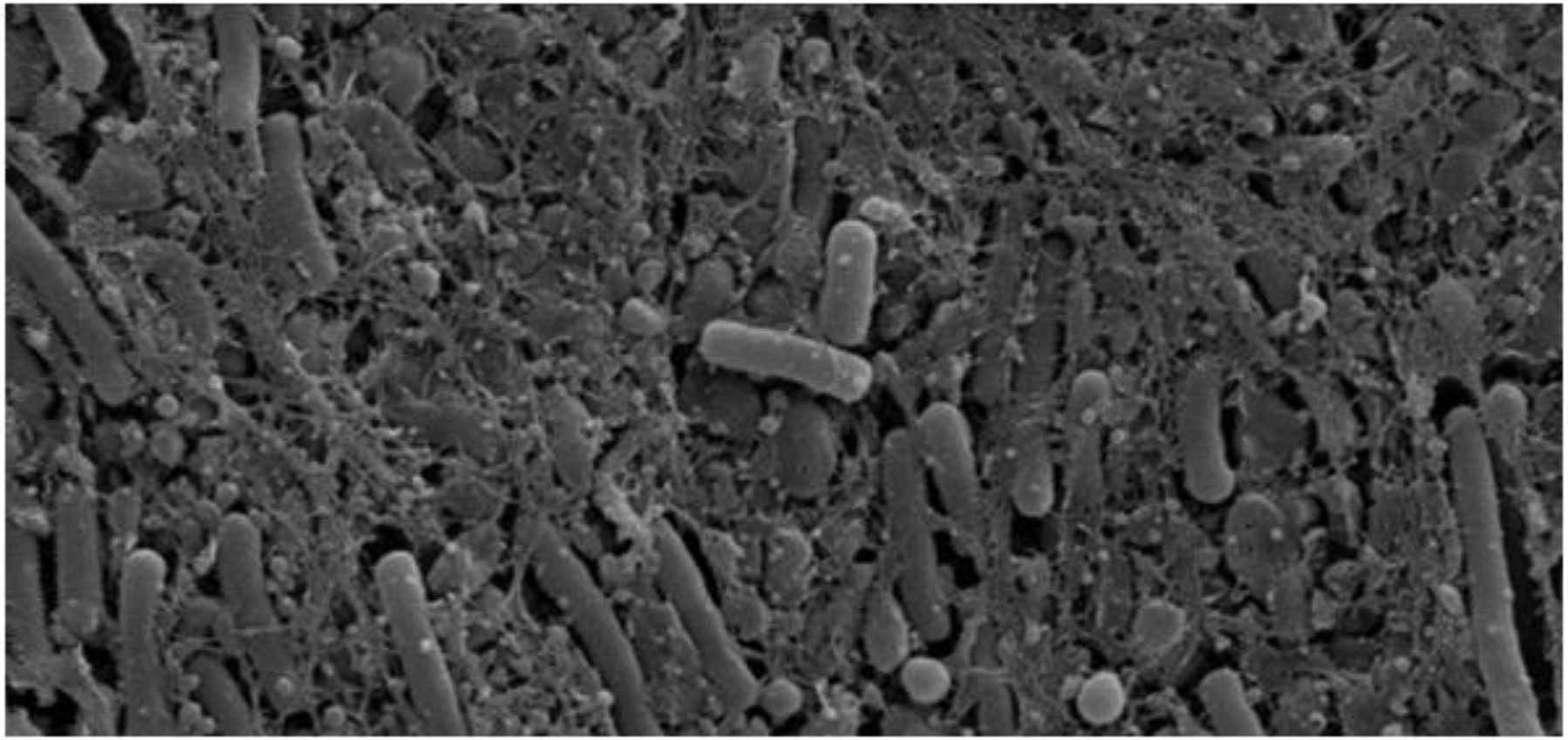


Figure 6. Six days old biofilm of C. difficile*, as viewed in a scanning electron microscope. Work available in the Creative Commons Public Domains, produced by Semenyuk et al. PLoS One, 2014. [4]*

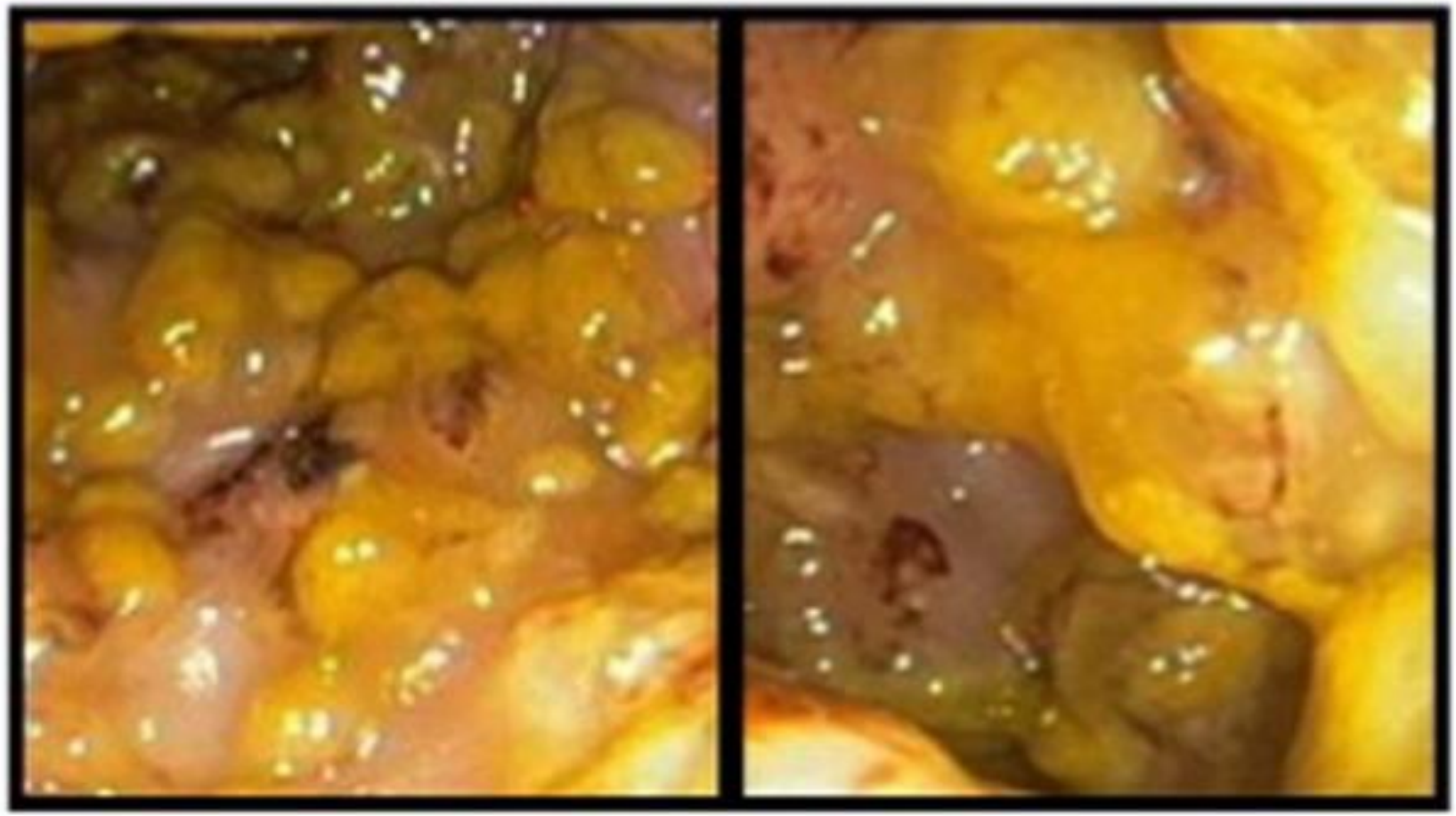
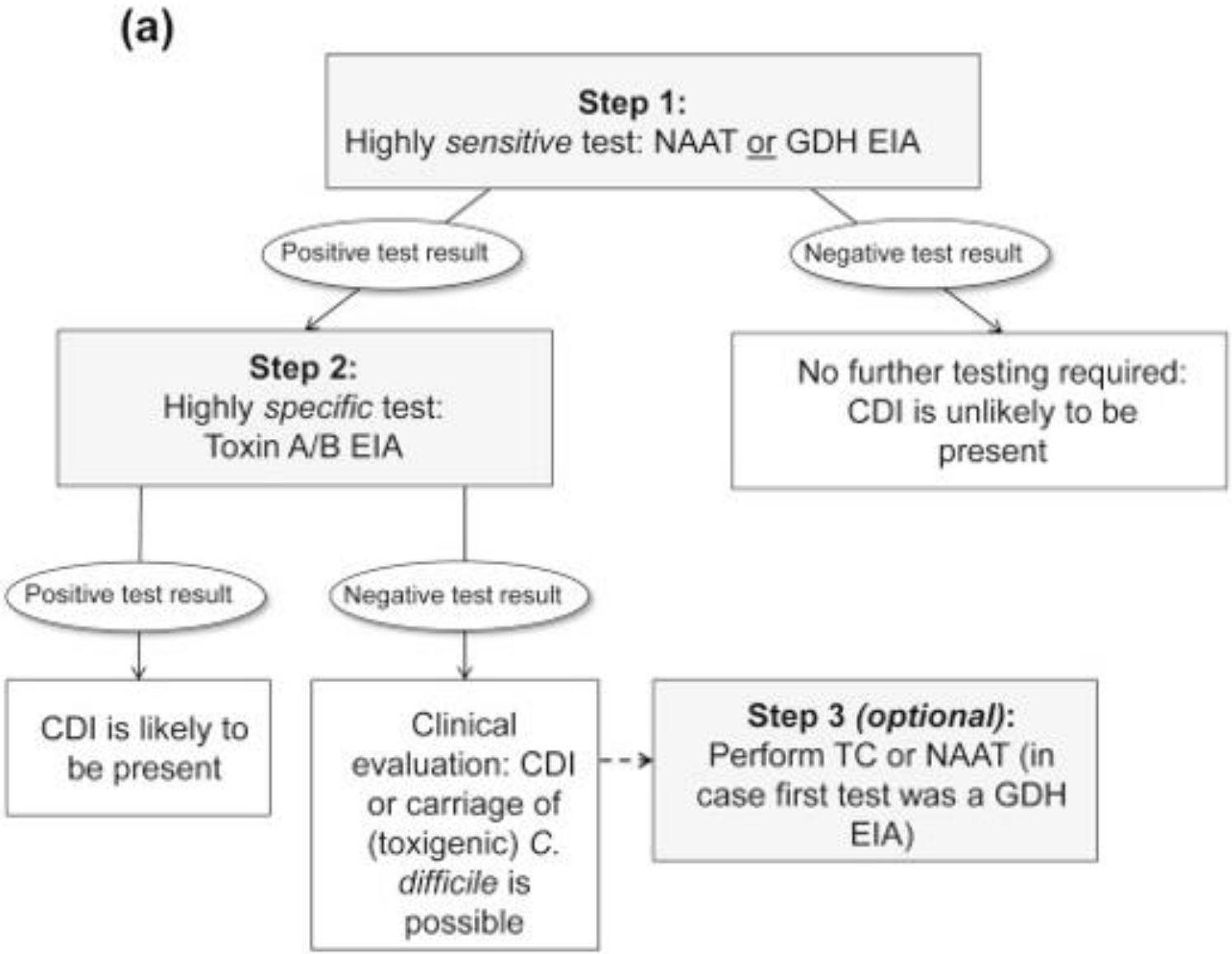


Figure 7. Pseudomembranes on the colonic mucosa, as viewed by flexible sigmoidoscopy. Reprinted with permission from Farooq et al 2015, [71] Copyright Elsevier.


(a)
Step 1:
Highly sensitive test: NAAT or GDH EIA
Positive test result
Negative test result
Step 2:
Highly specific test:
Toxin A/B EIA
No further testing required:
CDI is unlikely to be present
Positive test result
Negative test result
CDI is likely to be present
Clinical evaluation: CDI or carriage of (toxigenic) C. difficile is possible
Step 3 (optional):
Perform TC or NAAT (in case first test was a GDH EIA)

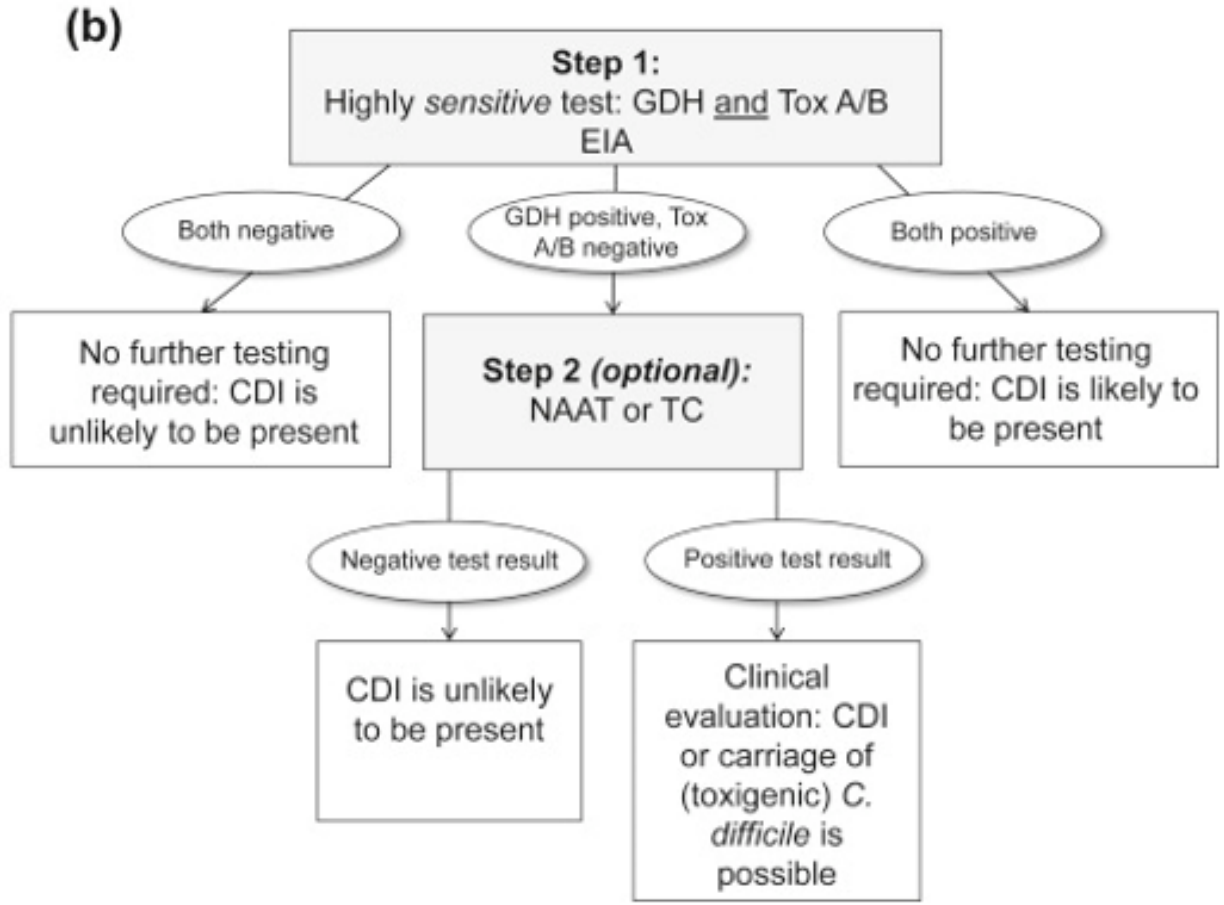


Figure 8. Two alternative (a and b) proposed algorithms in the current European guidelines for C. difficile *diagnostics, combining test of high sensitivity with tests of high specificity. Reproduced under the Creative Commons CC-BY-NC-ND license, from Crobach|et al, CMI, 2016. [103]*

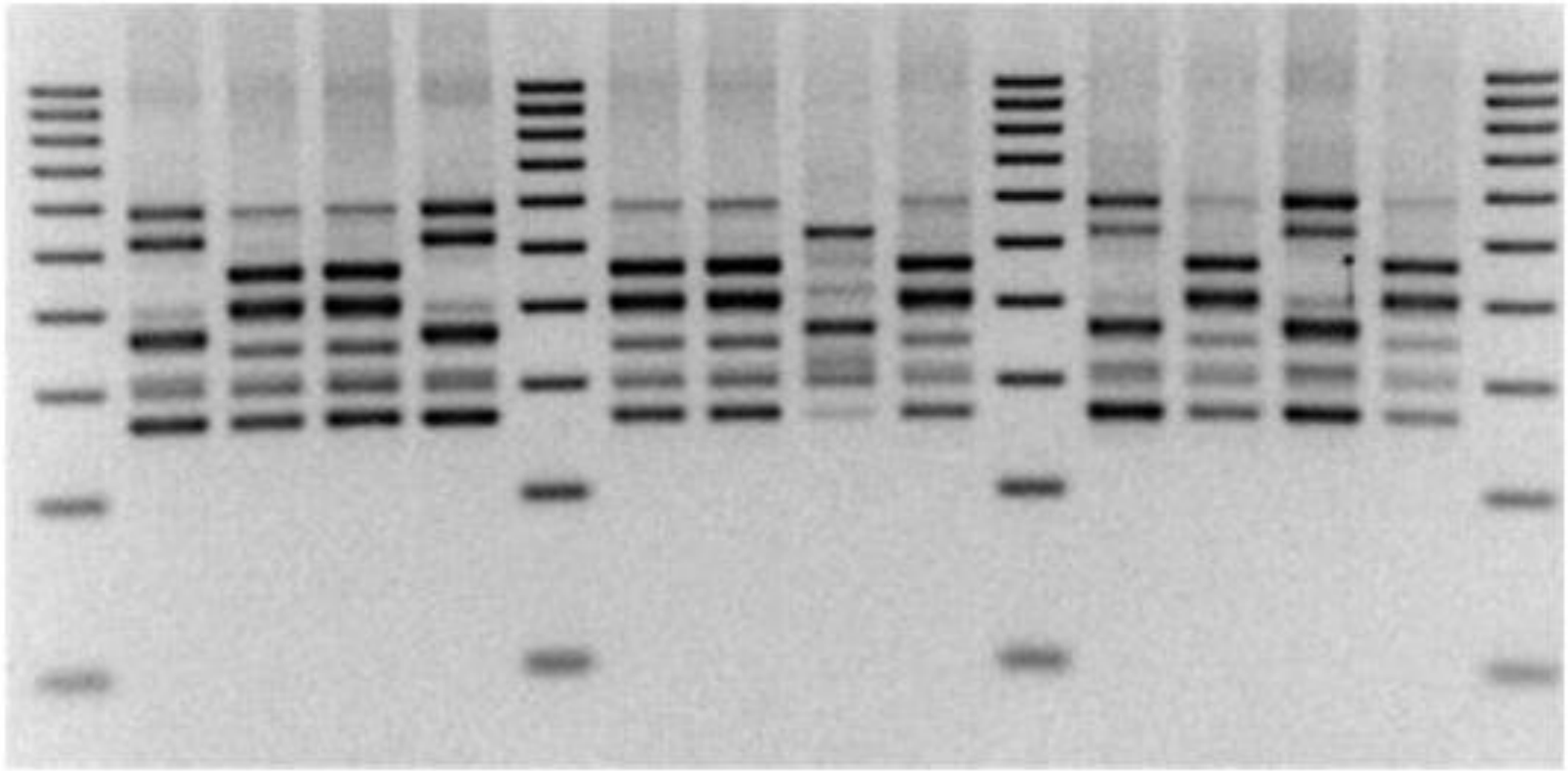


Figure 9. PCR ribotyping by agarosis gel electrophoresis, introduced in the mid-1990s. Ribosomal gene fragments are multiplied and then separated based on their size, resulting in different patterns for different strains. Reprinted with permission from Brazier, CMI, 2001. [117]

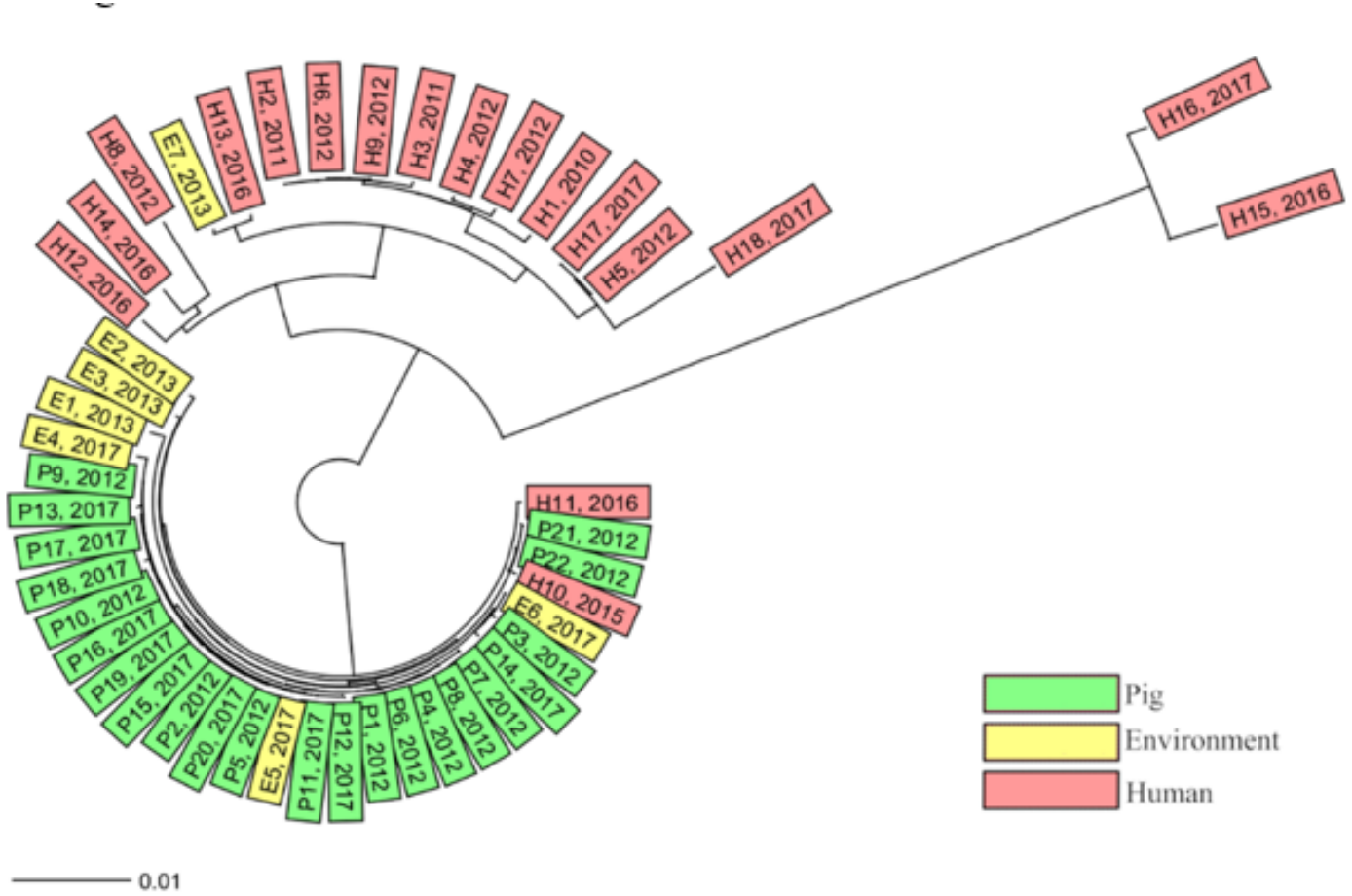


Figure 10. Visualisation of the genetic relatedness between isolates from a suspected cluster. All isolates are sequence type 35/ribotype 046, collected from humans as well as pigs and environmental sources between 2012 and 2017. Whole genome sequencing with cgMLST analysis revealed that some isolates were closely related while others were not. Available under the Creative Commons Attribution License, from Werner et al, PLoS One, 2020. [125]

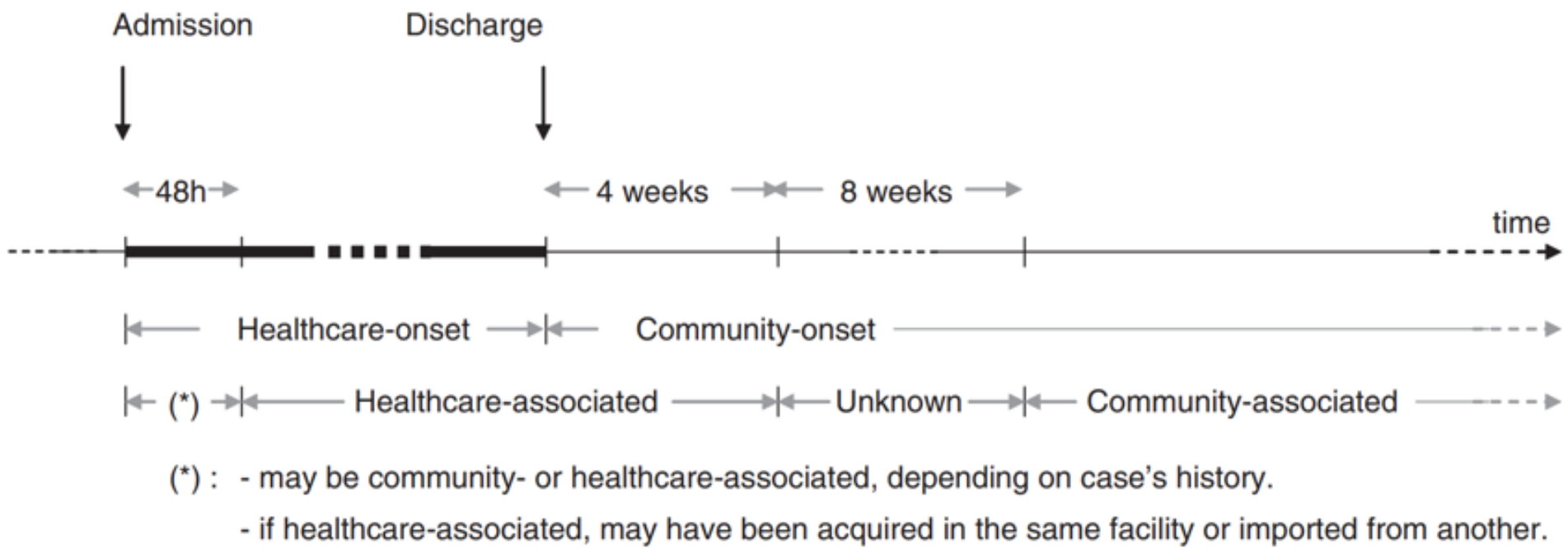


Figure 11. Current definitions recommended for surveillance of healthcare-facility-associated vs. community-associated C. difficile *infections, based on the time relation between symptom onset and hospital care. Reproduced with permission from Kuijper et al, CMI, 2006. [137]*

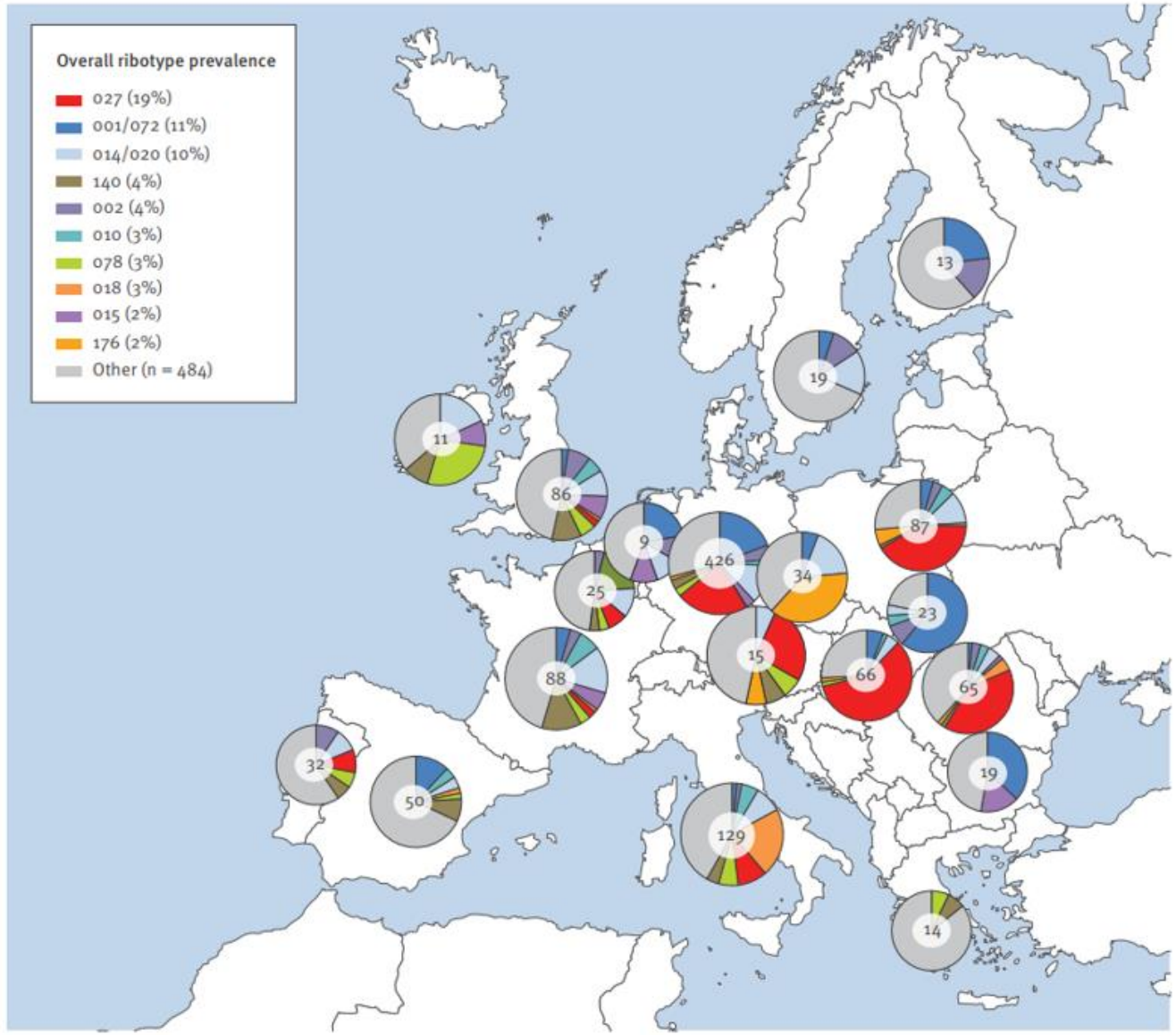


Figure 12. Distribution of ribotypes across Europe 2012-2013. Note the large differences between countries in the prevalence of RT027 (red). Available under the Creative Commons Attribution License, from Davies et al., Eurosurveill, 2016. [19]

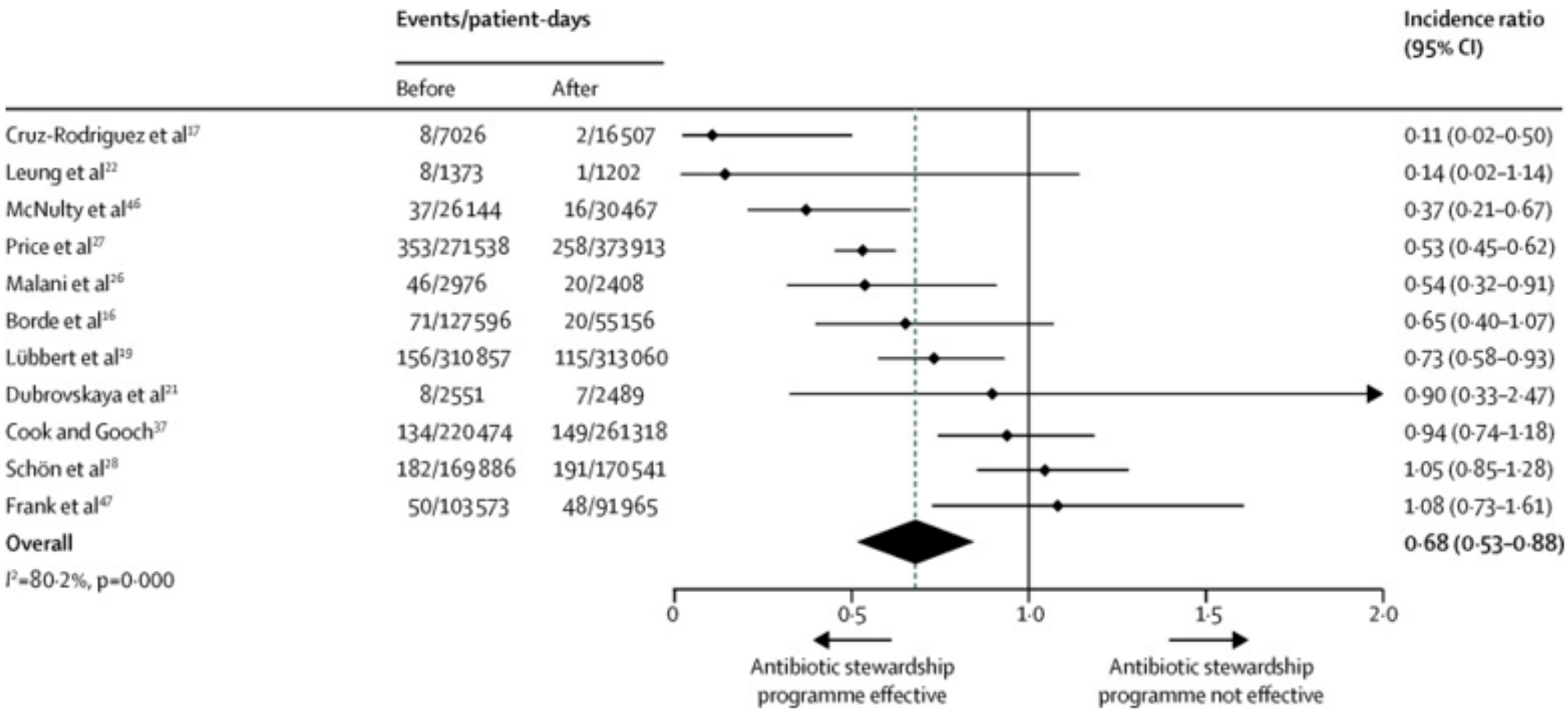


Figure 13. Forest plot of the effect of antibiotic stewardship programmes on C. difficile *infection incidence. The pooled incidence ratio results in an overall 32% decrease. Reproduced with permission from Baur et al., Lancet Infect Dis, 2017. [159]*

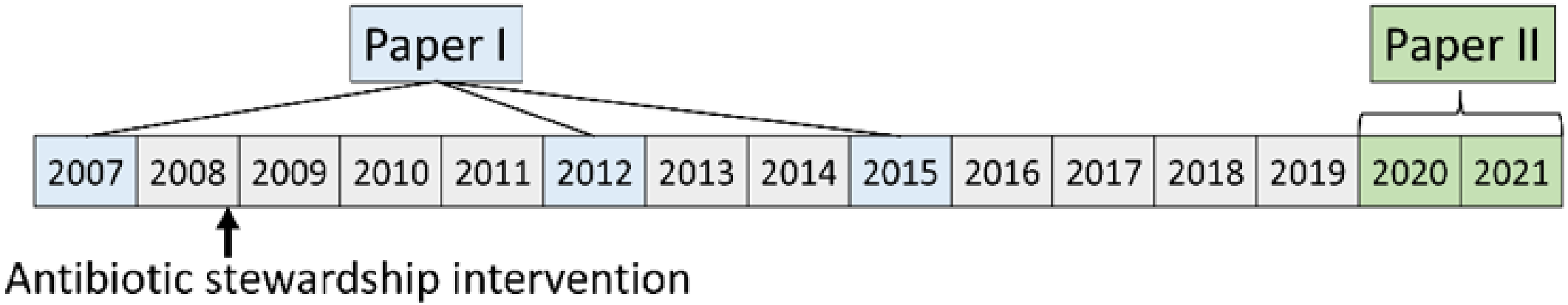
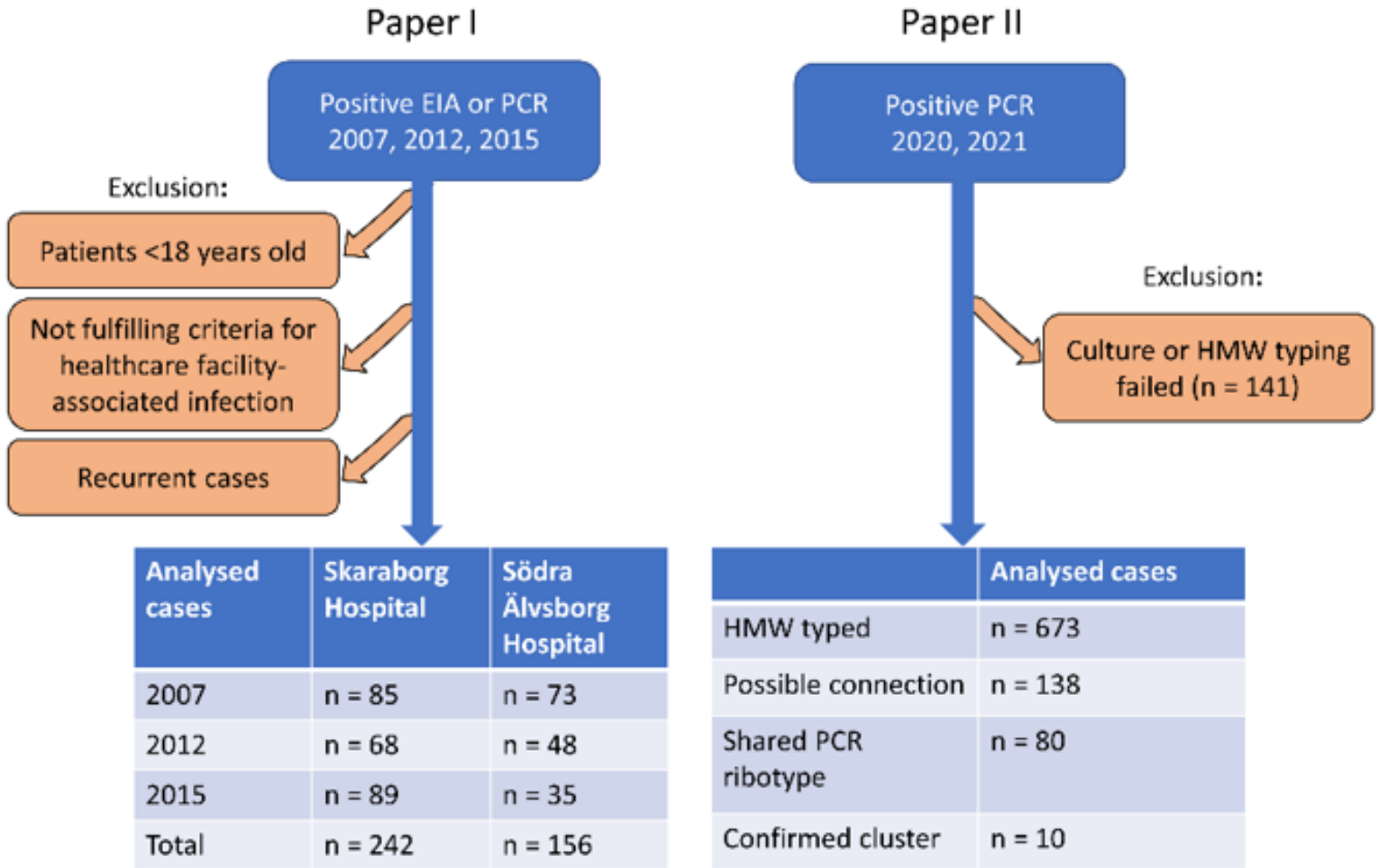


Figure 15. Years studied in Paper I and Paper II.



Analysed cases	Skaraborg Hospital	Södra Älvsborg Hospital
2007	n = 85	n = 73
2012	n = 68	n = 48
2015	n = 89	n = 35
Total	n = 242	n = 156

	Analysed cases
HMW typed	n = 673
Possible connection	n = 138
Shared PCR ribotype	n = 80
Confirmed cluster	n = 10

Figure 16. Overview of cases included and excluded in Paper I and Paper II. Patients from Skaraborg Hospital and Södra Älvsborg Hospital were studied in both papers.

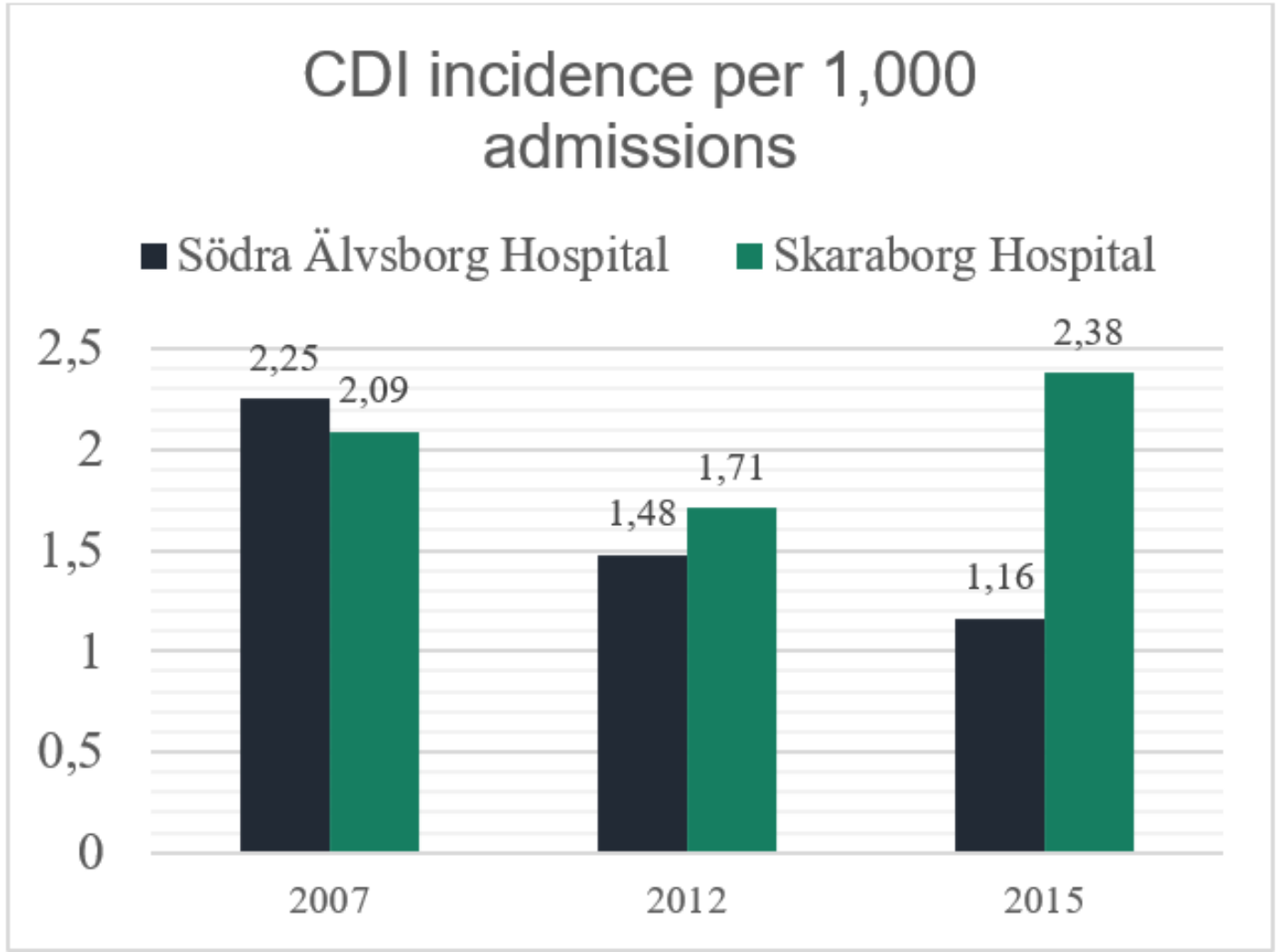


Figure 17. Incidence per 1,000 admissions of C. difficile *infections at the two hospitals in the years studied in Paper I.*

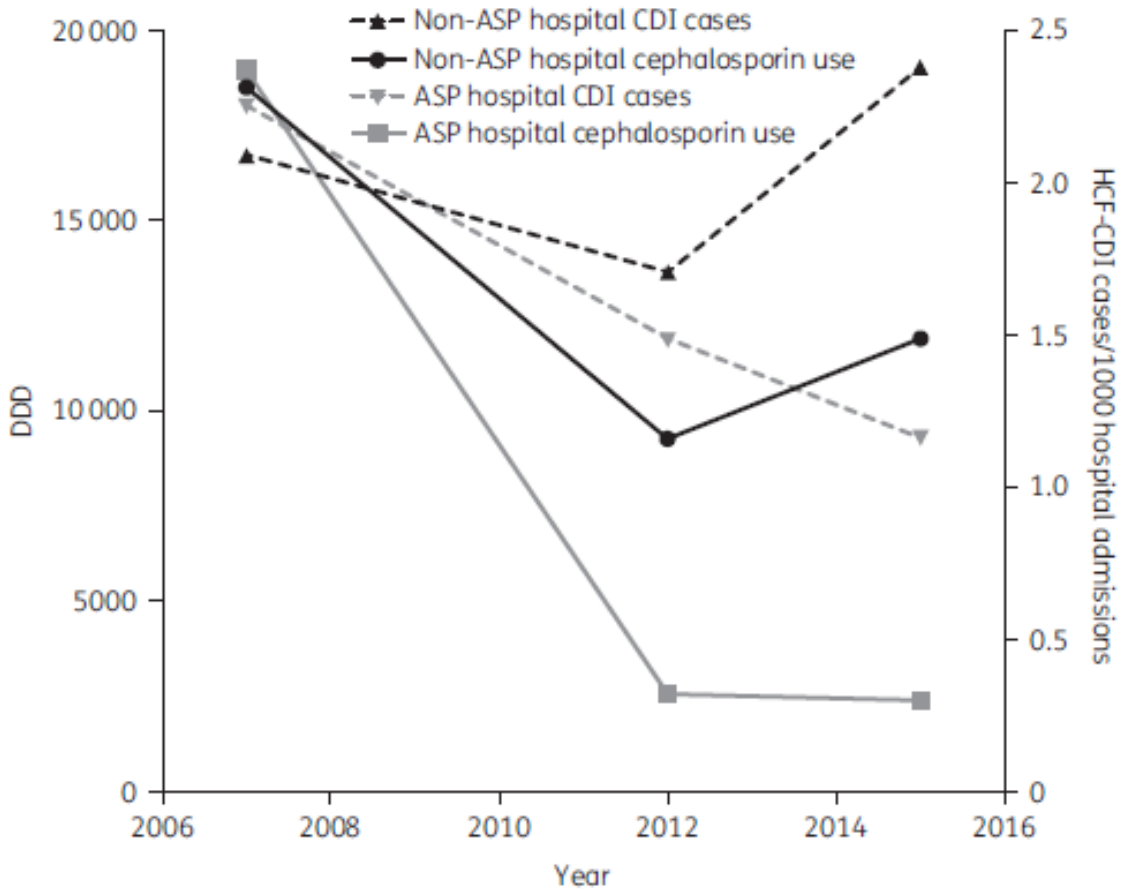


Figure 1. Cephalosporin use and incidence of HCF-CDI. Left *y*-axis shows use of cephalosporins and right *y*-axis shows incidence of HCF-CDI.

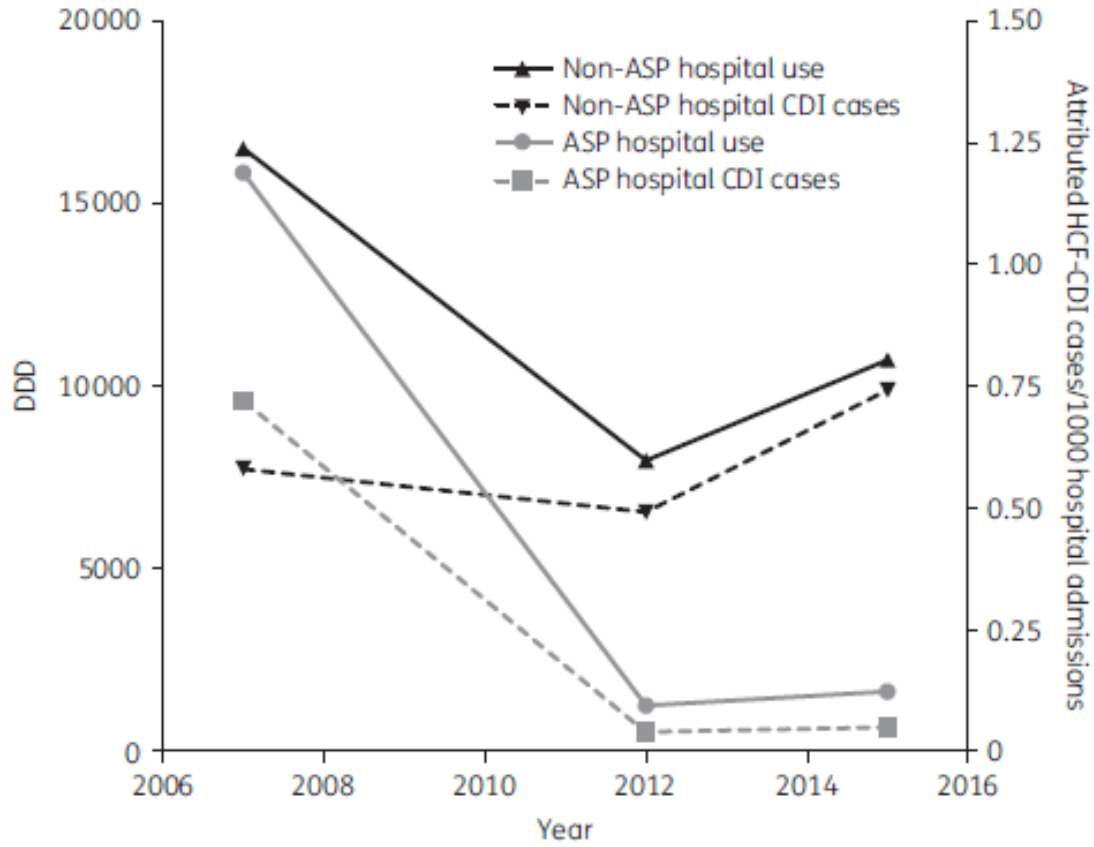


Figure 2. Use of iv cephalosporins and HCF-CDI cases attributed to iv cephalosporins. Left *y*-axis shows use of iv cephalosporins and right *y*-axis shows HCF-CDI cases attributed to iv cephalosporins.

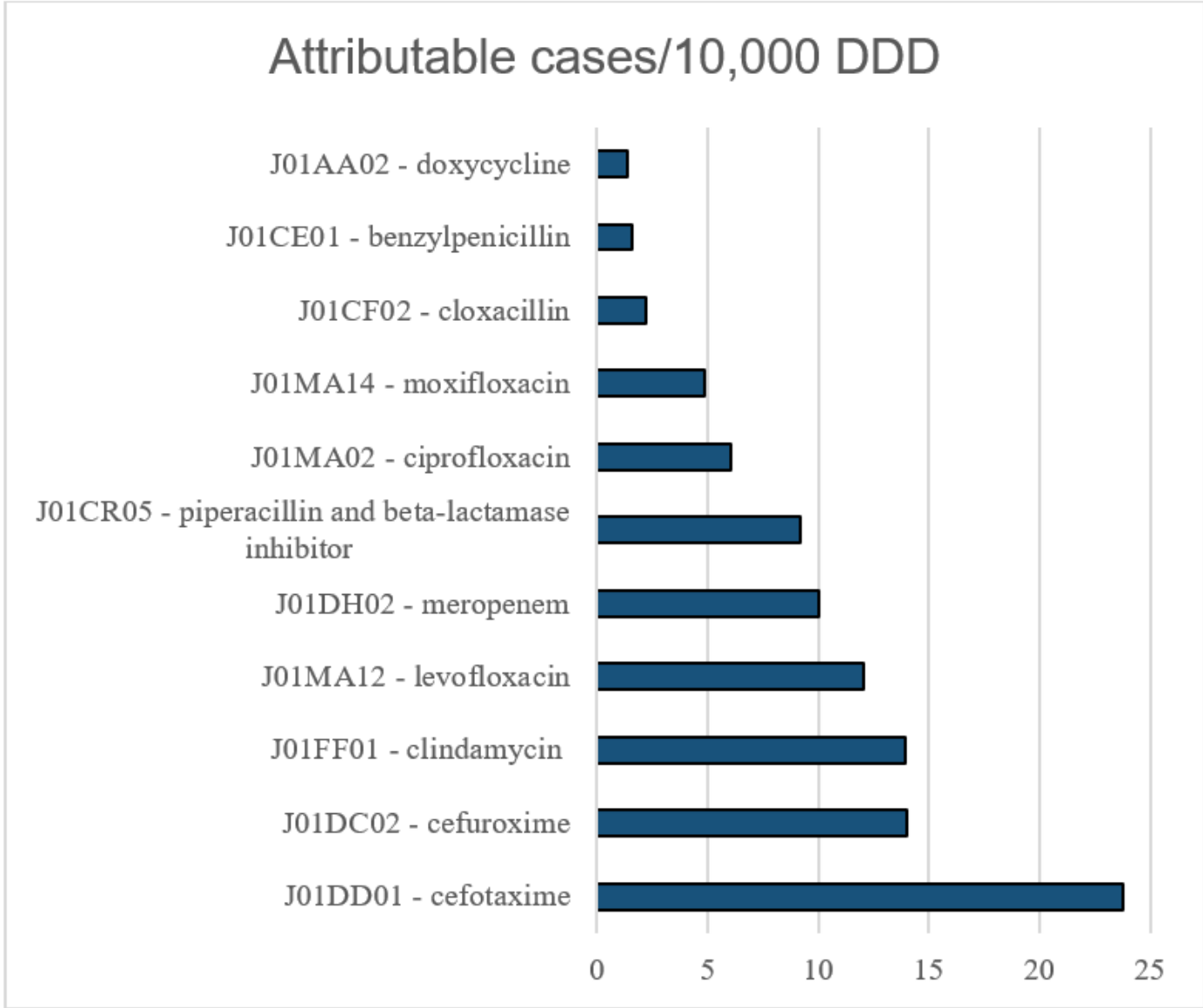


Figure 19. Healthcare-facility-associated C. difficile *infection cases attributable to a selection of different antibiotics related to their total consumption at Skaraborg Hospital and Södra Älvsborg Hospital in 2007, 2012, and 2015.*

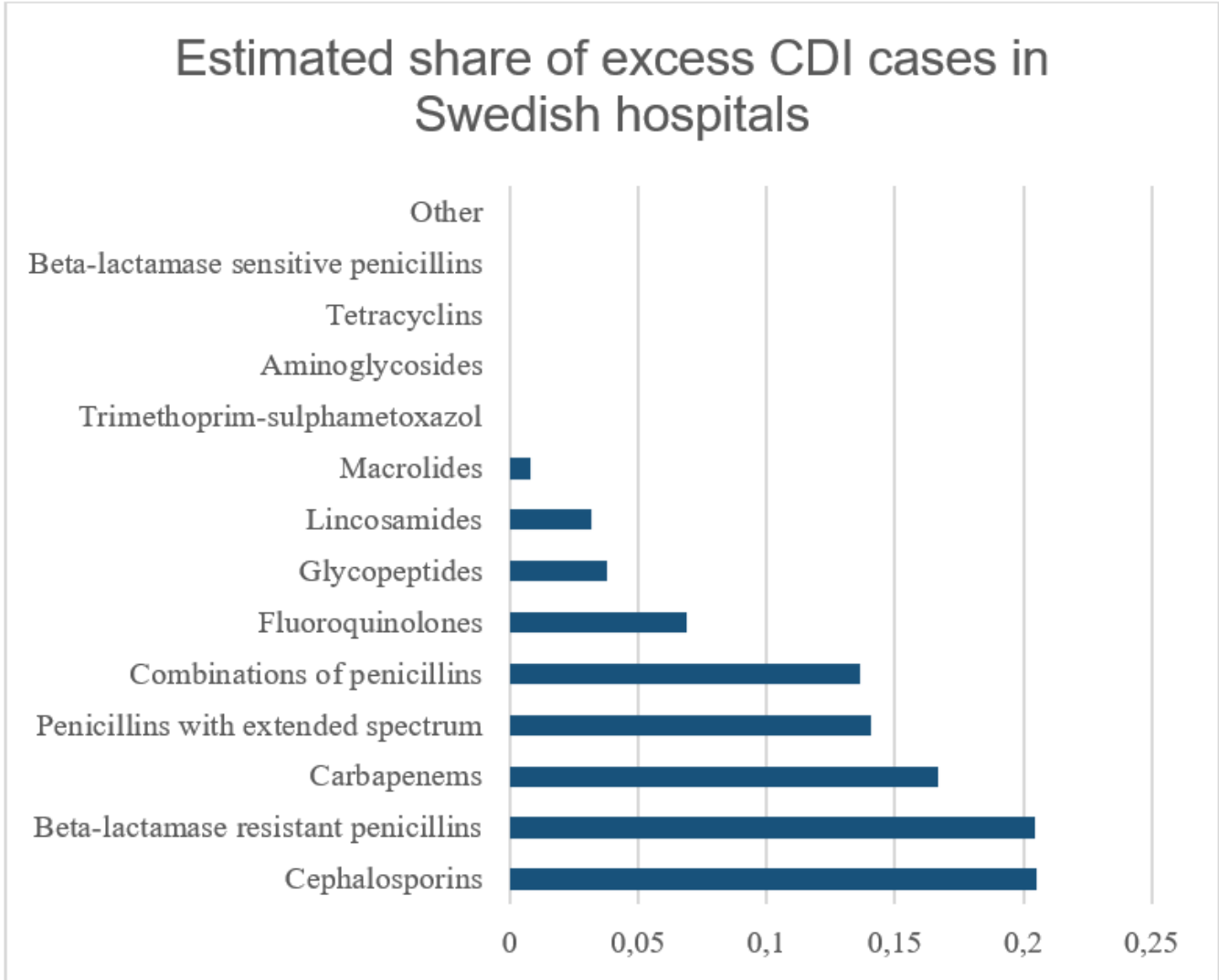
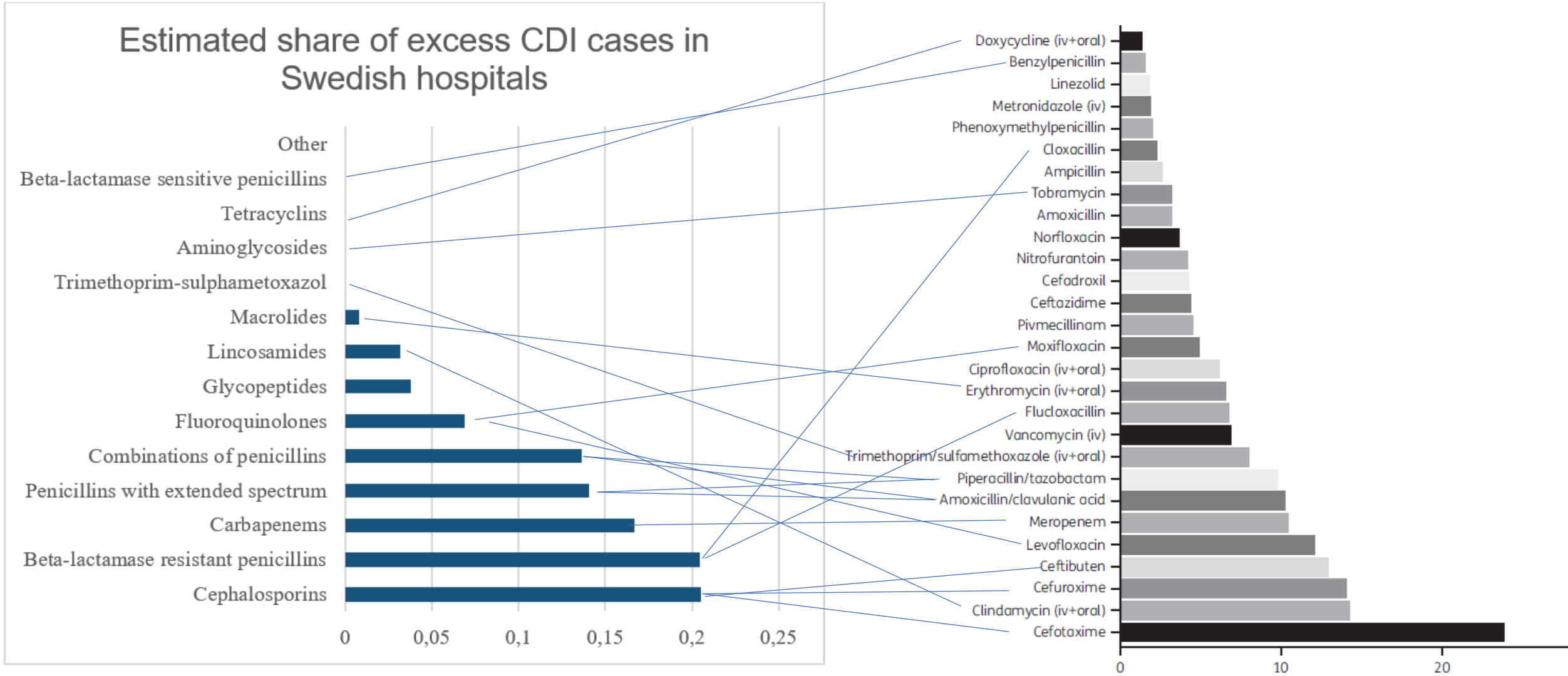


Figure 18. Estimated share of excess CDI cases in Swedish hospitals, based on Swedish data on hospital consumption in 2021 [192] and a meta-analysis of the risk increase of each type of antibiotic. [193] This estimation was used in Paper III for modelling the effects of an antibiotic stewardship programme.


Estimated share of excess CDI cases in Swedish hospitals
Other
Beta-lactamase sensitive penicillins
Tetracyclins
Aminoglycosides
Trimethoprim-sulphametoxazol
Macrolides
Lincosamides
Glycopeptides
Fluoroquinolones
Combinations of penicillins
Penicillins with extended spectrum
Carbapenems
Beta-lactamase resistant penicillins
Cephalosporins
0
0,05
0,1
0,15
0,2
0,25
Doxycycline (iv+oral)
Benzylpenicillin
Linezolid
Metronidazole (iv)
Phenoxymethylpenicillin
Cloxacillin
Ampicillin
Tobramycin
Amoxicillin
Norfloxacin
Nitrofurantoin
Cefadroxil
Ceftazidime
Pivmecillinam
Moxifloxacin
Ciprofloxacin (iv+oral)
Erythromycin (iv+oral)
Flucloxacillin
Vancomycin (iv)
Trimethoprim/sulfamethoxazole (iv+oral)
Piperacillin/tazobactam
Amoxicillin/clavulanic acid
Meropenem
Levofloxacin
Ceftibuten
Cefuroxime
Clindamycin (iv+oral)
Cefotaxime
0
10
20

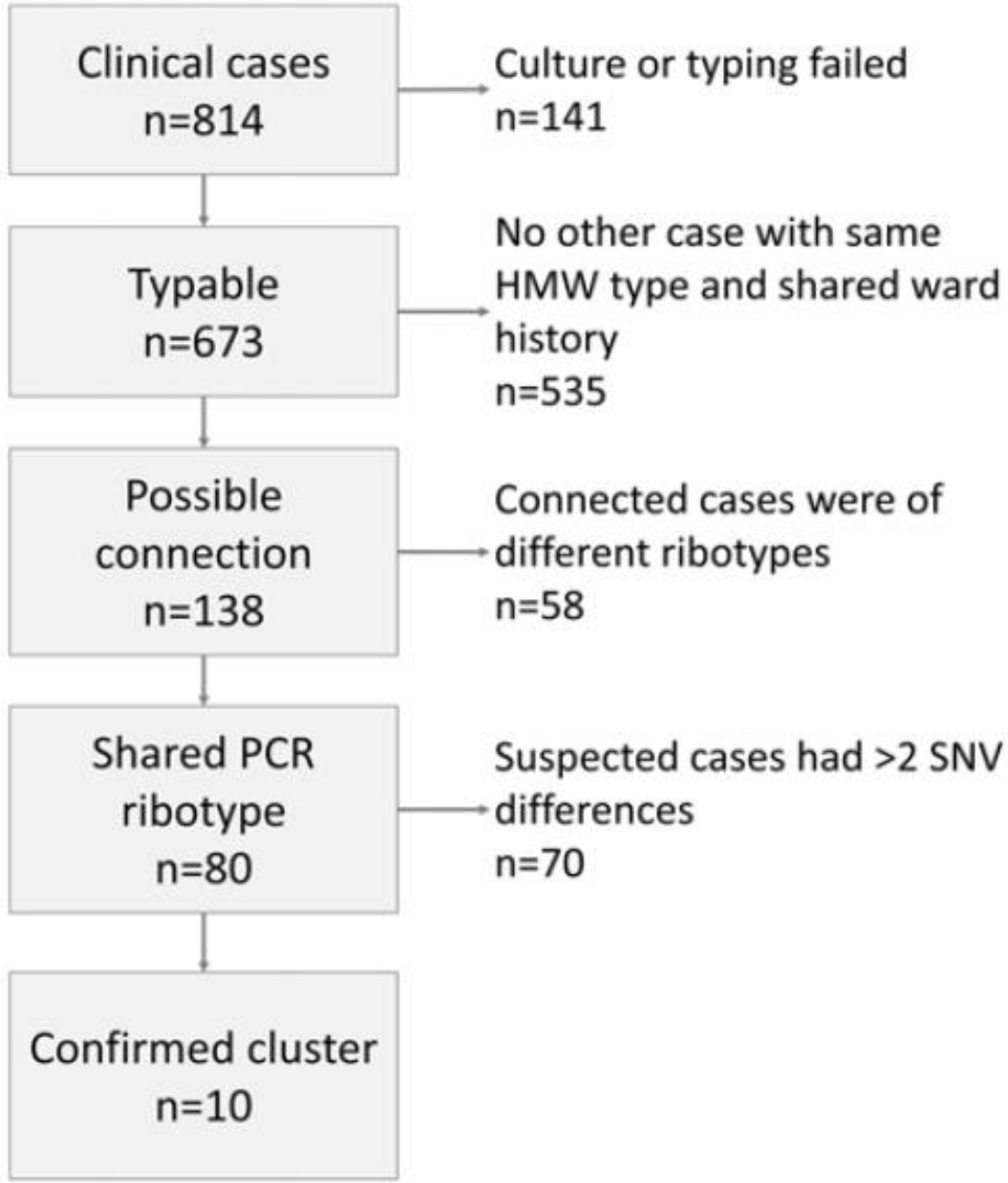


Figure 1. Flow chart depicting the steps for identifying transmission clusters.

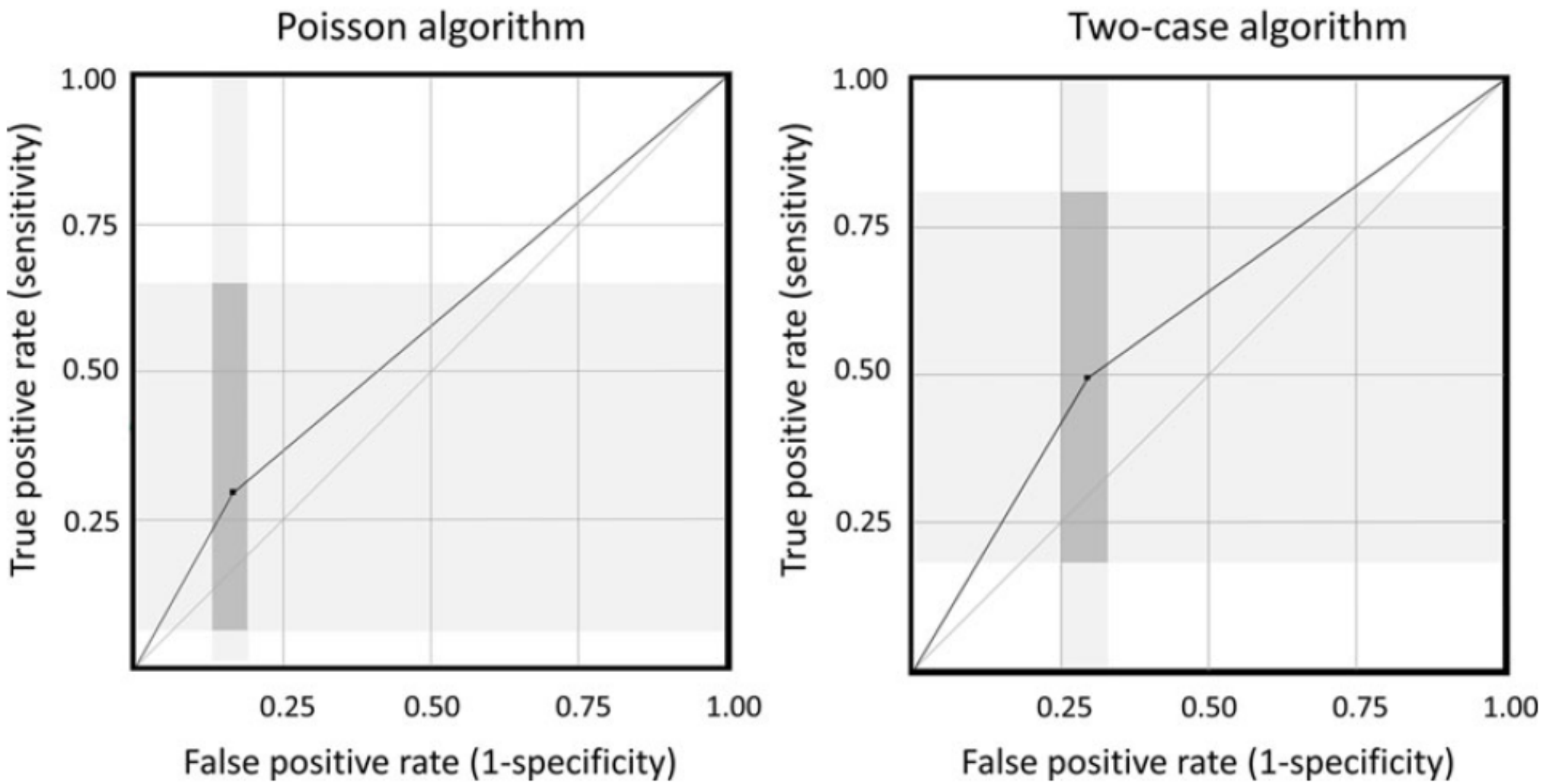
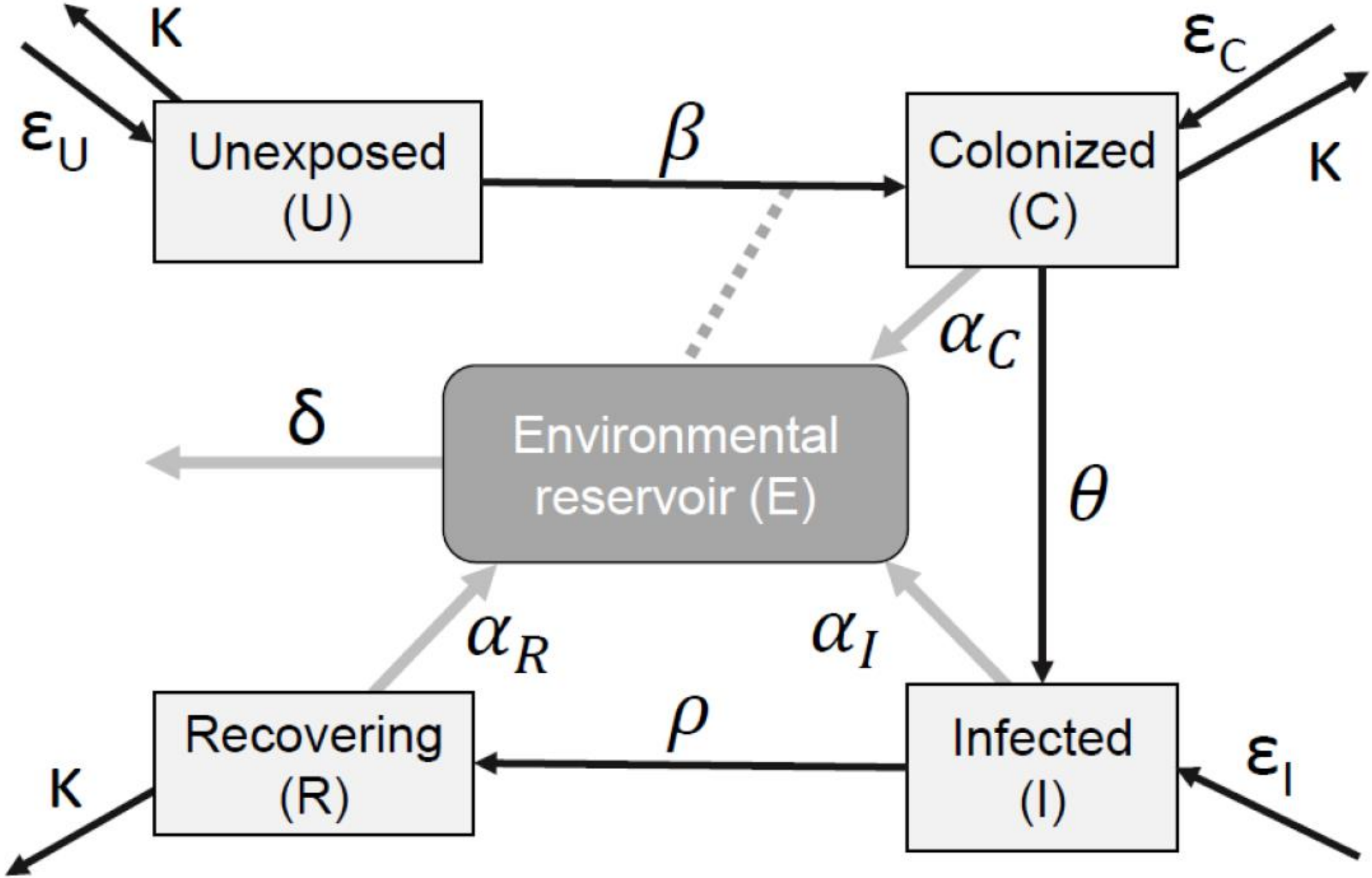

Poisson algorithm
Two-case algorithm
True positive rate (sensitivity)
False positive rate (1-specificity)
1.00
0.75
0.50
0.25
0.25
0.50
0.75
1.00

Table 1. Ward History and Early-Warning Algorithm Alerts for Patients in the Confirmed Clusters

Cluster (no. of cases, ribotype, ST)	Patient	SNV[2] Differences	Shared Ward	Days Between Shared Ward	Ward Where Test Was Taken	Poisson Alert	2-Case Alert
A (3 cases, RT014, ST 2)	S088	0–1	Surgical (general)	57	Surgical (gastrointestinal)	...	...
	S117				Medical (general)	...	...
	S245			223	Infectious diseases (outpatient)	...	...
B (2 cases, RT020, ST 2)	S225	0	Medical (nephro)	0	Medical (nephro)	Medical (nephro)	Medical (nephro)
	S238				Medical (general)	...	Medical (general)
C (3 cases, RT001, ST 3)	B125	0	Medical (nephro)	12	Infectious diseases	Infectious diseases	Infectious diseases
	B145		Medical (nephro)		Medical (nephro)	Medical (nephro)	Medical (nephro)
	B166		...	...	Neurology (stroke)	...	...
D (2 cases, RTx231, ST 11)[a]	B209	1	Surgical ward (mixed)	0	Medical (lung)	...	Medical (lung)
	B225				Medical (general)	...	...

Note. ST, sequence type; SNV, single-nucleotide variation.

[a]The "x" indicates that international nomenclature for the ribotype is missing.


κ
ε_U
Unexposed
(U)
β
Colonized
(C)
ε_C
κ
α_C
δ
Environmental
reservoir (E)
θ
α_R
α_I
Recovering
(R)
ρ
Infected
(I)
κ
ε_I

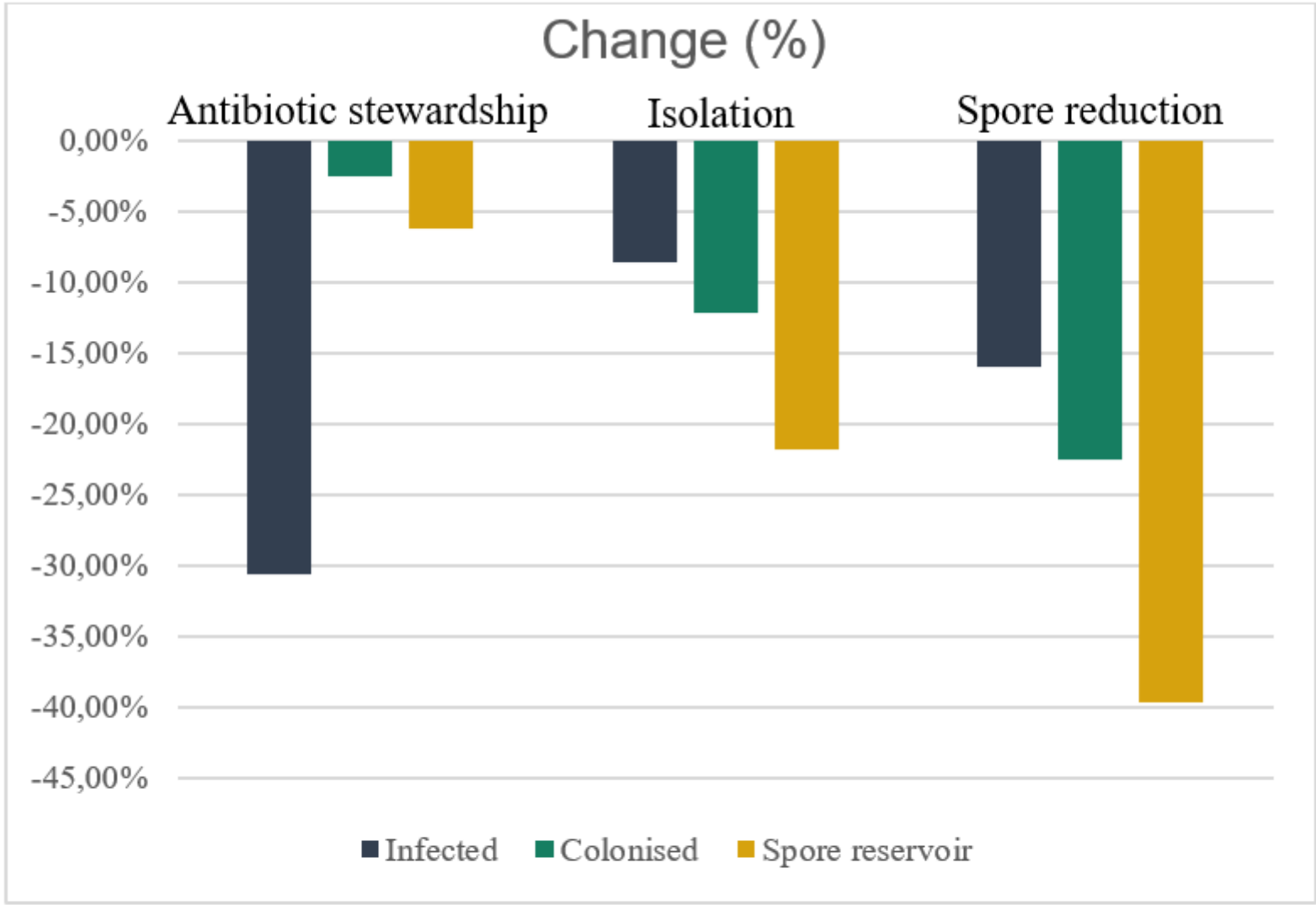


Figure 20. Changes in the number of infected and colonised patients and the environmental spore reservoir level after the interventions modelled in Paper III.

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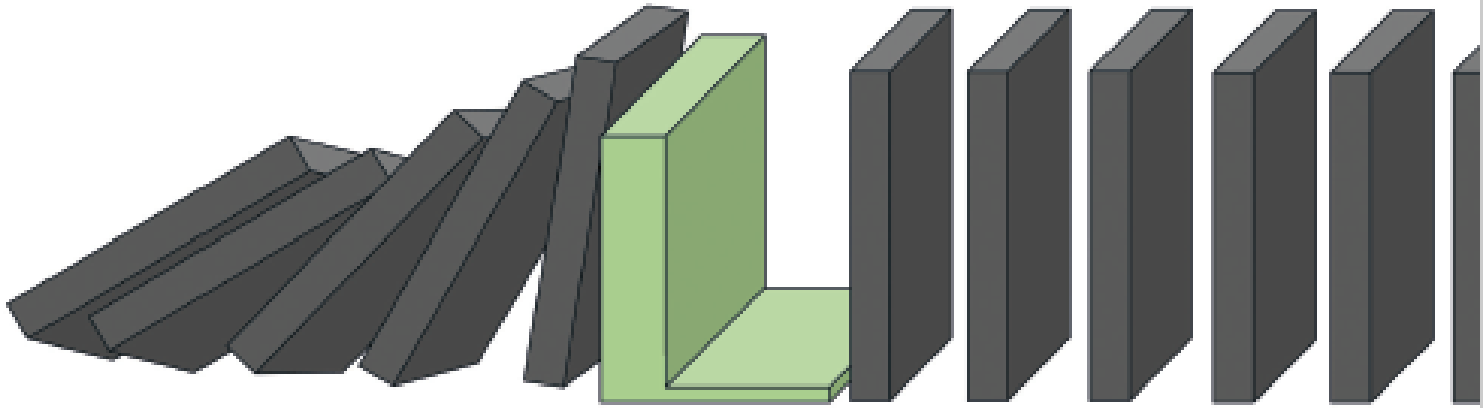

Clostridioides difficile: Preventive strategies

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