



# Occurrence and trends of *Clostridioides difficile* infections in hospitalized patients: a prospective multi-centre cohort study in six German university hospitals, 2016–2020

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## ARTICLE INFO

## Article history:

Received 16 April 2024

Accepted 9 June 2024

Available online 3 July 2024

## Keywords:

Epidemiology

*Clostridioides difficile*

Infection

Incidence

Germany



## SUMMARY

**Background:** For *Clostridioides difficile* infections (CDIs) in Germany no longitudinal multi-centre studies with standardized protocols for diagnosing CDI are available. Recent evaluations of general surveillance databases in Germany indicate a downward trend in CDI rates. We aimed to describe the actual burden and trends of CDI in German university hospitals from 2016 to 2020.

**Methods:** Our study was a prospective multi-centre study covering six German university hospitals. We report the data in total, stratified by year, by medical specialty as well as by CDI severity. Multi-variable regression analyses were performed to assess risk factors for severe CDI.

**Results:** We registered 3780 CDI cases among 1,436,352 patients. The median length of stay (LOS) of CDI cases was 20 days (interquartile range 11–37) compared with a general LOS of 4.2 days. In-hospital all-cause mortality in CDI patients was 11.7% ( $N = 444/3780$ ), while mortality attributed to CDI was 0.4% ( $N = 16/3761$ ). CDI recurrence rate was comparatively low at 7.2%. The incidence density of severe healthcare-associated healthcare onset (HAHO)-CDI showed a significant decrease from 2.25/10,000 patient days (pd) in 2016 to 1.49/10,000 pd in 2020 (trend calculation  $P=0.032$ ).

**Conclusions:** Compared with a European point-prevalence study in 2013/2014, where overall CDI incidence density was 11.2 cases/10,000 pd in Germany (EUCLID), we see in our study halved overall CDI rates of 5.6 cases/10,000 pd in 2020. Our study shows current data on the distribution of CDI cases in German university hospitals and thus provides international comparative data on the key indicators of CDI.

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## Introduction

Based on its impact on healthcare systems, *Clostridioides difficile* has been prioritized as a pathogen of the highest priority group for surveillance and epidemiological research, as it is associated with significant morbidity and mortality [1]. *C. difficile* is a spore-forming, obligate anaerobic, Gram-positive rod that causes disease through release of enterotoxins [2]. The clinical picture of *C. difficile* infection ranges from mild diarrhoea to pseudomembranous colitis, which in rare cases can be aggravated by a toxic megacolon. In the most severe form, the disease may lead to bowel perforation and death [3].

By the mid-2000s the epidemiology of *C. difficile* infection (CDI) changed dramatically, with increases in incidence and severity of disease in several countries. Largely attributed to the emergence of a more virulent strain (ribotype 027 (RT027)) CDI became a global public health challenge [4]. Results of a European point-prevalence study from 2011 to 2014 (EUCLID) revealed 7.0 cases (country range 0.7–28.7) of CDI per 10,000 patient-bed days (pd) with 10 cases/10,000 pd in Germany in hospitalized patients in 2011/12 and 11.2 cases/10,000 pd in 2013/14 [5].

Conversely, in the last decade a significant decrease in CDI incidence was described in the USA and England likely related to lower circulation of hypervirulent strains and reduced use of fluoroquinolones in community and healthcare centres [6,7]. In line with this, a recent analysis of the hospital coding of CDI in Germany showed a decrease of CDI from 2015 (6.8/10,000 pd) to 2021 (4.1/10,000 pd) [8]. However, the official reporting data in Germany cannot be evaluated without restrictions. According to the German Infection Protection Act (IfSG), only severe complicated CDI is reportable by the treating physicians

to the Robert Koch Institute (RKI), the German government's central scientific institution responsible for the surveillance of infectious diseases [9]. Because there is no general obligation to report CDI in Germany, the available official data on CDI are limited and under-reporting is likely. The above-mentioned hospital-coding data on CDI incidence in Germany are not based on studies that evaluate the patients in detail or verify the clinical diagnosis of CDI using predefined diagnostic criteria and databases are missing key figures of CDI such as mortality attributed to CDI, acquisition of CDI, seasonality and severity.

Thus, the aim of the present study was to describe the epidemiology and trends of CDI in a prospective, longitudinal multi-centre study by analysing patient demographics, incidence, severity, recurrence and in-hospital all-cause mortality as well as CDI attributable mortality 14 days after CDI diagnostics from 2016 to 2020 in six German university hospitals as part of the DZIF (German Centre for Infection Research) core network for the study of multi-drug-resistant bacterial organisms (R-Net).

## Methods

## Study design, centres, wards, patients

In this prospective multi-centre study, six German university hospitals participated in the CDI surveillance of the R-Net project, from October 2016 to July 2020. Study sites are located in the North, West, East, Southwest and Southeast of Germany and provide between 1300 and 3200 inpatient beds each.

All patients with microbiological detection of toxin-producing *C. difficile* in stool samples, performed using guideline-based diagnostic methodologies (see below) were screened by study personnel according to the study protocol

for possible inclusion. Patients were only included if they met one of the following criteria for CDI: (i) diarrhoea ( $\geq$  three unformed stools/24 h) or ileus or toxic megacolon and detection of toxin-producing *C. difficile*; or (ii) pseudomembranous colitis diagnosed by endoscopy or histopathology [10,11]. Certain medical disciplines including dermatology, obstetrics, ophthalmology, otorhinolaryngology and psychiatry, were excluded due to short hospital stays and low expected CDI incidences. We only enrolled cases in patients  $\geq 18$  years old.

According to the study protocol, recurrent CDI was defined as early recurrence with a new episode of CDI (using the same inclusion criteria as above)  $>2$  and  $<8$  weeks after the last case-defining event while being symptom-free ( $\geq 2$  days without diarrhoea) in the meantime. Recurrent *C. difficile* detection with diarrhoea within two weeks after the last case-defining event was not counted anew. This is in line with the ECDC CDI surveillance protocol and ESCMID guidelines [10–12]. Late recurrence was recorded as a new episode  $>8$  weeks and  $<12$  weeks after the last case-defining event while being symptom-free in the meantime. Recurrence was counted only once within 12 weeks of the first case event. After 12 weeks, a new case-defining episode was considered a new case.

Based on the ECDC CDI surveillance protocol, the acquisition of CDI was subdivided into community-associated (CA-CDI, onset before or in the first two days of hospital admission without hospital stay in the previous 12 weeks), healthcare-associated with community onset (HACO-CDI, symptom onset before or in the first two days of hospital admission with hospital stay in the previous four weeks), healthcare-associated with healthcare onset (HAHO-CDI, symptom onset  $\geq$  day 3 of and within hospital stay) and unknown association (symptom onset before or in the first two days of hospital admission without hospital stay in the previous four weeks but with hospital stay  $>4$  and  $\leq 12$  weeks prior to admission) [12]. Hospital stay was defined as  $\geq 1$  night and admission day was day 1. HACO- and HAHO-CDI combined are all healthcare-associated CDI (HA-CDI).

Severe CDI was defined by the presence of leucocytosis  $>15,000/\mu\text{L}$  and/or creatinine  $\geq 1.5$  mg/dL in the time interval  $\pm 2$  days after stool sample collection with a positive case-defining *C. difficile* test [13]. If no data were available, the criterion was considered not met. Based on the German Infection Protection Act (§ 6.1 a.b) [9] severe complicated CDI was defined as CDI with ileus, toxic megacolon, surgery, intensive care unit transfer, or death within 14 days of the date of specimen collection, each of which must have occurred in association with the CDI [9]. If a patient died within 14 days of diagnosis the attending physician had to confirm that death was due to CDI. These criteria widely overlap with ESCMID, IDSA and SHEA guidelines [10,11,13].

We recorded additionally whether CDI was the reason for admission to the hospital. Furthermore, length of stay (LOS) was recorded per patient from admission to discharge/death. Apart from the 14-day CDI associated deaths (as part of the definition criteria of severe complicated CDI) in-hospital all-cause mortality was recorded at the time of discharge from the hospital.

### CDI diagnostics

*C. difficile* testing was performed within 24 h of receiving the stool sample, and samples were stored at 4 °C until testing. In

the participating centres, different diagnostic algorithms were performed, all fulfilling the ESCMID criteria [10,11]. Details of the used assays are listed in the [Supplementary Table S1](#). The microbiological definition of CDI was fulfilled if either (i) glutamate dehydrogenase (GDH) testing and toxin A/B ELISA were positive, or (ii) GDH testing was positive, toxin A/B ELISA negative but toxin gene PCR or toxigenic culture were positive, or (iii) toxin gene PCR and toxin A/B ELISA were positive, or (iv) toxin gene PCR was positive and toxin A/B ELISA was negative.

### Statistics

In the descriptive analysis, number and percent or median and interquartile range were specified. Differences were tested by Chi-squared, Wilcoxon rank-sum or Kruskal–Wallis test, as appropriate. We reported the data in total and stratified by CDI severity as well as by year, hospital and medical specialty.

CDI incidence was calculated per 100 patients and incidence density was calculated per 10,000 pd. Trend analyses were performed as generalized estimating equation (GEE) model with Poisson regression for the monthly incidence densities of the wards, considering clusters in hospitals (for all HAHO-CDI, and stratified by HAHO-CDI severity). Multi-variable regression analyses were performed with GEE models to assess the difference between mild and non-mild CDI (severe + severe complicated CDI), as well as between severe cases with versus without complications (subgroup analysis). We calculated adjusted odds ratios (aORs) with 95% confidence interval (CI) using generalized estimating equation models to account for clusters (centres). All relevant parameters were added to the multi-variable model, then non-significant parameters were excluded stepwise backward by the smallest Chi-squared value and  $P < 0.05$  in type III score statistic.  $P$ -values  $< 0.05$  were considered significant. All analyses were exploratory in nature and performed with SPSS (version 25) and SAS (version 9.4).

### Ethics

The study was approved by the institutional ethics committees (approval number EA4/018/14). Signed informed consent was not required.

## Results

### Descriptive statistics

In the study period, 325 wards from six university hospitals in Germany took part in CDI surveillance, including 118 internal medicine wards, 126 surgical wards, 22 haematology–oncology wards and 59 other wards. The hospitals covered North (centre 6), East (centre 1), West (centre 3, centre 4), and Southwest Germany (centre 2, centre 5). During 13,781 surveillance months, we registered 1,436,352 patients and 6,800,059 pd and 3780 CDI cases. A flow chart of CDI cases can be found in [Supplementary Figure S1](#).

Of all CDI patients 47.4% ( $N = 1791$ ) were female and the median age was 70 years (interquartile range (IQR) 59–79). The median LOS of CDI cases was 20 days (IQR 11–37) compared with a general LOS of 4.2 days (of all patients admitted to the participating hospitals in our study period).

Of all CDI cases 84.4% were HA-CDI (3191/3780), 9.5% (359/3780) were CA-CDI and 4.1% (154/3780) had an unknown

Table I

Descriptive statistics of all *Clostridioides difficile* infection (CDI) cases as total and stratified by severity in mild, severe and severe complicated CDI

Parameter	Category	CDI total	Mild CDI	Severe CDI	Severe complicated CDI	P <sup>a</sup>
		N (%) / median (IQR)	N (%) / median (IQR)	N (%) / median (IQR)	N (%) / median (IQR)	
CDI cases		3780 (100%)	1833 (100%)	1902 (100%)	45 (100%)	
Sex	Male	1989 (52.6%)	892 (48.7%)	1067 (56.1%)	30 (66.7%)	<0.001
	Female	1791 (47.4%)	941 (51.3%)	835 (43.9%)	15 (33.3%)	
Age, years		70 (59–79)	67 (56–77)	72 (62–80)	69 (62–79)	<0.001
In-hospital all-cause mortality	Alive	3320 (87.8%)	1682 (91.8%)	1616 (85.0%)	22 (48.9%)	<0.001
	Deceased	444 (11.7%)	140 (7.6%)	281 (14.8%)	23 (51.1%)	
	Unknown	16 (0.4%)	11 (0.6%)	5 (0.3%)	0 (0.0%)	
LOS (days)		20 (11–37)	21 (11–38)	20 (11–36)	18 (11–36)	0.878
Recurrence	Initial manifestation	3026 (80.1%)	1491 (81.3%)	1503 (79.0%)	32 (71.1%)	0.166
	Early recurrence	273 (7.2%)	117 (6.4%)	151 (7.9%)	5 (11.1%)	
	Late recurrence	66 (1.7%)	28 (1.5%)	38 (2%)	0 (0%)	
	Unknown	415 (11%)	197 (10.7%)	210 (11%)	8 (17.8%)	
Acquisition	Missing data	76 (2%)	41 (2.2%)	33 (1.7%)	2 (4.4%)	0.004
	CA-CDI	359 (9.5%)	165 (9%)	186 (9.8%)	8 (17.8%)	
	HACO-CDI	811 (21.5%)	352 (19.2%)	445 (23.4%)	14 (31.1%)	
	HAHO-CDI	2380 (63%)	1193 (65.1%)	1168 (61.4%)	19 (42.2%)	
	Unknown	154 (4.1%)	82 (4.5%)	70 (3.7%)	2 (4.4%)	
Highest leucocyte count/ $\mu$ L $\pm$ 2 days of sampling		10,800 (6890–16,030)	8100 (5090–10,860)	15,630 (10,190–20,940)	15,900 (8750–29,400)	<0.001
Highest creatinine (mg/dL) $\pm$ 2 days of sampling		1.16 (0.79–2.21)	0.83 (0.67–1.07)	2.1 (1.26–3.49)	2.24 (1.7–3.8)	<0.001
Admission due to CDI	Unknown	197 (5.2%)	92 (5%)	103 (5.4%)	2 (4.4%)	<0.001
	No	3154 (83.5%)	1566 (85.5%)	1563 (82.2%)	25 (55.6%)	
	Yes	426 (11.3%)	173 (9.4%)	235 (12.4%)	18 (40%)	
Centre	1	1157 (30.6%)	539 (29.4%)	605 (31.8%)	13 (28.9%)	0.002
	2	560 (14.8%)	306 (16.7%)	248 (13%)	6 (13.3%)	
	3	530 (14%)	252 (13.7%)	268 (14.1%)	10 (22.2%)	
	4	594 (15.7%)	302 (16.5%)	283 (14.9%)	9 (20%)	
	5	347 (9.2%)	174 (9.5%)	167 (8.8%)	6 (13.3%)	
	6	592 (15.7%)	260 (14.2%)	331 (17.4%)	1 (2.2%)	
Ward type	ICU	499 (13.2%)	176 (9.6%)	301 (15.8%)	22 (48.9%)	<0.001
	Intermediate care	164 (4.3%)	68 (3.7%)	92 (4.8%)	4 (8.9%)	
	General ward	3090 (81.7%)	1569 (85.6%)	1502 (79%)	19 (42.2%)	
	Other	27 (0.7%)	20 (1.1%)	7 (0.4%)	0 (0%)	
Ward specialty	Surgery	688 (18.2%)	330 (18%)	348 (18.3%)	10 (22.2%)	<0.001
	Internal medicine	2237 (59.2%)	961 (52.4%)	1247 (65.6%)	29 (64.4%)	
	Haematology–oncology	478 (12.6%)	345 (18.8%)	128 (6.7%)	5 (11.1%)	
	Other	377 (10%)	197 (10.7%)	179 (9.4%)	1 (2.2%)	

Year	2016	2017	2018	2019	2020	115 (6.3%)	124 (6.5%)	1 (2.2%)	0.124
	240 (6.3%)	1054 (27.9%)	1054 (27.9%)	966 (25.6%)	466 (12.3%)	509 (27.8%)	530 (27.9%)	15 (33.3%)	
						485 (26.5%)	561 (29.5%)	8 (17.8%)	
						483 (26.4%)	466 (24.5%)	17 (37.8%)	
						241 (13.1%)	221 (11.6%)	4 (8.9%)	

CA-CDI, community-acquired CDI; HACO-CDI, hospital-associated with community-onset CDI; HAHO-CDI, healthcare-acquired healthcare-onset CDI; ICU, intensive care unit; IQR, interquartile range; LOS, Length of stay.

<sup>a</sup> P-values were calculated by Chi-squared or Kruskal–Wallis test, as appropriate. We compared in the table the different strata of the described parameters and P-values refer by line to the statistically significant differences between the groups.

association. In 11.3% of all cases (426/3777, missing values  $N = 3$ ) admission to the hospital was due to CDI. Most of the CDI cases (81.7%;  $N = 3090$ ) were diagnosed on general wards, followed by intensive care unit (13.2%;  $N = 499$ ) and intermediate-care wards (4.3%,  $N = 164$ ). In-hospital all-cause mortality in CDI patients was 11.7% ( $N = 444/3780$ ) (Table I). Mortality attributed to CDI was 0.4% ( $N = 16/3761$ , missing values  $N = 9$ ).

Of all CDI cases ( $N = 3780$ ), 1833 were classified as mild (48.5%), 1902 as severe (50.3%) and 45 as severe complicated CDI cases (1.2%) (Table I). Over half of the patients with severe complicated CDI (51.1%) died in the hospital (all-cause mortality), compared with 14.8% of those with severe CDI and 7.6% of those with mild CDI (Table I, Supplementary Figure S1).

Of the 45 patients with severe complicated disease, four (8.9%) developed ileus and nine (20%) a toxic megacolon, and 30 (66.7%) were admitted to ICU because of the CDI. Six (13.3%) had to undergo surgery due to CDI and 16 (35.6%) died of the CDI. Of these severe complicated cases, 18 (40%) were community-onset and admitted to hospital specifically because of their CDI. Patients with severe complicated CDI had higher leucocyte counts and higher creatinine levels in the two days around sampling, than severe CDI cases (Table I). Descriptive statistics of CDI cases stratified by the participating hospitals can be found in Supplementary Table S2.

#### CDI incidence in total and by specialty stratified for disease severity

The total CDI incidence was 0.263/100 patients (95% CI 0.251–0.272) (Table II) and varied among the hospitals from 0.181/100 patients (95% CI 0.160–0.196) to 0.430/100 patients (95% CI 0.382–0.466) (Supplementary Table S3).

Haematology–oncology wards showed the highest total CDI incidence of all specialties with 1.015/100 patients (95% CI 0.890–1.109). The highest incidence density of HAHO-CDI was also found on haematology–oncology wards (8.31/10,000 pd, 95% CI 7.46–9.23), mainly presenting as mild cases (6.16/10,000 pd, 95% CI 5.43–6.96). The incidence of HA-CDI was about nine-times higher than CA-CDI, i.e., 0.222 versus 0.025/100 patients (95% CI 0.211–0.230 and 0.021–0.028), respectively. The highest incidence density of severe HAHO-CDI cases was found on internal medicine wards (2.58/10,000 pd, 95% CI 2.39–2.78); this was even higher than the incidence density of mild HAHO-CDI cases in internal medicine wards (2.09/10,000 pd, 95% CI 1.93–2.27) (Table II).

#### Evolution of CDI epidemiology over time

Total CDI decreased from 0.3 cases/100 patients in 2016 to 0.26 cases/100 patients in 2020 and total CDI incidence density decreased from 6.34 cases/10,000 pd in 2016 to 5.56 cases/10,000 pd in 2020 (Supplementary Table S4). However, these observations were not statistically significant. But stratified by disease severity, a decreasing linear trend of severe HAHO-CDI incidence density from 2016 (2.25/10,000 pd) to 2020 (1.49/10,000 pd) was observed ( $P=0.032$ ) (Supplementary Table S5, Figure 1).

Seasonality of CDI incidence was not detected (Supplementary Table S6, Supplementary Figure S2). Also, there was no change in total CDI incidence over time in the

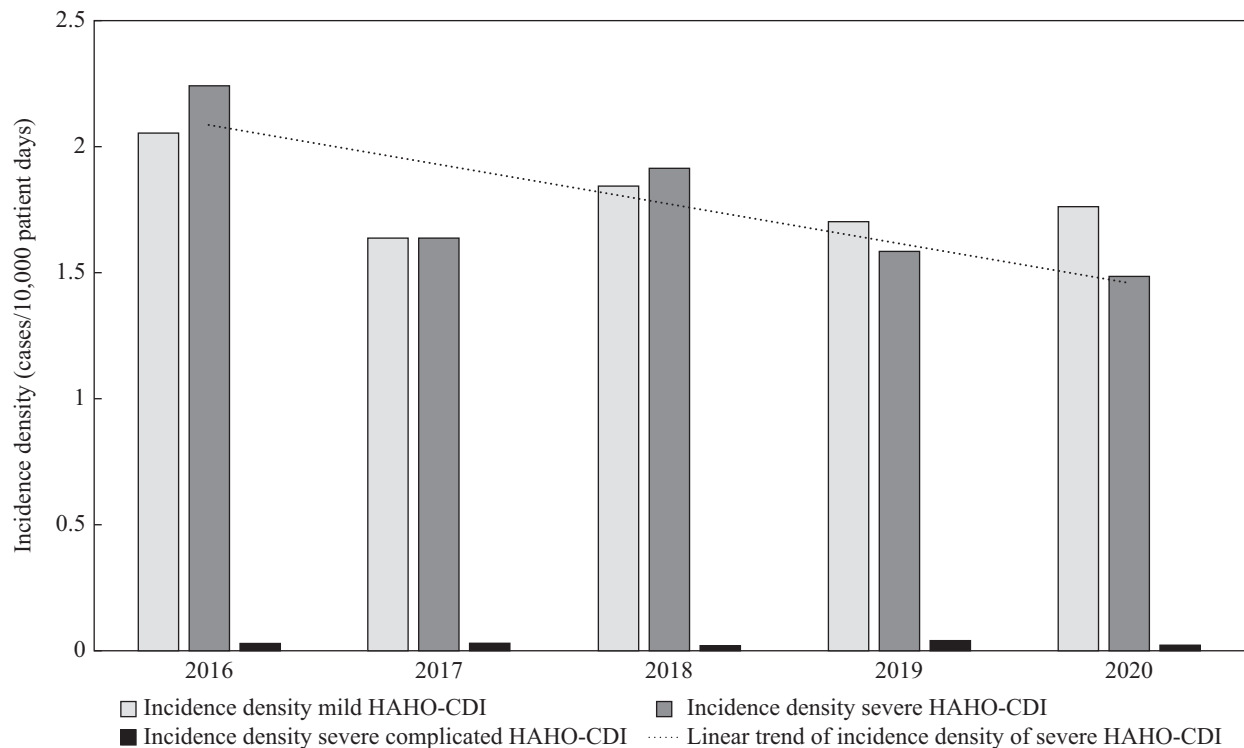


**Table II**  
*Clostridioides difficile* infection (CDI) incidence and incidence densities in total and by specialty

Parameter	CDI total	Surgery	Internal medicine	Haematology–oncology	Other
Wards	325	126	118	22	59
Surveillance months	13,781	5217	5027	1009	2528
Patients	1,436,352	518,120	565,665	47,107	305,460
Patient days	6,800,059	2,464,959	2,702,231	418,634	1,214,235
Incidence per 100 patients, incidence densities per 10,000 patient days (with 95% CI)					
CDI incidence <sup>a</sup>	0.263 (0.251–0.272)	0.133 (0.119–0.143)	0.395 (0.372–0.412)	1.015 (0.890–1.109)	0.123 (0.106–0.137)
CA-CDI incidence	0.025 (0.021–0.028)	0.009 (0.005–0.012)	0.046 (0.038–0.052)	0.034 (0.015–0.055)	0.013 (0.008–0.017)
HA-CDI incidence	0.222 (0.211–0.230)	0.117 (0.104–0.126)	0.325 (0.304–0.340)	0.913 (0.795–1.003)	0.104 (0.088–0.116)
HAHO-CDI incidence density	3.50 (3.36–3.64)	2.15 (1.97–2.35)	4.72 (4.46–4.98)	8.31 (7.46–9.23)	1.86 (1.63–2.12)
Mild CDI incidence <sup>a</sup>	0.128 (0.119–0.134)	0.064 (0.054–0.071)	0.170 (0.155–0.181)	0.732 (0.627–0.814)	0.064 (0.052–0.074)
Mild CA-CDI incidence	0.011 (0.009–0.013)	0.005 (0.003–0.007)	0.020 (0.015–0.024)	0.021 (0.007–0.039)	0.006 (0.003–0.009)
Mild HA-CDI incidence	0.108 (0.100–0.113)	0.055 (0.046–0.061)	0.138 (0.125–0.148)	0.660 (0.560–0.738)	0.055 (0.044–0.064)
Mild HAHO-CDI incidence density	1.75 (1.66–1.86)	1.01 (0.89–1.14)	2.09 (1.93–2.27)	6.16 (5.43–6.96)	0.99 (0.82–1.18)
Severe CDI incidence <sup>a</sup>	0.132 (0.124–0.139)	0.067 (0.058–0.075)	0.220 (0.203–0.233)	0.272 (0.209–0.323)	0.059 (0.047–0.068)
Severe CA-CDI incidence	0.013 (0.010–0.015)	0.003 (0.002–0.005)	0.025 (0.020–0.030)	0.011 (0.002–0.025)	0.007 (0.003–0.011)
Severe HA-CDI incidence	0.112 (0.105–0.118)	0.061 (0.052–0.068)	0.183 (0.167–0.194)	0.246 (0.187–0.295)	0.049 (0.038–0.057)
Severe HAHO-CDI incidence density	1.72 (1.62–1.82)	1.13 (1.00–1.27)	2.58 (2.39–2.78)	2.08 (1.66–2.56)	0.87 (0.71–1.06)
Severe complicated CDI incidence <sup>a</sup>	0.003 (0.002–0.004)	0.002 (0.001–0.004)	0.005 (0.003–0.007)	0.011 (0.002–0.025)	0.000 (0.000–0.002)
Severe complicated CA-CDI incidence	0.001 (0.000–0.001)	0.000 (0.000–0.001)	0.001 (0.000–0.002)	0.002 (0.000–0.012)	0.000 (0.000–0.001)
Severe complicated HA-CDI incidence	0.002 (0.001–0.003)	0.001 (0.000–0.003)	0.004 (0.002–0.006)	0.006 (0.001–0.019)	0.000 (0.000–0.002)
Severe complicated HAHO-CDI incidence density	0.03 (0.02–0.04)	0.02 (0.00–0.04)	0.04 (0.02–0.08)	0.07 (0.01–0.21)	0.00 (0.00–0.03)

Other incidences and incidence densities can be found in [Supplementary Table S4](#). CA-CDI, community-acquired CDI; CI, confidence interval; HA-CDI, all healthcare-associated CDI; HAHO-CDI, healthcare-acquired healthcare-onset CDI.

<sup>a</sup> CDI incidence includes cases with missing and unknown acquisition. These cases are not included in the reported CDI incidences by acquisition type.



**Figure 1.** Incidence density of mild, severe and severe complicated healthcare-associated with healthcare onset (HAHO) -*Clostridioides difficile* infection (CDI) cases from 2016 to 2020, Germany,  $N = 3780$  CDI cases. We observed a decreased linear trend in severe HAHO-CDI incidence density from 2016 to 2020 ( $P=0.0317$ ).

different medical specialties (trend calculation: internal medicine  $P=0.098$ , surgery  $P=0.350$ , haematology–oncology  $P=0.224$ , other specialties  $P=0.969$ ).

The ratio of female to male patients, patient age and LOS did not change in any consistent way between 2016 and 2020. The distribution of symptoms on admission, symptoms for severe complicated CDI definition and in-hospital all-cause mortality also remained unchanged; we recorded changes only in the ‘unknown/missing’ category of these variables (Table III).

### CDI recurrence

Among the CDI cases we observed 7.2% early recurrent cases and 1.7% late recurrent cases. The proportion of early recurrent cases increased with CDI severity (mild CDI 6.4% early recurrent cases, severe CDI 7.9%, severe complicated CDI 11.1%, Table I), but was stable over the surveillance period (Table III). Changes over time were only observed in the ‘unknown’ category.

The LOS of early recurrent CDI and initial manifestation did not differ (20 days (IQR 10–39) versus 20 days (IQR 11–36), while the LOS of late recurrent CDI was lower (14 days, IQR 7–38,  $P=0.008$ ) (Supplementary Table S7, Supplementary Figure S3).

### Risk factors for disease severity

Men had a higher chance of having severe or severe complicated CDI than women (aOR 1.37, 95% CI 1.23–1.52). With

each year of age, the odds of a non-mild CDI increased by 2% (aOR 1.02, 95% CI 1.01–1.03). Patients diagnosed with CDI in an ICU were almost twice as likely to suffer from a non-mild CDI (aOR 1.97, 95% CI 1.45–2.7). Patients whose CDI onset was at home, but who had been hospitalized during the previous four weeks (HACO-CDI) had a 38% higher chance of suffering from a severe or severe complicated CDI (aOR 1.38, 95% CI 1.25–1.52, Table IV).

Although patients with severe and severe complicated CDI were more often hospitalized due to their CDI (mild CDI 9.4% admission due to CDI, severe CDI 12.4%, severe complicated CDI 40%), the admission due to CDI did not enhance the chance of developing severe or severe complicated CDI (Table IV).

In order to differentiate between severe complicated and severe CDI cases, we performed a subgroup analysis excluding mild cases ( $N = 1947$ ). The chance of having severe complicated instead of severe CDI increased only by CDI diagnosis in an ICU (aOR 5.25, 95% CI 2.37–11.64). If the CDI was diagnosed not on an internal medicine, surgery or haematological/oncological ward, but on the ward of another specialty, the odds of severe complicated CDI was reduced by 77% (aOR 0.23, 95% CI 0.07–0.79).

### Discussion

In our study, the overall CDI incidence in German university hospitals was between 0.30 cases/100 patients in 2016 and 0.26 cases/100 patients in 2020. In comparison, surveillance data from the German CDAD-KISS show slightly higher and decreasing incidences in the 515 participating hospitals with 0.44

**Table III**  
*Clostridioides difficile* infection (CDI) cases stratified by surveillance year

Parameter	Category	2016	2017	2018	2019	2020	P <sup>b</sup>
Sex, age, LOS, admission due to CDI and laboratory parameters							
Sex	Male	133 (55.4%)	544 (51.6%)	571 (54.2%)	490 (50.7%)	251 (53.9%)	0.422
	Female	107 (44.6%)	510 (48.4%)	483 (45.8%)	476 (49.3%)	215 (46.1%)	
Age (in years, with IQR)		70 (60–79)	70 (58–79)	70 (60–79)	70 (59–79)	70 (59–79)	0.867
LOS (in days, with IQR)		20 (12–35)	19 (10–34)	22 (11–39)	21 (11–36)	21 (11–40)	0.014
Admission due to CDI	Unknown	15 (6.3%)	50 (4.7%)	46 (4.4%)	61 (6.3%)	25 (5.4%)	0.037
	No	198 (82.5%)	864 (82%)	889 (84.3%)	820 (85.2%)	383 (82.2%)	
	Yes	27 (11.3%)	140 (13.3%)	119 (11.3%)	82 (8.5%)	58 (12.4%)	
Highest leucocytes/μL ±2 days of sampling		10620 (7140–16,210)	11470 (7430–16,530)	11300 (7190–16,825)	10,360 (6420–15,430)	9740 (5710–14,990)	<0.001
Highest creatinine (mg/dL) ±2 days of sampling		1.08 (0.77–1.94)	1.2 (0.79–2.20)	1.2 (0.80–2.44)	1.15 (0.78–2.20)	1.03 (0.76–2.30)	0.186
Distribution of symptoms at the time of diagnosis							
Diarrhoea	No	3 (1.3%)	10 (0.9%)	10 (0.9%)	4 (0.4%)	7 (1.5%)	0.304
	Yes	237 (98.8%)	1044 (99.1%)	1044 (99.1%)	962 (99.6%)	459 (98.5%)	
Toxic megacolon	No	240 (100%)	1053 (99.9%)	1054 (100%)	966 (100%)	466 (100%)	0.629
	Yes	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	
Colitis	No	237 (98.8%)	1040 (98.7%)	1043 (99%)	961 (99.5%)	460 (98.7%)	0.431
	Yes	3 (1.3%)	14 (1.3%)	11 (1%)	5 (0.5%)	6 (1.3%)	
Ileus	No	240 (100%)	1051 (99.7%)	1054 (100%)	966 (100%)	465 (99.8%)	0.192
	Yes	0 (0%)	3 (0.3%)	0 (0%)	0 (0%)	1 (0.2%)	
Distribution of symptoms for severe complicated CDI and in-hospital all-cause mortality							
Ileus associated with CDI <sup>a</sup>	Unknown	19 (7.9%)	90 (8.5%)	58 (5.5%)	48 (5%)	28 (6%)	0.038
	No	221 (92.1%)	962 (91.3%)	996 (94.5%)	915 (94.9%)	437 (93.8%)	
	Yes	0 (0%)	2 (0.2%)	0 (0%)	1 (0.1%)	1 (0.2%)	
Toxic megacolon associated with CDI <sup>a</sup>	Unknown	19 (7.9%)	91 (8.6%)	56 (5.3%)	49 (5.1%)	28 (6%)	0.019
	No	220 (91.7%)	960 (91.1%)	995 (94.6%)	911 (94.5%)	437 (94%)	
	Yes	1 (0.4%)	3 (0.3%)	1 (0.1%)	4 (0.4%)	0 (0%)	
ICU transfer due to CDI complications <sup>a</sup>	Unknown	19 (7.9%)	25 (2.4%)	51 (4.8%)	53 (5.5%)	28 (6%)	<0.001
	No	221 (92.1%)	1019 (96.7%)	996 (94.5%)	897 (93.2%)	437 (93.8%)	
	Yes	0 (0%)	10 (0.9%)	7 (0.7%)	12 (1.2%)	1 (0.2%)	
Surgery due to CDI <sup>a</sup>	Unknown	19 (7.9%)	26 (2.5%)	48 (4.6%)	53 (5.5%)	28 (6%)	<0.001
	No	220 (91.7%)	1021 (97.1%)	1002 (95.4%)	906 (94.4%)	438 (94%)	
	Yes	1 (0.4%)	4 (0.4%)	0 (0%)	1 (0.1%)	0 (0%)	
Deceased due to CDI <sup>a</sup>	Unknown	23 (9.6%)	28 (2.7%)	42 (4%)	50 (5.2%)	27 (5.8%)	<0.001
	No	217 (90.4%)	1018 (96.7%)	999 (95.7%)	907 (94.4%)	434 (93.7%)	
	Yes	0 (0%)	7 (0.7%)	3 (0.3%)	4 (0.4%)	2 (0.4%)	
In-hospital all-cause mortality	Unknown	0 (0%)	0 (0%)	2 (0.2%)	8 (0.8%)	6 (1.3%)	0.011
	Alive	213 (88.8%)	927 (88%)	919 (87.2%)	856 (88.6%)	405 (86.9%)	
	Dead	27 (11.3%)	127 (12%)	133 (12.6%)	102 (10.6%)	55 (11.8%)	
CDI by centre							
Centre 1		79 (32.9%)	281 (26.7%)	310 (29.4%)	335 (34.7%)	152 (32.6%)	<0.001
Centre 2		26 (10.8%)	186 (17.6%)	128 (12.1%)	142 (14.7%)	78 (16.7%)	



Centre 3	28 (11.7%)	149 (14.1%)	142 (13.5%)	145 (15%)	66 (14.2%)
Centre 4	23 (9.6%)	170 (16.1%)	200 (19%)	129 (13.4%)	72 (15.5%)
Centre 5	24 (10%)	95 (9%)	101 (9.6%)	73 (7.6%)	54 (11.6%)
Centre 6	60 (25%)	173 (16.4%)	173 (16.4%)	142 (14.7%)	44 (9.4%)
CDI by recurrence					
Initial manifestation	209 (87.1%)	908 (86.1%)	813 (77.1%)	728 (75.4%)	368 (79%)
Early recurrence	16 (6.7%)	77 (7.3%)	86 (8.2%)	66 (6.8%)	28 (6%)
Late recurrence	4 (1.7%)	17 (1.6%)	17 (1.6%)	18 (1.9%)	10 (2.1%)
Unknown	11 (4.6%)	52 (4.9%)	138 (13.1%)	154 (15.9%)	60 (12.9%)
CDI by specialty					
Internal medicine	143 (59.6%)	589 (55.9%)	623 (59.1%)	601 (62.2%)	281 (60.3%)
Surgery	56 (23.3%)	213 (20.2%)	183 (17.4%)	163 (16.9%)	73 (15.7%)
Haematology–oncology	24 (10%)	121 (11.5%)	135 (12.8%)	125 (12.9%)	73 (15.7%)
Other	17 (7.1%)	131 (12.4%)	113 (10.7%)	77 (8%)	39 (8.4%)

CA, community-associated; CI, confidence interval; HA, healthcare-associated; HAHO, healthcare-associated healthcare-onset; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

<sup>a</sup> Evaluated 14 days after diagnosis.

<sup>b</sup> P-values were calculated by Chi-squared or Kruskal–Wallis test, as appropriate. We compared in the table the different strata of the described parameters and P-values refer by line to the statistically significant differences between the groups.

cases/100 patients in 2016 to 0.29 cases/100 patients in 2020 [14]. The difference in CDI incidence might be due to hospital structure (university hospitals in our study versus general hospitals).

Recent analysis of further surveillance databases in Germany confirmed that the overall CDI incidence density decreased from 6.8 cases/10,000 pd in 2015 to 4.1 cases/10,000 pd in 2021 [8,15,16]. In our data on overall CDI incidence and overall incidence density there was no significant decrease from October 2016 to July 2020, only HAHO severe CDI cases showed a significant decrease over our study period. The other mentioned reports analyse data until the end of 2020 and 2021, respectively. Therefore, additional to a broader data collection they cover a larger time span of the COVID pandemic, which may have led to significantly lower CDI incidences in 2020 and 2021 due to contact precautions [17].

Compared with the data from a European point-prevalence study in 2011/12 and 2013/14, where rates of 10 cases/10,000 pd and 11.2 cases/10,000 pd were recorded in Germany, we saw in our study a drop in the total CDI incidence density to 6.3 cases/10,000 pd (2016) and 5.6 cases/10,000 pd (2020), respectively.

In an international context the hospital incidence density of HA-CDI in our study appears to be in the middle range with 4.69 (CI 4.53–4.86) per 10,000 pd (Supplementary Table S1). In a systematic literature review from 2021 including articles from 2009 to 2019 the highest incidence density in Europe was reported in Poland (HA-CDI: 6.18 per 10,000 patient days), the lowest from the UK, at 1.99 per 10,000 patient days [18]. Nevertheless, international data on CDI incidence (densities) are difficult to compare due to differences in study design, definitions and settings.

As discussed previously, the main likely explanations for the decreasing CDI incidence in Germany might be improved adherence to infection control measures, systematic training of infectious disease specialists over the last decade and the implementation of several concerted national activities aimed at the reduction of antibiotic consumption [8]. With this effort, overall antibiotic consumption in German hospitals (recorded by the antimicrobial consumption surveillance of the Robert Koch Institute) decreased steadily from 55.38 defined daily doses/100 pd in 2015 to 49.74 defined daily doses/100 pd in 2021 [19]. Additionally, a reduction in the number of hypervirulent RT027 strains might be a cause for the decrease of CDI. In Germany, the nationwide prevalence of RT027 was <1% prior to 2010 but increased continuously thereafter, reaching 21.7% in 2013 [20,21]. Since then, RT027 as well as RT001, another important nosocomial strain, decreased considerably in Germany [22,23]. Both the increased antibiotic/antimicrobial stewardship (ABS/AMS) efforts and the reduction in (nosocomial) hypervirulent ribotypes potentially have the greatest impact on severe hospital-associated CDI cases (compared with mild cases or cases from the ambulant sector). This is consistent with the observation in our study where we found a significant decrease from 2016 to 2020 (only) in the severe HAHO-CDI case group, as well as with data from other countries [6,7].

Early CDI recurrence rate in our study was 7.2%. Data from the Federal Health Monitoring (GBE-Bund) and CDAD-KISS report comparable rates of recurrence of 5.8 and 6.5%, respectively for 2016–2019 [14,15]. Nevertheless, globally the rate of recurrence is estimated to be higher at approximately

**Table IV**

Multi-variable model for risk factors for severe and severe complicated *Clostridioides difficile* infection (CDI) compared with mild CDI

Parameter	Category	aOR (95% CI)	P	Type-III test P
Sex	male	1.37 (1.23–1.52)	<0.001	0.023
	female	1=Ref.		
Age (years)		1.02 (1.01–1.03)	<0.001	0.017
Ward type	ICU	1.97 (1.45–2.70)	<0.001	0.024
HACO-CDI		1.38 (1.25–1.52)	<0.001	0.025

All CDI were considered independent of association (total cohort,  $N = 3780$ ). Parameters considered in the model: age, length of stay, CDI recurrence (as category: initial manifestation, early recurrence, late recurrence, unknown), and as binary variables: sex, surveillance year, specialties (internal medicine, surgery, haematology–oncology and other), ward types (intensive care unit, intermediate care, general), acquisition types (CA-CDI, HAHO-CDI, HACO-CDI), admission due to CDI, seasons (spring, summer, autumn, winter). aOR, adjusted odds ratio; CA, community associated; CI, confidence interval; HACO, hospital-associated with community-onset; HAHO, healthcare-associated healthcare-onset.

10–20% (median 17%) of all CDI cases [18]. Our study and the German database evaluations mentioned above only record hospitalized patient cases and could therefore potentially underestimate the rate of recurrence.

The average LOS for CDI cases in our study was 20 days compared with an average LOS of 4.2 days (of all patients in our surveillance period) and remained constant over time. According to the German Hospital Association, the average length of stay in German hospitals in 2019 was 7.2 days [24]. A recently published case–control study showed similar data in the USA, with 17.2 days in CDI patients versus 5.2 days in non-CDI patients, underscoring the economic impact of CDI infections [25]. Cases of late recurrence showed in our study a shorter LOS of only 14 days. Late recurrence was more often a new episode with a separate hospital admission and LOS in this group might therefore be shorter than in the early recurrence group (20 days), where the recurrence occurred within the same hospital stay.

In our hospital setting we did not observe a seasonality of the incidence of CDI. In a German evaluation from 2000 to 2009 of laboratory data on *C. difficile* toxin-positive stool samples, the relative number of positive isolates was also not related to individual months [26]. Nevertheless, earlier studies have demonstrated seasonal variability in rates of CDI characterized by a peak in spring and lower frequencies of CDI in summer/autumn [27]. Driving factors for the observed seasonality are not fully understood but might be due to seasonal fluctuations in antibiotic consumption [28] and local environmental influences or contaminated food [27]. Furthermore, seasonality can be related to testing density which changes over the year, often due to winter peaks of other gastro-intestinal pathogens [29]. These factors were by-and-large stable in our hospital setting.

Besides male sex, CDI acquired on an ICU and age, healthcare-associated community-onset CDI was a risk factor for severe or severe complicated CDI. This might be explained by the longer time to treatment/diagnosis in patients who are potentially at risk (due to the fact that they have been

hospitalized in the last four weeks). The higher risk in ICU is likely due to patient type on ICU that tend to be multi-morbid and often receive antibiotic therapy).

Our study has several limitations. First, we missed all cases in <18-year-old patients but may still have overestimated CDI incidence due to exclusion of specialties with low expected CDI incidence. Second, different diagnostic testing algorithms and awareness of medical staff in different centres may have varied and could have led to underestimation of CDI cases as more testing is associated with the diagnosis of more CDI cases [29,30]. We only recorded hospitalized cases in university hospitals and presumably significantly underestimated the actual number of community-acquired CDIs as well as the number of recurrent CDI cases because the recording was based on the written medical history and previous discharge letters in the patients' files. Our data did not record the ribotypes underlying the CDI cases, nor did we analyse changes in staff awareness over the period. Furthermore, we did not investigate the transmission of cases epidemiologically and did not record cross-infections, thus we cannot make any final statements about the reasons for the reduction in *C. difficile* cases. The COVID-19 pandemic began at the end of our study period and may have had an impact on CDI data due to the changed patient population and changed hospital admission rates [17]. The impact of the pandemic on our data was not evaluated due to the minimal time overlap of four months (April–July 2020).

A subset of the data was previously published, analysing the association of ward-level antibiotic consumption with hospital-onset CDI [31].

In conclusion, for the first time, we can evaluate CDI data collected in a prospective multi-centre study for Germany and confirm incidence density was decreasing in severe HAHO-CDI from 2016 to 2020. Furthermore, our study provides up-to-date epidemiological data on patient demographics, severity, CDI recurrence, in-hospital all-cause mortality and CDI-attributed mortality.

## Acknowledgements

We thank all other members of the R-Net Study Group: M.J.G.T. Vehreschild, Cologne, Tübingen; M. Buhl, Tübingen, Nürnberg; M. Fritzenwanker, Giessen; H. Götz, Freiburg; H. Grundmann, Freiburg; C. Hennelly, Freiburg; S. Herold, Giessen; F. Hölzl, Tübingen; L. Künstle, Tübingen; A. Lang, Lübeck; D. Lenke, Lübeck; F. Meis, Giessen; L. A. P. Diaz, Berlin; G. Pilarski, Berlin; S. Proske, Cologne; J. Schmiedel, Giessen; N. Thoma, Berlin; D. Tobys, Cologne; B. Walinski, Tübingen.

## Author contributions

A.M.R.: local site coordinator, study design, surveillance protocol, local data collection, supervision of data collection in partner sites, data analysis, drafting the manuscript. A.M.: local clinical advisor, local data collection, surveillance and drafting the manuscript. M.B.: database set-up, supervision of data collection in partner sites. T.C.: local principal investigator. A.D.: microbiological analysis. S.E.: local site co-ordinator, local data collection. J.F.: local site co-ordinator, local data collection. P.G.: local principal investigator, study design, surveillance protocol. G.H.: microbiological analysis. S.H.: local data collection, local

clinical advisor. C.I.: microbiological analysis. N.K.: local site coordinator, local data collection. E.K.: local clinical advisor, local data collection. S.P.: microbiological analysis. E.P.: microbiological analysis. J.R.: local principal investigator. C.S.: local site coordinator, microbiological analysis. F.S.: d analysis. H.S.: principal investigator of the study, local principal investigator, study design, surveillance protocol. M.S.B.: supervision of antibiotic consumption data collection in partner sites. E.T.: local principal investigator. J.T.: data collection, local clinical advisor. L.B.: local site coordinator, local data collection. S.V.W.: local site coordinator, isolate management. W.V.K.: local principal investigator, study design, surveillance protocol. N.J.: study design, surveillance protocol, microbiological analysis and drafting the manuscript. All authors revised the manuscript.

### Conflict of interest statement

S.E. reports grants from German Centre for Infection Research (DZIF), during the conduct of the study. J.F. reports grants from Bundesministerium für Bildung und Forschung, during the conduct of the study. The work in the multi-centre cohort was supported by the German Centre for Infection Research (DZIF). Grant ID HZI 8039808824. P.G. reports grants from Government, during the conduct of the study. C.I. reports personal fees and other from MSD Sharp and Dohme, personal fees from Shionogi, non-financial support from Eumedica, during the conduct of the study; grants from German Federal Ministry of Education and Research (BMBF), outside the submitted work. E.K. has received payments for lectures, presentations, etc., antibiotic stewardship and other courses from the German Society for Infectiology (Deutsche Gesellschaft für Infektiologie); has received support for attending meetings and/or travel for ECCMID conference by Gilead; has a leadership role, namely deputy head of section antibiotic stewardship at German Society for Infectiology and at guideline group antibiotic stewardship. S.P. has received grants from German Centre for Infection Research (DZIF). J.R. received grants from BMBF and DZIF, during the conduct of the study. H.S. – the institution has received funding from German Centre for Infection Research (DZIF); has received consulting fees from Debiopharm and Shionogi; has received payments for lecture or presentation from Gilead, MSD, and Shionogi. L.B. reports personal fees from Eumedica, outside the submitted work. S.V.W. has received funding by German Centre for Infection Research (DZIF) (TTU 08.811) during the conduct of the study; has received consulting fees from Institute for Quality and Efficiency in Health Care (IQWiG) and non-financial support from BD, Heidelberg, Germany, outside the submitted work. W.V.K. – institution has received funding from the German Centre for Infection Research (DZIF); has received consulting fees from Gilead and Stiftung Warentest; has received payment for lectures from Landesärztekammer Baden-Württemberg, Akademie für Infektionsmedizin, Berufsverband Deutscher Internisten, SANA Kliniken AG. All other authors report no conflicts of interest.

### Funding sources

The study was supported by the German Center for Infection Research (DZIF) as TTU 08.811.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhin.2024.06.007>.

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