

Electronic Supplementary Material

Article title: Costs and outcomes of *Clostridioides difficile* infections in Germany: A retrospective health claims data analysis

Authors: Katharina Schley¹, Kirstin Heinrich², Jennifer C. Moisi³, Dennis Häckl⁴, Dominik Obermüller⁵, Gordon Brestrich¹, Christof von Eiff¹, Thomas Weinke⁶

Author affiliations:

¹ Pfizer Pharma GmbH, Friedrichstrasse 110 - 10117 Berlin, Germany

² Pfizer Inc., Patient & Health Impact, New York, NY 10017, United States of America

³ Pfizer Vaccines, Medical Development and Scientific/Clinical Affairs, 23 av du Dr Lannelongue 75014 Paris, France

⁴ WIG2 GmbH, Markt 8, 04109 Leipzig, Germany

⁵ InGef–Institute for Applied Health Research Berlin GmbH, Otto-Ostrowski-Str. 5, 10249 Berlin, Germany

⁶ Ernst von Bergmann Klinikum, Charlottenstraße 72, 14467 Potsdam, Germany

Corresponding author: Katharina Schley | Katharina.Schley@pfizer.com

Supplemental information on study design and population

The focus of the cohort study described in this article is the economic (i.e., healthcare costs and healthcare resource utilization) and clinical (i.e., excess all-cause mortality attributable to *Clostridioides difficile* infection [CDI], clinical consequences, and subsequent treatment) burden of CDI. This cohort study was part of a larger study design for which results will be reported separately. The larger study involved other objectives, including CDI incidence estimation for which different definitions were used to identify CDI cases in the InGef (Institute for Applied Health Research Berlin GmbH) research database; these are presented below in Table S1.

Table S1. Other CDI definitions used in the larger study for incidence objectives

CDI definition	Criteria
CDI broad definition	Main inpatient diagnosis with ICD-10-GM code A04.7
	AND/OR
	Secondary inpatient diagnosis with ICD-10-GM code A04.7
CDI strict definition	AND/OR
	Verified outpatient diagnosis with ICD-10-GM code A04.7
	AND/OR
CDI strict definition	Main inpatient diagnosis with ICD-10-GM code A04.7
	AND/OR
	Secondary inpatient diagnosis with ICD-10-GM code A04.7
CDI strict definition	AND/OR
	Verified outpatient diagnosis with ICD-10-GM code A04.7 AND
	prescription of either metronidazole (ATC code J01XD01), vancomycin (ATC code J01XA01), or fidaxomicin (ATC code A07AA12) in the same quarter AND laboratory test for confirmation of CDI with EBM code 32151, 32700, 32707, 32722, or 32723 in the same quarter

ATC Anatomical Therapeutic Chemical Classification; *CDI Clostridioides difficile* infection; *EBM* German physician fee schedule or Einheitlicher Bewertungsmaßstab; *ICD-10-GM* International Classification of Diseases, 10th Revision, German Modification; *InGef* Institute for Applied Health Research Berlin GmbH.

Table S2. Most common *a priori*-defined risk factors in both CDI cases and matched non-CDI controls from exploratory analysis after propensity score matching

Risk factors after propensity score matching	CDI cases and matched non-CDI controls N=76,710	
	n	%
PPI/H2 antagonists	46,709	60.9
Immunosuppressants	16,788	21.9
Gastroesophageal reflux disease	14,762	19.2
Diverticulosis of the intestine	11,680	15.2
Chemotherapy	6,141	8.0
Chronic inflammatory bowel disease	2,214	2.9
Radiation therapy	2,043	2.7
Irritable bowel syndrome	1,476	1.9

CDI *Clostridioides difficile* infection; H2 histamine₂-receptor; PPI proton pump inhibitor.

Table S3. CDI-related risk factors for the exploratory assessment

Category	Code	Description
Comorbidities: verified ambulatory or secondary inpatient diagnosis	I10	Essential (primary) hypertension
	E78	Disorders of lipoprotein metabolism and other lipidemias
	E87	Other disorders of fluid, electrolyte and acid-base balance
	I50	Heart failure
	N39	Other disorders of urinary system
	Z92	Personal history of medical treatment
	I25	Chronic ischemic heart disease
	N18	Chronic kidney disease
	E11	Type 2 diabetes mellitus
	M54	Dorsalgia
	I48	Atrial fibrillation and flutter
	R32	Unspecified urinary incontinence
	R26	Abnormalities of gait and mobility
	Z74	Problems related to care provider dependency
	F32	Major depressive disorder, single episode
	H52	Disorders of refraction and accommodation
	Z96	Presence of other functional implants
	E86	Volume depletion
	Z25	Need for immunization against other single viral diseases
	K29	Gastritis and duodenitis
	E79	Disorders of purine and pyrimidine metabolism
	Z95	Presence of cardiac and vascular implants and grafts
	J44	Other chronic obstructive pulmonary disease
	R52	Pain, unspecified
	M17	Osteoarthritis of knee
	E66	Overweight and obesity
	A09	Infectious gastroenteritis and colitis, unspecified
	B96	Other bacterial agents as the cause of diseases classified elsewhere
	E14	Unspecified diabetes mellitus
	I70	Atherosclerosis
	F03	Unspecified dementia
	M47	Spondylosis
	R15	Fecal incontinence
	L89	Pressure ulcer
	J96	Respiratory failure, not elsewhere classified
	I11	Hypertensive heart disease
	I83	Varicose veins of lower extremities
	A04	Other bacterial intestinal infections
	N19	Unspecified kidney failure
	M81	Osteoporosis without current pathological fracture
	J18	Pneumonia, unspecified organism
	K59	Other functional intestinal disorders
	R60	Edema, not elsewhere classified
	U50	Motor function impairment
	K21	Gastroesophageal reflux disease
	N40	Enlarged prostate
	D64	Other anemias
	E03	Other hypothyroidism
	G47	Sleep disorders
	K76	Other diseases of liver
	B95	Strep as the cause of diseases classified elsewhere

	D62	Acute posthemorrhagic anemia
	E04	Other nontoxic goiter
	F45	Somatoform disorders
	I67	Other cerebrovascular diseases
	I69	Sequelae of cerebrovascular disease
	J06	Acute upper resp infections of multiple and unspecified sites
	J40	Bronchitis, not specified as acute or chronic
	K57	Diverticular disease of intestine
	L30	Other and unspecified dermatitis
	M16	Osteoarthritis of hip
	M53	Other and unspecified dorsopathies, not elsewhere classified
	R10	Abdominal and pelvic pain
	R54	Age-related physical debility
	Z00	Encounter for general exam w/o complaint, suspected or reported diagnosis
	Z12	Encounter for screening for malignant neoplasms
Comorbidities: primary inpatient diagnosis	I50	Heart failure
	J18	Pneumonia, unspecified organism
	I63	Cerebral infarction
	S72	Fracture of femur
	B96	Other bacterial agents as the cause of diseases classified elsewhere
	B95	Strep as the cause of diseases classified elsewhere
	J91	Pleural effusion in conditions classified elsewhere
	J44	Other chronic obstructive pulmonary disease
	A41	Other sepsis
	I70	Atherosclerosis
	N39	Other disorders of urinary system
	R65	Symptoms and signs specifically associated with sys inflammation and infection
	I21	ST-elevation and non-ST-elevation myocardial infarction (STEMI, NSTEMI)
	N17	Acute kidney failure
	E11	Type 2 diabetes mellitus
	D63	Anemia in chronic diseases classified elsewhere
	E86	Volume depletion
	I48	Atrial fibrillation and flutter
	K57	Diverticular disease of intestine
	I25	Chronic ischemic heart disease
	A09	Infectious gastroenteritis and colitis, unspecified
	K59	Other functional intestinal disorders
	Y57	Drugs and medicines causing adverse effects in therapeutic use
	I67	Other cerebrovascular diseases
	S71	Open wound of hip and thigh
	J15	Bacterial pneumonia, not elsewhere classified
	G47	Sleep disorders
	M46	Other inflammatory spondylopathies
	M16	Osteoarthritis of hip
	J96	Respiratory failure, not elsewhere classified
	N13	Obstructive and reflux uropathy
	R07	Pain in throat and chest
Comedications: prescribed antibiotics	J01MA02	Ciprofloxacin
	J01DC02	Cefuroxim
	J01CR04	Sultamicillin
	J01CR02	Amoxicillin and enzyme inhibitors

J01FF01	Clindamycin
J01EE01	Sulfamethoxazole and trimethoprim
J01CA04	Amoxicillin
J01MA12	Levofloxacin
J01DD13	Cefpodoxim
J01MA14	Moxifloxacin
J01FA09	Clarithromycin
J01DD08	Cefixime
J01XE01	Nitrofurantoin
J01FA10	Azithromycin
J01FA06	Roxithromycin
J01XX01	Fosfomycin
J01AA02	Doxycycline
J01DC04	Cefaclor
J01CE02	Phenoxymethylpenicillin
J01XA01	Vancomycin
J01MA01	Ofloxacin
J01GB03	Gentamicin
J01MA06	Norfloxacin

CDI Clostridioides difficile infection.

Includes *ICD-10-GM* (International Classification of Diseases, 10th Revision, German Modification) or *ATC* (Anatomical Therapeutic Chemical Classification) codes.

Table S4. HCRU analysis on inpatient and outpatient visits and length of hospital stay for CDI cases and matched non-CDI controls

Time period	HCRU parameter	CDI cases ^a						Matched non-CDI controls ^b						<i>p</i> value from t-test	Difference in means
		Mean	SD	Per patient -time ^c	Q1	Median	Q3	Mean	SD	Per patient -time ^c	Q1	Median	Q3		
One year after the index date	Outpatient visits	32	38	51	6	24	45	34	28	37	18	29	44	<0.001	-2
	Inpatient visits	3	2	4	1	2	4	1	2	1	0	0	2	0	2
	Length of hospital stay (days)	46	50	73	17	32	58	11	29	11	0	0	10	0	36
Two years after the index date	Outpatient visits	87	73	64	47	71	103	69	52	52	38	60	87	<0.001	17
	Inpatient visits	5	4	3	2	4	6	2	3	1	0	1	3	0	3
	Length of hospital stay (days)	68	87	50	21	44	81	19	49	14	0	4	19	0	49
Three years after the index date	Outpatient visits	125	106	55	68	101	148	103	75	46	58	89	129	<0.001	22
	Inpatient visits	6	5	3	2	4	8	3	4	1	0	1	4	<0.001	3
	Length of hospital stay (days)	82	123	36	24	51	93	25	61	11	0	8	27	<0.001	58

CDI *Clostridioides difficile* infection; HCRU healthcare resource utilization; Q1 first quartile; Q3 third quartile; SD standard deviation.

^a Based on incident CDI cases diagnosed between 2013–2016, 2013–2015, and 2013–2014, respectively.

^b Based on 1:4 propensity score matching of CDI cases to non-CDI controls.

^c Mortality-adjustment per patient per time period.