Epidemiologia e fattori di rischio per infezione da *C. difficile*

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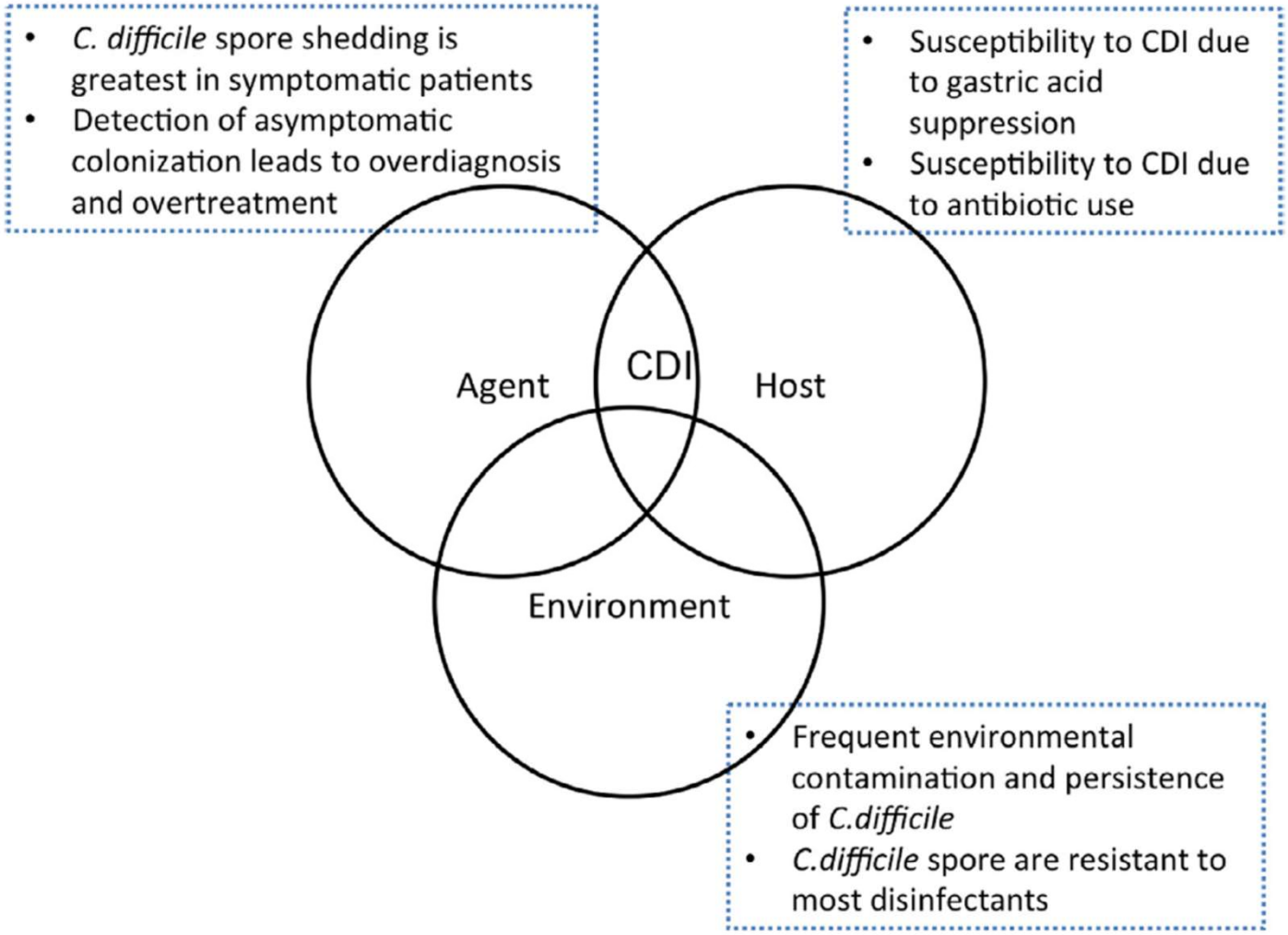
C. difficile infection epidemiological triad



N. Blanco et al. American Journal of Infection Control. 2021.

Country-weighted prevalence and estimated incidence of healthcare-associated infections (HAI) by type of HAI in European acute care hospitals (n = 19,626) and long-term care facilities (n = 3,858), 30 EU/EEA countries, 2016–2017

Type of HAI	Acute care hospitals								Long-term care facilities							
	HAI in PPS sample		Country-weighted HAI prevalence		Estimated HAI on a given day, EU/EEA[a]		Estimated annual HAI, EU/EEA[a]		HAI in PPS sample		Country-weighted HAI prevalence		Estimated HAI on a given day, EU/EEA[a]		Estimated annual HAI, EU/EEA[a]	
	N	% total	n	95% cCI	N	95% cCI	n	95% cCI	n	% total	%	95% cCI	n	95% cCI	n	95% cCI
Respiratory tract infection																
Pneumonia	4,200	21.4	1.26	0.96–1.68	18,935	14,398–25,265	862,084	567,728–1 283,203	143	3.7	0.15	0.06–0.32	4,948	1,946–10 658	112,868	44,390–243,134
Other lower respiratory tract infection[b]	838	4.3	0.24	0.15–0.41	3,568	2,208–6,192	183,232	91,731–376,990	847	22.0	0.88	0.59–1.14	29,010	19,412–37,826	1,058,853	708,542–1 380,653
Common cold/ influenza	NI	NA	NA	NA	NA	NA	NA	NA	290	7.5	0.29	0.13–0.51	9,678	4,368–16,782	441,543	199,312–765,693
Urinary tract infection	3,710	18.9	1.10	0.85–1.43	16,491	12,822–21,455	869,941	572,105–1,278,951	1,233	32.0	1.29	0.87–1.66	42,687	28,898–54,825	1,298,388	878,983–1,667,596
Surgical site infection	3,601	18.3	1.08	0.81–1.44	16,130	12,185–21,715	518,182	293,036–858,222	66	1.7	0.09	0.03–0.20	2,829	944–6,500	57,366	19,133–131,803
Bloodstream infection	2,116	10.8	0.69	0.48–1.00	10,294	7,241–15,097	375,050	227,552–613,624	19	0.5	0.04	0.01–0.07	1,168	193–2,389	23,692	3,908–48,442
Gastrointestinal infection																
Clostridium difficile infection	951	4.8	0.32	0.21–0.51	4,786	3,105–7,721	189,526	105,154–340,978	37	1.0	0.05	0.01–0.14	1,787	424–4,755	18,118	4,296–48,206
gastrointestinal infection	792	4.0	0.24	0.14–0.41)	3,549	2,108–6,166	144,926	64,880–312,212	75	1.9	0.1	0.03–0.20	3,187	1,012–6,473	145,409	46,184–295,333
Skin and soft tissue infection	823	4.2	0.21	0.13–0.36	3,146	1,900–5,451	108,269	45,149–242,816	828	21.5	0.83	0.51–1.19	27,459	17,021–39,307	626,415	388,293–896,687
Eye, ear, nose or mouth infection	557	2.8	0.16	0.09–0.35	2,400	1,278–5 194	123,091	54,155–303,206	183	4.7	0.17	0.08–0.31	5,712	2,707–10,369	173,733	82,323–315,390
Systemic infection	1,069	5.4	0.29	0.17–0.52	4,388	2,586–7,799	251,237	110,732–549,877	35	0.9	0.04	0.01–0.08	1,223	286–2,534	37,201	8,691–77,061
Other infection	969	4.9	0.30	0.19–0.50	4,518	2,867–7,574	154,138	65,647–332,357	102	2.6	0.12	0.04–0.24	3,878	1,366–8,077	117,958	41,556–245,683
All types of HAI, EU/EEA[a]	19,626	100	NA	NA	88,204	62,697–129,630	3,779,677	2,197,869–6,492,437	3,858	100	NA	NA	133,565	78,576–200,494	4,111,544	2,425,610–6,115,682
All types of HAI, EU/EEA, corrected after validation	**NA**	**NA**	**NA**	**NA**	**104,177**	**74,743–152,575**	**4,464,159**	**2,620,139–7,641,606**	**NA**	**NA**	**NA**	**NA**	**143,565**	**64,736–260,655**	**4,422,629**	**1,998,384–7,950,784**

SURVEILLANCE AND OUTBREAK REPORT

Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017

Carl Suetens[1], Katrien Latour[2], Tommi Kärki[3], Enrico Ricchizzi[3], Pete Kinross[1], Maria Luisa Moro[3], Béatrice Jans[2], Susan Hopkins[4], Sonja Hansen[5], Outi Lyytikäinen[6], Jacqui Reilly[7,8], Aleksander Deptula[9], Walter Zingg[10], Diamantis Plachouras[1], Dominique L Monnet[1], the Healthcare-Associated Infections Prevalence Study Group[11]

- **Le infezioni gastro-intestinali rappresentano l'8,9% di tutte le HAI**
- **CDI rappresenta il 44.6% delle infezioni gastrointestinali**
- **CDI il 4.9% di tutte le HAIs (Healthcare-associated infections)**

Burden of *Clostridioides difficile* infection - a systematic review of the epidemiology of primary and recurrent CDI

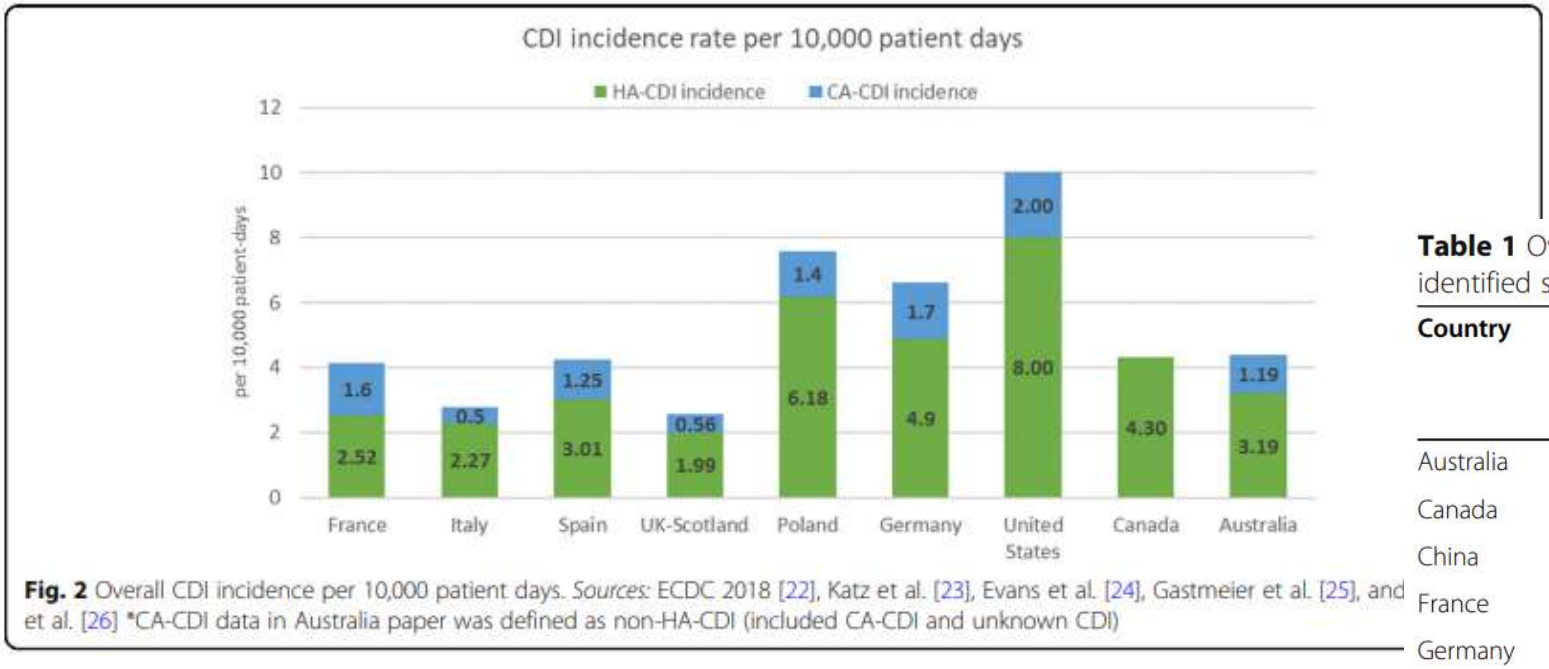


Fig. 2 Overall CDI incidence per 10,000 patient days. *Sources:* ECDC 2018 [22], Katz et al. [23], Evans et al. [24], Gastmeier et al. [25], and et al. [26] *CA-CDI data in Australia paper was defined as non-HA-CDI (included CA-CDI and unknown CDI)

- **Incidence rates between countries showed considerable variation**
- **The levels of difference may be attributed to variances in reporting practices and other factors such as the definitions used across territories and publications.**
- CDI has a substantial incidence globally, with evidence suggesting higher rates for HA-CDI cases than for CA-CDI;
- on average, CA-CDI rates were reported as being 31.6% of HA-CDI rates.

Finn et al. BMC Infectious Diseases. 2021.

Table 1 Overall incidence per 10,000 patient days from all identified studies and large size studies

Country	All identified studies			Large size studies		
	No.	Incidence		No.	Incidence	
		Median	Range		Median	Range
Australia	4	3.96	2.33–8.00	2	3.92	3.25–4.03
Canada	2	6.08	5.95–6.20	1	6.2	6.2
China	0	N/A	N/A	0	N/A	N/A
France	3	3.41	1.10–4.12	3	3.41	1.10–4.12
Germany	2	7.00	6.60–7.40	2	7	6.60–7.40
Italy	10	3.65	0.30–23.40	7	3.1	0.30–23.40
Japan	0	N/A	N/A	0	N/A	N/A
Poland	2	7.88	6.10–9.60	1	7.58	N/A
Spain	3	2.33	0.52–4.26	1	4.26	N/A
United Kingdom	5	7.10	2.32–74.40	4	4.82	2.32–19.80
United States	6	3.70	2.30–15.60	4	3.45	2.30–15.60
Overall	37	4.08	0.30–74.40	25	3.97	0.30–23.40

Abbreviations: *N/A* Not applicable, *No.* Number of key studies reporting outcome

The COMBACTE-CDI Project

Combating Bacterial Resistance in Europe-CDI (COMBACTE-CDI) aimed to develop a detailed understanding of the epidemiology and clinical impact of CDI across multiple European countries

- WP1 objectives: Epidemiology of *C. Difficile*
  - Quantification of the burden of CDI in the whole healthcare economy (hospital and community patients) in the EU; contemporaneous comparison with animal and food isolates with those within human health

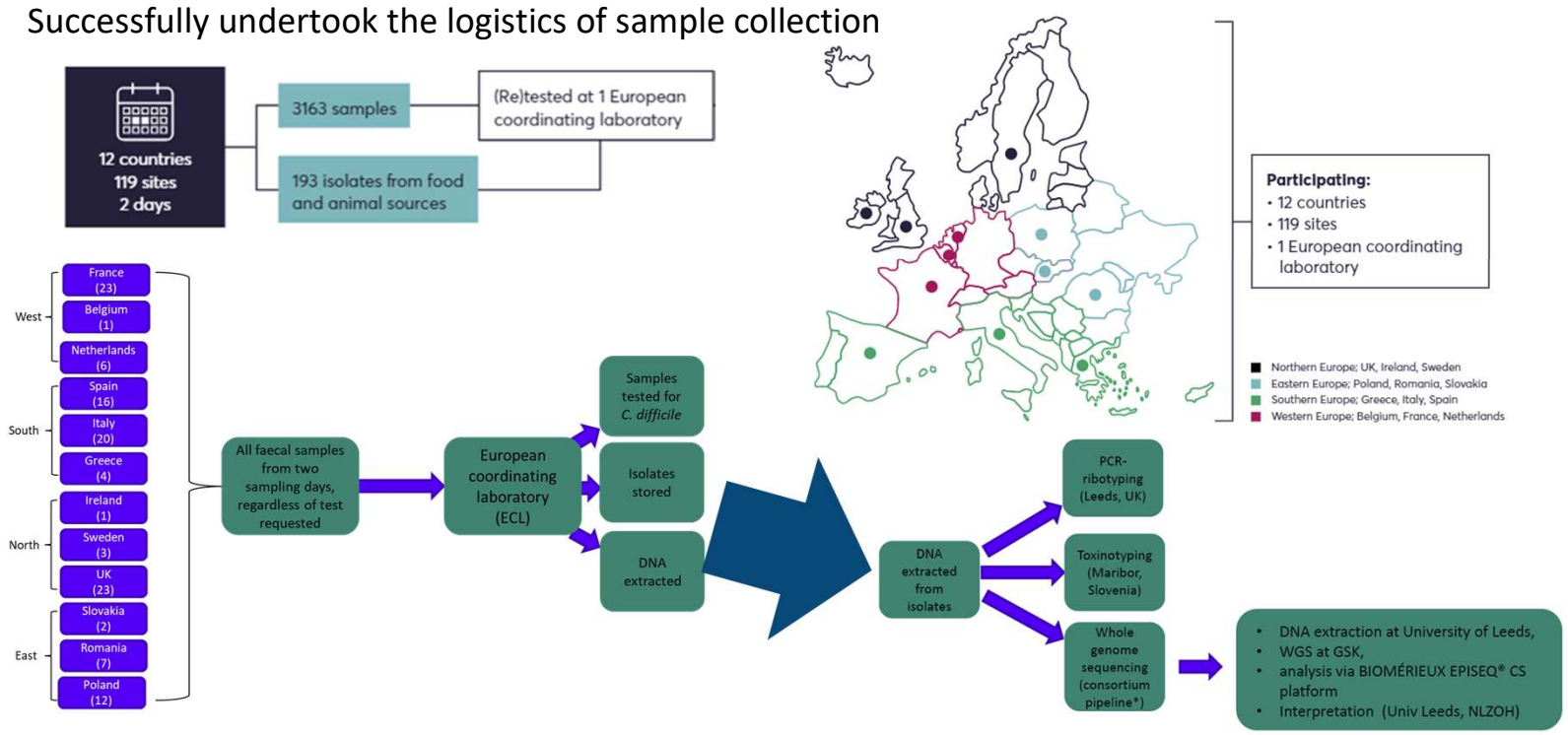
- WP2 objectives: Assessment of current practices (guidelines, testing, surveillance, treatment, cost)
  - To understand current CDI practice across the EU, quantify the economic impact of CDI treatment options/interventions, and develop a best-practice model for *C. difficile* infection prevention, diagnosis, treatment and surveillance

Viprey VF et al. COMBACTE-CDI consortium. European survey on the current surveillance practices, management guidelines, treatment pathways and heterogeneity of testing of Clostridioides difficile, 2018-2019: results from The Combatting Bacterial Resistance in Europe CDI (COMBACTE-CDI). J Hosp Infect. 2023.

COMBACTE-CDI project

1: Identifying the true burden of CDI across healthcare economies

- Successfully undertook the logistics of sample collection



COMBACTE-CDI project

Key achievements

1: Identifying the true burden of CDI across healthcare economies

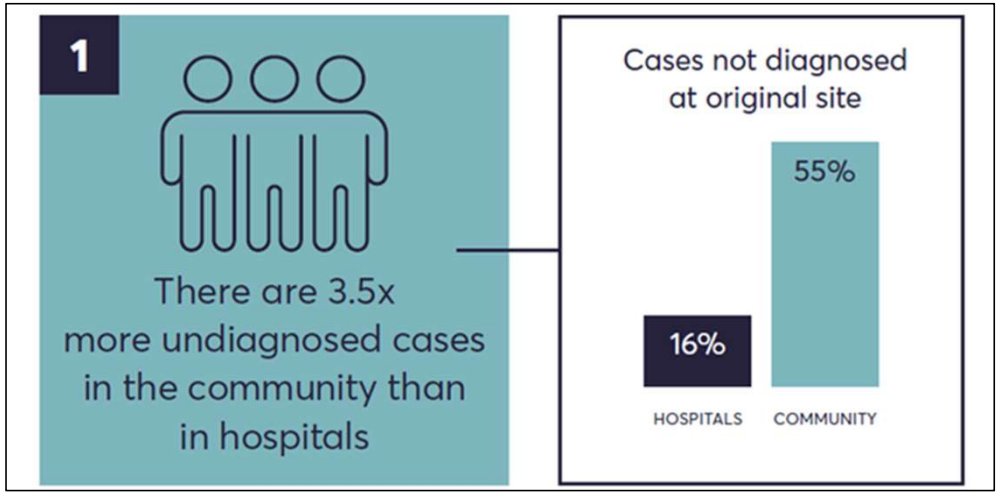
- **Up to date:** previous data is 10 years old (ECDC point-prevalence study 2011-2012)
- Uniquely includes both community and hospital onset cases

CDI positivity rate (% of samples)

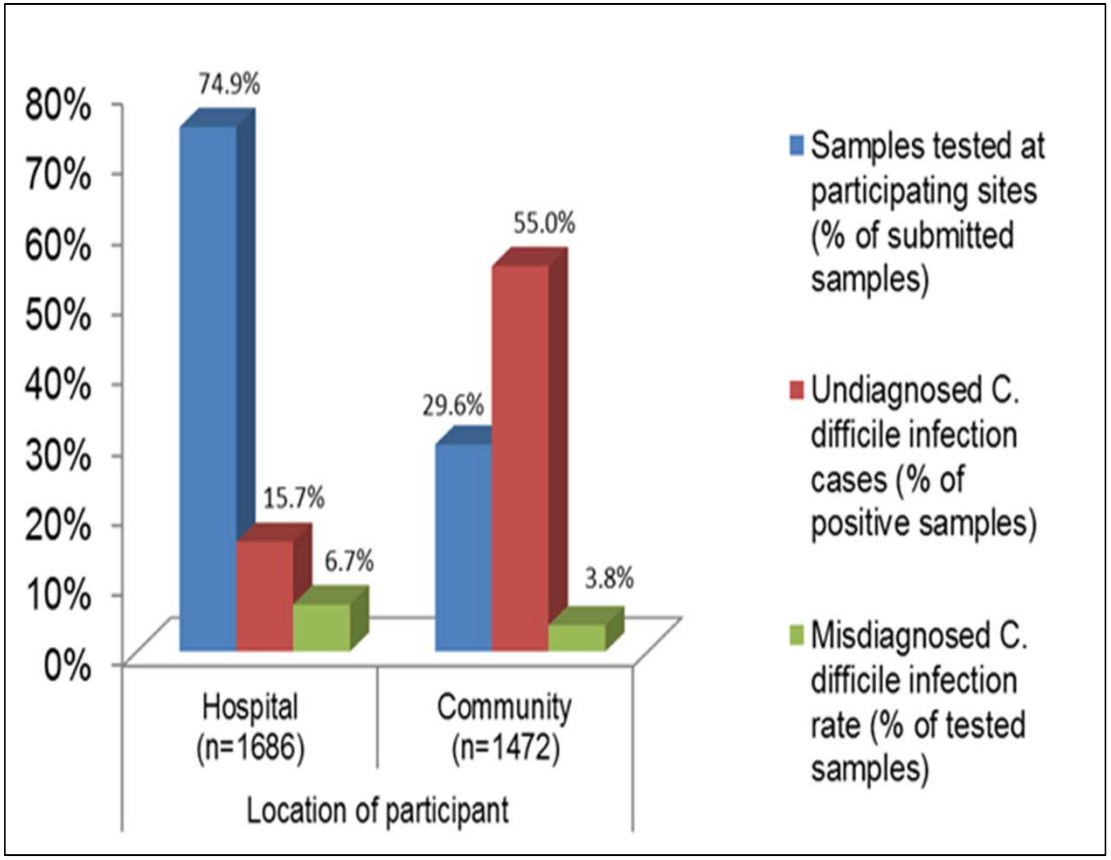
4.4%
[country range 0-16%]

1.3%
[country range 0-2%]

- **Identified three times more undiagnosed adults in the community compared to hospital due to lack of clinical suspicion.**
  - Patient benefit from driving forward better diagnosis especially in the community
  - Demonstrates where burden of disease is for targeted approach by pharmaceutical and diagnostic manufacturers



Key differences between hospital & community cases

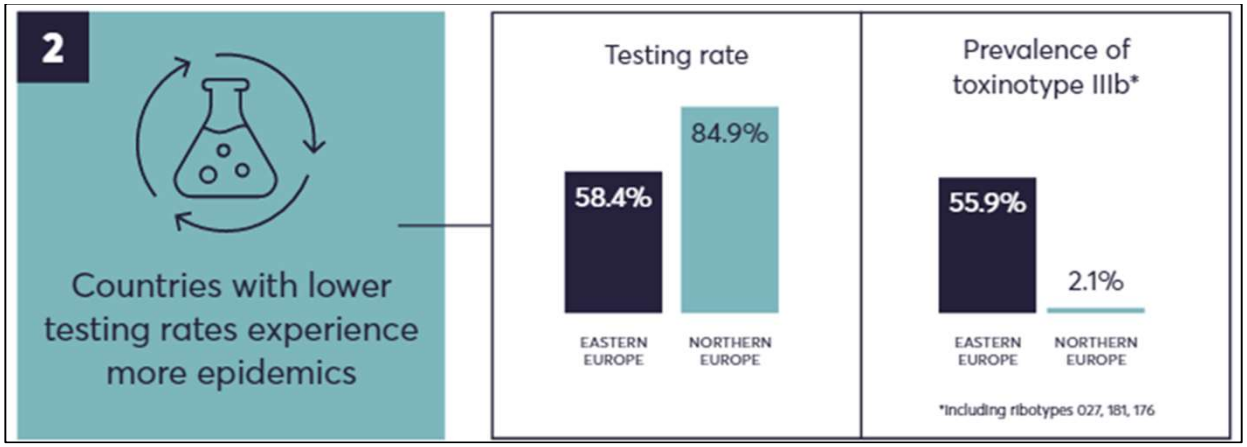


CDI is not only a hospital infection, but also a community problem. Testing is very poor in community and would be improved so that patients will be identified earlier and treated earlier

Viprey VF et al. COMBACTE-CDI consortium. European survey on the current surveillance practices, management guidelines, treatment pathways and heterogeneity of testing of Clostridioides difficile, 2018-2019: results from The Combatting Bacterial Resistance in Europe CDI (COMBACTE-CDI). J Hosp Infect. 2023.

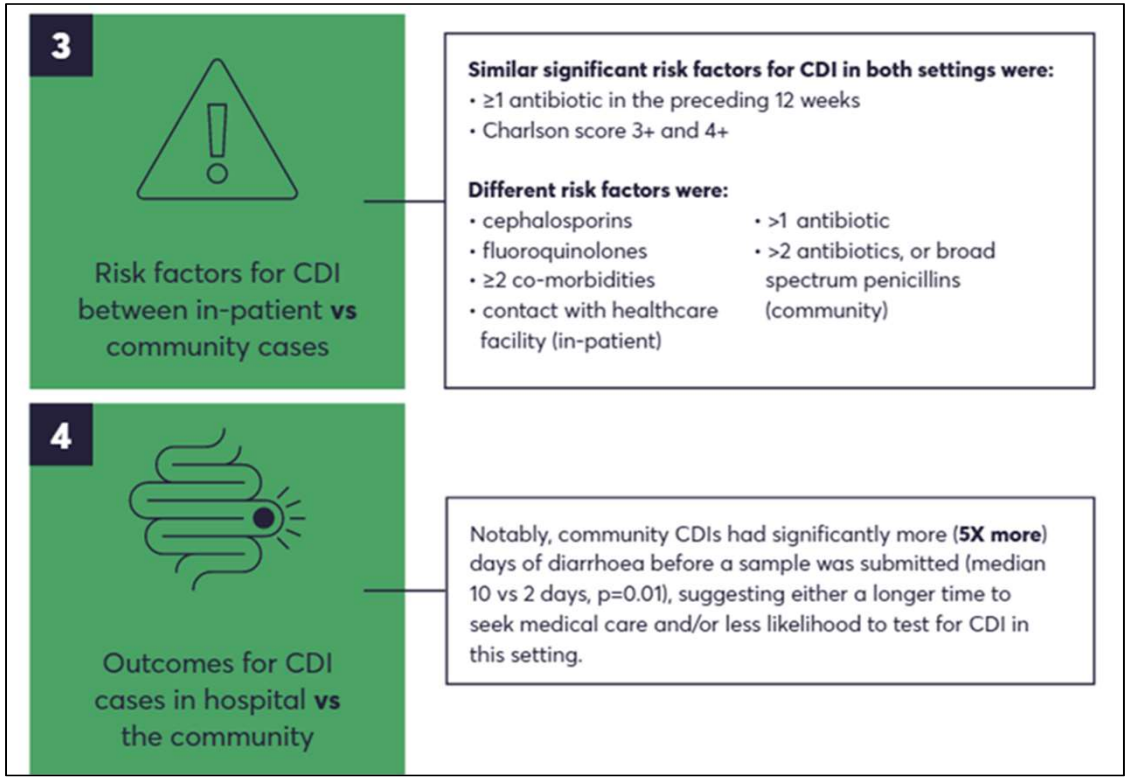
Countries with lower testing rates in hospitals experience more epidemics

- Uniquely showed that epidemic strains were higher in the community in those same countries

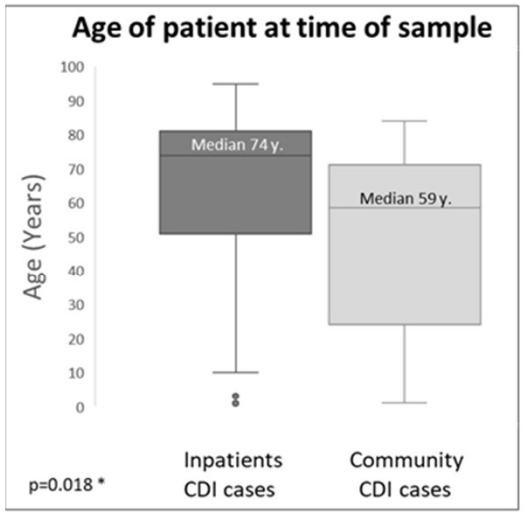


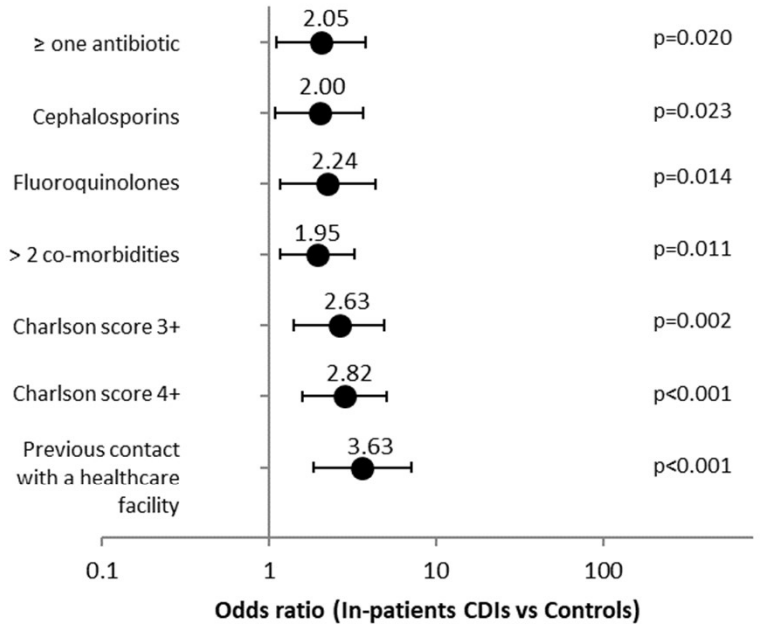
Identified key differences and similarities between cases

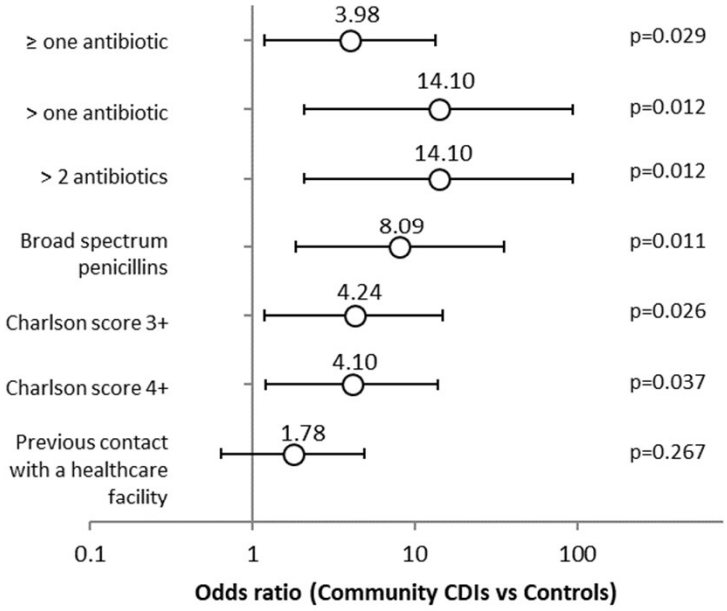
- Exposure to antibiotics is a risk factor in both settings, but which antibiotics differs
  - Different prescribing practices in different settings
  - Increasing numbers of co-morbidities were a risk factor for patients in both the hospital and community

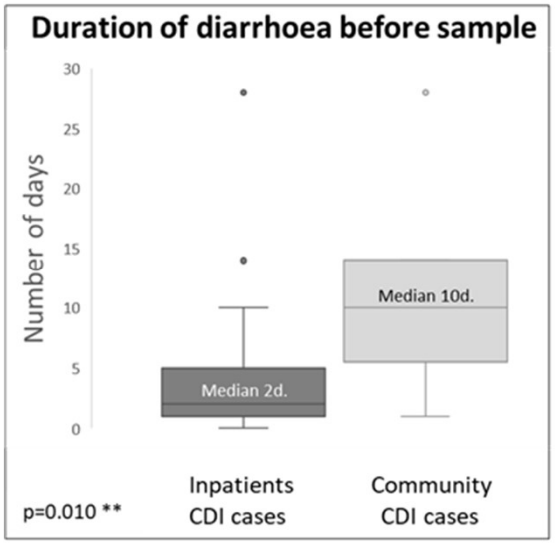


- Key differences between hospital & community cases





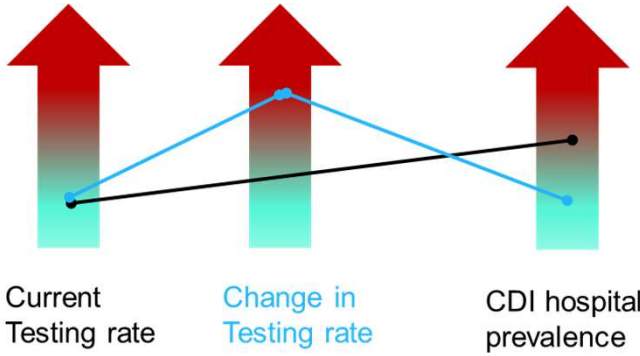




COMBACTE-CDI project

- 2. Dynamic transmission model

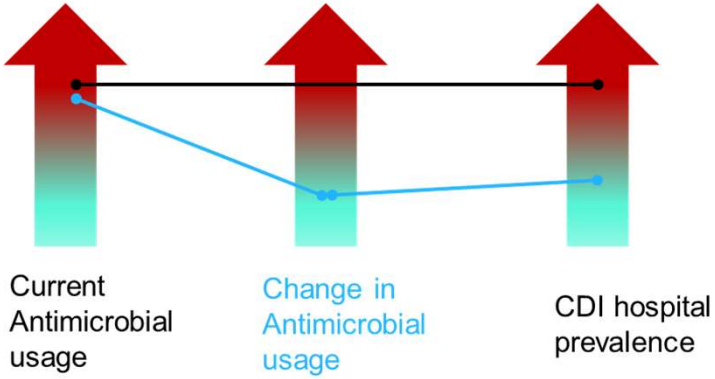
Demonstrated that the true incidence of colonized and infected cases in the hospital setting within different European countries can be predicted by accounting for differences in national sampling and testing rates



Low testing rate = missed opportunity to detect and treat patient leading to increased CDI hospital prevalence

The model predicts that

- many European countries are significantly underestimating the incidence of CDI (lack of testing)
- that countries with high antimicrobial use are making this worse
- that decreased antimicrobial use and increased testing could result in a reduction in CDI incidence in hospitals



High antimicrobial usage rate = increased CDI hospital prevalence

Shows that a reduction in disease through greater control of testing and antimicrobial usage rate is achievable

Hospital-acquired infection

symptomatic cases: the most recognizable sources of transmission.

CDI transmission between **symptomatic patients** has been studied in Oxfordshire, UK, using detailed epidemiological data and WGS of consecutive isolates

- ✓ 45% of new cases were genetically distinct from all previous cases
- ✓ 13% of infected individuals had recent ward contact with a previous sequence matched case.

Alternative sources of *C. difficile* in the healthcare setting:

- untested symptomatic patients
- asymptomatic patients
- environmental contamination
- health-care workers

Eyre, D. W. et al. N. Engl. J. Med. 2013.

Hospital-acquired infection

asymptomatic carriers

a study published in 2013 from Pittsburgh, USA, demonstrated:

✓ 10.4% of inpatients carried C. difficile regardless of their symptom profile.

Major role for asymptomatic patients in transmitting *C. difficile*.

At present, no proven intervention to eliminate *C. difficile* in such individuals is available, and the resource implications for global sampling and source isolation of asymptomatic patients are daunting.

health-care workers

- ✓ Poor hand hygiene have previously been shown to play a part in CDI transmission.
- ✓ Asymptomatic intestinal *C. difficile* carriage in health-care workers is generally uncommon

Curry, S. R. et al. Clin. Infect. Dis. 57, 1094–1102 (2013).
Clabots et al. J. Infect. Dis. 166, 561–567 (1992)
Rutala et al. Healthc. Infect. 18, 18–22 (2013). 79.
Friedman, N. D. et al. BMC Infect. Dis. 13, 459 (2013).

Hospital-acquired infection

Isolation of symptomatic patients with CDI and control of epidemic strains might **no longer be sufficient** to further reduce the burden of disease.

Focus on:

- asymptomatic patients
- untested patients
- controlling exposure to antibiotics

Community-associated and community-onset CDI

Defined as those with symptom onset in the community (or within 48h of hospital admission) without a history of hospitalization within the previous 12 weeks

- ❑ Human reservoirs.
- ❑ Environmental reservoirs

Community-associated and community-onset CDI

Human reservoirs

- ~50% CA-CDIs have **outpatient health-care exposure** in the weeks before infection.

- CA-CDI is also well-recognized in **residents of long-term care (LTC)** facilities.

A meta-analysis including nine studies, mainly from North America, demonstrated a 14.8% rate of asymptomatic carriage of toxigenic strains in LTC residents.
Colonization with toxigenic strains was associated with:

- previous CDI
- prior hospitalization
- antimicrobial use.

- Previously, a survey in Germany demonstrated an approximate fivefold increase in *C. difficile* colonization of LTC residents compared with elderly people living in their own homes.

Jury, L. A. et al. PLoS ONE 8, e70175 (2013).
Arvand, M. et al. PloS ONE 7, e30183 (2012).
Ziakas, P. D. et al. PloS ONE 10, e0117195 (2015).

Community-associated and community-onset CDI

Environmental reservoirs

FOODBORNE

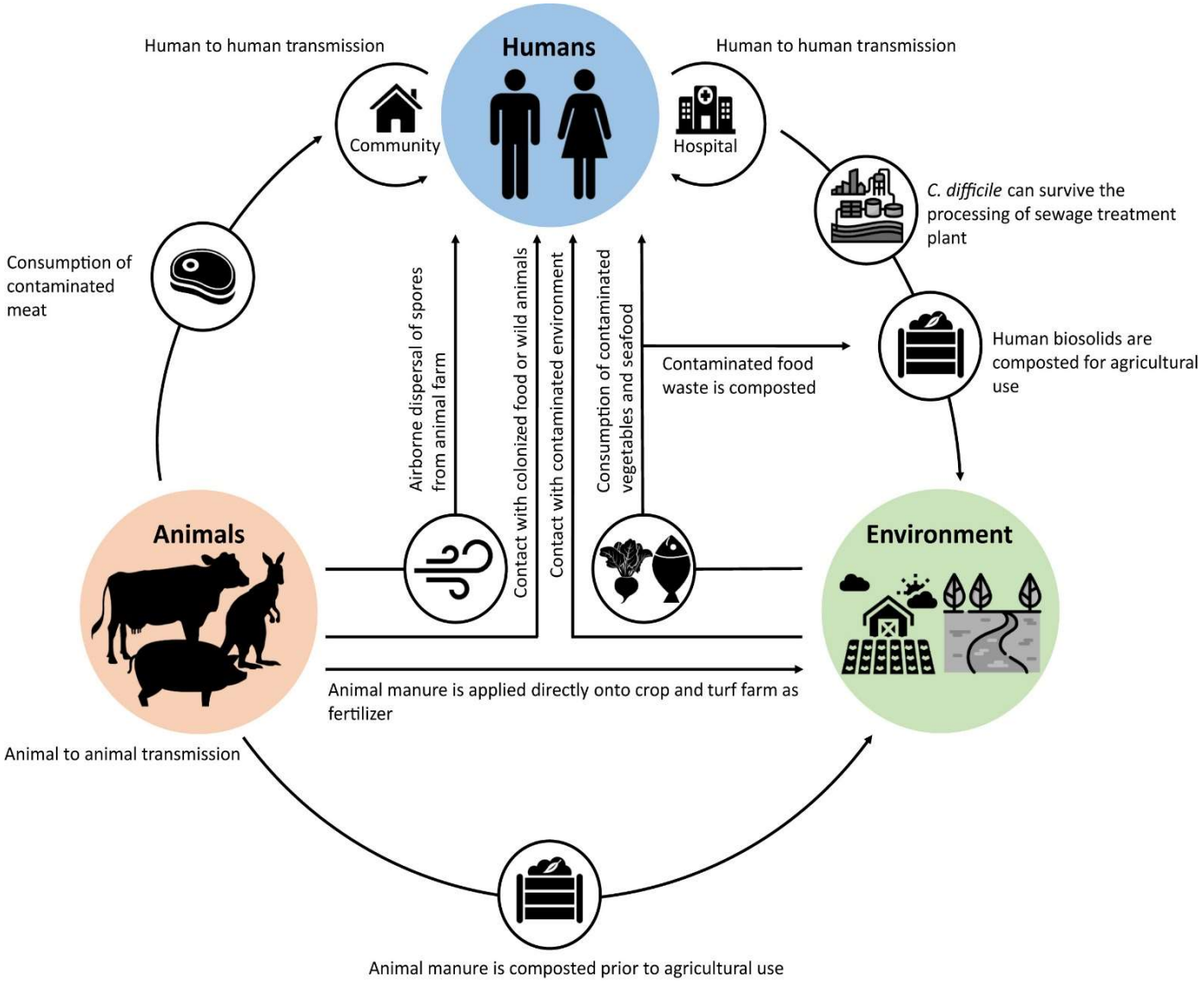
The reported prevalence of *C. difficile* in 'off-the-shelf ' foods is generally low but extremely variable (0–42%), with ground meat, shellfish, vegetables and pre-packed salads most commonly contaminated.

No food-related outbreaks have been reported.

ENVIRONMENT

C. difficile has also been recovered from water and soil

A small US study demonstrated toxigenic *C. difficile* on 25 of 63 (39.7%) of shoe swabs.



Gould et al. Clin. Infect. Dis. 2010.
Al Saif, et al. J. Med. Microbiol. 1996.
Alam, M. J et al. Anaerobe. 2014.

From 31 December 2019, when the World Health Organization was informed of an outbreak of respiratory disease affecting the city of Wuhan, the world has been shaken by the most profound health crisis of the last several decades.

Adoption of **heterogeneous therapeutic management approaches**, often without clear distinction between evidence-based data and expert opinion in informing treatment choices

The high number of hospitalizations and shortage of beds **challenged compliance with infection control and antibiotic stewardship programs** in most health-care facilities

Many health-care facilities gave priority to the protection of their healthcare workers from COVID-19, **reducing attention to the prevention of other bacterial infections transmitted by interpersonal contact**

Most of the early recommendations for management of COVID-19 patients considered the use of empirical antibiotic treatment, resulting in **large usage of antimicrobials in COVID-19 patients**

Huttner BD et al. Clin. Microbiol. Infect. 2020.

A systematic review and meta-analysis was to assess the proportion of COVID-19 patients with CDI

We included studies reporting data on CDI occurring in patients with a confirmed diagnosis of COVID-19. We pooled proportion of CDI patients using a random effects model.

13 studies were included in the systematic review. All the studies retrospectively collected data between February 2020 and February 2021.

The reported CDI incidence rates ranged from 1.4 to 2.7 CDI cases per 10,000 patient-days.

Seven studies reported data on the number of COVID-19 patients who developed CDI and the total number of COVID-19 patients in the study period and were included in the meta-analysis, **comprising 23,697 COVID-19 patients.**

The overall pooled proportion of COVID-19 patients who had CDI was 1% [95% confidence interval: 1-2].

Among studies reporting CDI occurrence in patients with and without COVID-19, the majority of them reported reduced or unchanged CDI rates compared to pre-COVID period.

Granata G, Petrosillo N et al. Anaerobe. 2021.

Study aim was to assess the incidence of CDI in hospitalized COVID-19 patients, to describe the clinical characteristics and outcomes of COVID-19 patients with CDI and to identify risk factors for the onset of CDI in COVID-19 patients

Observational, retrospective, national multicenter, case-control study with 1:3 matching.

The study was performed in 8 acute-care Italian hospitals admitting COVID-19 patients, between February 2020 and July 2020

List of participating centres
IRCCS Istituto Nazionale Malattie Infettive "L. Spallanzani", Rome (co-ordinating centre)
Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome
ASST Grande Ospedale Metropolitano Niguarda, Milan
Ospedale di Piacenza "Guglielmo da Saliceto", Piacenza
Ospedale di Cremona, Cremona
Policlinico Sant'Orsola-Malpighi, Bologna
Azienda Ospedaliero-Universitaria Careggi, Florence
Unità Operativa Complessa di Malattie Infettive, Rimini, Forlì and Cesena

Journal of *Clinical Medicine*

MDPI

Article

The Burden of Clostridioides Difficile Infection during the COVID-19 Pandemic: A Retrospective Case-Control Study in Italian Hospitals (CloVid)

Guido Granata [1,*], Alessandro Bartoloni [2], Mauro Codeluppi [3], Ilaria Contadini [4], Francesco Cristini [4], Massimo Fantoni [5], Alice Ferraresi [6], Chiara Fornabaio [6], Sara Grasselli [3], Filippo Lagi [2], Luca Masucci [5], Massimo Puoti [7], Alessandro Raimondi [7], Eleonora Taddei [8], Filippo Fabio Trapani [9], Pierluigi Viale [9], Stuart Johnson [10], Nicola Petrosillo [1] and on behalf of the CloVid Study Group [†]

Hospitalized adult patients with COVID-19 and CDI were identified from the databases of the participant centers

Cases were defined as COVID-19 patients with CDI; **controls were COVID-19 patients without CDI**

Cases were matched 1:3 with controls. Demographic, epidemiological and clinical data were collected

Controls were matched to cases according to the following criteria:

1. Same gender
2. Hospitalization in the same hospital and in the same unit
3. Same date of hospital admission ± 7 days
4. Same age ± 3 years

All cases and controls were followed up to 30 days from their hospital discharge to assess for new onset of diarrhea, recurrence of CDI, and mortality at 30 days from the hospital discharge.

The incidence of CDI among all COVID-19 patients admitted to the participating hospitals was calculated using as numerator the number of CDI cases and as denominator the number of days of hospitalization of the COVID-19 patients (x 10,000).

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CDI incidence among COVID-19 patients

During the study period **a total of 40,315 patients were admitted to the 8 participant hospitals**; **of these, 8,402 were COVID-19 patients**
The mean hospital stay for COVID-19 patients was 13.8 days (range 1-59 days).

38 CDI cases were identified, including 32 hospital-onset CDI (HO-CDI) and 6 community onset, healthcare-associated CDI (CO-HCA-CDI) cases.

Therefore, **during the study period 32 COVID-19 patients developed HO-CDI, corresponding to a HO-CDI incidence of 2,7 x 10,000 patient days** ranging in the hospitals from 0.7 to 12.3 x 10,000 patient days

Participant Infectious Disease Units	Number of admitted COVID-19 cases	Mean hospital stay for COVID-19 cases	Number of hospital-onset CDI cases among COVID-19 patients	Hospital-onset CDI incidence among COVID-19 patients (per 10,000 patient days)
#1	646	18	4	3,4
#2	789	13,4	11	10,4
#3	901	17,3	2	1,2
#4	1760	11,8	5	2,4
#5	2187	13,1	2	0,7
#6	1097	16,9	3	1,6
#7	178	9,1	2	12,3
#8	844	10,6	3	3,3

Clinical features of *Clostridioides difficile* infection in COVID-19 patients

Among the 38 COVID-19 patients with CDI, 23 (60.5%) patients were female

The **mean age was 79 years**, ranging between 53 and 97 years.

The mean age-adjusted **Charlson co-morbidity index (CCI) at admission was 6.6**

36 out of 38 **(94.7%) CDI patients had a primary CDI**, and 2 (5.3%) a recurrence

In 32 out of 38 (84.2%), **the diarrhea onset and the CDI diagnosis occurred after the COVID-19 diagnosis**

23 (60.5%), 11 (**28.9%**) and 4 (**10.5%**) had mild, **severe and complicated CDI**, respectively

The **mean length of the in-hospital stay was 35 days**, ranging between 1 and 96 days

Regarding risk factors for CDI before the admission 21/38 (55.2%), 25/38 (65.7%) and 8/38 (21%) CDI patients received antibiotics, proton pump inhibitors and steroids in the previous two months, respectively

Regarding COVID-19 severity during the hospitalization, 7 (18.4%), 15 (39.4%), 12 (31.5%), 3 (7.8%) and 1 (2.6%) had asymptomatic, mild pneumonia, severe pneumonia, ARDS and septic shock, respectively

As of medications administered for COVID-19 during the hospital stay, 35 (92.1%), 25 (65.7%), 26 (68.4%), 14 (36.8%) and 9 (23.6%) patients received low molecular weight heparin, PPI, chloroquine, lopinavir or darunavir and steroids

Additionally, **32/38 (84.2%) CDI patients were treated with broad-spectrum antimicrobials**
The most common antimicrobial class was **beta-lactam** which were administered in 21 (**55.2%**) patients. **Macrolides** (**specifically azithromycin**), **carbapenems**, **glycopeptides** and **quinolones** were administered in 12 (**31.5%**), 11 (**28.9%**), 5 (**13.1%**), 4 (**10.5%**) patients, respectively

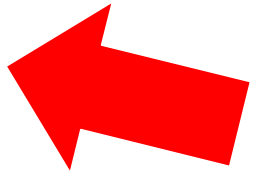
during the hospital stay 18/38 (**47.3%) CDI patients developed a bacterial infection**, including 9 urinary tract infection, 5 sepsis, 2 abdominal infections and 2 bacterial pneumonia

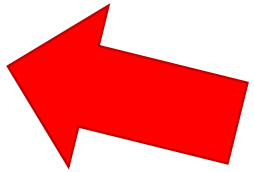
About outcomes, 19/38 (50%) recovered and were discharged without complications; 8/38 (21.1%) developed complications during the hospitalization, including 7 patients with prolonged bedrest syndrome and 1 with decompensated chronic heart failure

11 out of 38 (28.9%) patients died in the hospital. CDI was the main cause of death in 1 of these patients, while septic shock, respiratory failure and heart failure were considered the main cause of death in 7, 2 and 1 patients, respectively

The outcome COVID-19 patients with CDI

	COVID-19 with CDI	**COVID-19**		
Patients outcome				
• Recovered without complications	19 (50%)	74 (64.9%)	p: 0.01	0.4 (0.1 – 0.8)
• Recovered with complications	8 (21.0%)	8 (7.0%)	ns	
• Deceased	11 (28.9%)	25 (21.9%)	ns	
Total length of in-hospital stay (days)	35 (range: 1-96)	19.4 (range: 1-88)	p: 0.0007	





Conclusions

- Focused antibiotic stewardship interventions can prevent *C. difficile* infections and help in their management in a variety of ways
- *C. difficile* infection is first a clinical diagnosis. Early and targeted testing for *C. difficile* infection is crucial. Community onset CDI.
- Future, optimized approaches for specific subgroups of high-risk patients