# What is the role of the asymptomatic carrier in environmental contamination with *C. difficile* spores and nosocomial transmission, and can we do anything to prevent it?



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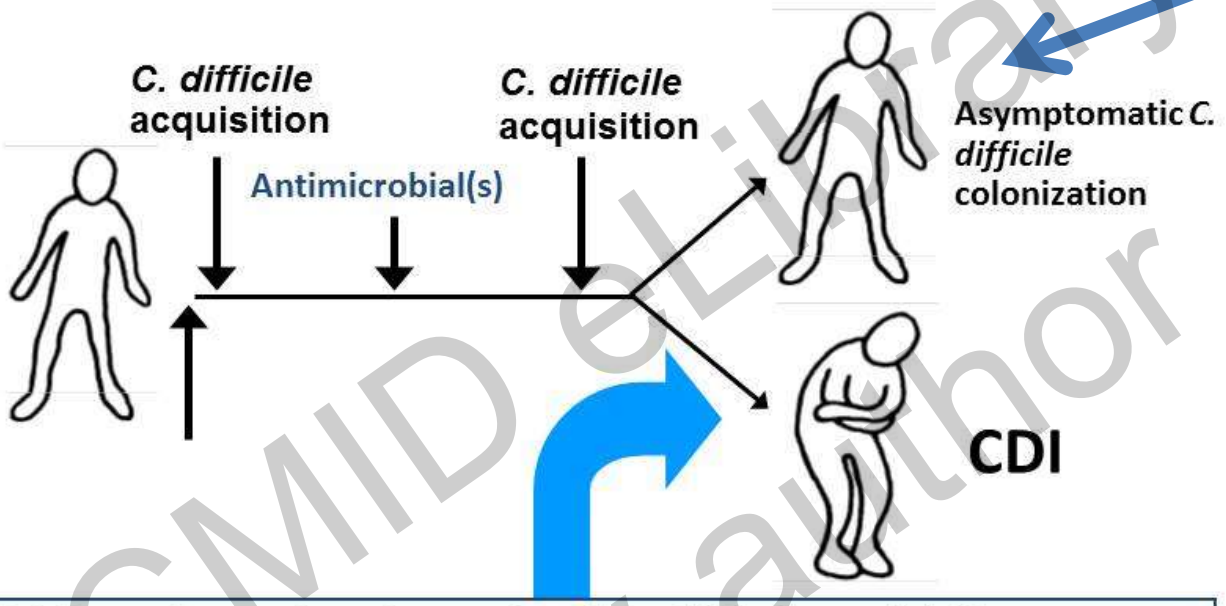
# Overview of session

1. Introduction to asymptomatic carriage
2. Studies of asymptomatic carriers
3. Extant guidance 2018
4. Conclusions

# 1. Introduction to asymptomatic carriage

# Figure 1. Current Pathogenesis Model for CDI




*Kyne L et al. N Engl J Med. 2000:342;390.*

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https://www.infectiousdiseaseadvisor.com/infectious-diseases/clostridium-difficile-infection/article/609175/

# Asymptomatic carriage of *C. difficile*

- Some people carry *C. difficile* in their gut without having any symptoms
- Asymptomatic carriage upon hospitalisation was **8.1%** in pooled meta-analysis (2005-2014); **3-26%** among acute inpatients, **5-7%** among elderly in long-term care facilities.
- For adults with no recent healthcare exposure colonisation is **2%**
- There is uncertainty with regards to the management of asymptomatic carriers (incl. screening and control of spread of spores from carriers)

# 2. Studies of asymptomatic carriers

# Risk factors for asymptomatic carriage

**Table II**
Characteristics associated with rectal carriage of *Clostridium difficile* in hospitalized patients with no symptoms of *C. difficile* infection

| Factor | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Used antibiotics in the previous 3 months | 6.16 | 1.36–27.9 | 4.49 | 0.95–21.3 |
| *C. difficile* infection (CDI) in previous 3 months | 5.95 | 1.49–23.7 | 3.14 | 0.70–14.0 |
| Length of stay >14 days | 3.68 | 1.33–10.1 | 1.99 | 0.64–6.12 |

OR, odds ratio; CI, confidence interval.
[a] For other factors in Table I.

Guerrero et al, 2013

- Risk factors for asymptomatic colonisation have been associated with previous antibiotic exposure, healthcare exposure and previous CDI.
- Colonisation rates on admission to hospital :
  - Acute hospital: 4%-21% (TCD)
  - Acute geriatric hospital: 2% (TCD)

# Ribotype distributions in carriers vs CDI cases

**Table 4. Five Most Common Toxigenic *Clostridium difficile* Strains From Asymptomatic Carriers, Protocol A, and Protocol B**

| Asymptomatic Carriers (n = 40) | | Protocol A (n = 74) | | Protocol B (n = 49) | |
|---|---|---|---|---|---|
| Strain[a] | No. | Strain[a] | No. | Strain[a] | No. |
| 014/020*,*** | 14 (35%) | 027 | 23 (31%) | 027 | 8 (16%) |
| 012*,** | 10 (25%) | 106/174 | 9 (12%) | WU42 | 8 (16%) |
| 053* | 4 (10%) | 014/020 | 7 (9%) | 014/020 | 6 (12%) |
| 077 | 3 (8%) | 002 | 7 (9%) | 001 | 4 (8%) |
| 027*,*** | 1 (3%) | 005 | 4 (5%) | 106/174 | 3 (6%) |

[a] Strain name is the polymerase chain reaction ribotype. If the strain did not match to a ribotype, the Washington University (WU) strain number is provided. If unable to discriminate between different ribotypes, both ribotypes the strain matched to are provided.

* $P \leq .005$, asymptomatic carriers compared with protocol A.

** $P < .001$, asymptomatic carriers compared with protocol B.

*** $P \leq .03$, asymptomatic carriers compared with protocol B.

Overall 15% of patients were colonised with TCD on admission

Protocol A/B : identified patients with symptomatic CDI

Alasmari et al. 2014

# Ribotype distribution in hospital and community CDI cases, and carriers

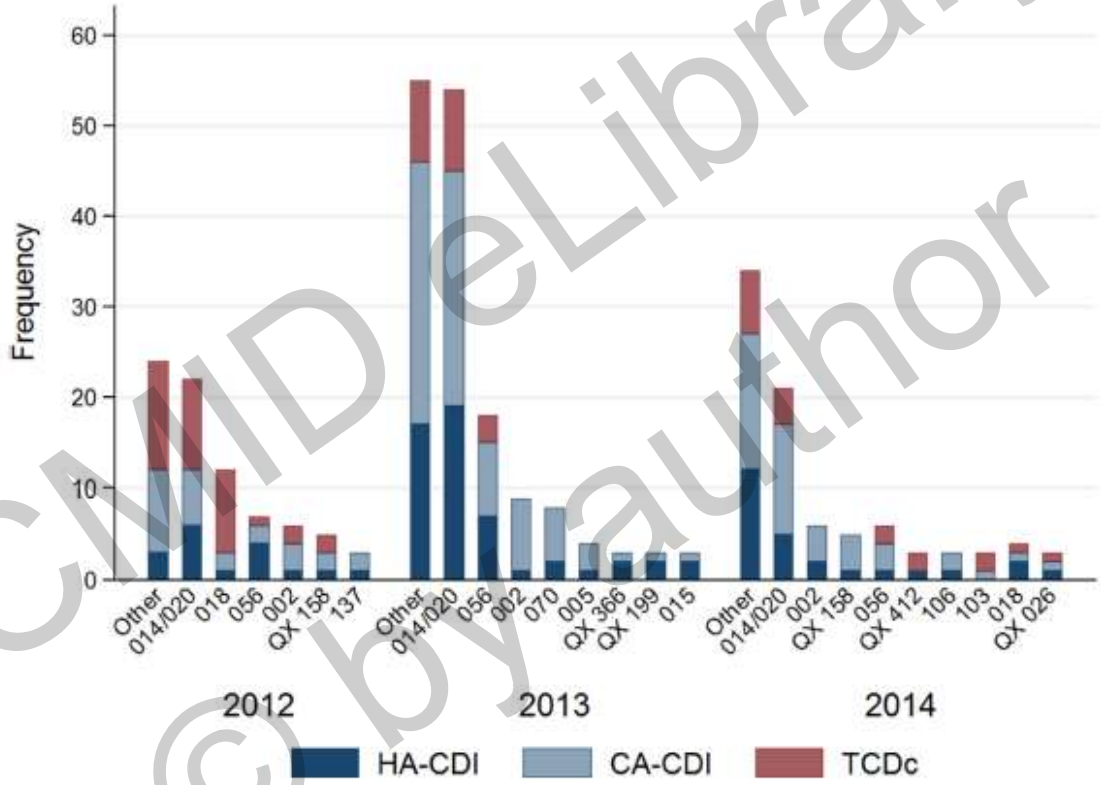



**FIG 1** Distribution of ribotypes by year among symptomatic HA-CDI and CA-CDI patients and asymptomatic toxigenic *C. difficile*-colonized (TCDc) patients. Ribotypes found at a frequency of less than 3 isolates in a year were grouped into the other category.

# Development of CDI following asymptomatic colonisation (or contamination)

**Table 3** Clinical impact of *Clostridium difficile* colonization in adults

| Country | Study year | Follow-up duration | Clinical impact | Refs |
|---|---|---|---|---|
| | | | **Development of *C. difficile* infection** | |
| USA | 1983–1993 | 9 wk–20 mo | 1.0% (2/192) CdC vs. 3.6% (22/618) no CdC | 29 |
| USA | 1991 | 5 mo | 47% (9/19) tCdC | 40 |
| Israel | 1998 | 5 mo | 51.3% (19/37) CdC at admission vs. 12.0% (28/234) no CdC ($p < 0.0001$) | 30 |
| Taiwan | 2011 | 6 mo | 17.9% (5/28) tCdC vs. 1.4% (2/140) no tCdC ($p = 0.002$) | 9 |
| Taiwan | 2011–2012 | 18 mo | 14.1% (11/79) tCdC vs. 0.9% (3/328) no CdC, 0% (0/34) ntCdC ($p < 0.001$) | 8 |
| | | | **Contamination** | |
| USA | 2008 | 90 d | 17% (3/18) CdC: skin and/or environmental contamination | 42 |
| USA | 2006 | 3 mo | Carriers *vs.* noncarriers: skin (61% vs. 19%; $p = 0.001$) or environmental contamination (59% vs. 24%; $p = 0.004$) | 23 |

CdC = *C. difficile* colonization; ntCdC = nontoxigenic CdC; tCdC = toxigenic CdC.



Hung et al. 2014

# Protective effect of *C. difficile* colonisation

•Incubation period 2-3 days (median), but one study showed that 7% had been colonised > 1 week before developing CDI (Curry et al, 2013)

•Earlier studies showed that being colonised over longer time periods has a **protective effect against CDI** (Kyne et al, 2000, Shim et al 1998)

•It is possible that risk of **progression** from colonisation to infection **decreases over time due to boosting of serum antibodies against toxin A and B** (Kyne et al, 2001)

•Colonisation with non-toxigenic strains may be protective against symptomatic CDI due to competition for nutrients or access to the mucosal surface (Shim et al. 1998, Sambol et al. 2001)

# Effect of antibiotics on progression from colonised to infected states

- The **individual risk of symptomatic CDI** was found to be higher in patients admitted to a room **where a previous patient without CDI was administered antibiotics**, suggesting induced shedding of *C. difficile* from asymptomatic carriers (Brown et al. 2015)

- **Ward-level antibiotic abx prescribing** (among CDI and non-CDI patients) was a risk factor for CDI that was independent of the risk from antibiotics and other factors in individual patients (Freedberg et al. 2016).

# Increased shedding of spores after recovery from symptomatic CDI

- **Shedding of C. difficile spores into the environment** is high after resolution of diarrhoea/end of treatment for CDI (Bobulsky et al. CID 2008)

- The frequency of **skin contamination** and **environmental shedding** remained high at the time of resolution of diarrhoea (60% and 37%, respectively), decreased at the end of treatment, and increased again 1–4 weeks after treatment (58% and 50%, respectively) (Sethi et al. 2010)

# Colonised children as a source of *C. difficile*

- By 2–3 years of age, approximately 1%–3% of children are asymptomatic carriers of *C. difficile*

- Young children are unlikely to have *C. difficile infection*

- Nontoxigenic strains are more common than toxigenic strains among colonized infants and colonisation is transient.

- Asymptomatically colonized infants and children may serve as a source of transmission of the organism to adults, leading to *C. difficile infection* among adult contacts (Wilcox et al 2008, Rosseau et al 2011, Stoesser et al 2011)

# The environment as a source of *C. difficile*

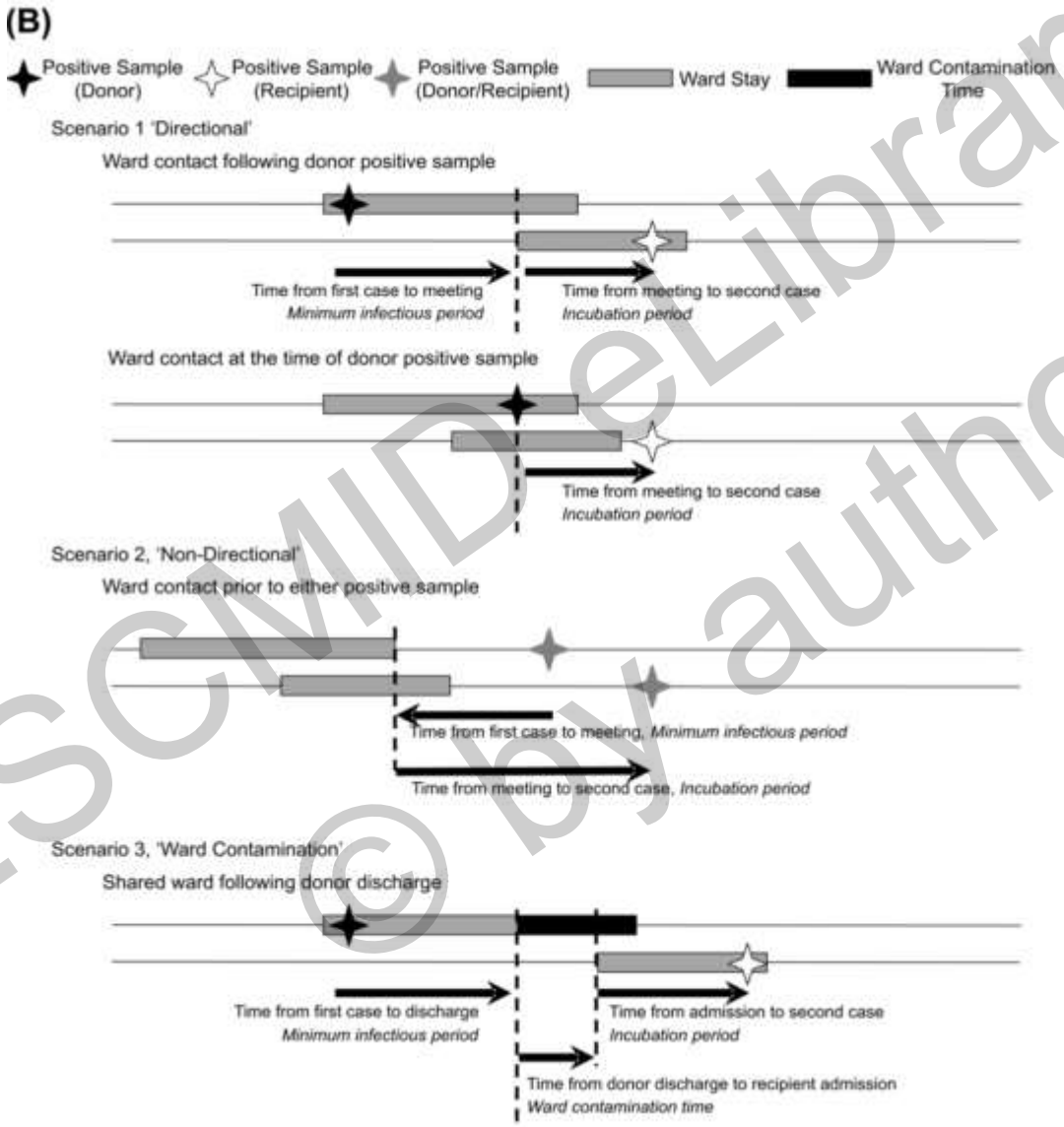
- Based on WGS only 2-7% of new cases acquire *C. difficile* from contaminated environments (Curry et al, 2013, Eyre et al 2013).

•Outbreak in which high-risk fomites (care equipment e.g. blood pressure cuffs, thermometers and stethoscope) shared between patients contributed to transmission (Brooks et al 1992).

•Mathematical modelling estimated that environmental contamination with spores only contributes to 10% of new CDI cases (Starr et al. 2009).

•Effectiveness of sporicidal agents have mostly been demonstrated in outbreak settings when implemented concurrently with other interventions (McMullen et al 2007, Orenstein et al 2011).

# Scenarios for ward-based contacts with symptomatic CDI cases leading to transmission

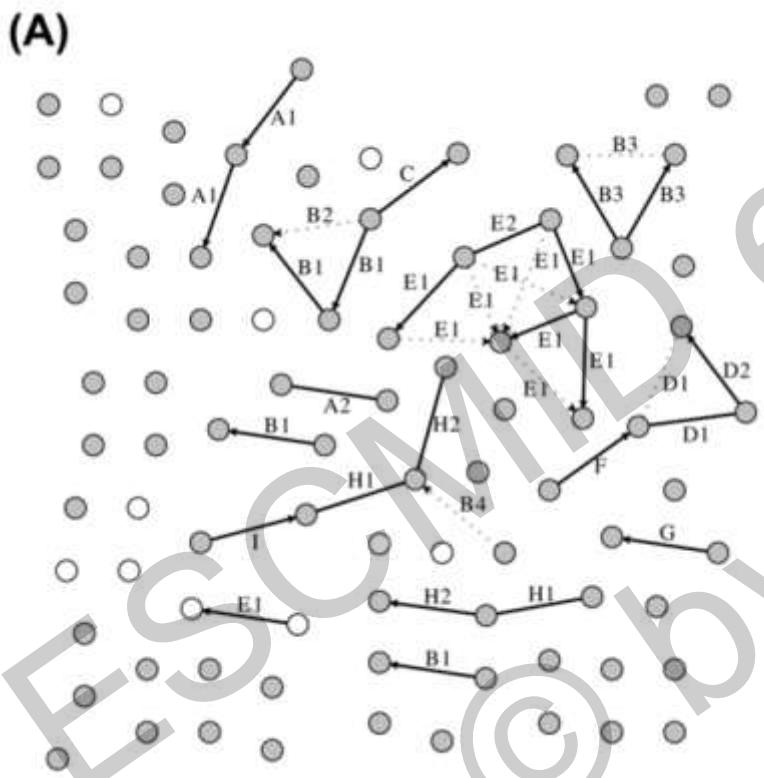



DIRECTIONAL

NON-DIRECTIONAL

WARD CONTAMINATION

# How do people acquire CDI in hospital in endemic settings?




Walker et al. 2012

<u>MLST typing showed:</u>
Overall, only 25% of new cases could be linked to previous symptomatic CDI inpatients -

Specialist surgery – 6%
Acute elderly medicine –28%
Haematology/oncology – 29%
Renal/transplant – 37%

***Conclusions:*** In an endemic setting with well-implemented infection control measures, ward-based contact with symptomatic enzyme-immunoassay-positive patients cannot account for most new CDI cases.

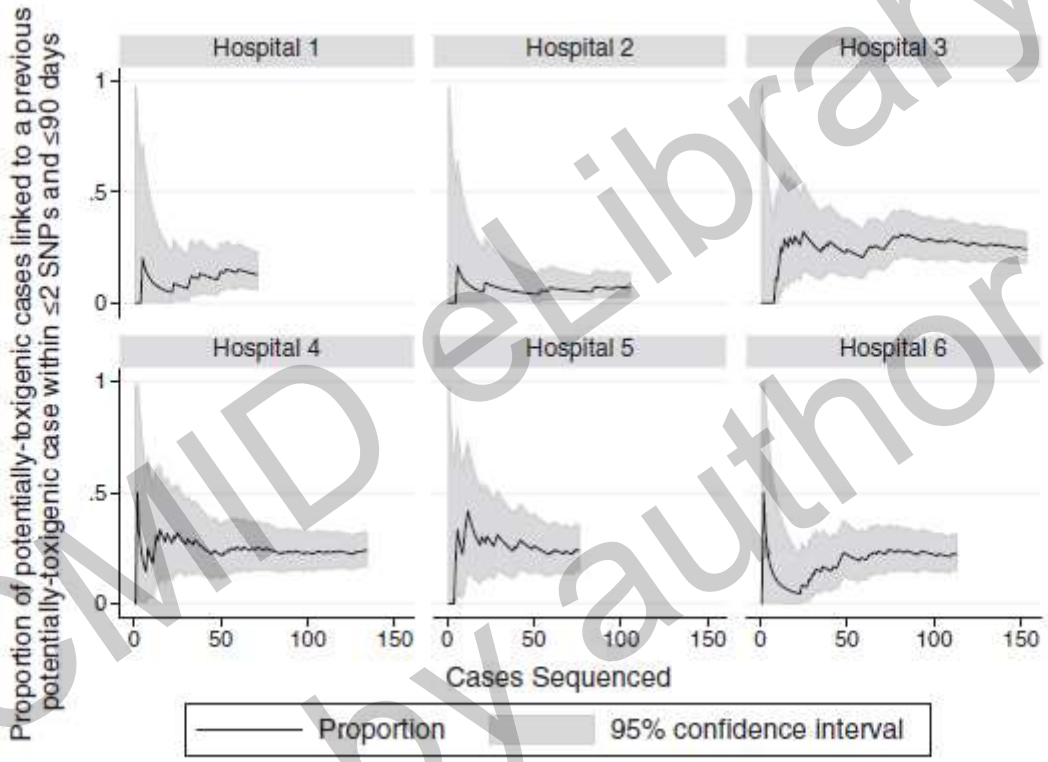
# HA-CDI acquisition in endemic setting (US)


Curry et al. 2013

MLVA typing showed:

- 30% of new cases were associated with CDI patients (4% using same rooms)
- 29% of new cases were associated with asymptomatic carriers (4% using same rooms).
- Concluded identification and isolation of carriers may be necessary to further reduce transmission of C. difficile

# Multi-centre study using WGS to identify HA-CDI acquisition (UK)




Eyre et al 2017

**Figure 2.** Proportion of potentially toxigenic cases linked to a previous potentially toxigenic case by hospital and number of sequences obtained. Abbreviation: SNP, single-nucleotide polymorphism.



- 20% of CDI patients were linked to previous CDI patients (< 2 SNP difference) (range 7-26%).
- Variation among ribotypes (57% of RT 027 cases were linked).

# Mathematical modelling of screening and contact precautions for carriers

- Mathematical modelling studies have suggested that reductions in CDI incidence by 10%–25% could be achieved by identifying and isolating carriers upon hospital admission (Grigoras et al. 2016, Lanzas et al, 2014)
- Exposed individuals who have not yet been colonised will be missed in screening tests (Yakob et al, 2013)
- 'Screening + isolation' approach was tested in a hospital in Quebec with high incidence of CDI (Longtin et al 2016)
  - Significant decrease in incidence
  - Sustained for at least 1 year after the study.

# Basic research gaps - colonisation

- What enables *C. difficile* to colonize patients?
- What are the triggers for sporulation and germination of *C. difficile* in the GI tract?
- Is there a nutritional niche that allows colonization?
- What is the role of mucosal/systemic immunity in preventing symptomatic CDI?
- What causes *C. difficile* colonization to end?
- What are the factors in infants and young children that influence susceptibility to infection vs. colonization?

# 3. Extant guidance 2018

# CDI Guidance Scotland 2017

## Asymptomatic carriers

Health Protection Scotland

- Testing of stools from asymptomatic carriers is not recommended (IB)
- Routine screening of asymptomatic persons for CDI is not recommended (no evidence)
- Transmission based precautions (or other interventions) are not recommended for carriers (insufficient evidence)

# ESCMID guidance 2018

## Recommendations relating to asymptomatic carriers

| Categories of recommendations | Recommendations relating to asymptomatic carriers |
|---|---|
| Diagnostic testing | No* |
| Surveillance | No |
| Screening | No** |
| Hand hygiene | No |
| PPE | No |
| Contact precautions | No |
| Environmental cleaning and disinfection | No |
| Infrastructure changes | No |
| Antibiotic stewardship | No |
| Education | Yes |

*The ESCMID Diagnostic Guidance (Crobach et al. 2016) addresses issues relating to ambiguous test results

** No recommendations given and reasons indicated.

# ESCMID Guidance 2018

Screening

## Does screening help to identify colonised patients?

***Recommendation for outbreak and endemic settings***

4. We do not recommend screening for *C. difficile to identify colonised/carrier* patients as a way of altering the risk of developing CDI in either colonized subjects or other patients and thus reducing CDI-rates (conditional recommendation, low level of evidence in the endemic setting).

## Should Healthcare workers be screened?

***Recommendation for outbreak and endemic settings***

5. We do not recommend HCW screening for *C. difficile gut colonization as a routine* control measure for CDI (strong recommendation, very low level of evidence in the endemic setting).

# ESCMID Guidance 2018

## Environmental control

### Does environmental disinfection of rooms of CDI patients decrease transmission of C. difficile?

***Recommendation for the outbreak setting***

14. Introduce daily environmental sporicidal disinfection and terminal disinfection of rooms of patients with CDI to decrease the transmission of CDI (strong recommendation, very low quality of evidence).

### Are no-touch disinfection systems effective in reducing contamination?

**Recommendation for outbreak and endemic settings**

17. The panel concludes that both in the outbreak and the endemic setting, no touch disinfection systems may be effective in reducing transmission/ incidence of CDI (very low quality of evidence).

# ESCMID Guidance 2018

## Education – Environmental control

**Does specific education enhance thoroughness of cleaning aimed at prevent CDI?**

Education of environmental service personnel proved to be of particular importance for prevention of CDI as reducing environmental *C. difficile contamination was* associated with lower *C. difficile prevalence in hospitals.*

Environmental service personnel require repeated training and regular quality control measurements (e.g. by labelling of surface areas before cleaning with a fluorescence marker) to ensure sustained high quality cleaning.

# CDI guidance IDSA/SHEA 2018

**Should asymptomatic carriers be tested and isolated?**

- No recommendation on screening for asymptomatic carriage
- No recommendation on contact precautions

**Is there a role of asymptomatic testing - Should repeat testing be allowed for asymptomatic patients?**

- Do not retest during the same episode
- Do not test asymptomatic patients (unless it is part of an epi study)

# 4. Discussion and conclusions

# Discussion and conclusions (1)

- There is conflicting evidence regarding the contribution of asymptomatic carriage to the epidemiology and spread of CDI; which may also vary with burden of disease, ribotype and healthcare setting.

- Multi-centre studies in different hospital settings are needed to support the "screening-isolation" approach more widely.

- Currently national guidelines generally agree on recommendations re. **asymptomatic carriers:**
  - **No testing**
  - **No screening**
  - **No contact precautions**
- Education, environmental measures and standard infection control precautions and antimicrobial stewardship should be in place **to prevent and control spread of *C. diificile* spores and development of CDI.**

# Discussion and conclusions (2)

- Even if sufficient evidence will be produced to support the implementation of a 'screening-isolation' approach; this will need to be assessed against public health principles for approval and funding (UK principles abbreviated here):

1. The epidemiology and natural history of the condition, including **latency period**, risk factors and disease markers, should be known
2. There should be a safe, accurate and validated **screening test available**
3. There should be agreed evidence-based strategies **for effective intervention or treatment** for identified individuals.
4. **Implementation should be underpinned by a complete screening programme** (test, diagnostic procedures, treatment/ intervention) that is **clinically, socially and ethically acceptable to health professionals and the public**

# Questions

Q1:

Do you test asymptomatic patients for presence of *C. difficile*?

- A) yes
- B) no

# Questions

Q2:

Do you screen for asymptomatic carriers of *C. difficile*?

- A) yes
- B) no

# Questions

Q2:

Do you isolate carriers positive for toxigenic *C. difficile?*

- A) yes
- B) no

Thank you for your attention