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Surveillance des infections à *Clostridium difficile* en Europe : pourquoi tant de différences?

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Déclaration d'intérêts de 2012 à 2015

- **Intérêts financiers : Alère, Astellas, bioMérieux, Roche, Sanofi-Pasteur, Theradiag**
- **Liens durables ou permanents : Aucun**
- **Interventions ponctuelles : Astellas**
- **Intérêts indirects : Aucun**

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : ECKERT Catherine

Titre : Surveillance des infections à *Clostridium difficile* en Europe : pourquoi tant de différences?

☐ L'orateur ne souhaite pas répondre

Consultant ou membre d'un conseil scientifique	☐ OUI	☑ NON
Conférencier ou auteur/rédacteur rémunéré d'articles ou documents Alère, Astellas	☑ OUI	☐ NON
Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations Alère, Astellas	☑ OUI	☐ NON
Investigateur principal d'une recherche ou d'une étude clinique COMMUNODIFF (Alère)	☑ OUI	☐ NON

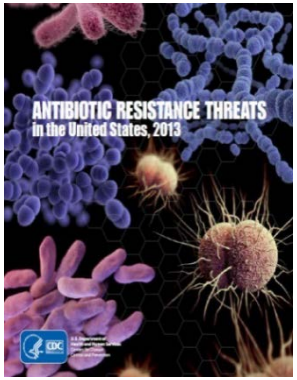
Points abordés

- **Prévalence et incidence des ICD**
- **Facteurs influençant l'incidence**
  - Densité de prescription
  - Méthodes diagnostiques
  - PCR ribotypes
  - Surveillance
- **Vers une surveillance standardisée européenne**
  - Projet ECDIS-net
  - Etude pilote

Prévalence et incidence des ICD

POIDS DES ICD EN EUROPE ET AUX ETATS-UNIS

- **Etats-Unis**



  - 453 000 ICD/an[1]

(IC 95% 397 100 – 508 500, HA et CO, HA ≥ 4 j, tous ES)

  - 29 300 décès
  - 1er agent responsable d'IAS (12,5%) [2]
  - Menace urgente (CDC)

- **Europe**

  - 124 000 ICD/an

(IC 95% 61 000 – 285 000, HA=CDI ≥ 3 j, ES court séjour)

  - Mortalité attribuable: 3% (3 700 décès attrib./an)
  - 8ème agent responsable d'IAS (5,4%) [3]

[1]Lessa , NEJM 2015, 372, 825; [2] Magill SS, NEJM 2014; 370, 1198-208
[3]http://www.ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-antimicrobial-use-pps.pdf

Prévalence et incidence des ICD

PLACE DES ICD DANS LES IAS

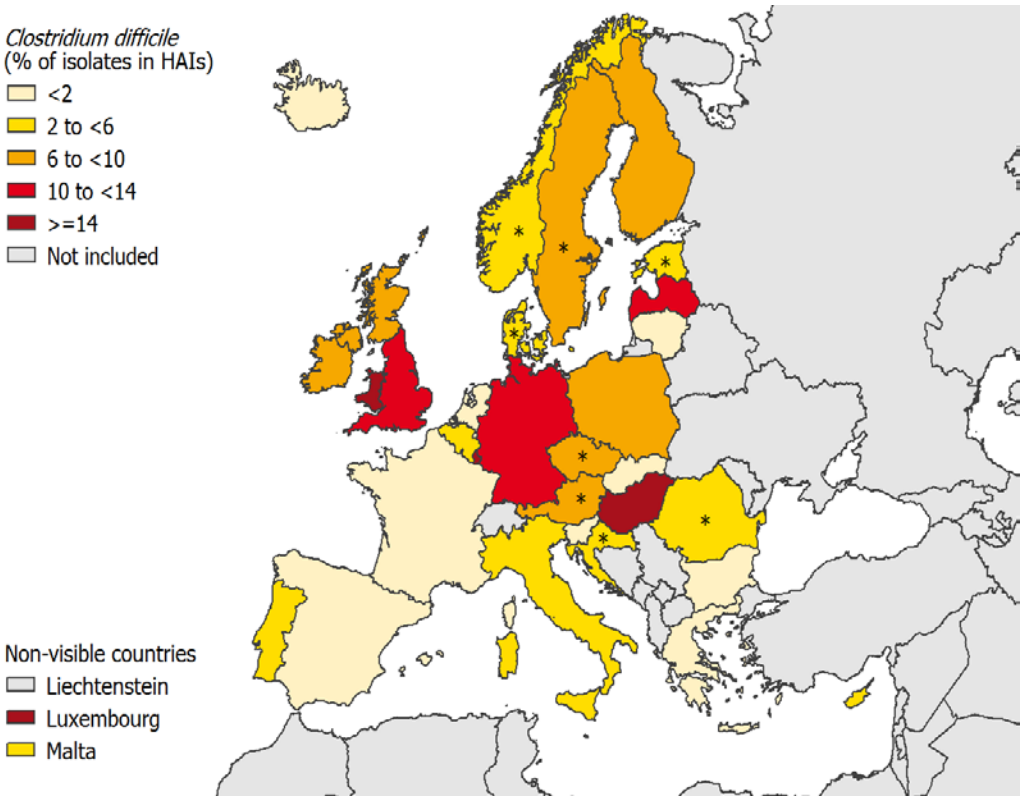
	Etats-Unis (2010)	Europe (2012)	France (2012)
Nb ES	183	1149	1938
Prévalence IAS	4,0%	6,0%	5,1%
Infections gastro-intestinales (%)	17,1% (3e rang)	7,7% (5e rang)	4,3% (7e rang)
dont *C. difficile*	70,9%	48%	43,5 %
Fréquence de *C. difficile* parmi les germe responsables d'IN	12,1% (1er rang)	5,4% (8e rang)	2,7% (9e rang)

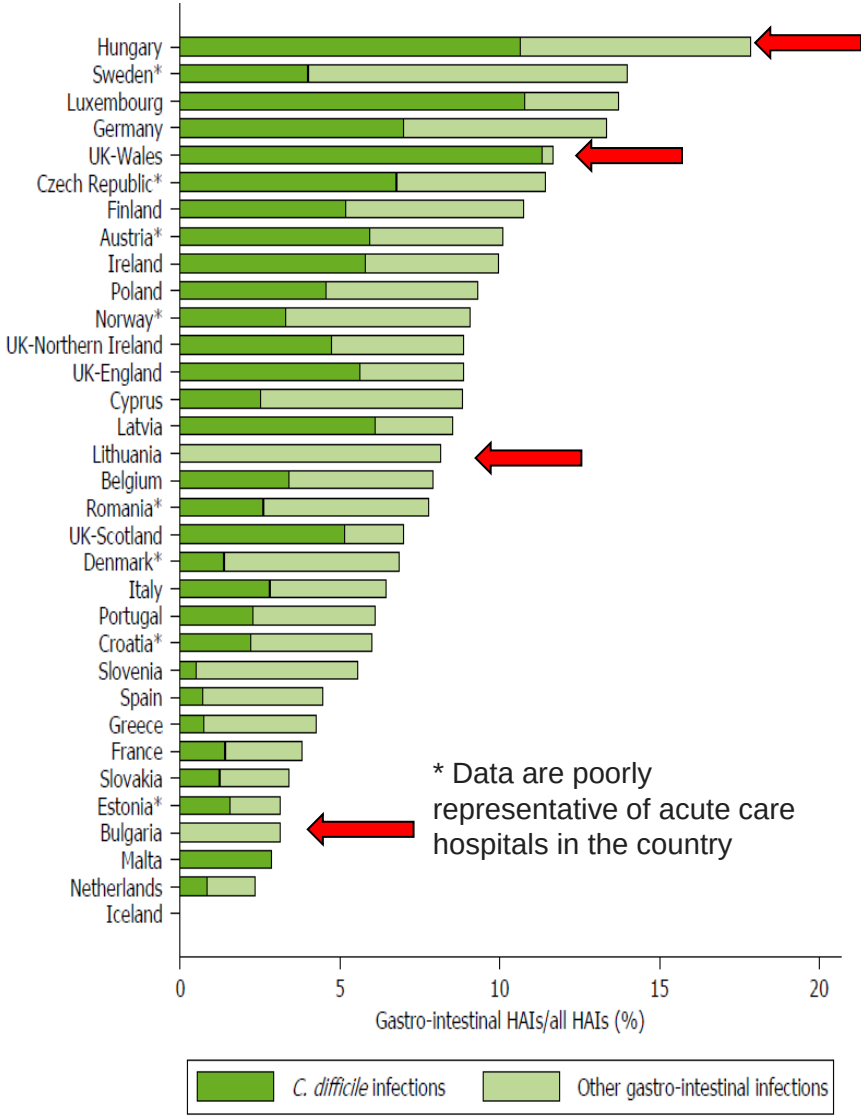
Magill SS, NEJM 2014; 370, 1198-208
http:/www.invs.sante.fr/content
http://www.ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-antimicrobial-use-pps.pdf

Prévalence et incidence des ICD

POIDS DES ICD EN EUROPE

% *C. difficile* parmi les germes responsables d'IAS





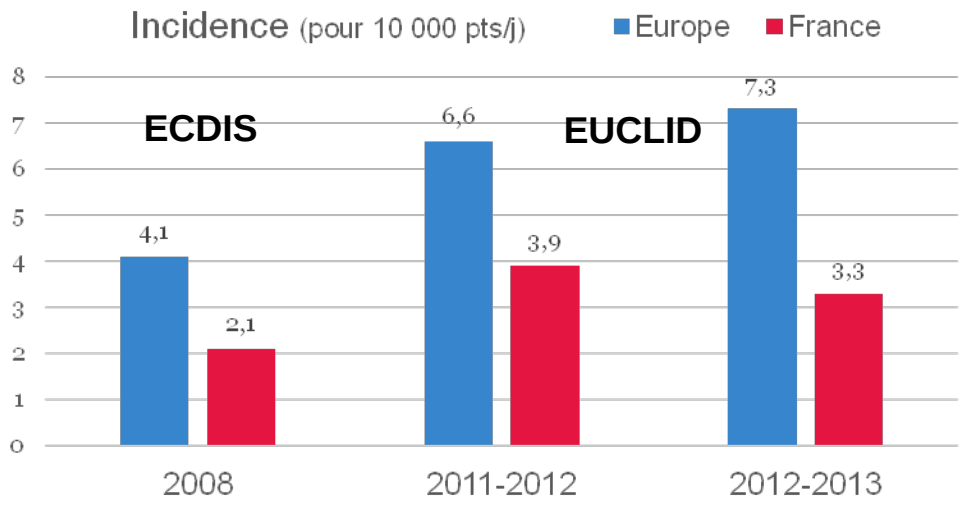
Source: ECDC, 2013. Available from: http://www.ecdc.europa.eu/en/publications/Publications/healthcare-associated-infections-antimicrobial-use-PPS.pdf

Prévalence et incidence des ICD

INCIDENCE DES ICD

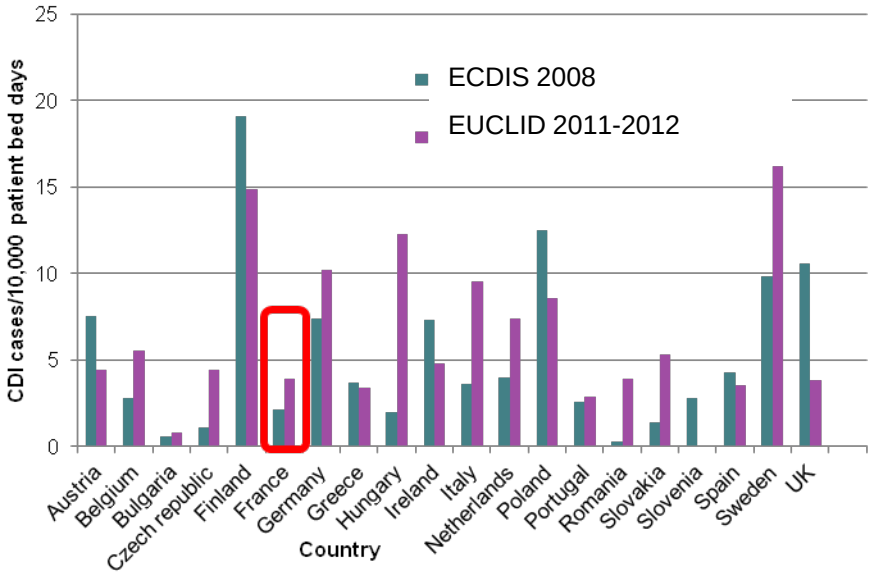
L'incidence continue d'augmenter en Europe [1–3]

- Amélioration des techniques diagnostiques
- Sensibilisation croissante des cliniciens
- Diffusion du clone NAP1/027/BI en Europe de l'Est



106 ES
36 pays

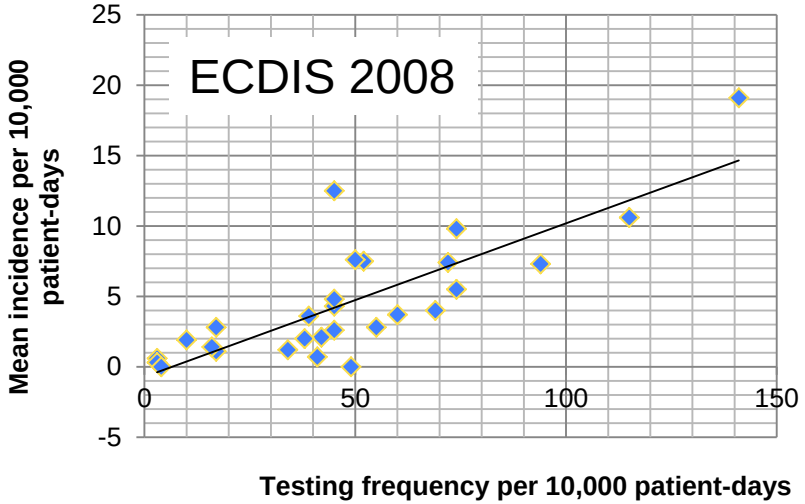
482 ES
20 pays



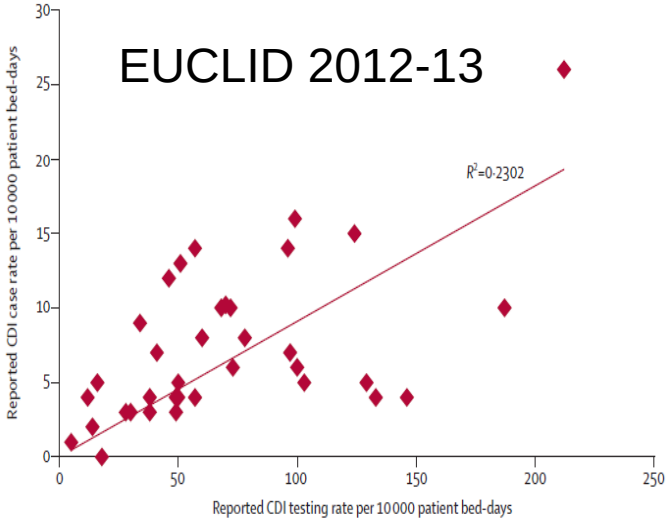
1. Bauer *et al* Lancet 2011
2. Davies *et al* Lancet 2014
3. Barbut *et al* Presse med 2015

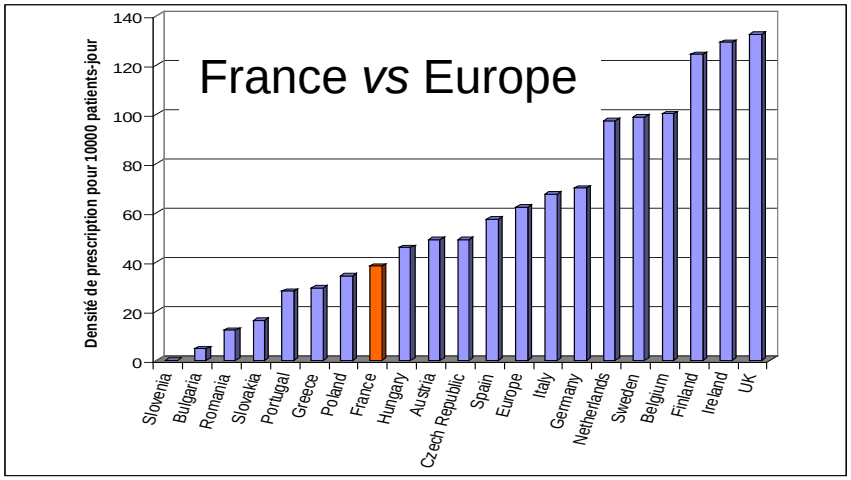
Facteurs influençant l'incidence

INCIDENCE ET DENSITE DE PRESCRIPTION



Adapté d'après Bauer *et al.* Lancet 2011;377:63–73





- Variation de la densité de prescription d'un facteur 48 K. Davies, ECCMID 2012, LB 2968

- La densité de prescription est de 36,3 ± 25,2 pour 10 000 pts-j

  Barbut *et al* Presse med 2015

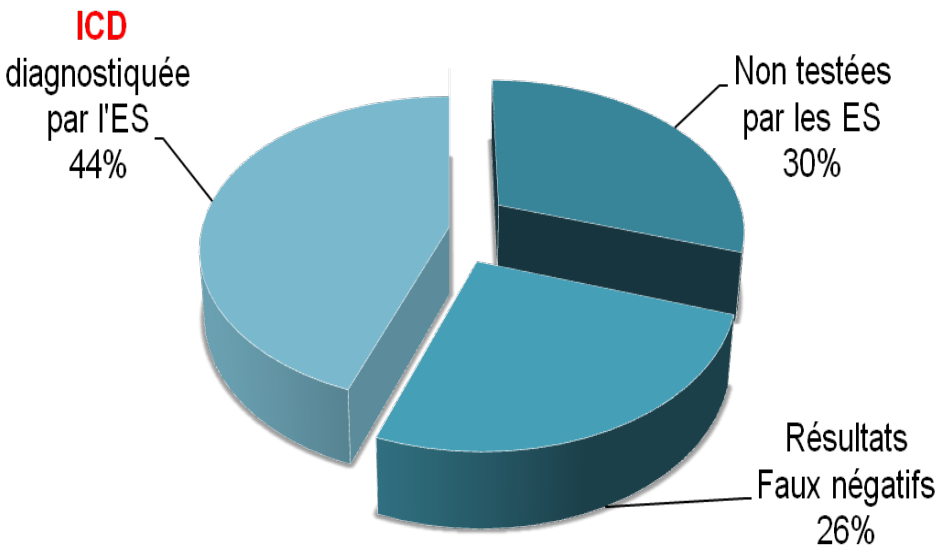
- Moyenne basse de l'Europe (65,8 pour 10 000 pts-j)

  Davies *et al* Lancet 2014

Facteurs influençant l'incidence

LE SOUS-DIAGNOSTIC DES ICD EST MAJEUR EN FRANCE

- Etude EUCLID 2012/13 : prévalence de *C. difficile* dans toutes les selles diarrhéiques envoyées au laboratoire, indépendamment de la demande du clinicien
- Analyse de 651 selles (70 ES) par le CNR
- 9,7% des échantillons positifs à *C. difficile* toxinogène

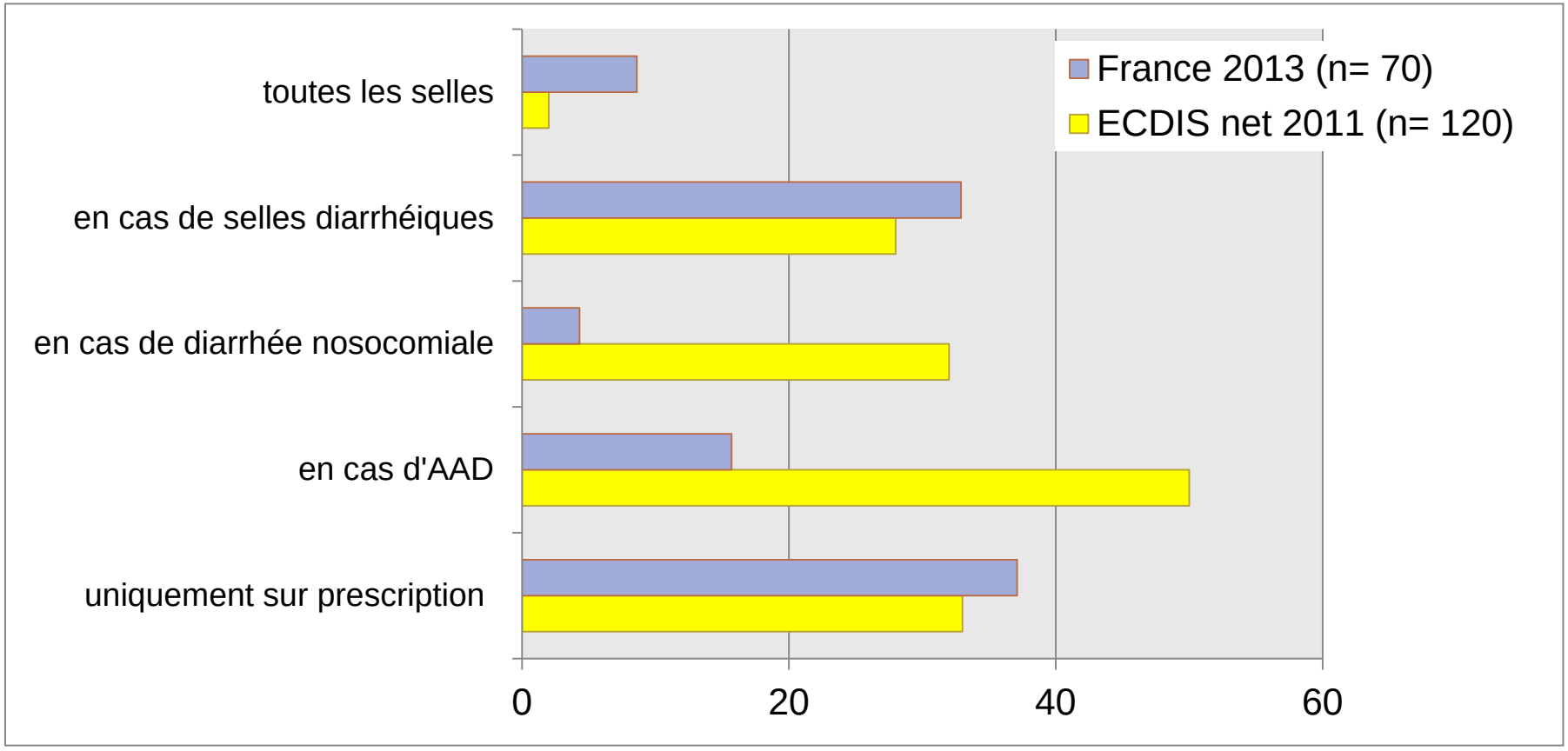


➢ **55,6% des ICD NON diagnostiquées par l'ES**

Barbut *et al.* Presse médicale 2015

Facteurs influençant l'incidence

CRITERES DE RECHERCHE DE *C. difficile*



Van Nood *et al.* for the 'European *Clostridium difficile* Infection Surveillance' network (ECDIS-net) on behalf all participants 2015, Manuscrit soumis

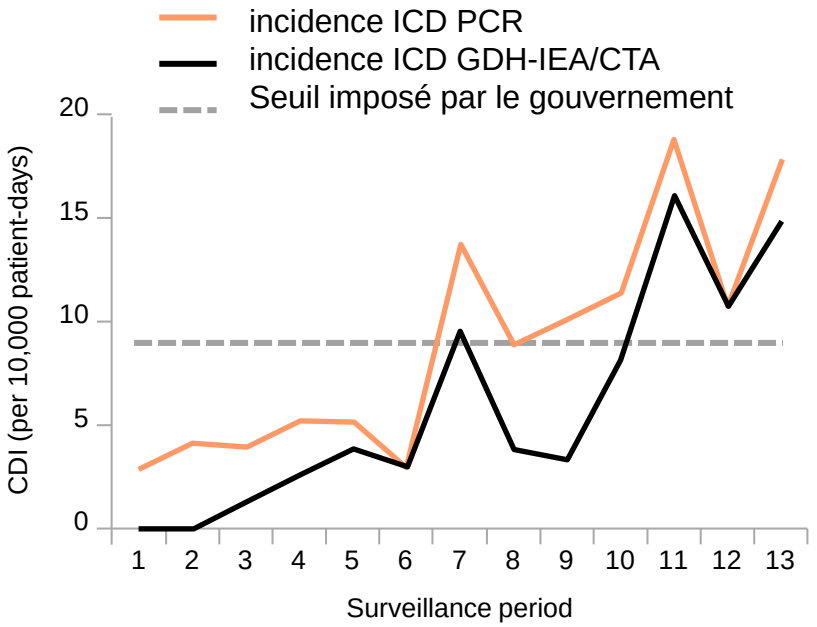
Facteurs influençant l'incidence

L'INCIDENCE DEPEND DES METHODES DIAGNOSTIQUES

Evolution de la prévalence et de l'incidence des ICD après utilisation d'un test EIA et de la PCR pendant des périodes de 3 mois[1]

	EIA	PCR	p
No. of lab specimens	2,579	2,534	
Mean no. (%) positive	167 (6.5)	382 (15.1)	<0.001
CDI rates*	4.9	10.3	<0.001

*Cases per 10,000 patient-days



- 8.9/10,000 JH (PCR) vs 5.8/10,000 JH (GDH-toxin + CTA)[2]
- Peut faire passer l'incidence au delà des seuils imposés par le gouvernement[2]
- Standardisation des méthodes diagnostiques nécessaire pour interpréter les taux[2]

➢ **Le passage à la PCR augmente l'incidence des ICD**

1. Fong *et al.* Infect Control Hosp Epidemiol 2011;32:932–3;
2. Longtin *et al.* Clin Infect Dis 2013;56:67–73.

CTA, cytotoxicity assay; EIA, enzyme immunoassay; PCR, polymerase chain reaction

Facteurs influençant l'incidence

CATEGORISATION DES ALGORITHMES

	Test de dépistage	Test de confirmation	Remarques
Optimale	Méthode moléculaire	Détection des toxines (EIA)	Rapide Individualisation des pts avec toxines libres
	GDH et détection des toxines (EIA)	Méthode moléculaire (ou culture toxigénique)	
Sub-optimale	GDH	Méthode moléculaire (ou culture toxigénique)	Très sensible mais ne permet pas d'identifier les pts avec des toxines libres
	Méthode moléculaire	Aucun	
Incomplète	Autres algorithmes		

Van Dorp *et al.* 2015 Manuscrit accepté

Facteurs influençant l'incidence

CATEGORISATION DES ALGORITHMES

Données disponibles pour 2011 et 2014[1]

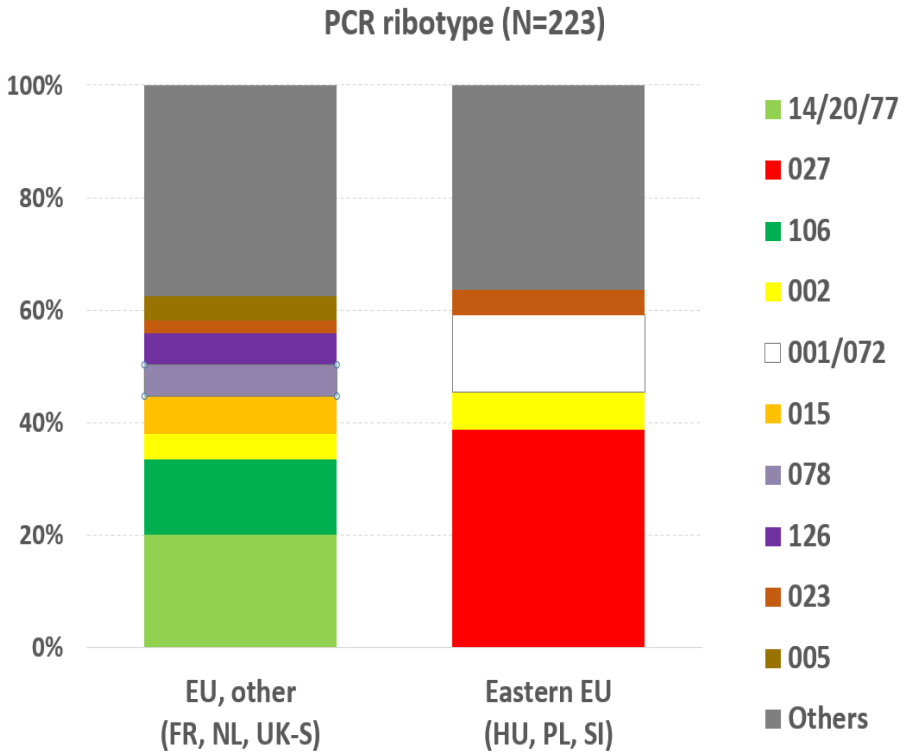
	2011		2014	
Algorithme	n	%	n	%
Optimal	15	19%	37	46%
Acceptable	8	10%	12	15%
Incomplet	58	72%	32	40%
Total	81	100%	81	100%

Van Nood *et al.* for the 'European *Clostridium difficile* Infection Surveillance' network (ECDIS-net) on behalf all participants 2016, Manuscrit soumis

Facteurs influençant l'incidence

DISTRIBUTION DES PCR-RIBOTYPES

- **Très grande diversité de PCR-Ribotypes (PR) en Europe**
  - 138 PR différents (20 pays) vs 65 en 2008 (26 pays) (Bauer *et al.* Lancet 2008)
- **Majorité des pays (14/16): grande variété de PR sans clone dominant**
  - République Tchèque → PR 176 (35%)
  - Italie→ 2 PR: 018 (22%) et 356 (17%)
- **PR 027 = le plus fréquent (18%) mais → 88% isolés dans 4 pays**
  - Allemagne (43% du total)
  - Hongrie (17%)
  - Pologne (16%)
  - Roumanie (12%)



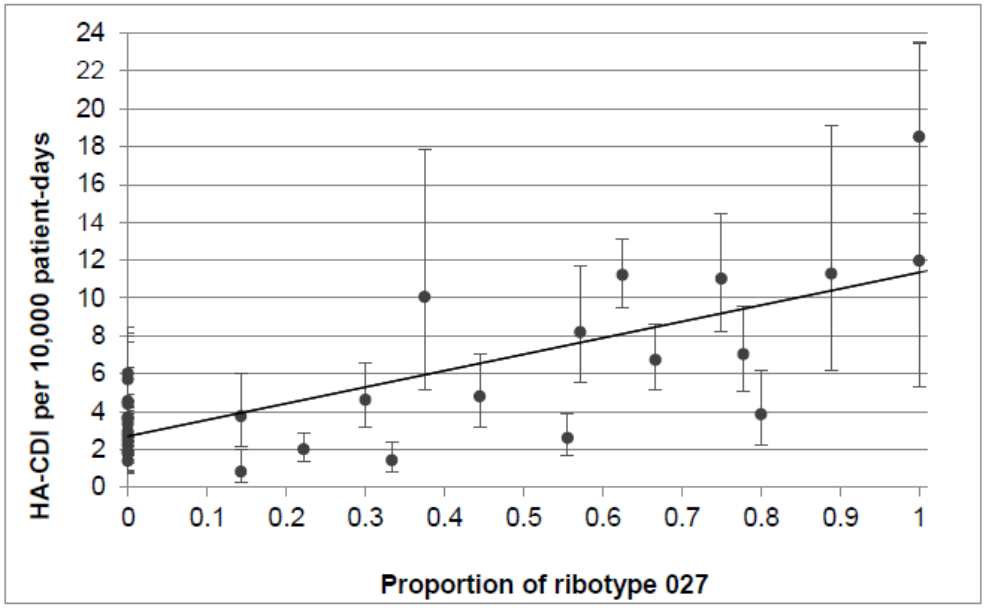
➢ **France 2,8% des souches**
(Eckert *et al.* Poster 350 RICAI 2015)

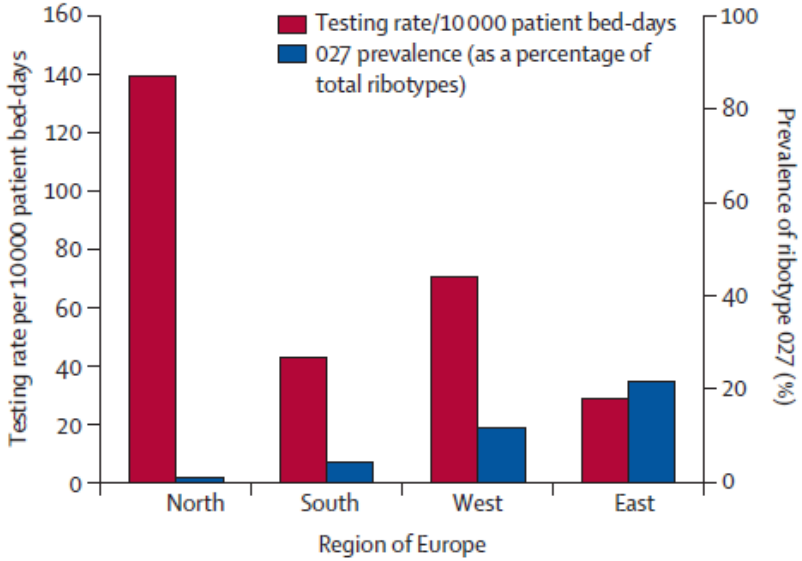
D'après Wilcox M., communication personnelle, ECCMID 2014

*'Eastern EU' as defined in Hajdu A. CDI in Eastern Europe: challenges and opportunities for surveillance. ECCMID 2016

Facteurs influençant l'incidence

L'INCIDENCE DEPEND DE LA PREVALENCE DU CLONE 027





- **Corrélation inverse entre la densité de prescription et la prevalence du PR 027**

Davies *et al.* Lancet Inf. Dis 2014, 14, 1208-19
Van Dorp *et al.* Eurosurveillance 2016, sous presse

Facteurs influençant l'incidence

VARIABILITE DE LA SURVEILLANCE DES ICD EN EUROPE

Pays	Numérateur	Dénominateur	Déf. ECDC	Type de surveillance	Période	Public reporting
France	Formes sévères, épidémies (e-sin)	Non	Oui	Obligatoire	Année	Non
Belgique	Toute ICD	JH	Oui	Obligatoire (141 ES)	Min 1 semestre	Non
Angleterre	Toute ICD	JH	+/-	Obligatoire (tout ES)	Année	Oui
Allemagne	Toute ICD (Kiss CDAD) + formes sévères épidémies (Survnet)	JH	Oui	Volontaire	Année	Non
Pays Bas	Toute ICD	JH	Oui	Volontaire (20 ES sentinelles)	Année	Non

Vers une surveillance standardisée européenne

PANORAMA DES ACTIVITES DE L'ECDC POUR LA SURVEILLANCE DES ICD

2006
Définition des cas d'ICD (ESGCD/ECDC)

2007
ECDC lance la première étude de surveillance des ICD (ECDIS, 2008-2009)

2008
Recommendations pour limiter la diffusion des ICD
(Vonberg *et al*. CMI 2008)

2010-2014
Projet ECDIS-Net ("Supporting capacity building for surveillance of CDI at European level"):
→ améliorer les capacités des laboratoires (formation, ribotypage, CEQ)
→ méthodes standardisées de surveillance (revue des méthodes existantes, développement d'un protocole EU)

2013
Etude pilote V1

2015
Finalisation du protocole de surveillance

2016
Etude pilote V2

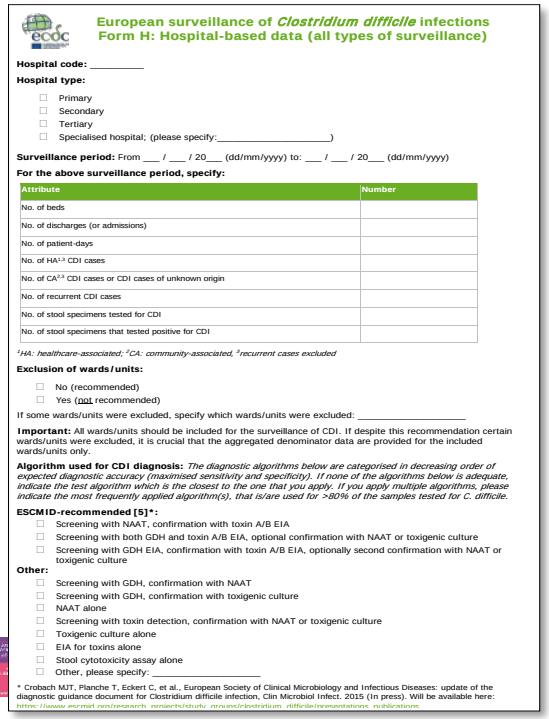
Vers une surveillance standardisée européenne

PROTOCOLE STANDARDISE DE SURVEILLANCE DES ICD, ECDIS-net

3 options

- **"Minimal" :** données aggrégées de l'hôpital (numérateur dénominateur), algorithme diagnostique et densité de prescription
- **"Light" :** minimal + données cliniques pour chaque cas
- **"Enhanced":** light + données microbiologiques (e.g. PCR-ribotype, résistance)

Form H = Minimal



European surveillance of *Clostridium difficile* infections
Form H: Hospital-based data (all types of surveillance)

Hospital code: _____

Hospital type:

- ☐ Primary
- ☐ Secondary
- ☐ Tertiary
- ☐ Specialised hospital; (please specify:_____)

Surveillance period: From ___ / ___ / 20___ (dd/mm/yyyy) to: ___ / ___ / 20___ (dd/mm/yyyy)

For the above surveillance period, specify:

Attribute	Number
No. of beds	
No. of discharges (or admissions)	
No. of patient-days	
No. of HA[1,3] CDI cases	
No. of CA[2,3] CDI cases or CDI cases of unknown origin	
No. of recurrent CDI cases	
No. of stool specimens tested for CDI	
No. of stool specimens that tested positive for CDI	

[1]*HA: healthcare-associated;* [2]*CA: community-associated,* [3]*recurrent cases excluded*

Exclusion of wards/units:

- ☐ No (recommended)
- ☐ Yes (not recommended)

If some wards/units were excluded, specify which wards/units were excluded: _____

Important: All wards/units should be included for the surveillance of CDI. If despite this recommendation certain wards/units were excluded, it is crucial that the aggregated denominator data are provided for the included wards/units only.

Algorithm used for CDI diagnosis: *The diagnostic algorithms below are categorised in decreasing order of expected diagnostic accuracy (maximised sensitivity and specificity). If none of the algorithms below is adequate, indicate the test algorithm which is the closest to the one that you apply. If you apply multiple algorithms, please indicate the most frequently applied algorithm(s), that is/are used for >80% of the samples tested for C. difficile.*

ESCMID-recommended [5]*:

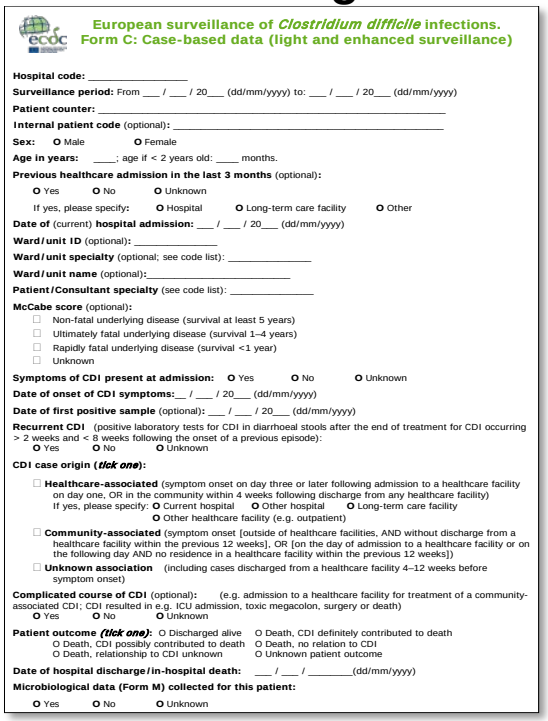
- ☐ Screening with NAAT, confirmation with toxin A/B EIA
- ☐ Screening with both GDH and toxin A/B EIA, optional confirmation with NAAT or toxigenic culture
- ☐ Screening with GDH EIA, confirmation with toxin A/B EIA, optionally second confirmation with NAAT or toxigenic culture

Other:

- ☐ Screening with GDH, confirmation with NAAT
- ☐ Screening with GDH, confirmation with toxigenic culture
- ☐ NAAT alone
- ☐ Screening with toxin detection, confirmation with NAAT or toxigenic culture
- ☐ Toxigenic culture alone
- ☐ EIA for toxins alone
- ☐ Stool cytotoxicity assay alone
- ☐ Other, please specify: _____

* Crobach MJT, Planche T, Eckert C, et al., European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for Clostridium difficile infection, Clin Microbiol Infect. 2015 (In press). Will be available here: https://www.escmid.org/research_projects/study_groups/clostridium_difficile/presentations_publications/

+ Form C = Light



European surveillance of *Clostridium difficile* infections.
Form C: Case-based data (light and enhanced surveillance)

Hospital code: _____

Surveillance period: From ___ / ___ / 20___ (dd/mm/yyyy) to: ___ / ___ / 20___ (dd/mm/yyyy)

Patient counter: _____

Internal patient code (optional)**:** _____

Sex: O Male O Female

Age in years: ____; age if < 2 years old: ____ months.

Previous healthcare admission in the last 3 months (optional)**:**

O Yes O No O Unknown

If yes, please specify**:** O Hospital O Long-term care facility O Other

Date of (current) **hospital admission:** ___ / ___ / 20___ (dd/mm/yyyy)

Ward/unit ID (optional)**:** _____

Ward/unit specialty (optional; see code list): _____

Ward/unit name (optional)**:** _____

Patient/Consultant specialty (see code list): _____

McCabe score (optional)**:**

- ☐ Non-fatal underlying disease (survival at least 5 years)
- ☐ Ultimately fatal underlying disease (survival 1–4 years)
- ☐ Rapidly fatal underlying disease (survival <1 year)
- ☐ Unknown

Symptoms of CDI present at admission: O Yes O No O Unknown

Date of onset of CDI symptoms:__ / ___ / 20___ (dd/mm/yyyy)

Date of first positive sample (optional)**:** ___ / ___ / 20___ (dd/mm/yyyy)

Recurrent CDI (positive laboratory tests for CDI in diarrhoeal stools after the end of treatment for CDI occurring > 2 weeks and < 8 weeks following the onset of a previous episode)**:**
O Yes O No O Unknown

CDI case origin (*tick one*):

- ☐ **Healthcare-associated** (symptom onset on day three or later following admission to a healthcare facility on day one, OR in the community within 4 weeks following discharge from any healthcare facility)
  If yes, please specify: O Current hospital O Other hospital O Long-term care facility O Other healthcare facility (e.g. outpatient)
- ☐ **Community-associated** (symptom onset [outside of healthcare facilities, AND without discharge from a healthcare facility within the previous 12 weeks], OR [on the day of admission to a healthcare facility or on the following day AND no residence in a healthcare facility within the previous 12 weeks])
- ☐ **Unknown association** (including cases discharged from a healthcare facility 4–12 weeks before symptom onset)

Complicated course of CDI (optional)**:** (e.g. admission to a healthcare facility for treatment of a community-associated CDI; CDI resulted in e.g. ICU admission, toxic megacolon, surgery or death)
O Yes O No O Unknown

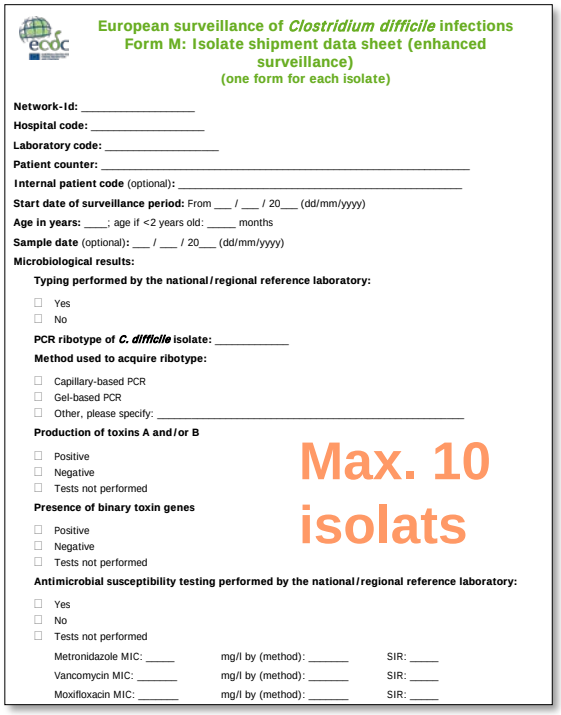
Patient outcome *(tick one)*: O Discharged alive O Death, CDI definitely contributed to death O Death, CDI possibly contributed to death O Death, no relation to CDI O Death, relationship to CDI unknown O Unknown patient outcome

Date of hospital discharge/in-hospital death: ___ / ___ / _____(dd/mm/yyyy)

Microbiological data (Form M) collected for this patient:

O Yes O No O Unknown

+ Form M = Enhanced



European surveillance of *Clostridium difficile* infections
Form M: Isolate shipment data sheet (enhanced surveillance)
(one form for each isolate)

Network-Id: _____

Hospital code: _____

Laboratory code: _____

Patient counter: _____

Internal patient code (optional)**:** _____

Start date of surveillance period: From ___ / ___ / 20___ (dd/mm/yyyy)

Age in years: ____; age if <2 years old: _____ months

Sample date (optional)**:** ___ / ___ / 20___ (dd/mm/yyyy)

Microbiological results:

Typing performed by the national/regional reference laboratory:

- ☐ Yes
- ☐ No

PCR ribotype of *C. difficile* isolate: _____

Method used to acquire ribotype:

- ☐ Capillary-based PCR
- ☐ Gel-based PCR
- ☐ Other, please specify: _____

Production of toxins A and/or B

- ☐ Positive
- ☐ Negative
- ☐ Tests not performed

Presence of binary toxin genes

- ☐ Positive
- ☐ Negative
- ☐ Tests not performed

Antimicrobial susceptibility testing performed by the national/regional reference laboratory:

- ☐ Yes
- ☐ No
- ☐ Tests not performed

Metronidazole MIC: _____ mg/l by (method): _____ SIR: _____

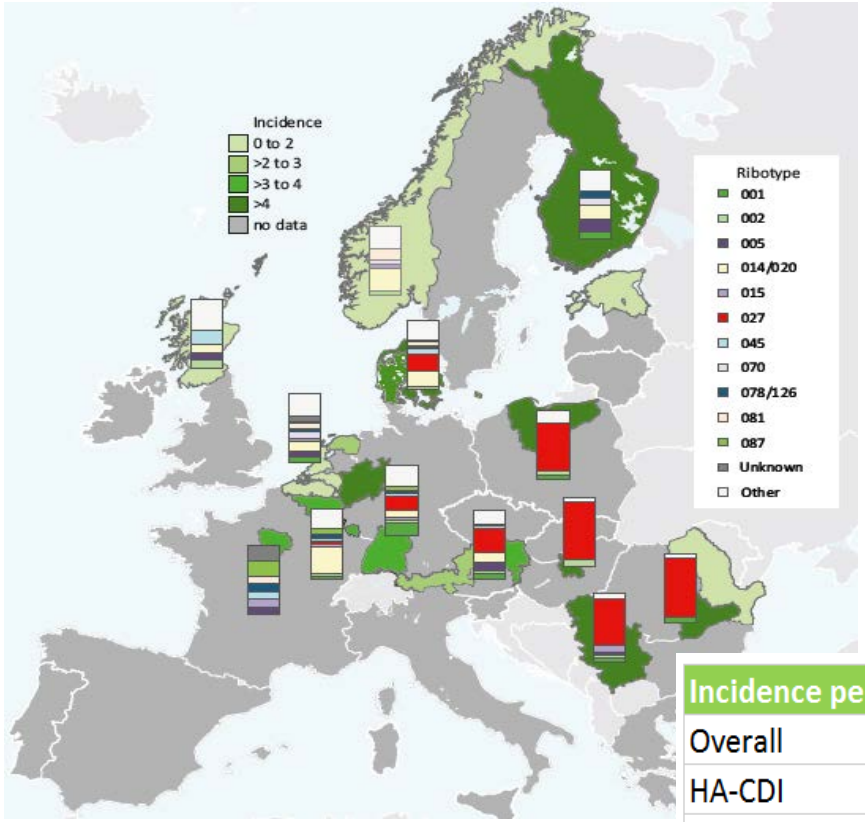
Vancomycin MIC: _____ mg/l by (method): _____ SIR: _____

Moxifloxacin MIC: _____ mg/l by (method): _____ SIR: _____

Max. 10 isolats

Vers une surveillance standardisée européenne

PROJET ECDIS-Net : ETUDE PILOTE V1, 2013



N=14 pays, N=37 ES
3 mois

→ 027 : 30%

Incidence per 10 000 patient-days	Median	IQR	Range
Overall	6.0	3.1 – 8.5	0.8 – 27.4
HA-CDI	3.7	2.0 – 6.6	0.6 – 18.5
Recurrent CDI	0.3	0.04 – 1.2	0.0 – 9.0
CA-CDI or unknown origin	0.9	0.5 – 0.5	0.0 – 8.5

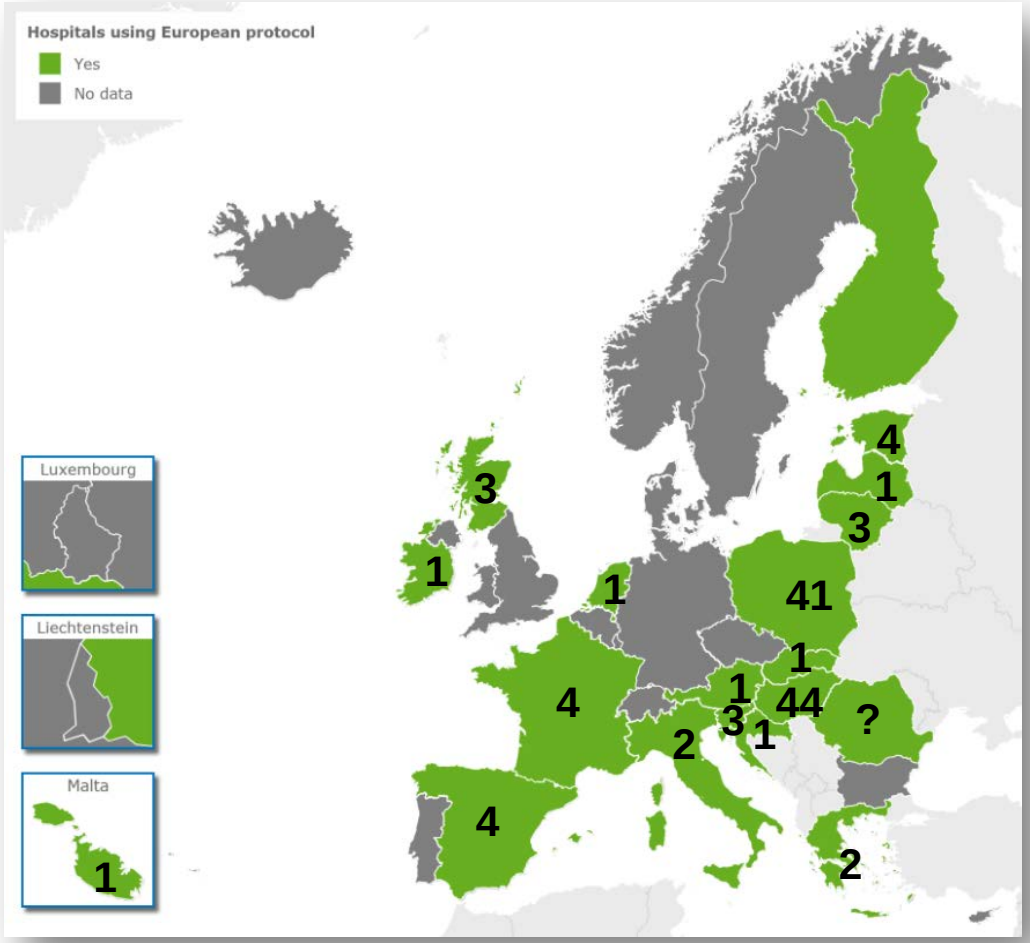
van Dorp *et al.* Eurosurveillance, 2016 (sous presse)

IQR= interquartile range, **HA= Healthcare-Associated:** symptoms >48 h following admission to a healthcare facility or symptoms in the community < 4 weeks following discharge from a healthcare facility, **CA= Community-Associated:** symptoms while outside a healthcare facility, and without discharge from a healthcare facility <12 weeks or with onset of symptoms <48 h following admission to a healthcare facility without residence in a healthcare facility <12 weeks, **Recurrence:** recurrent episode >2 weeks and ≤8 weeks after onset of previous episode

Vers une surveillance standardisée européenne

ETUDE PILOTE V2 , 2016

- **Jan-Fév 2016**: 1 mois minimum
- 17 pays, 117 ES:
  - Protocole “Minimal”: 2
  - Protocole “Light” (case-based): 79
  - Protocole “Enhanced” (+ microbiological data): 36
- 1125 cas d’ICD
- PCR ribotype : 223

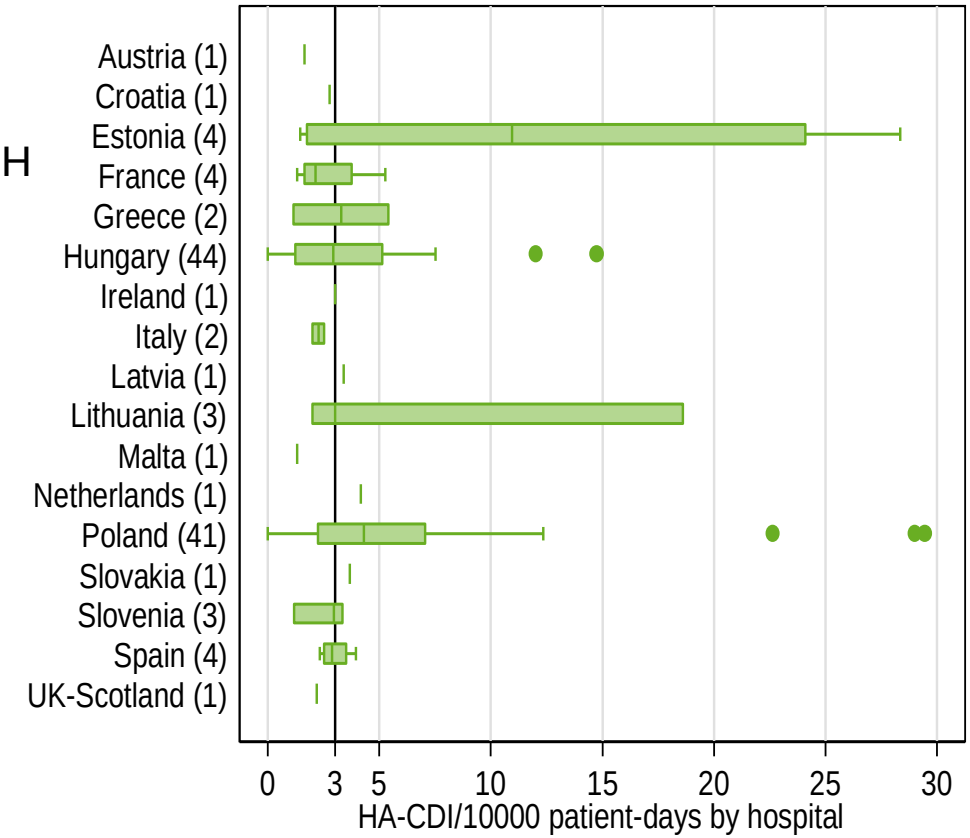


Vers une surveillance standardisée européenne

INCIDENCE ET MORTALITE

- **ICD associés aux soins (HA) ICD:**
  - Médiane: **3,0 HA-ICD/10 000 JH**
    IQR 1,7 – 5,4
  - Moyenne poolée: 3,9 HA-ICD/10 000 JH
- **Total (HA + community-associated) ICD:**
  - Médiane: **3,8 ICD/10 000 JH**
    IQR 2,3 – 6,6
  - Moyenne poolée: 4,6 ICD/10 000 JH
- **Récidives ICD:**
  - Moyenne poolée: 0,5 ICD/10 000 JH
- **Mortalité intra hospitalière: 195 (18,8%)**
  - Non reliée: 83 (68%)
  - Possiblement reliée: 32 (26%)
  - Certainement reliée: 7 (6%)

➔ Mortalité attribuable = **6%**



Conclusions

- **L'incidence dépend de nombreux facteurs**
  - La densité de prescription
  - Les stratégies diagnostiques
  - L'épidémiologie locale (épidémie, ribotype…)
  - La méthode de surveillance

- **Grande variabilité de modalité de surveillance des ICD en Europe**
  - Absence de données d'incidence en France

- **Nécessité d'ajuster les taux sur ces facteurs confondants**

Remerciements

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CDI case

A patient to whom one or more of the following criteria applies:

-Diarrheal stools or toxic megacolon, and **a positive laboratory assay for *C. difficile* tcdA and/or tcdB in stools or a toxin-producing *C. difficile* organism detected in stool via culture or other means**

-Pseudomembranous colitis revealed by lower gastrointestinal endoscopy

-Colonic histopathology characteristic of CDI (with or without diarrhea) on a specimen obtained during endoscopy, colectomy or autopsy

Recurrent CDI

- An episode of CDI (return of diarrheal stools with a positive laboratory test after the end of treatment) >2 weeks and ≤8 weeks following the onset of a previous episode (CDI cases with onset later than 8 weeks after the onset of a previous episode were included as new CDI cases)

Healthcare-associated CDI

- A case of CDI with onset of symptoms at least 48 hours following admission to a healthcare facility or with onset of symptoms in the community within 4 weeks following discharge from a healthcare facility

Community-associated CDI

- A case of CDI with onset of symptoms outside a healthcare facility or within 48 hours after admission to a healthcare facility, without residence in a healthcare facility within the previous 12 weeks

Complicated course of CDI

CDI leading to any of the following:

-Admission to an intensive care unit for treatment of CDI or its complications (e.g. for shock requiring vasopressor therapy)

-Surgery (colectomy) for toxic megacolon, perforation or refractory colitis

-Death within 30 days after diagnosis if CDI is either a primary or contributing cause