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Results of the European *Clostridium difficile* survey (ECDIS)

Martijn Bauer, MD; on behalf of the ECDIS Study Group and local coordinators

Clostridium difficile infection in Europe: a hospital-based survey

Martijn P Bauer, Daan W Notermans, Birgit H B van Benthem, Jon S Brazier, Mark H Wilcox, Maja Rupnik, Dominique L Monnet, Jaap T van Dissel, Ed J Kuijper, for the ECDIS Study Group*

Lancet 2011; 377: 63–73

Contributors

The study was designed by DWN, BHBB, MHW, and EJK, with support of DLM, on behalf of ECDC, and members of European Study group of *Clostridium difficile*, on behalf of European Society for Clinical Microbiology and Infectious Diseases. JSB and MR were responsible for PCR ribotyping and toxinotyping of strains, respectively. MPB did the study as principle coordinator, using support of DWN as principal investigator and EJK as microbiological coordinator. DLM helped in selecting national coordinators. BHBB and JTvD supervised clinical data collection and data analysis. MPB analysed the data and wrote the first draft of the article. All authors contributed substantially to the submitted version.

ECDIS study group

*=national coordinator. †=local coordinator.

Austria—F Allerberger. (AGES–Institut für medizinische Mikrobiologie und Hygiene, Wien). G Hartmann† (Hospital Feldkirch, Feldkirch). M Hell† (University Hospital Salzburg, Salzburg). A Wechsler-Fördös† (Hospital Rudolfstiftung, Wien). *Belgium:* M Delmee*† (University of Louvain, Brussels). B Gordts† (St Jan Hospital, Brugge). K Laffineur† (St Luc Hospital, Namur) *Bulgaria:* K Ivanova* (National Ref Lab for Anaerobes, Sofia). M Marina† (National Center of Infectious & Parasitic Diseases for the Queen Giovanna University Hospital, Sofia). E Dzhigosheva† (Saint Anna-University Multi-specialization Hospital for Activ Treatment, Sofia) G Filefski† (1st Multi-specialization Hospital for Activ Treatment, Sofia). *Croatia:* B Matica* (Institute of Public Health Andrija Stampar, Zagreb). D Golubic† (County Hospital Cakovec, Cakovec). V Punda-Polic† (Split University Hospital, Split). A Tambic Andrasevic† (University Hospital for Infectious Diseases Zagreb, Zagreb). *Cyprus:* P Maikanti-Charalampous*† (Nicosia General Hospital, Nicosia). D Bagazouni (Nicosia General Hospital, Nicosia). *Czech Republic:* O Nyč* (Hospital FN Motol Prague, Prague). I. Mejzlíkova† (Hospital U svate Anny FN Brno, Brno) I. Geigerova† (Hospital FN Plzen Prague, Plzen–Lichotin). *Denmark:* KEP Olsen* (Statens Serum Institut, Copenhagen). I Brock† (Hvidovre Hospital, Hvidovre). H Holt† (Odense Universitetshospital, Odense). M Kragh Thomsen† (Regionshospitalet Viborg, Viborg). *Estonia:* M Jyrna-Ellam*† (North-Estonian Regional Hospital and North Estonia Medical Centre, Tallinn). *Finland:* A Virolainen-Julkunen* (KTL [National Public Health Institute], Helsinki). J Mikkola† (Central Hospital of Kanta-Häme, Hämeenlinna). E Mattila† (Helsinki University Central Hospital [Meilahti], Helsinki). M Broas† (Lapland Central Hospital [Infection Control Unit], Rovaniemi). *Former Yugoslav Republic of Macedonia:* M Petrovska* (Institute of Microbiology and Parasitology, Skopje). *France:* F Barbut* (Hôpital Saint-Antoine, Paris). D Descamps† (Centre hospitalier de Béthune, Béthune). J P Canone† (Centre hospitalier de Lens, Lens). V Lalande† (CHU Saint-Antoine, Paris) L Lemée† (CHU de Rouen-Charles Nicolle, Rouen). I. Cavalié† (CHU de Toulouse, Toulouse). *Germany:* N Kleinkauf* (Robert Koch-Institut, Berlin). A Kola† (Paulinenhaus Krankenanstalt e.V, Berlin). R Knüfermann† (Paulinenhaus Krankenanstalt e.V, Berlin). M Kist† (Universitätsklinikum Freiburg, Freiburg). I Fenner† (Albertinenkrankenhaus, Hamburg). A Rodloff† (Universitätsklinikum Leipzig, Leipzig). C von Eichel-Streiber† (Institut für Medizinische Mikrobiologie und Hygiene, Mainz). S Borgmann† (Krankenhaus Tirschenreuth, Tirschenreuth). R Michael† (Krankenhaus Tirschenreuth, Tirschenreuth). *Greece:* E Malamou-Lada* (General Hospital of Athens). M Orfanidou† (G. Gennimatas General Hospital of Athens, Athens). A Avlami† (Laiko General Hospital, Athens). M Kanellopoulou† (Sismanoglion General Hospital, Athens). *Hungary:* E Nagy* (Faculty of Medicine, University of Szeged, Szeged). M Konkoly-Thege† (St István and St László Municipal Hospital, Budapest). G Terhes† (University Hospital of Szeged, Szeged). S Lenke† (St György Hospital, Székesfehérvár). *Iceland:* H Hardarson*† (Landspitali University Hospital, Reykjavik). H Hardardottir (Landspitali University Hospital, Reykjavik) *Ireland:* F Fitzpatrick* (Health Protection Surveillance Centre, Dublin) M Skally* (Health Protection Surveillance Centre, Dublin). E Smyth† (Beaumont Hospital, Dublin). L Fenelon† (St Vincents University Hospital, Dublin). K Schaffer† (St Vincents University Hospital, Dublin). M Cormican† (University College Hospital, Galway) *Italy:* P Mastrantonio* (Istituto Superiore di Sanità [National Institute of Health], Rome). A Raglio† (Ospedali Riuniti di Bergamo, Bergamo). P Nicoletti† (Azienda Ospedaliera Careggi, Firenze). G Dettori† (Azienda Ospedaliera Universitaria, Parma). P Mazzella†, (Policlinico Universitario, Università Cattolica del Sacro Cuore, Roma). T Zaccaria† (Azienda Ospedaliera S.Giovanni Battista di Torino, Torino). *Latvia:* A O Balode* (Central laboratory, Paul Stradins Clinical University Hospital, Riga). K Aksenoka† (Paul Stradins Clinical University Hospital, Riga). G Zvingelis† (Riga 1st City Hospital, Riga). M Liepins† (Riga City Hospital Gailezers, Riga). *Liechtenstein:* C Lee* (Labormed. Zentrum Dr. Risch, Schaan). *Luxembourg:* J Mossong* (Laboratoire National de Santé, Luxembourg). J Even (Laboratoire National de Santé, Luxembourg) A Hakim† (Clinique Sainte Thérèse, Luxembourg). Malta: P Caruana* (Mater Dei Hospital, Msida). *Netherlands:* E J Kuijper*† (Leiden University Medical Centre, Leiden). S B Debast† (Meander Medical Centre, Amersfoort). P Bloembergen† (Isala klinieken, Zwolle). C Harmanus (Leiden University Medical Centre, Leiden). I Sanders (Leiden University Medical Centre, Leiden) *Norway:* A Ingrebretsen*† (Rikshospitalet University Hospital, Oslo). BG Iversen* (Norwegian Institute of Public Health, Oslo). P A Jenum† (Asker and Baerum Hospital, Rud). J E Afset† (St Olav Hospital/Trondheim University Hospital, Trondheim) *Poland:* H Pituch* (Medical University of Warsaw, Warsaw) J Pawlowska† (Province Hospital Plock, Plock). H Pituch† (The Infant Jesus Teaching Hospital, Warsaw). H Pituch† (Public Central Clinic Hospital, Warsaw). *Portugal:* C Furtado* (Instituto Nacional de Saude Dr. Ricardo Jorge, Lisboa). R Guiomar Moreira* (Instituto Nacional de Saude Dr Ricardo Jorge, Lisboa); J Machado* (Instituto Nacional de Saude Dr. Ricardo Jorge, Lisboa). I. Sancho† (Hospital Fernando Fonseca, Amadora). G Ribeiro† (Hospital da Universidade de Coimbra, Coimbra). H Ramos† (Hospital Geral de Santo António, Porto). *Romania:* D Lemeni* (Cantacuzino Institute, Bucarest). R Serban* (The Institute for Public Health Bucharest, Bucarest). M Ciocîrlan† (Fundeni Clinic Institute, Bucharest). A Rafila† (Matei Bals Institute for Infectious Diseases, Bucharest). G Lesanu† (Grigore Alexandrescu Emergency Clinical Hospital for Children, Bucharest). E Danaila† (Military Central Emergency Hospital, Bucharest). E Szekely† (Targu-Mures Emergency Hospital, Targu-Mures). *Slovakia:* R Melková* (Slovak Medical University, Bratislava). E Novakova† (Martinska Fakultna Nemocnica, Martin). L Glosova† (Fakultna Nemocnica Trencin, Trencin). E Novakova† (Nemocnica s Poliklinikou Zilina, Zilina). *Slovenia:* M Rupnik* (Institute of Public Health, Maribor). T Lejko Zupanc† (University Clinical Centre, Ljubljana). B Kotnik Kevorkijan† (University Clinical Centre, Maribor). G Lesnicar† (Hospital, Celje). *Spain:* E Bouza* (Hospital General Universitario Gregorio Marañón, Madrid). I. Alcalá Hernández† (Hospital General Universitario Gregorio Marañón, Madrid). J Abarca† (Hospital Clinico San Carlos-Complejo Hospitalario, Madrid). A Mena Ribas† (Hospital Son Dureta-Complejo Hospitalario, Palma de Mallorca). I Sanfeliú Sala† (Corporació Sanitària Parc Taulí, Sabadell [Barcelona]). MI García García† (Hospital Universitario de Salamanca-Hospital Clínico y Hospital Virgen de la Vega, Salamanca). *Sweden:* T Åkerlund* (Swedish Institute of Infectious Disease Control, Solna). M Wullt† (Malmö Allmänna Sjukhus, Malmö). T Norén† (Universitetssjukhuset Örebro, Örebro). A Weintraub† (Södersjukhuset, Stockholm). C Nord† (Södersjukhuset, Stockholm). *Switzerland:* A F Widmer*† (University Hospital, Basel). A Widmer† (Claraspital, Basel). A Widmer† (Felix Platter Spital, Basel). *Turkey:* B Levent * (Refik Saydam National Hygiene Center, Ankara). S Kacar† (Yuksek Ihtisas Hospital, Ankara). G Hascelik† (Hacettepe University Medical Faculty, Ankara). B Sener† (Hacettepe University Medical Faculty, Ankara). O Azap (Baskent University Hospital, Ankara). H Arslan† (Baskent University Hospital, Ankara). M. Siniras† (Uludag University, Bursa). H Akalin† (Uludag University, Bursa). N Ulger† (Marmara University, Kadikoy, Istanbul). G Soyletir† (Marmara University, Kadikoy, Istanbul). M Petrovska† (Institute of Microbiology and Parasitology, Skopje) *United Kingdom–England:* M Wilcox*† (Leeds General Infirmary, Leeds). B Patel *† (Health Protection Agency, London; Northwick Park Hospital, Harrow; Central Middlesex Hospital, London). *United Kingdom–Northern Ireland:* P Rooney† (Belfast City Hospital, Belfast). *United Kingdom–Scotland:* C Wiuff* (Health Protection Scotland, Glasgow). A Gibb† (Royal Infirmary of Edinburgh, Edinburgh). J Coia† (Stobhill Hospital, Glasgow). *European Centre for Disease Prevention and Control:* A Navarro Torné (European Centre for Disease Prevention and Control, Stockholm, Sweden). P Tüll (European Centre for Disease Prevention and Control, Stockholm, Sweden).

Conflicts of interest

The authors declared no conflicts of interest.

Participating laboratories/ hospitals

Methods

November 2008, follow-up February 2009

Patients >2 years suspected of CDI or inpatients developing diarrhoea after ≥3 days of admission

CDI case definition: compatible clinical picture and positive stool test for *C. difficile* toxin

Of every first 10 patients per hospital:

- questionnaires on inclusion and 3 months follow-up
- stools cultured locally
- isolates sent to Leiden University Medical Centre for PCR-ribotyping and testing for presence of toxin genes

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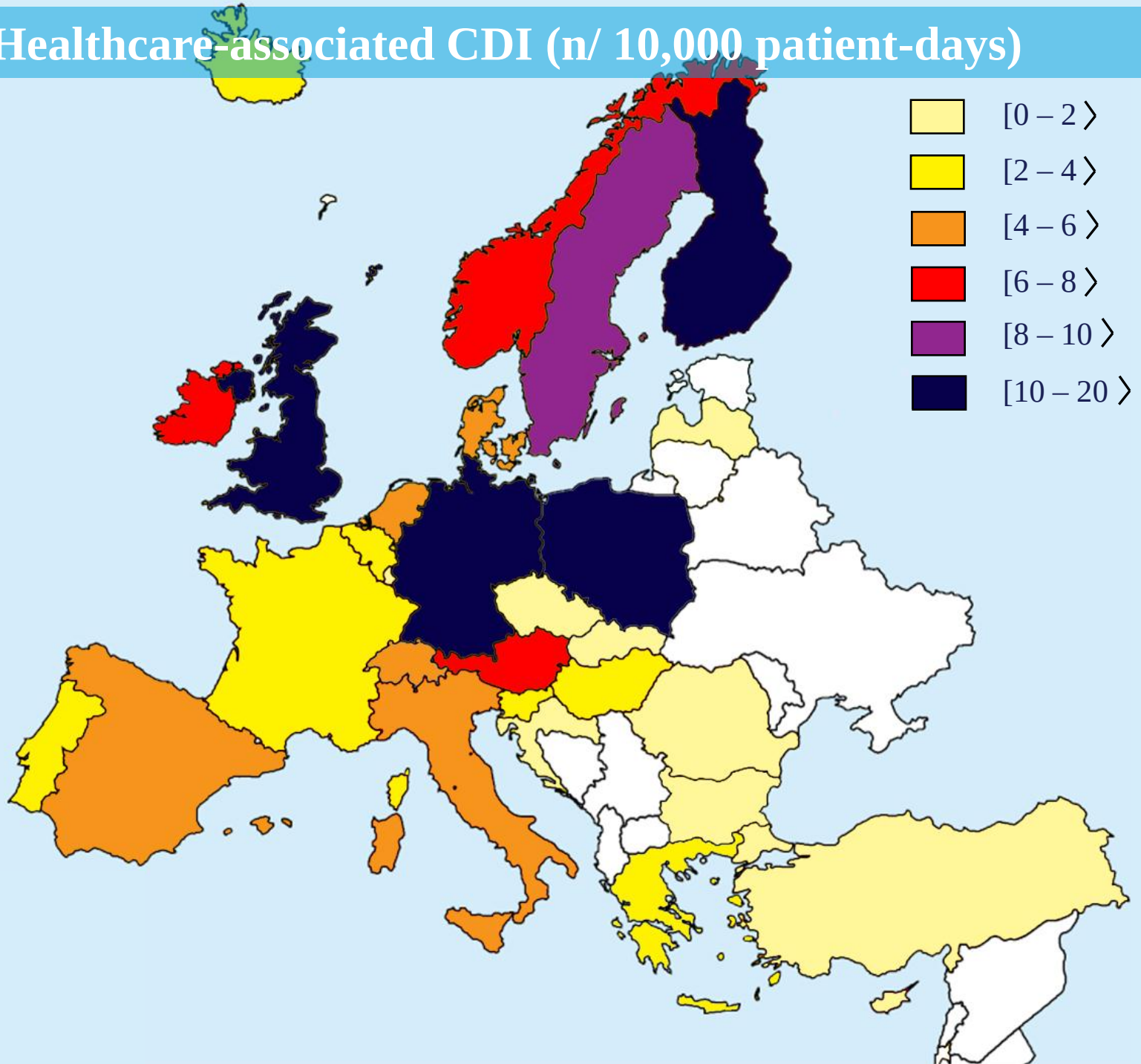
Analysis

Incidence rates of healthcare-associated CDI: (number of CDI cases x proportion of healthcare-associated CDI)/ patients-days or admissions

Odds ratios of patient and pathogen characteristics and outcome parameters (i.e., severe CDI and recurrence)

Relevant variables analyzed by logistic regression

Healthcare-associated CDI (n/ 10,000 patient-days)



Patient characteristics

- 509 included, 484 in follow-up
- 80% healthcare-associated
- Age median 71 (IQR 56 – 81) yr
- 44% severe comorbidity, 50% immunocompromised
- 16% episodes of CDI in previous 8 weeks
- 79% antibiotics in previous month, 92% in previous 3 months
- 28% diarrhoea > 1 week
- 4% ileus
- 29% last leukocyte count ≥ 15 · 10^9/L

Follow-up after 3 months

- 7% ICU admissions
  - 23% CDI contributive or primary cause
- 0.7% colectomies for CDI
- 22% died
  - 40% CDI contributive or primary cause
- 18% recurrent CDI

Determinants of severe CDI

	Univariate		Multivariate	
Characteristic	OR	95%CI	OR	95%CI
Age ≥ 65 years	4.87	1.88 – 12.63	3.44	1.12 – 10.52
Healthcare-associated	3.29	0.99 – 10.90		
Severe comorbidity	1.17	0.61 – 2.23		
Heart disease	1.52	0.60 – 3.85		
Pulmonary disease	2.52	1.16 – 5.50		
Antibiotics during previous month:				
aminopenicillin + βL inh.	2.05	1.01 – 4.14		
3rd or 4th generation fluoroquinolone	2.85	1.08 – 7.55		
macrolide	2.59	0.91 – 7.36		
Episodes of CDI in previous 8 weeks	0.84	0.31 – 2.24		
PCR-ribotype:				
027	4.18	1.03 – 17.05	5.56	1.29 – 23.92
015	5.78	1.59 – 20.95	9.06	2.31 – 35.47
018	7.10	2.53 – 19.94	7.20	2.45 – 21.14

Determinants of recurrent CDI

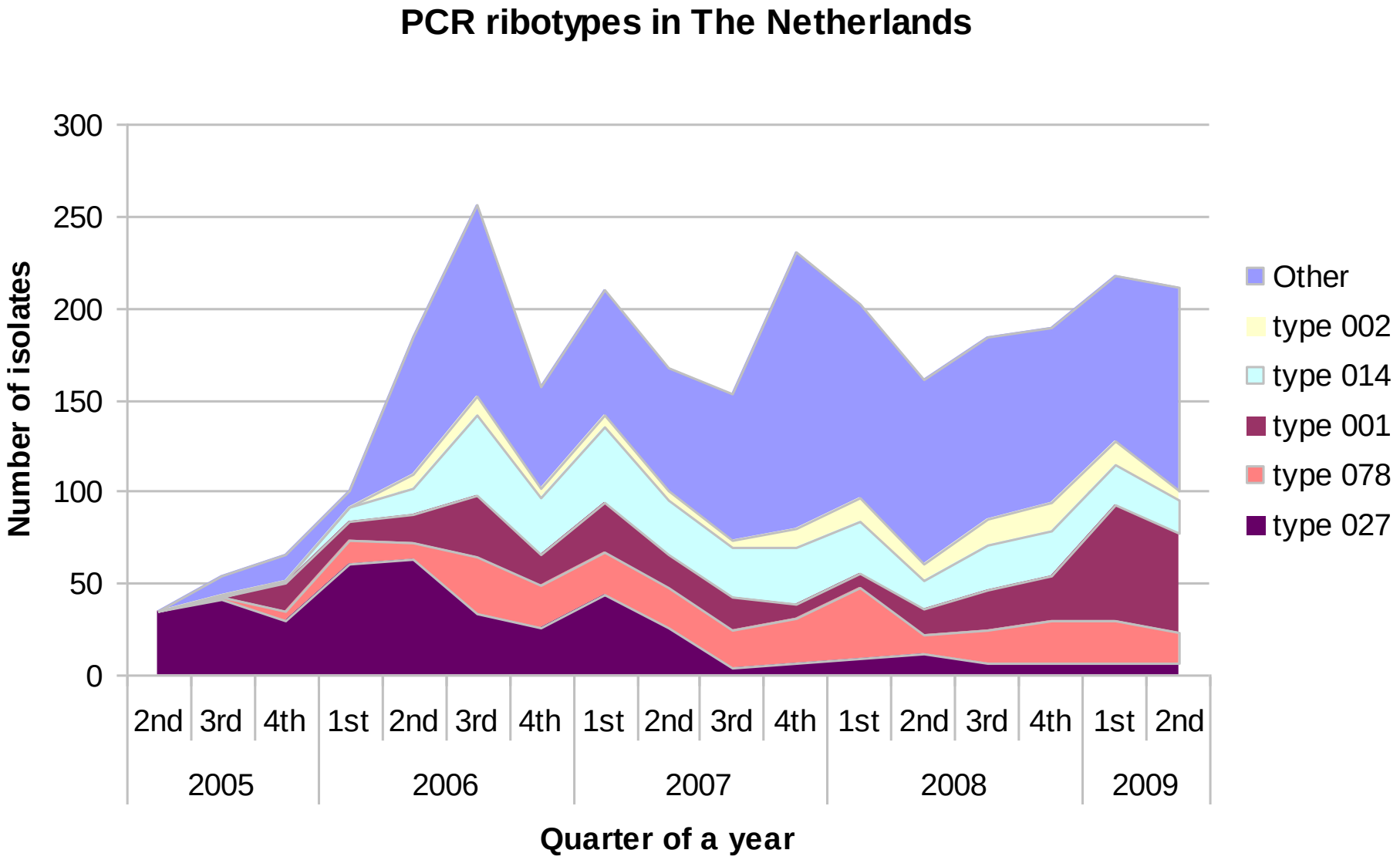
	Univariate		Multivariate	
Characteristic	OR	95%CI	OR	95%CI
Age ≥ 65 years	1.88	1.11 – 3.17	1.98	1.10 – 3.59
Healthcare-associated	1.95	0.96 – 3.93		
Severe comorbidity	1.32	0.81 – 2.17		
Antibiotics during previous month:				
antipseudomonal penicillin + βL inh.	1.74	0.81 – 3.75		
ceftazidime	2.12	1.19 – 3.78	2.22	1.16 – 4.26
glycopeptide	1.92	0.85 – 4.35		
Episodes of CDI in previous 8 weeks	2.34	1.27 – 4.30	2.75	1.46 – 5.19

Conclusions – surveillance Nov 2008

- The incidence of CDI varied widely in Europe
- Many PCR-ribotypes, in particular 014, 001 and 078
- Most cases healthcare-associated
- The classical risks old age, comorbidity and antibiotic use
- During follow-up, 22% of patients died (40% CDI contributive)
- Severe disease in elderly, PCR-ribotypes 015, 018 and 027
- Recurrent disease in elderly, ceftazidime use and number of prior episodes of CDI
- Clinical characteristics of CDI were not strongly correlated with a complicated course or recurrence of disease

Limitations of study method

- Patients/ samples representative for whole country?
  - maximum of 10 patients per hospital
  - selection of hospitals
- Local toxin tests, culture methods and data retrieval varied
- Cases defined by toxin test, not culture
- Distribution across Europe: higher incidence or higher awareness?


PCR ribotypes in The Netherlands
Number of isolates
300
250
200
150
100
50
0
2nd
3rd
4th
1st
2nd
3rd
4th
1st
2nd
3rd
4th
1st
2nd
3rd
4th
1st
2nd
2005
2006
2007
2008
2009
Quarter of a year
Other
type 002
type 014
type 001
type 078
type 027

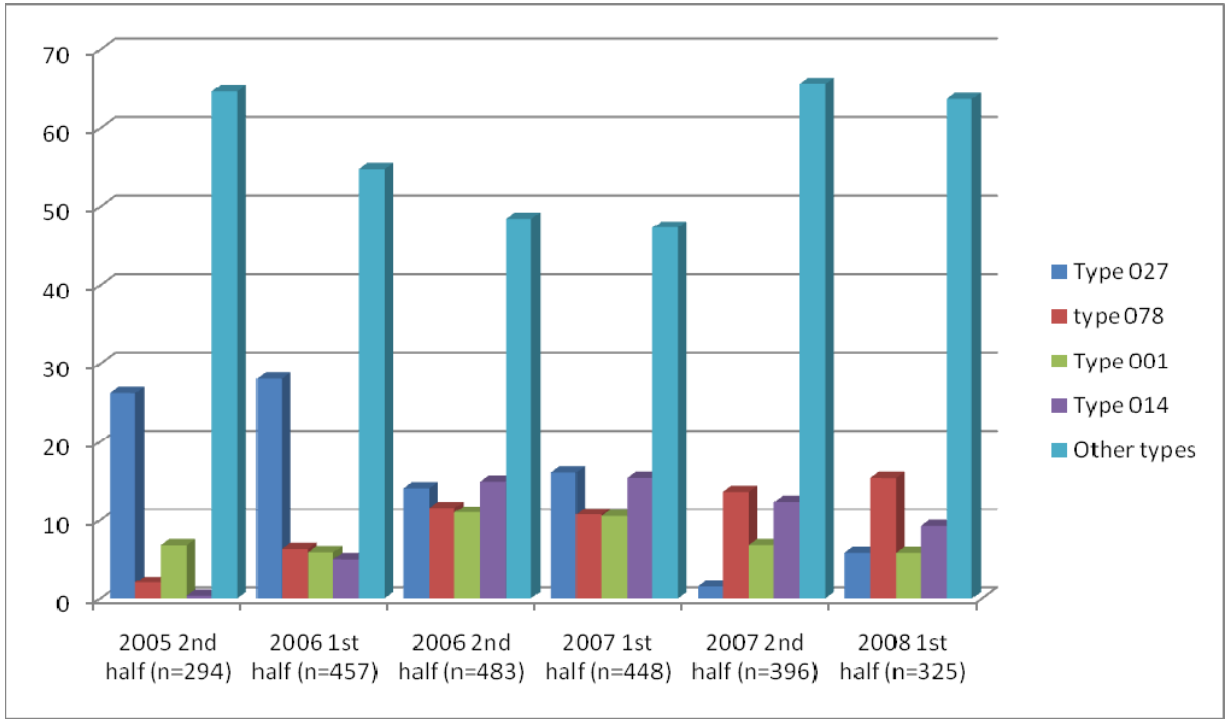
Emergence of *Clostridium difficile* Infection Due to a New Hypervirulent Strain, Polymerase Chain Reaction Ribotype 078

Clinical Infectious Diseases 2008; 47:1162–70

Abraham Goorhuis,[1] Dennis Bakker,[1] Jeroen Corver,[1] Sylvia B. Debast,[3] Celine Harmanus,[1] Daan W. Notermans,[2] Aldert A. Bergwerff,[4] Frido W. Dekker,[5] and Ed J. Kuijper[1]

Departments of [1]Medical Microbiology and [2]Clinical Epidemiology, Leiden University Medical Center, Leiden, [3]Center for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, [4]Department of Medical Microbiology, Meander Medical Center, Amersfoort, and [5]Department of Veterinary Medicine, University of Utrecht, Utrecht, The Netherlands

Type 078 similar severe CDI as Type 027, but at a younger population and more frequently CA



Emerging *Clostridium difficile* 078

Clinical

- Attributable mortality within 30 days: 3.8%
- Complications: 9.6%
- Relapse rate: 15.8%
- Severe diarrhoea as 027, but affects younger patients

Characteristics of the strain

– *tcdA* and *tcdB*	Positive
– *tcdC*	39 bp deletion
– *tcdC*	mutation at 184, stopcodon
– *ermB*	Negative
– Binary toxin	Positive

Genotyping of the strain

– PCR-ribotyping	078
– Toxinotyping	V
– Further subtyping	MLVA?

The Netherlands, Northern Ireland

US: third most common prevalent type in CA-CDI
European study 2005: 11th type
France: 3,25% in 2006 to 11% in 2007

Antibiotics and CDI due to Types 078 and 027

Risk factor	Proportion of patients with CDI (%)		
	Type 078	Type 027	Other types
Antibiotic therapy			
Any	44/52 (84.6)	110/123 (89.4)	425/501 (84.8)
Penicillins	23/51 (45.1)	55/122 (45.1)	236/478 (49.4)
Cephalosporins			
All	22/51 (43.1)	68/121 (56.2)[d]	201/477 (42.1)
First generation	1/48 (2.1)	8/121 (6.6)	34/456 (7.5)
Second generation	9/48 (18.8)	36/112 (32.1)[d]	85/456 (18.6)
Third generation	10/48 (20.8)	21/112 (18.8)	91/456 (20.0)
Fluoroquinolones	15/51 (29.4)[c]	37/122 (30.3)[d]	95/480 (19.8)
Macrolides and clindamycin	6/51 (11.8)	15/121 (12.4)[c]	94/480 (19.6)
Aminoglycosides	9/51 (17.6)	6/123 (4.9)[a]	52/481 (10.8)
Carbapenems	4/51 (7.8)	4/120 (3.3)	23/473 (4.9)
Vancomycin	4/51 (7.8)	18/123 (14.6)[c]	43/479 (9.0)
Metronidazole	6/51 (11.8)	16/121 (13.2)	41/480 (8.5)
Sulfonamides and trimethoprim	7/51 (13.7)	11/121 (9.1)	68/478 (14.2)

Clostridium difficile PCR ribotype 078 toxinotype V found in diarrhoeal pigs identical to isolates from affected humans

Environmental Microbiology (2008)

Sylvia B. Debast,[1] Leo A. M. G. van Leengoed,[2]
Abraham Goorhuis,[3] Celine Harmanus,[3]
Ed J. Kuijper[3] and Aldert A. Bergwerff[4]*

Two herds with outbreaks of diarrhoea in piglets (1 year)

Yellow to orange watery diarrhoea

High morbidity (80%), low mortality (12%), growth rates were affected

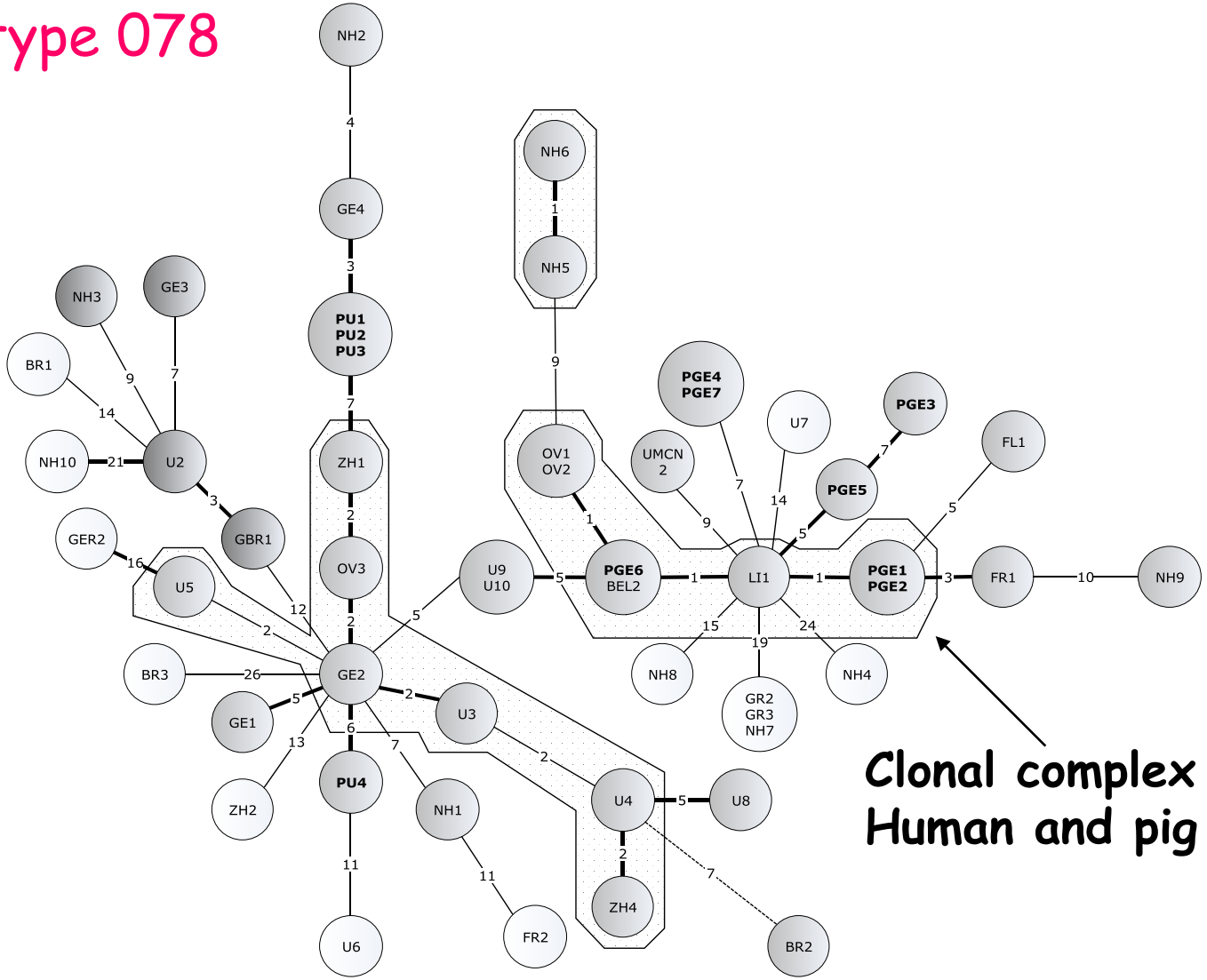
Periparturient medication of sows with trimethoprim-sulfadiazin, vaccination and use of amoxicilline:

Exsudative fibrino-haemorragic colitis of colon, but no necrotic lesions in mucosa of small intestine *(C. perfringens).* Mesocolonic oedema.

Cultures for C. perfringens negative.

No Isospora suis or rotavirus.

MLVA type 078



Clonal complex with Human and pig isolates

MLVA of 65 *Clostridium difficile* Type 078 isolates: 54 human isolates and 11 porcine isolates.

CLOSTRIDIUM DIFFICILE IN A FARROWING PEN

Hopman, N.E.M., Keessen, E.C., Harmanus, C, van Leengoed, L.A.G.M., Kuijper, E, Lipman, L.J.A.

- Dutch pig-breeding farm with 200 sows
- All sampled 72 newborn piglets, irrespective of the presence of diarrhoea, acquired C. difficile 078 within two days after birth. Within this herd, just one ribotype, CD ribotype 078, was isolated from neonatal piglets, sows and from the environment (floor, air) of the piglets.
- None of the 38 piglets born by caesarean section became positive for the presence of CD 078

Relatedness of human and animal *Clostridium difficile* PCR Ribotype 078 isolates

(collaboration with Mark Wilcox, Leeds)

101 human isolates

44 Northern Ireland

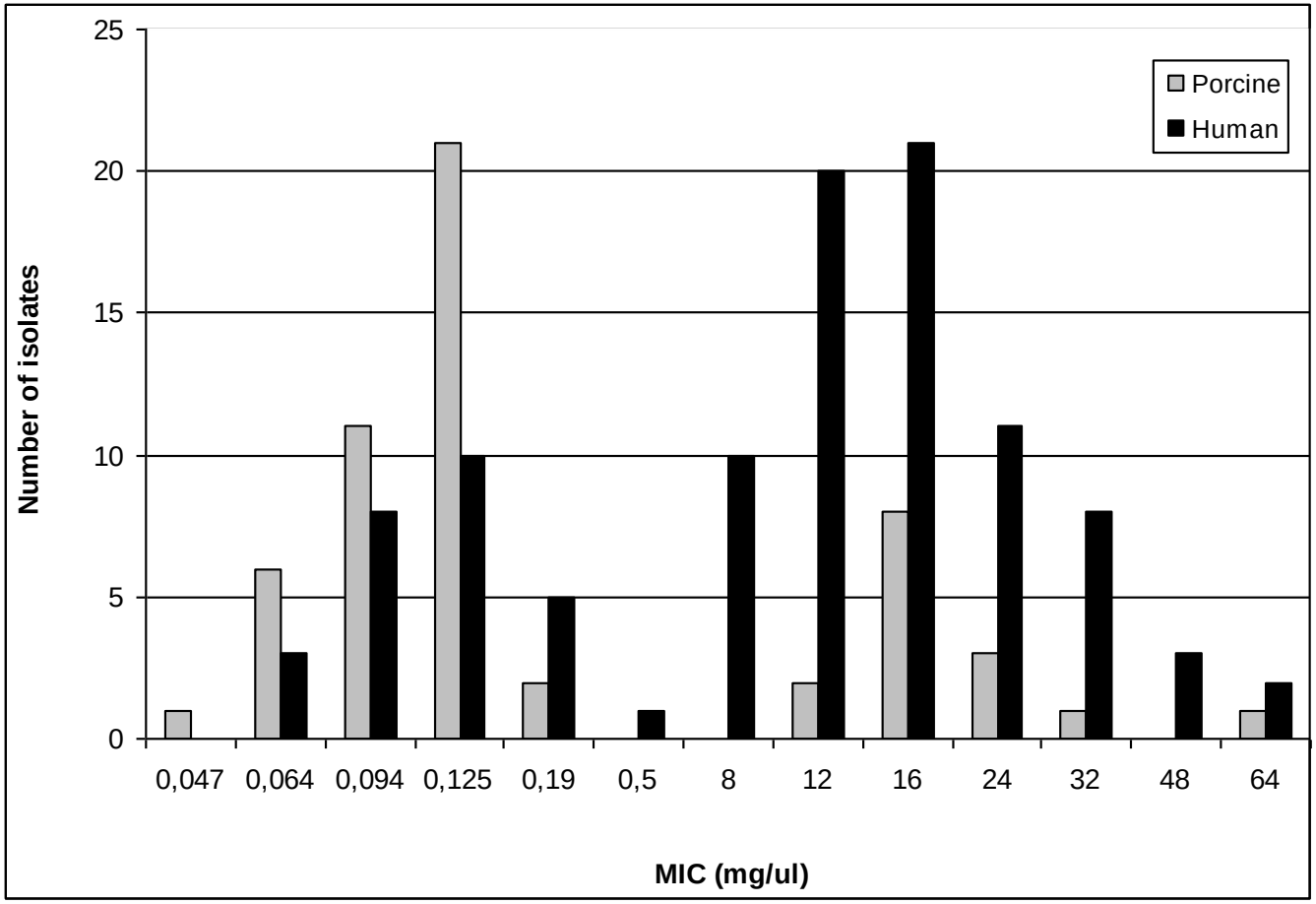
20 other parts UK

3 Ireland

34 The Netherlands

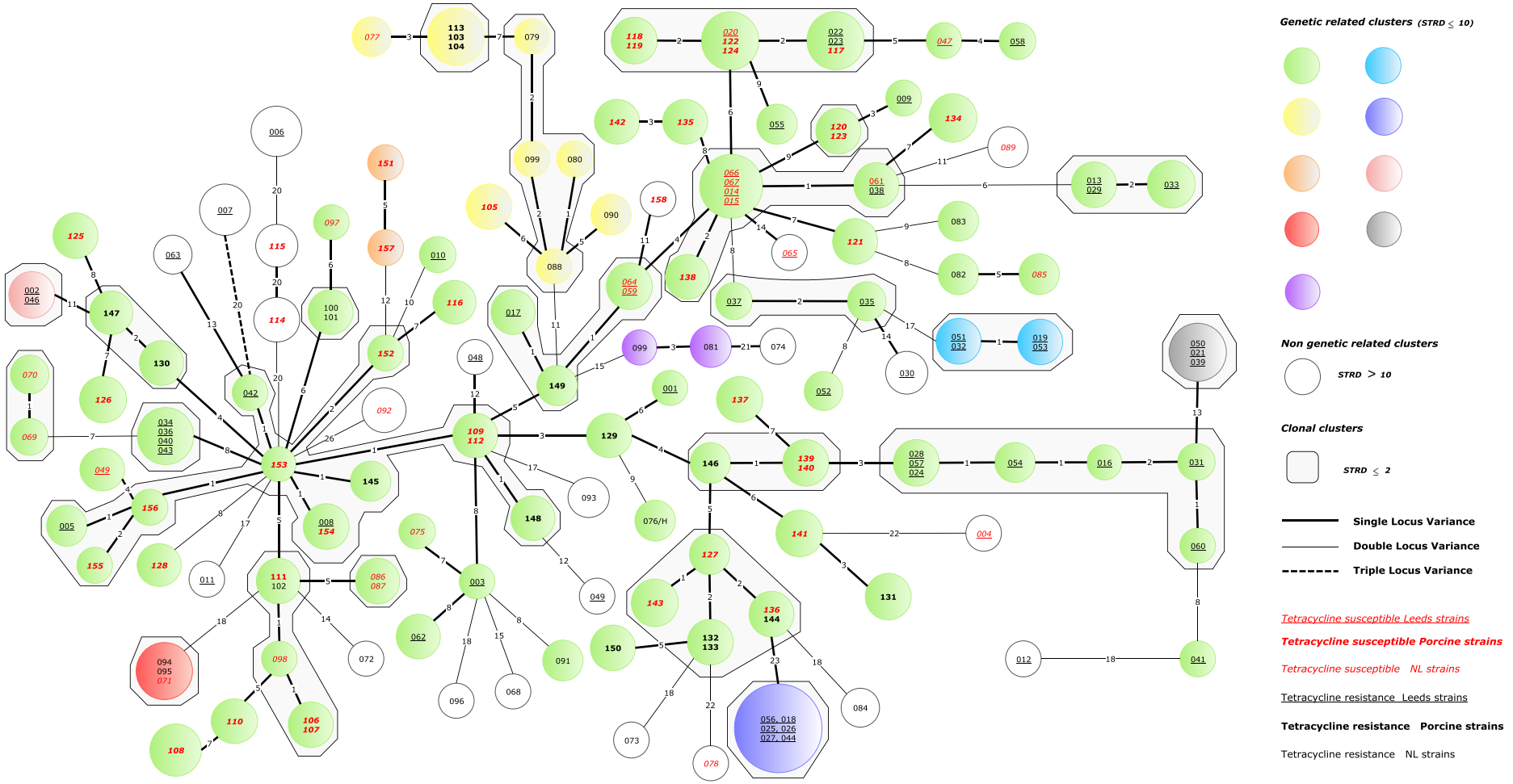
56 porcine isolates

11 different pigfarms in 2006-2009



74% of human type 078 strains, 27% porcine type 078 strains were resistant to tetracycline (MIC≥ 8 mg/l); $p<0.05$.

All tetracycline resitant strains had Tn916-like transposon



23 CC (STRD ≤ 2);

5 CC human and animal isolates, 5 porcine, 13 human (6 specific region)
12 CC only tetracycline resistant isolates, 3 tetra susceptible, 8 mixed

Interspecies transmission:

Supporting capacity building for surveillance of *Clostridium difficile* infections at European level *(2010-2013)*

Tenderer: Ed J. Kuijper,
Department of Medical Microbiology, Leiden University Medical Centre, Leiden, the Netherlands

ECDC: Carl Suetens

Investigator: drs. Marjolein Hensgens, LUMC/ RIVM, The Netherlands

Manager: Walter Zuijderduin, LUMC, Leiden

Website: www.ecdisnet.eu

Website: www.ecdisnet.eu

ECDIS-Net

Supporting capacity building for surveillance of C. difficile

ESGCD ESCMID STUDY GROUP FOR CLOSTRIDIUM DIFFICILE

European Society of Clinical Microbiology and Infectious Diseases

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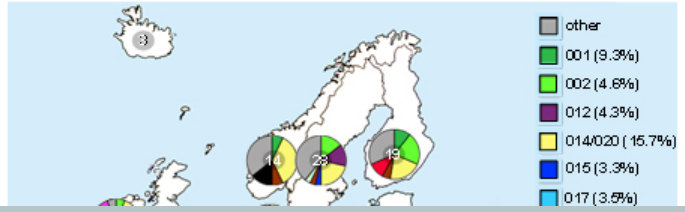
Supporting capacity building for surveillance of Clostridium difficile infections at European level (2010-2014)

Clostridium difficile infections (CDI) are an important healthcare problem across Europe. To improve recognition and awareness, and to enable surveillance at a European level, the European Centre of Disease Prevention and Control (ECDC) funded an upcoming project to enhance laboratory capacity for CDI detection and surveillance in Europe (2010-2014). This project will not be a duplication of the previous European *Clostridium difficile* infection study (ECDIS), but instead will be used to strengthen the network and capacity building for CDI surveillance on national and European level. We have therefore called the new project "European Clostridium difficile infection surveillance network (ECDIS-net)".

Background

After the recognition of a new hypervirulent *Clostridium difficile* strain, PCR ribotype 027, in 2005 in Europe, the ESCMID Study Group on *Clostridium difficile* (ESGCD) contacted ECDC leading to several actions. A background document on CDI was written, guidance documents were published, and a first pan-European surveillance study, the "European Clostridium Infection Survey (ECDIS)" was performed in 2008-2009. Results of this study have been published in Lancet (Bauer et al. *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet. 2011;377:63-73). Based on the results of the ECDIS study, it was decided to provide support for further capacity building for surveillance of CDI across Europe.



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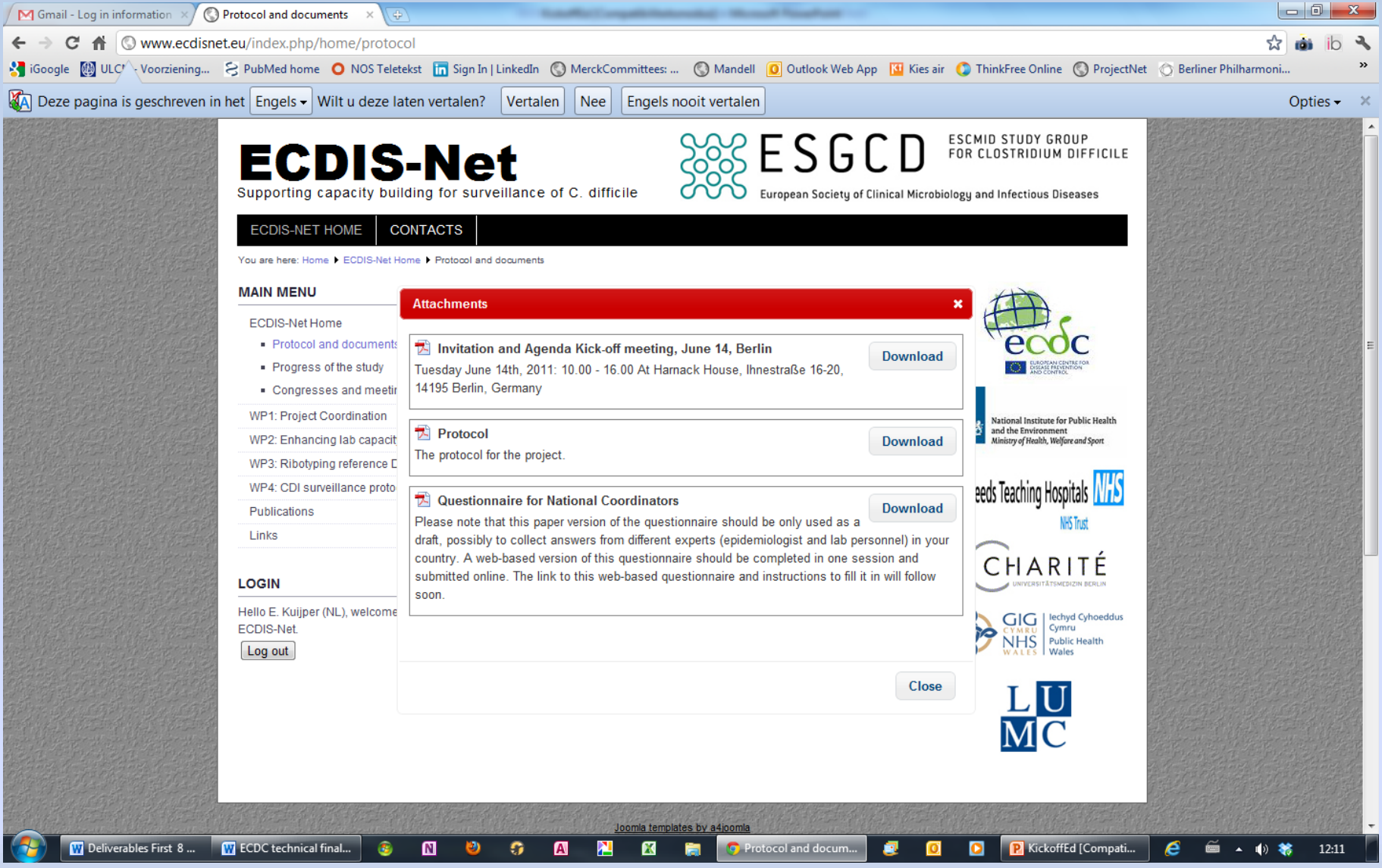
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Attachments
Invitation and Agenda Kick-off meeting, June 14, Berlin
Tuesday June 14th, 2011: 10.00 - 16.00 At Harnack House, Ihnestraße 16-20, 14195 Berlin, Germany
Download
Protocol
The protocol for the project.
Download
Questionnaire for National Coordinators
Please note that this paper version of the questionnaire should be only used as a draft, possibly to collect answers from different experts (epidemiologist and lab personnel) in your country. A web-based version of this questionnaire should be completed in one session and submitted online. The link to this web-based questionnaire and instructions to fill it in will follow soon.
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Supporting capacity building for surveillance of *Clostridium difficile* infections at European level

- To enhance the laboratory capacity for detection and surveillance of *Clostridium difficile* in European Member States (MS), Norway, Iceland and Liechtenstein.
- To build up and maintain a European ribotyping nomenclature reference database for *Clostridium difficile*.
- To develop a enhanced CDI surveillance protocol.

Coordinators

Beneficiary Number	Beneficiary name	Resonsible coordinator	Country	Leader of WP	Participating in WP
1	Leiden University Medical Center, Leiden	E.J.Kuijper	NL	1	2,3,4
2	Leeds Teaching Hospitals NHS Trust, & Health Protection Agency	M.H.Wilcox		1	2,3,4
3	Center for Infectious Diseases Control (Cib), RIVM, Bilthoven	D.W Notermans	NL	2	3,4
4	Anaerobe Reference Laboratory, Cardiff, Wales	V. Hall		3	2,,4
5	Charité - Universitätsmedizin Berlin	P. Gastmeier	Germany	4	2,3

Supporting capacity building for surveillance of *Clostridium difficile* infections at European level: Other participants

- National Public Health Institute, Helsinki (A. Virolaine , Outi Lyytikäinen)
- University of Szeged, Szeged (E. Nagy)
- National Institute of Health (ISS), Rome (P. Mastrantonio)
- National Reference centre for HAI, Sofia (Rossitza Vatcheva-Dobrevska and K. Ivanova)
- AGES-Institut für medizinische Mikrobiologie und Hygiene, Vienna (A. Indra)
- University College Dublin and Health Protection Surveillance Centre (HPSC), Dublin (L. Kyne and F. Fitzpatrick)
- Institut de Veille Sanitaire, Saint-Maurice Cedex (F. Barbut)
- Health Protection Scotland, Glasgow (Camilla Wiuff)
- Department of Epidemiology, Swedish Institute for Infectious Disease Control (Johan Struwe)

Work packages

Work package	Coordinators	Time period
(1) Project Coordination	Mark Wilcox and Ed Kuijper (Leeds and Leiden)	0-36 months
(2) Enhancing laboratory capacity for CDI detection in EU Member States.	Daan Notermans (RIVM, The Netherlands)	0-24 months
(3) Establishing a European ribotyping nomenclature reference database for *Clostridium difficile* in close collaboration with ECDC (TESSy).	Val Hall (Cardiff, Wales)	4-24 months
(4) To develop a European enhanced CDI surveillance protocol	Petra Gastmeier (Charité, Berlin)	0-24 months
Perform a feasibility study by implementing the protocol in at least 6 Member States	Petra and others	24-36 months

Work package 1; Project Coordination

Work package leaders: dr. Ed Kuijper (Leiden) and prof. Mark Wilcox (Leeds)

- Objective 1. Set up a project coordination group and a network of representatives from each EU Member State, EU-MS, Norway, Iceland and Liechtenstein and candidate countrie
- Objective 2. Communication between the consortium members and TESSY at ECDC.
- Objective 3. Budgetary control.
- Objective 4. Consortium reporting to the ECDC

Work package 2: Enhancing laboratory capacity for CDI detection in EU Member States.

Work package leader: dr. Daan Notermans, CIb, RIVM, Bilthoven, The Netherlands.

- Objective 1. Set up a network of CDI-reference labs
- Objective 2. Perform an assessment of MS primary diagnostic laboratory capacity for *Clostridium difficile* and for typing capacity (ribotyping of CD isolates) and the need for training.
- Objective 3. A proposal for standard operating procedures (SOPs) for the routine culture of *Clostridium difficile* isolates
- Objective 4. A training module will be designed for culturing *C. difficile* and a re-assessment will be performed after implementation of the training module

Web based questionniare
(Dr. Daan Notermans, RIVM, The Netherlands)

- National coordinators of 32 countries were requested to select at random 10% of all laboratories to participate in a questionnairre on laboratory diagnostics
- Minimum of 3 laboratories
- 31 coordinators replied
- 12/30 (38%) national guidelines to test for CDI
- 22/30 (71%) of the countries had a laboratory capable to type *C. difficile*
- 14/27 (52%) had "national reference laboratories" officially funded
- 20/22 laboratories performed PCR ribotyping
- 48 and 58% responded that training for culturing and typing was needed

ECDIS-net training module at Leiden University, 14 and 15 March 2012

Programme:

Day 1:

10.00 – 11.00	Registration with tea and coffee		
11.00 – 11.15	Welcome		dr. Ed Kuijper
11.15 – 11.30	Practical issues hotels / travel expenses		Walter Zuiderduin
11.30 – 12.00	Methods of identification and typing of *C. difficile*	(lecture)	dr. Ed Kuijper
12.00 – 12.30	Agarose gel based PCR-ribotyping		dr. Val Hall
12.30 – 13.00	Capillary gel based PCR-ribotyping		dr. Warren Fawley
13.00 – 14.00	Lunch		
14.00 – 16.30	Practical demonstration: identification and typing of *C. difficile*		(all)

Day 2:

09.00 – 09.30	European SOP for isolation of *C. difficile**	dr. Daan Notermans
09.30 – 10.15	European ribotyping nomenclature & reference database	prof. Mark Wilcox
10.15 – 10.30	Coffee	
10.30 – 12.30	Practical demonstration of agarose based PCR ribotyping	(all)
12.30 – 13.30	Lunch	
13.30 – 15.30	Practical demonstration of capillary PCR ribotyping	(all)
15.30 – 15.45	Wrap-up and closure	dr. Ed Kuijper

Work package 3; Establishing a European ribotyping nomenclature reference database for *Clostridium difficile* in close collaboration with ECDC (TESSy).

Work package leader: dr.Val Hall, ARU, Cardiff, UK.

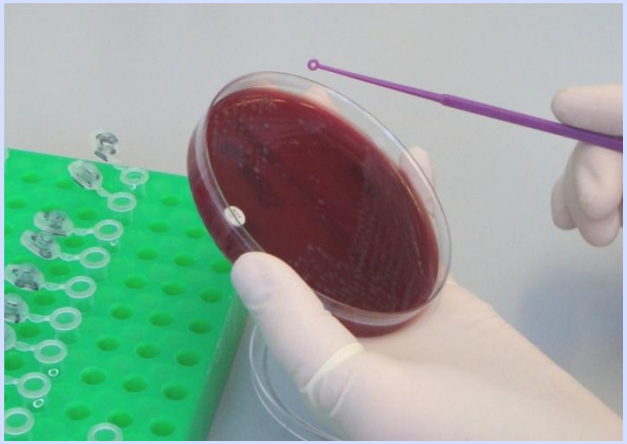
- Objective 1. Build up and maintain a ribotyping nomenclature reference database for *Clostridium difficile*.
- Objective 2. Provide free of charge service to MS reference laboratories for sharing *C. difficile* reference strains.
- Objective 3. Provide a written document on SOPs and propose a guideline for the ribotyping of *Clostridium difficile isolates* in EU
- Objective 4. Provide External Quality Assesment (EQA) for national reference laboratories in the MS for ribotyping and assessment of antimicrobial resistance of *C. difficile* strains (yearly or 6-monthly

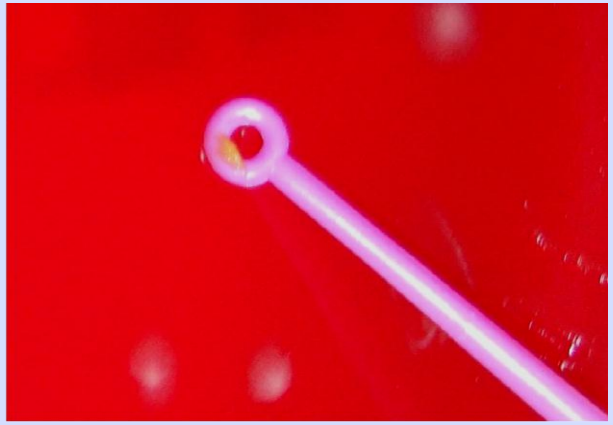
ARU collection of >15,000 *C. difficile* isolates

- 345 distinct ribotypes recognised
  - >1000 isolates of types 001, 027 & 106.
  - 100-1000 isolates of 13 ribotypes.
  - 11-100 isolates of 53 ribotypes.
  - <5 isolates of 226 ribotypes.
- Most common types are in the ECDC/Leeds collection.

PCR-ribotyping agarose gel method

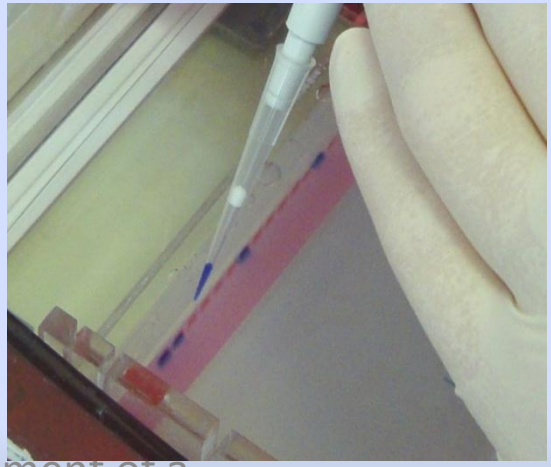
1. Extract DNA from pure culture (<24h old) in 5% Chelex-100 resin. Heat at 100°C 12min.
2. Centrifuge, use supernate as template.
3. Amplify with O'Neill 16S – 23S primers.

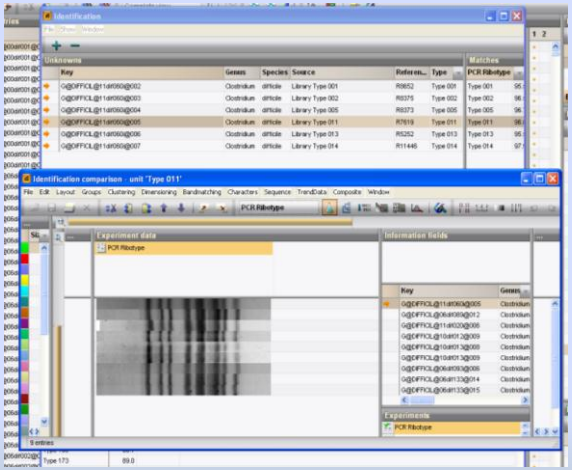




PCR-ribotyping agarose gel method

4. Concentrate amplicons at 75°C for ~45min.
5. Separate amplicons in Metaphor agarose gel (3%) with 100-1000bp ladder, 3h @ 60mA.
6. Capture image. Save as .tif file.
7. Use GelCompar / Bionumerics to compare band patterns with library of known ribotypes.

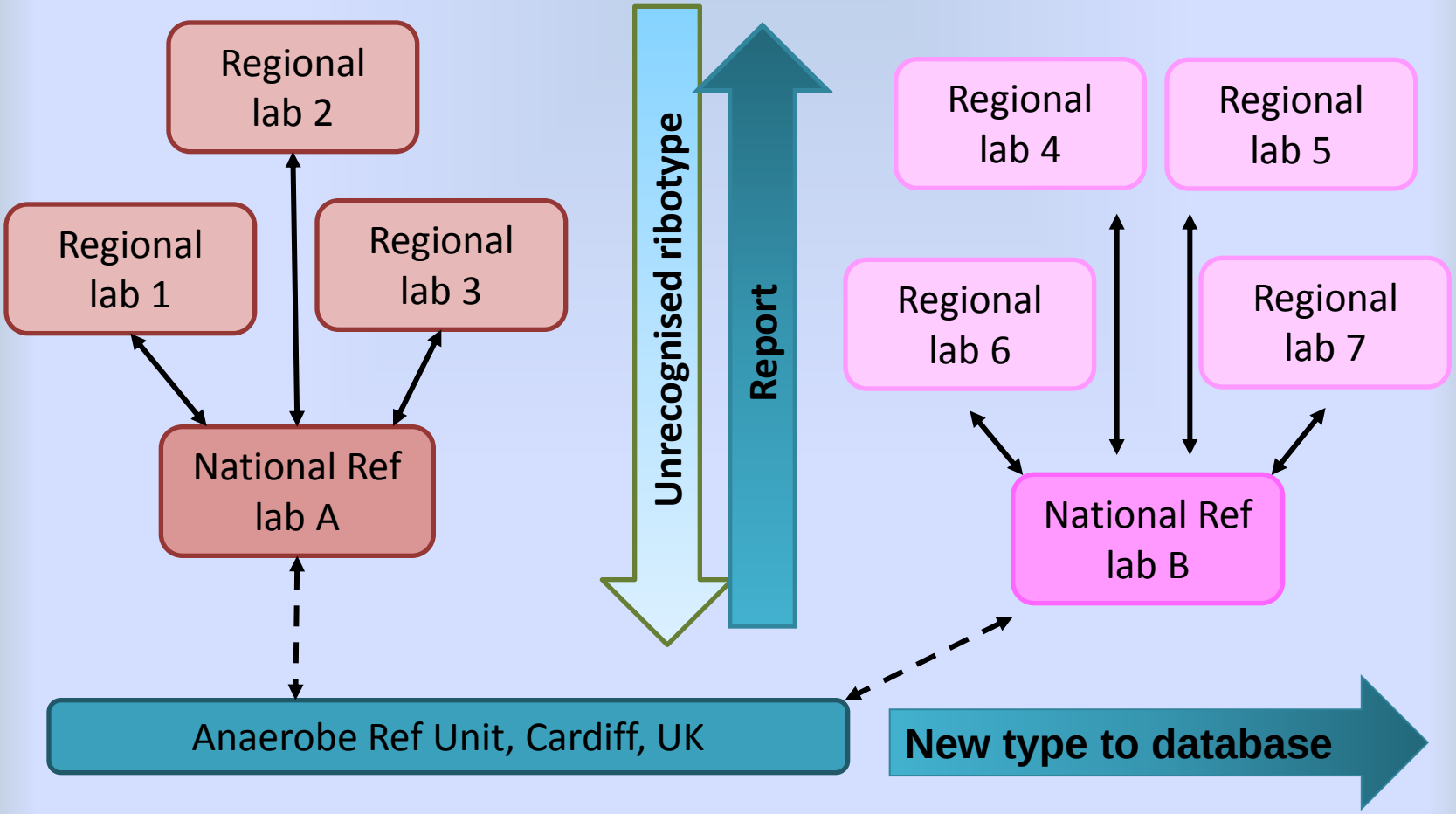




Agarose- vs. capillary-gel methods

- **Agarose gel method**
  - Only basic equipment needed
  - Proven technology
  - Database of 345 types established
  - Database not easily shared
  - Analysis is labour-intensive
  - Less practical for large numbers of isolates
- **Capillary gel method**
  - High cost equipment
  - Evaluations in progress
  - Database to be constructed
  - Practical for inter-lab use
  - Less subjective analysis
  - Larger throughput possible

Proposed network of typing labs



Establishment of a European ribotyping nomenclature reference database for *C. difficile*

CDC/PHAC/LUMC/Leeds *C. difficile* Typing Study

Dr. Duncan McCannel (CDC)
Dr. Michael Mulvey (PHAC)
Dr. Ed Kuijper (Leiden)
Prof. Mark Wilcox (Leeds)

Aims

- Compare PFGE with PCR ribotyping on a selected number of well defined *C. difficile* strains
- Characterization of international set of reference *C. difficile* strains
- Optimization of protocol for capillary gel electrophoresis PCR ribotyping

PFGE and PCR ribotyping

- Leeds/Leiden collection (70 most frequently found isolates in Europe)
- CDC: PFGE (*Sma*I, *Eag*I, *Mlu*I), PCR (*cdtB*, lok1/3, *tcdC*), PCR-Ribotyping (CGE+agarose)
- PHAC: PFGE (*Sma*I), PCR (*tcdA*, *tcdB*, *tcdC*, *cdtB*, *tpi*), PCR-Ribotyping (agarose)
- Results; too many discrepancies and unclear nomenclature of PFGE

Results Leeds/Leiden collection

- Agreement of genetical characterization of Leeds/Leiden strains with exceptions of Types 078 and 126. Subtypes of 019 and 027?
- Disagreement of phenotypical characterization of toxin production A and B with presence of TcdA and TcdB
- Pilot (n=50) CE-PCR ribotyping using home made protocols: good agreement

Capillary gel electrophoresis PCR ribotyping

- Standardization of the protocol nearly achieved
- Interlaboratory exchangeable files
- Import in Bionumerics deserves more attention

Plans

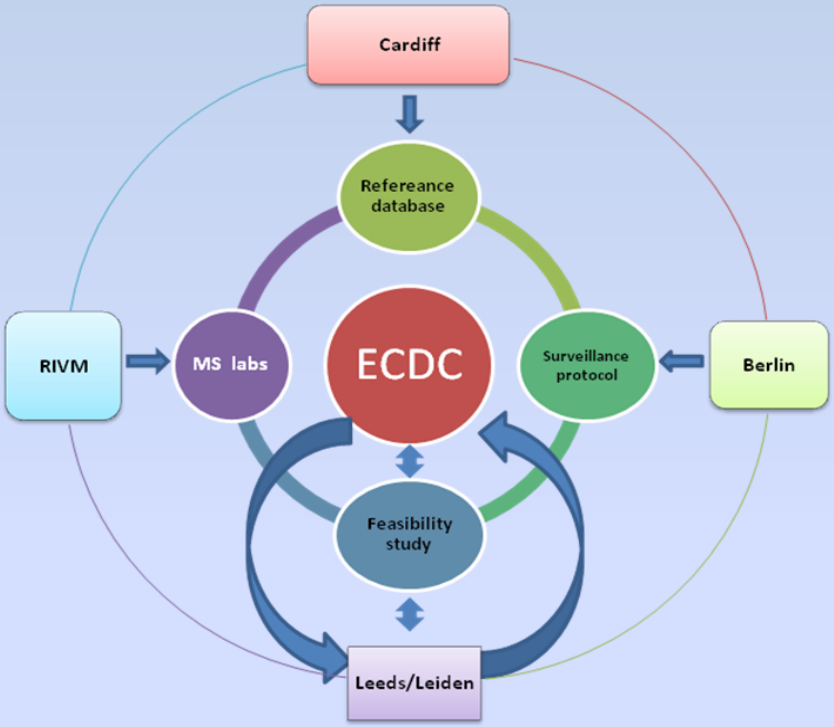
- New protocol of CE-PCR ribotyping is currently completed
- Val Hall: validated 70 reference strains
- Further expansion of database by Leeds, LUMC and Wales
- Open library accesable

Work package 4: To develop a European enhanced CDI surveillance protocol

Work package leader: Prof. Dr. Petra Gastmeier, Charité - Universitätsmedizin Berlin, Germany.

- Objective 1: Review methods and data of existing national CDI surveillance protocoll
- Objective 2: Call an expert meeting to develop a European enhanced CDI surveillance protocol with case based epidemiological and microbiological (typing) data for infections.
- Objective 3: Perform a feasibility study by implementing the protocol in at least 6 Member States (3 with high experience and 3 with no prior experience).
- Objective 4: Presentation and agreement of the enhanced protocol during the annual *Clostridium difficile* network meeting

Components and interdependencies



RIVM: Centre for Infectious Diseases Control (Cib), RIVM, Bilthoven
Berlin: Charité - Universitätsmedizin Berlin
Cardiff: Anaerobe Reference Laboratory, University Hospital of Wales
Leiden: Leiden University Medical Center, Leiden
Leeds: Leeds Teaching Hospitals NHS Trust, Univ. of Leeds & Health Protection Agency

Deliverables First 8 months

Deliverable	WP	Months of the project	coordinator
Minutes of project launch meeting ECDC	1	3	Dr. Ed Kuijper/prof. Mark Wilcox
Preparing web based questionnaire for surveillance	*4*	*3*	*Prof.Petra Gastmeier*
List with candidate Laboratories	2	3	Dr. Daan Notermans
Report on candidate laboraties	2	4	Dr. Daan Notermans
Written document for training module	2	4-6	Dr. Daan Notermans
Kick off meting with all MS participants	1	4-6	Dr. Ed Kuijper/prof. Mark Wilcox
Report on kick-off meeting	1	6	dr. Ed Kuijper
Proposal for SOP and guidelines for PCR ribotyping	3	6	Dr. Val Hall
Performing a review for CDI surveillance by web questionniare	*4*	*7*	*Prof. Petra Gastmeier*
Manuscript on CDI surveillance in Europe	*4*	*8*	*Prof. Petra Gastmeier*