JNI 17es Journées Nationales d'Infectiologie

du mardi 7 au jeudi 9 juin 2016
Lille Grand Palais

Lille
et l'interrégion Nord-Pas-de-Calais-Picardie

Managing CDI : what can we learn from the English experience?

Dr David R Jenkins
Consultant Medical Microbiologist and Infection Control Doctor
University Hospitals of Leicester NHS Trust,
And
Honorary Reader, University of Leicester Medical School

University Hospitals of Leicester NHS
NHS Trust

Caring at its Best

Disclosures

- Director, Healthcare Infection Prevention Ltd
- Speaker fees: Astellas, EUSA Pharma
- Advisory panel fees: Astellas, MSD, Novartis

Outline

- Features of Clostridium difficile infection (CDI)
- CDI in England
- CDI treatment options
- Real-world experience of fidaxomicin use:
  - Seven-centre study, UK

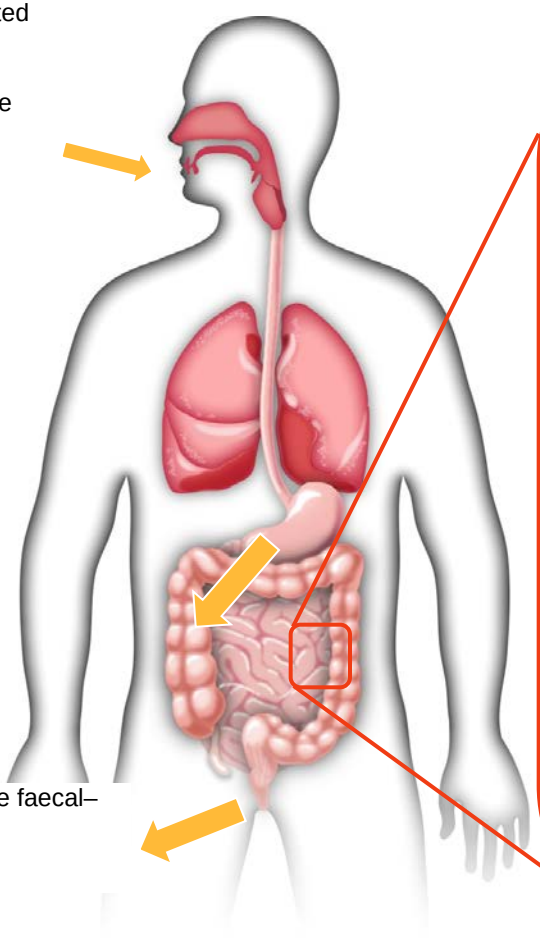
Features of Clostridium difficile infection (CDI)

The disease cycle of *C. difficile* infection (CDI)

1. Ingestion of spores transmitted from other patients, via hands of healthcare personnel and the environment

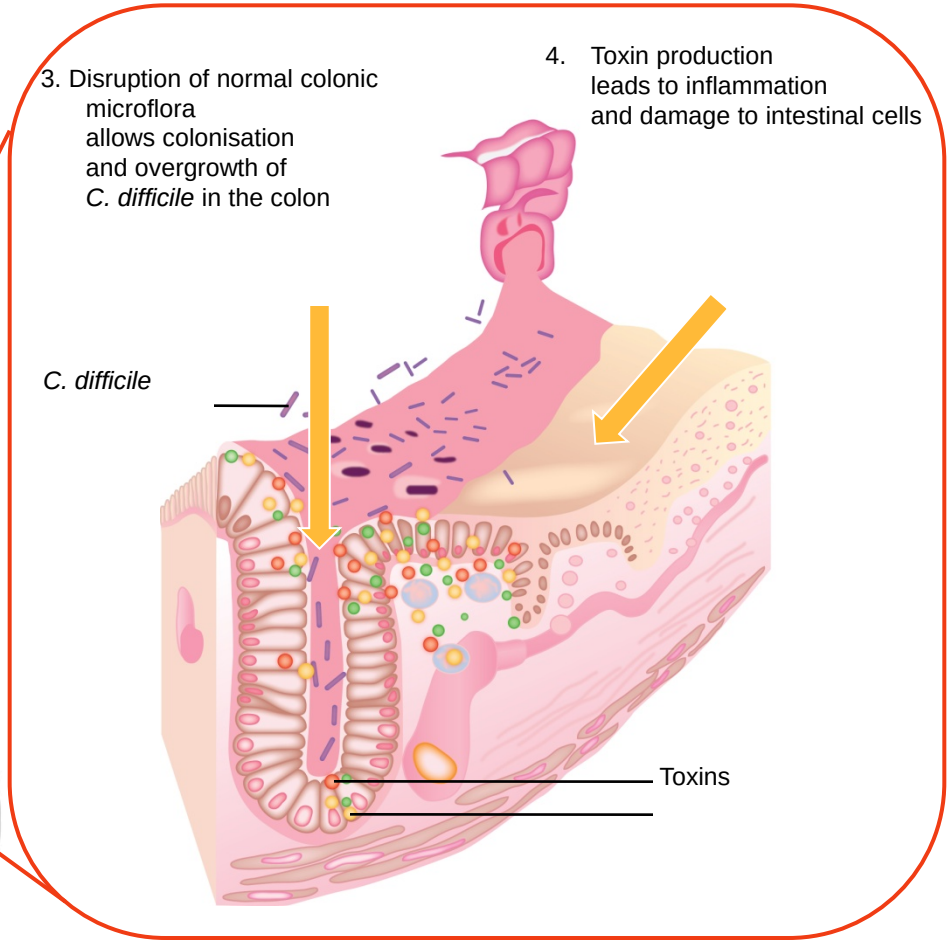
2. Germination into growing (vegetative) cells

5. Transmission of spores via the faecal–oral route



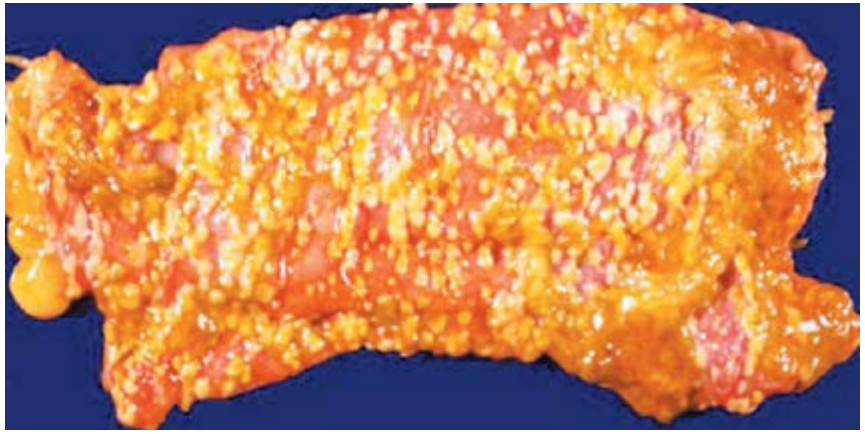
3. Disruption of normal colonic microflora allows colonisation and overgrowth of *C. difficile* in the colon

4. Toxin production leads to inflammation and damage to intestinal cells

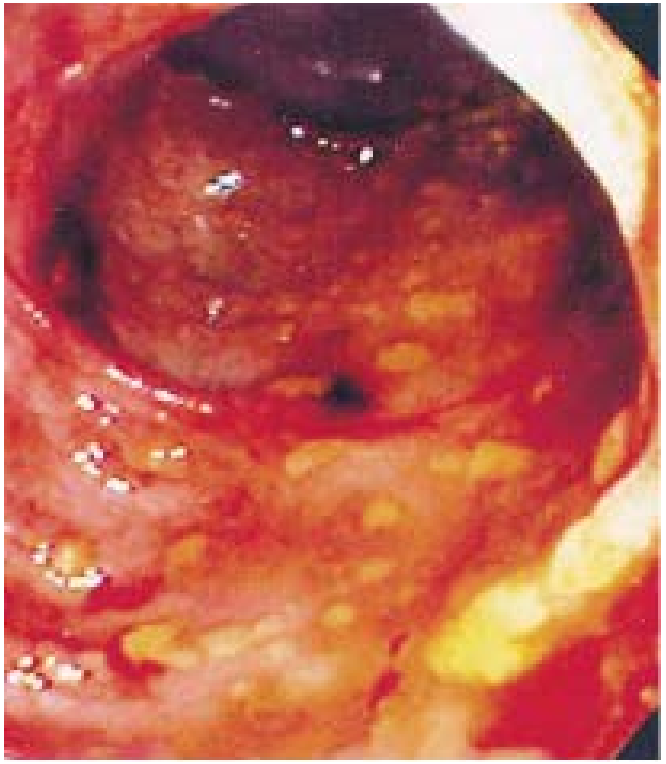


Sunenshine RH, et al. Cleve Clin J Med 2006;73:187–97.

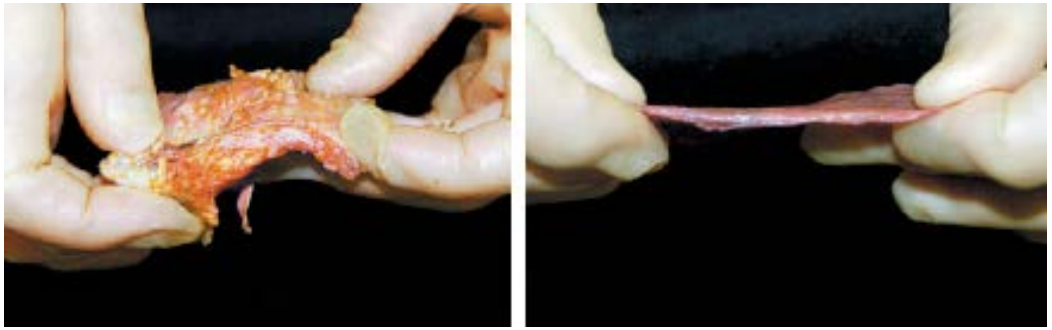
The effect of *C difficile* infection on the large bowel



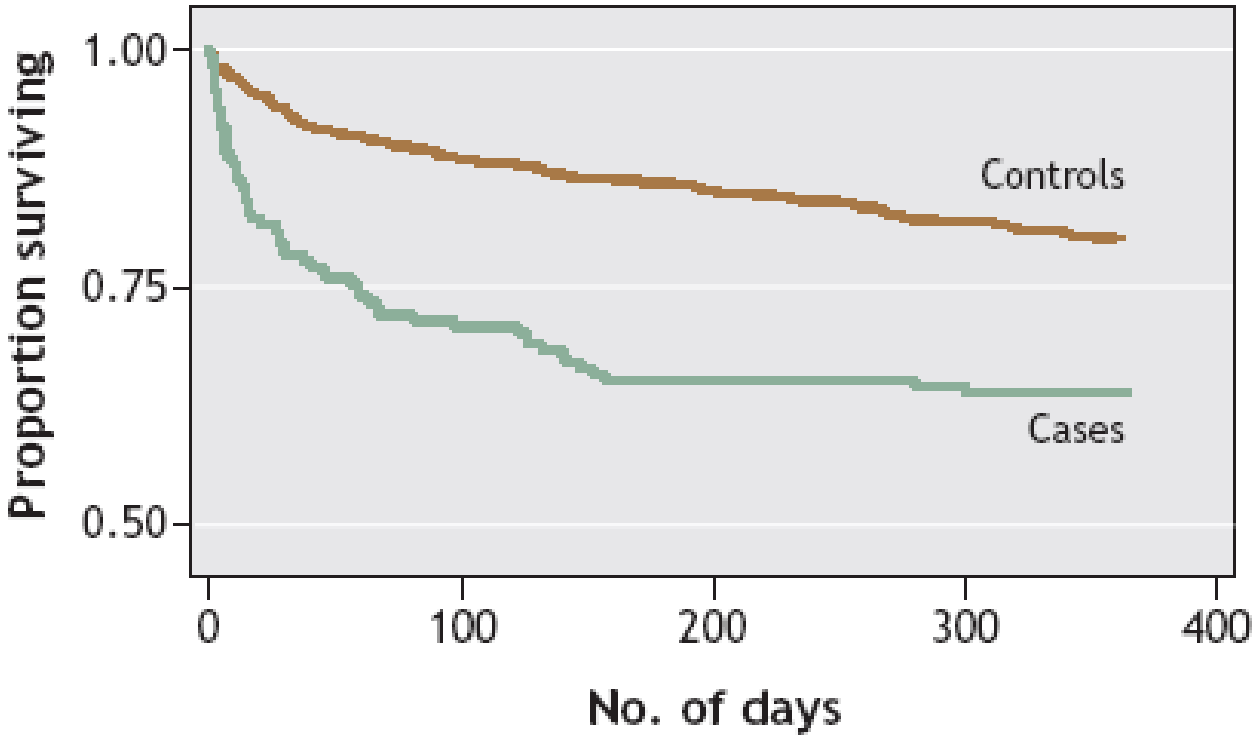
Wolf PL & Kasyan A. NEJM 2005;353:23



Triadafilopoulos G. NEJM 2002;346:333



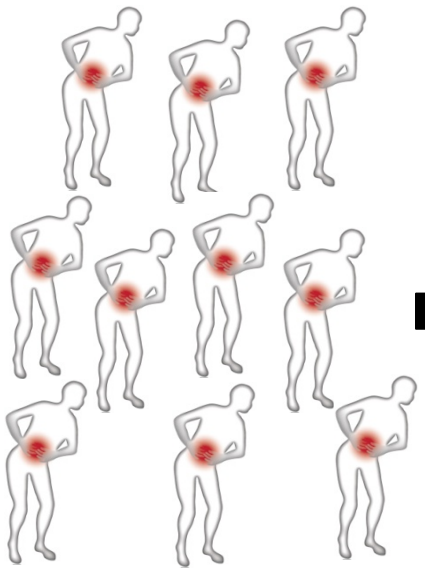
The lethal impact of *C difficile* BI/NAP1/027 infection



Kaplan–Meier plot showing probability of death since diagnosis among inpatients in whom nosocomial Clostridium difficile-associated disease (CDAD) developed and among matched control subjects without CDAD. No. of days = time since diagnosis of CDAD (cases) or time since reaching the same interval after admission (controls).

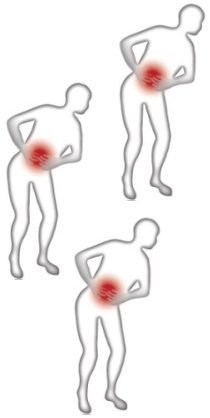
Pepin J et al. CMAJ 2005;173: 1037-1042.

The incidence of recurrent CDI



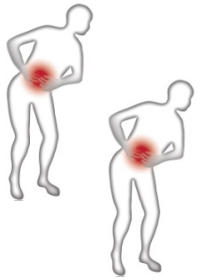
Initial episode of CDI

1st recurrence of CDI



Up to 25% of patients have recurrent CDI1–3

Recurrence(s) of CDI

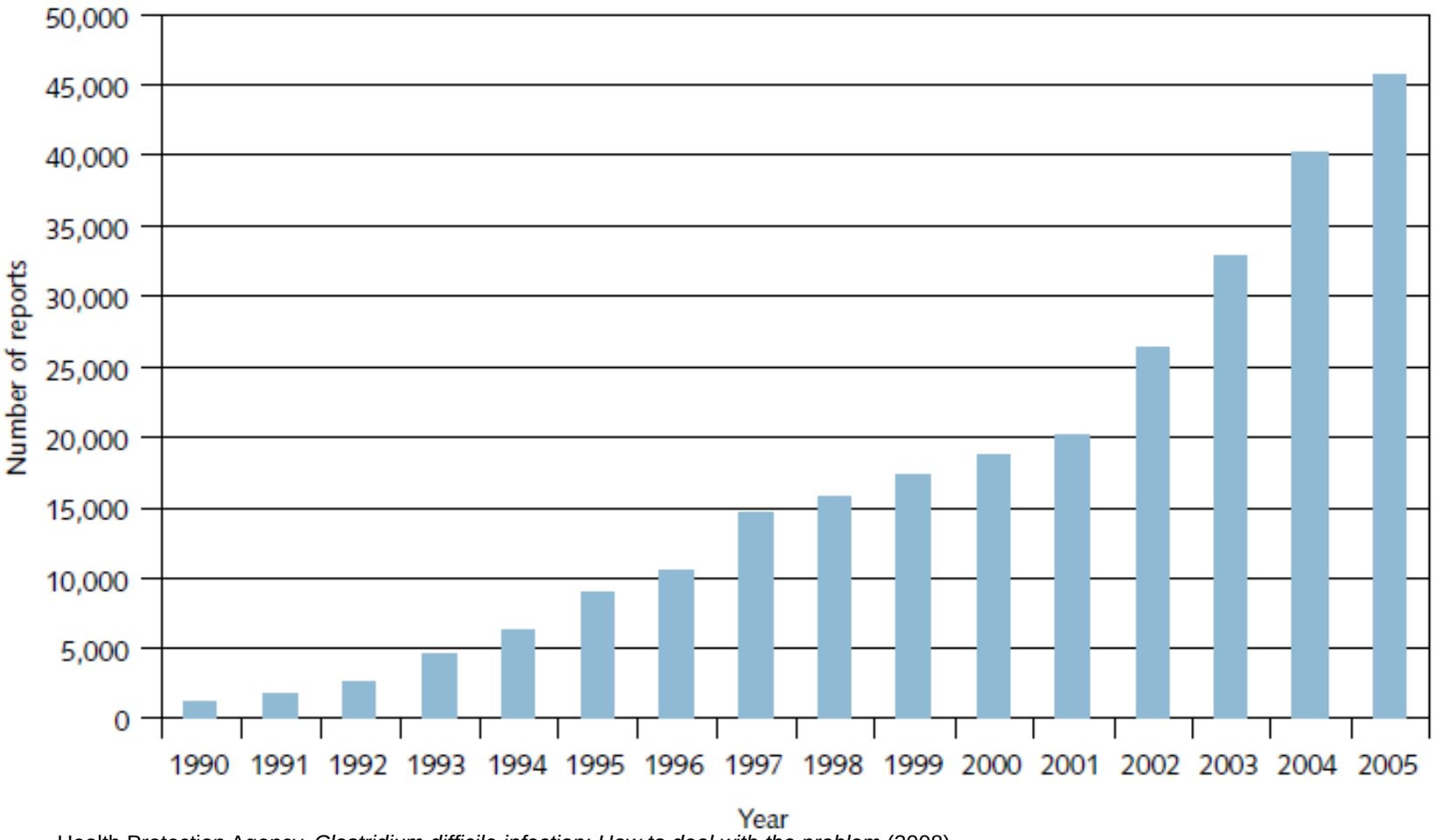


~45–65% of patients have further recurrences4,5

1. Louie TJ, et al. N Engl J Med 2011;364:422–31;
2. Lowy I, et al. N Engl J Med 2010;362:197–205;
3. Johnson S, et al. Clin Infect Dis 2014;59:345–54;
4. McFarland LV, et al. Am J Gastroenterol 2002;97:1769–75;
5. McFarland LV, et al. JAMA 1994;271:1913–8.

Clostridium difficile infection in England

Clostridium difficile infections reported to voluntary surveillance scheme, England, 1990 to 2005



Health Protection Agency. *Clostridium difficile infection: How to deal with the problem* (2008)

Clostridium difficile public health policy initiatives, England – key milestone

2007 - Mandatory enhanced surveillance of C. difficile infection for NHS acute trusts

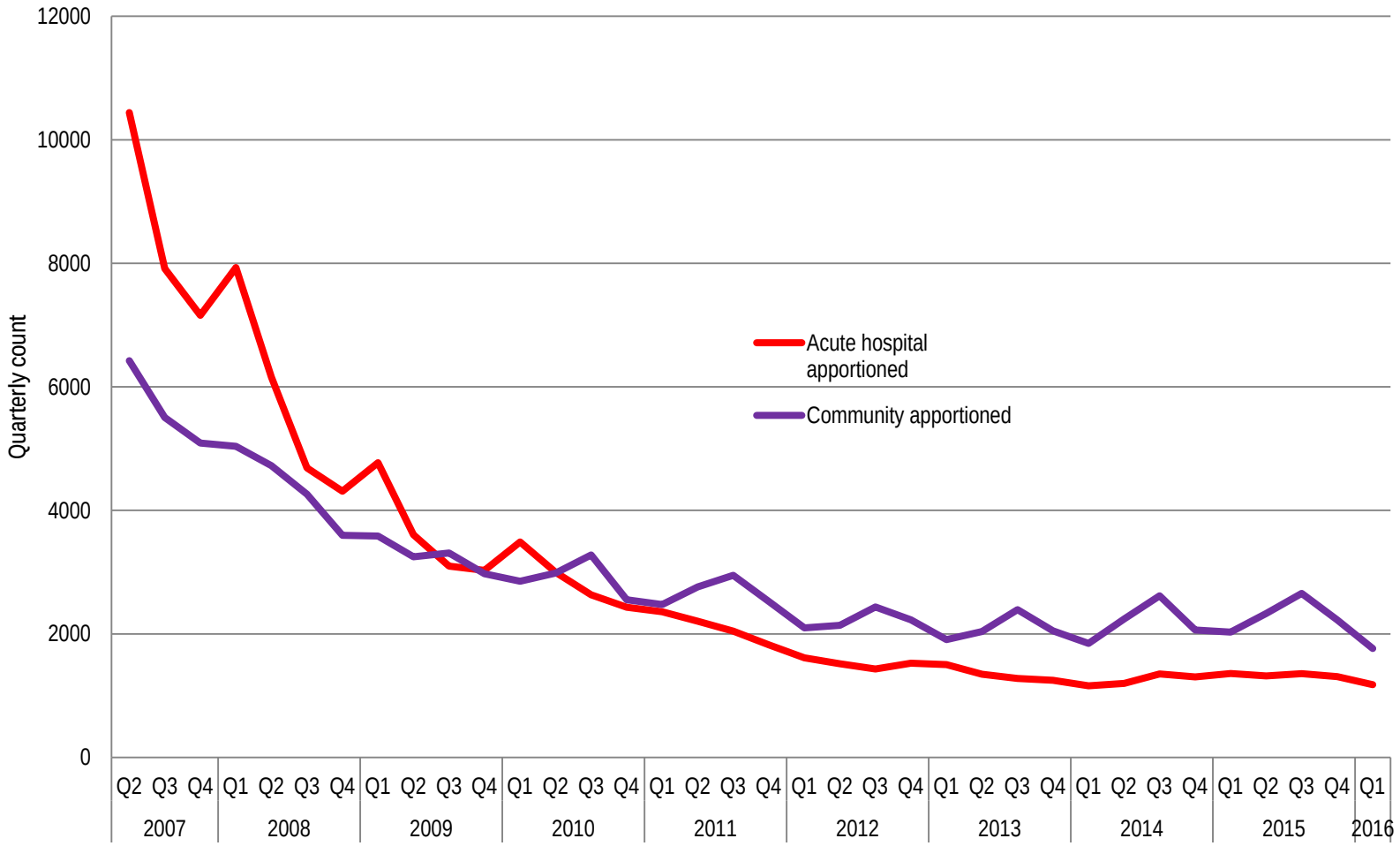
2007 - *Saving Lives: Reducing infection, delivering clean and safe care. High Impact Intervention No. 7 – Care bundle to reduce the risk from Clostridium difficile* (Department of Health)

2008 - *Clostridium difficile infection: How to deal with the problem*

2012 - *Updated Guidance on the Diagnosis and Reporting of Clostridium Difficile*

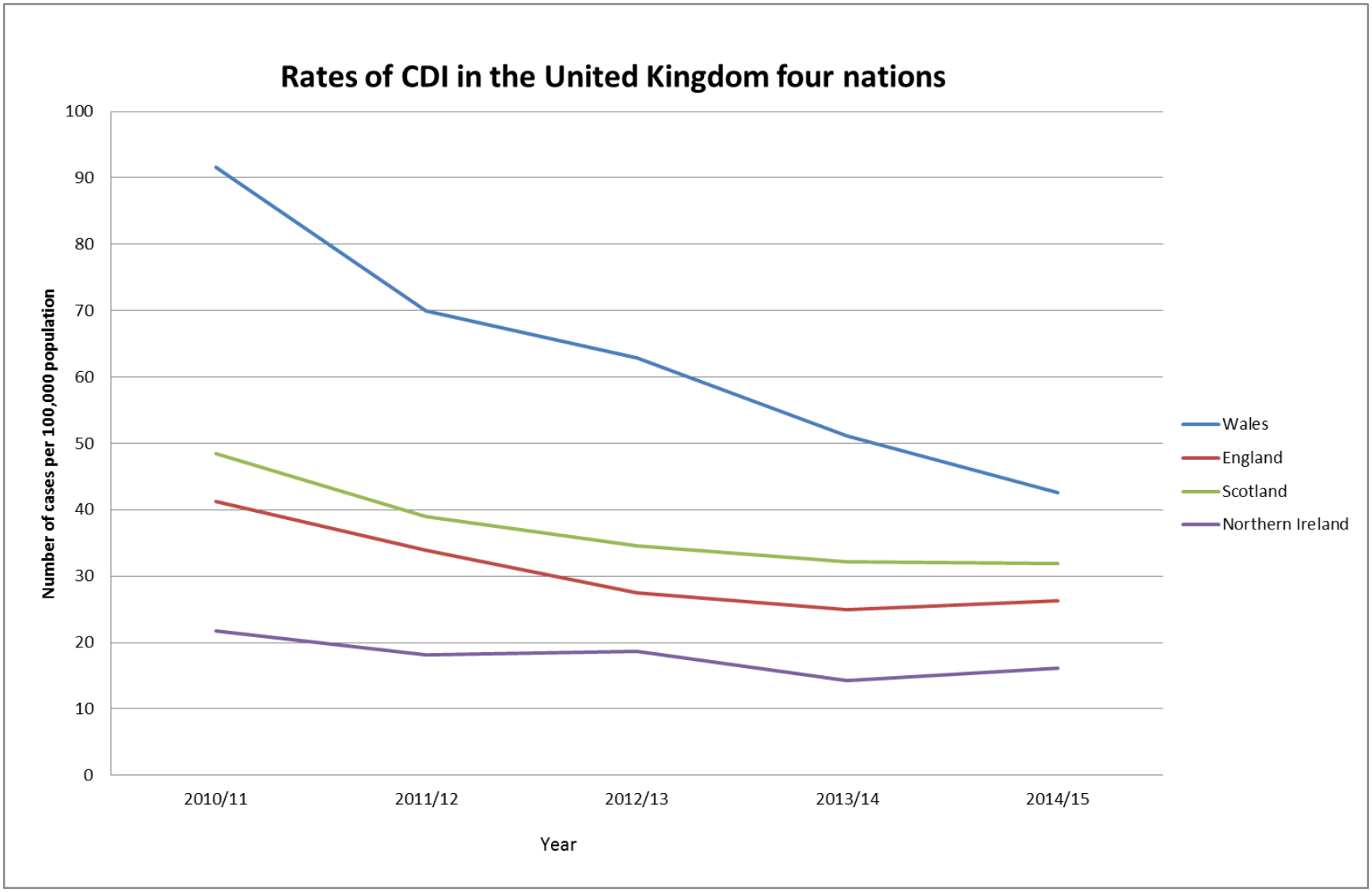
2013 – NHS England sets reduction targets with big fines for failure

Quarterly count of Clostridium difficile infections in England, 2007 to 2016



Data source: https://www.gov.uk/government/collections/clostridium-difficile-guidance-data-and-analysis#epidemiology

A comparison of CDI rates in the four UK administrations



CDI treatment options

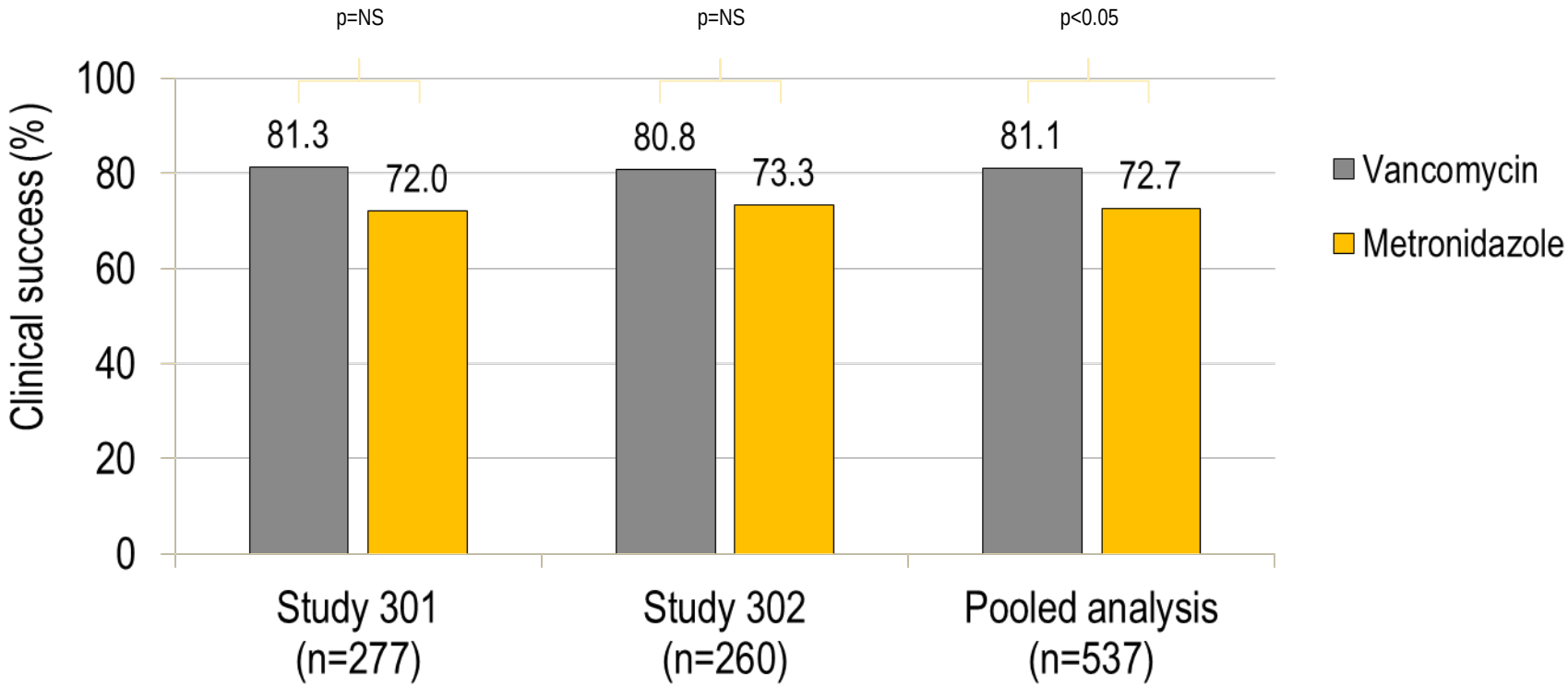
First lines treatment of CDI

- Metronidazole
- Vancomycin
- Fidaxomicin

(Faecal transplant – evidence base is for recurrent disease only)

Rates of clinical success for metronidazole and vancomycin

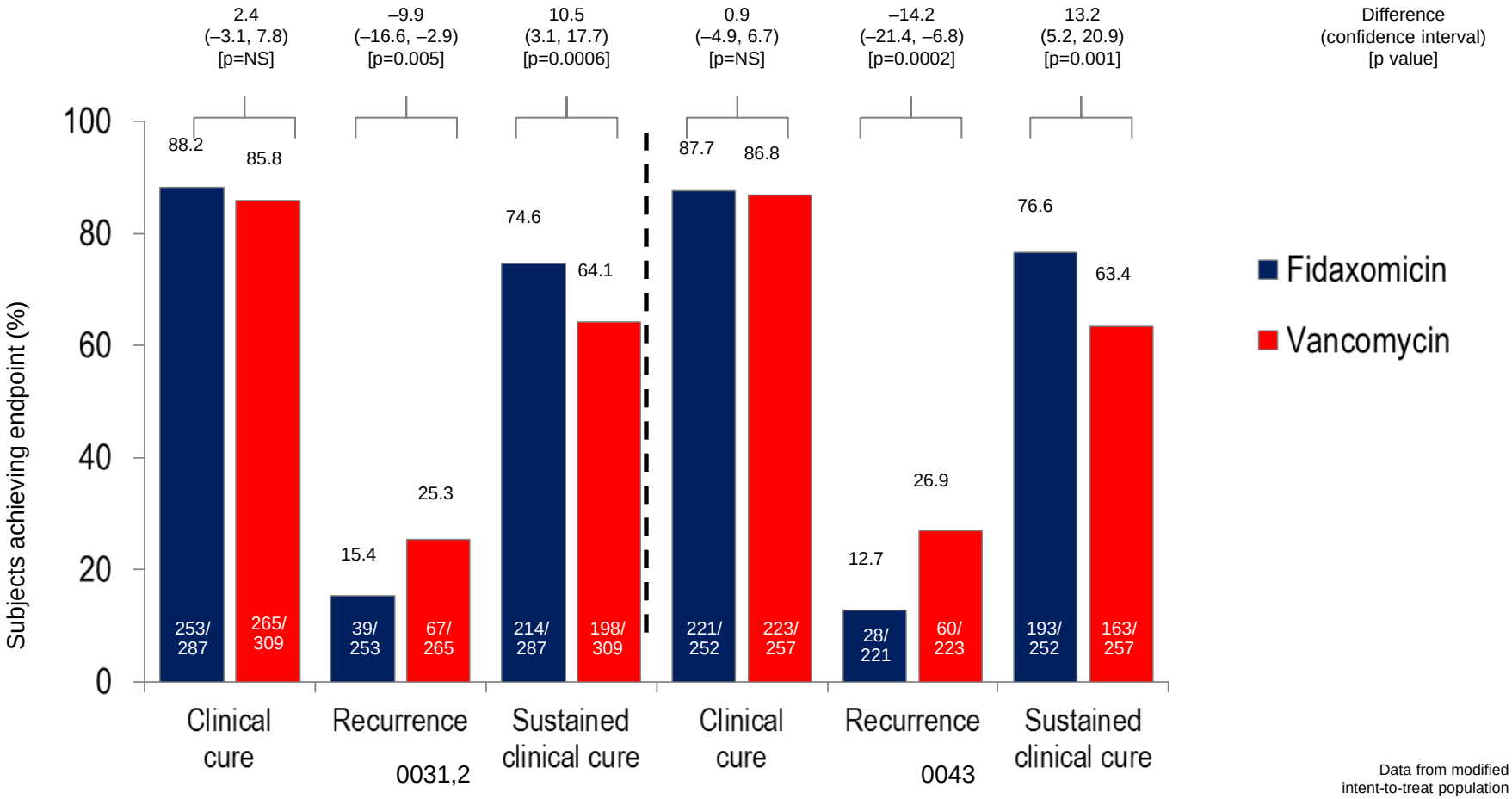
Rates of clinical success in two identical multicentre, randomised, double-blind, parallel-group trials



Johnson S, et al. Clin Infect Dis 2014;59:345–54.

Clinical success was defined as diarrhoea resolution and absence of severe abdominal discomfort due to CDI on Day 10; NS, not significant

Fidaxomicin phase 3 trial results



Data from modified intent-to-treat population

NS, not significant;
Study 003: USA, Canada;
Study 004: Belgium, Canada, France, Germany, Italy,
Spain, Sweden, UK, USA

1. European Public Assessment Report, 22 September 2011 (EMA/857570/2011);
2. Louie TJ, et al. N Engl J Med 2011;364:422–31;
3. Cornely OA, et al. Lancet Infect Dis 2012;12:281–9.

Real-world experience of fidaxomicin use: Seven-centre study, UK

“Can it work? Does it work? Is it worth it?”

	Question	Methodology	Caveats
Efficacy	Can a treatment work (under ideal circumstances)?	Randomised clinical trials	Excludes many patients who do not fit trial criteria; clinical practice should be rigorous
Effectiveness	Does a treatment work in (non-ideal) real life?	Observational studies of routine clinical settings	Includes all patient, healthcare practitioner and organisational variables
Efficiency	Is a treatment worth its cost to individuals or society?	Health economic studies	Takes into account the strengths and weaknesses of alternative options

Haynes B BMJ 319;1999:652-3

Efficacy versus effectiveness

“What works well at the Sloan Kettering (a high tech cancer centre) may not work very well in Kettering (a small UK community hospital).”

Brian Haynes *professor of clinical epidemiology and medicine*
McMaster University Health Sciences Center, Ontario, Canada

Haynes, B. BMJ 319;1999:652-3

Fidaxomicin local service evaluation seven-centre study

Objective

- To collect robust real-world data to understand the cost-effectiveness of fidaxomicin when introduced in routine practice
  - Local treatment of CDI
  - Local rates of CDI recurrence
  - Local resource use associated with CDI management
  - Costs of managing CDI recurrence

Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259

Fidaxomicin local service evaluation seven-centre study

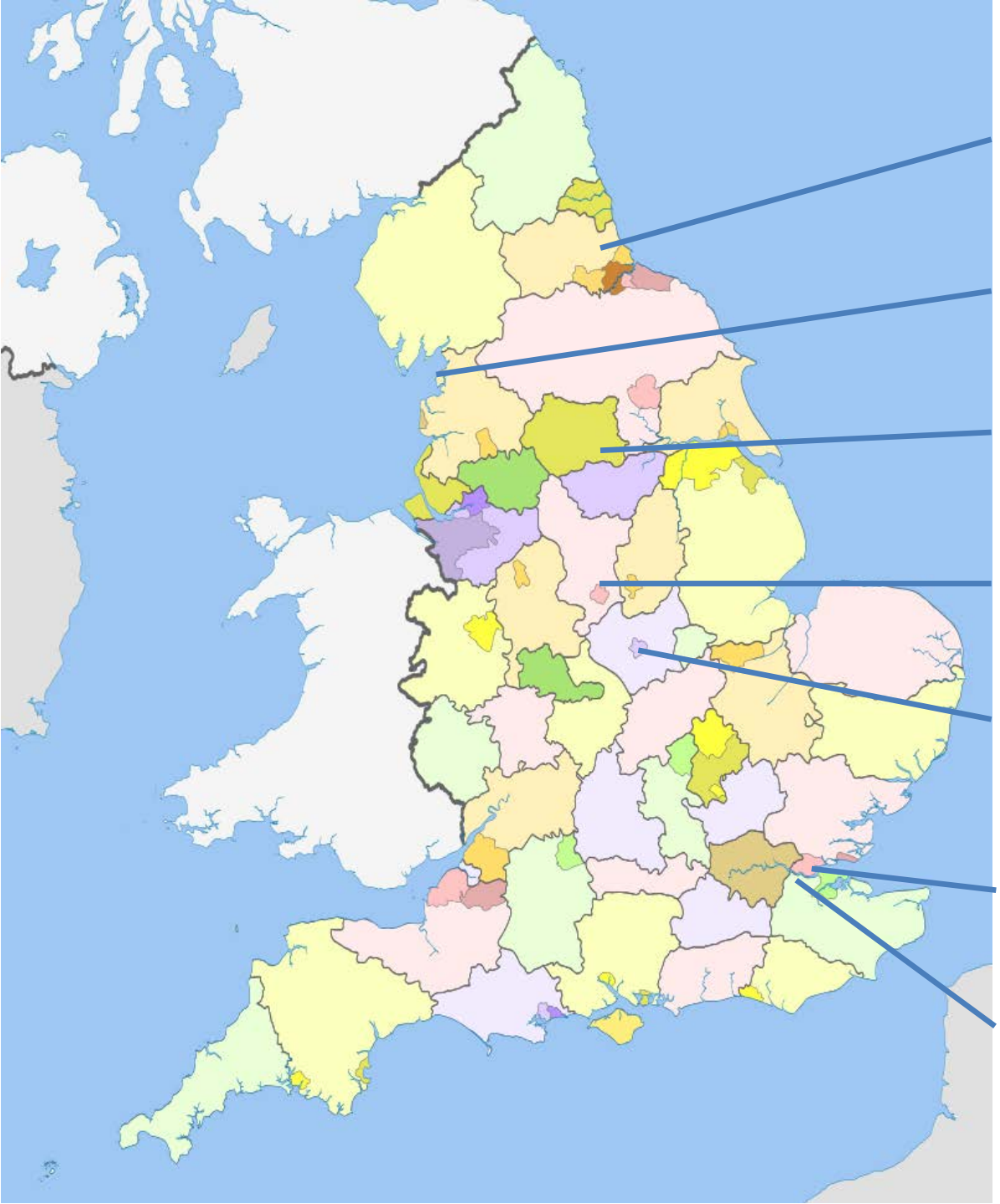
- **Seven centres introducing fidaxomicin between July 2012–July 2013**
- Retrospective data collection on CDI episodes occurring 12 months before (pre-FDX) and after (post-FDX) the introduction of fidaxomicin
- Pre-fidaxomicin treatment: vancomycin or metronidazole
- Inclusion criteria
  - All hospitalised patients aged ≥18 years with primary CDI (and no CDI in previous 3 months)
- Recurrence
  - In-patient diarrhoea requiring treatment at any time within subsequent 3 months after initial episode
- Data collected
  - Patient characteristics, CDI severity, treatment, place of acquisition, date of onset/resolution, resource use and cost utilisation (length of stay, procedures, readmissions)

Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259

Authors and affiliations

Hospital	Author
Leeds Teaching Hospitals NHS Trust	Philip Howard Jonathan Sandoe
Guy's and St Thomas' NHS Foundation Trust	Simon Goldenberg Paul Wade
County Durham & Darlington NHS Foundation Trust	Stuart Brown Deepa Nayar
University Hospitals of Morecambe Bay NHS Foundation Trust	Monika Pasztor
St George's Healthcare NHS Trust	Tim Planche Laura Whitney
Derby Hospitals NHS Foundation Trust	Deborah Gnanarajah
University Hospitals of Leicester NHS Trust	David Jenkins, Leslene Edwards

Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259



County Durham & Darlington NHS Foundation Trust

University Hospitals of Morecambe Bay NHS Foundation Trust

Leeds Teaching Hospitals NHS Trust

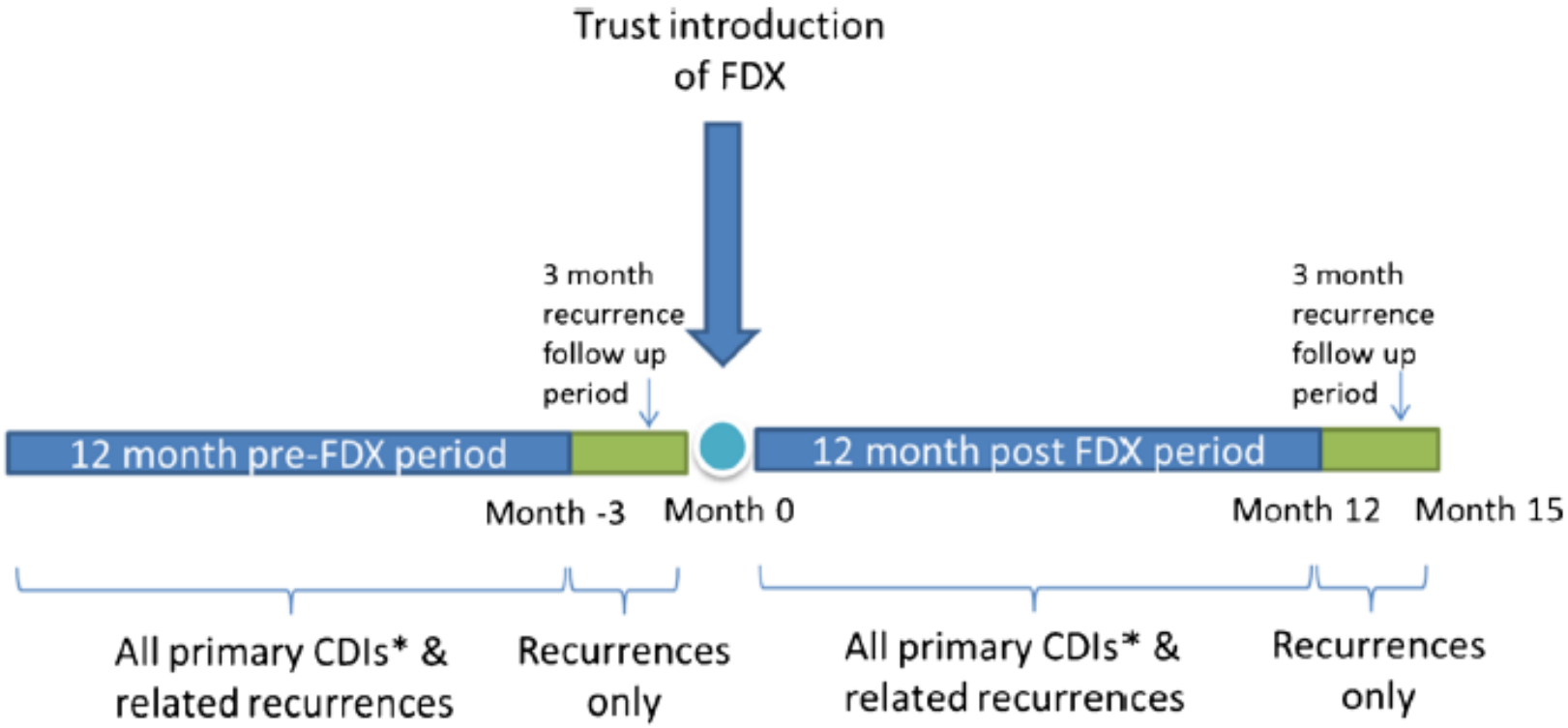
Derby Hospitals NHS Foundation Trust

University Hospitals of Leicester NHS Trust

Guy's and St Thomas' NHS Foundation Trust

St George's Healthcare NHS Trust

Study design



*primary CDI confirmed by checking for CDIs in previous 3 months

Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259

CDI diagnosis and fidaxomicin use policies

Diagnosis

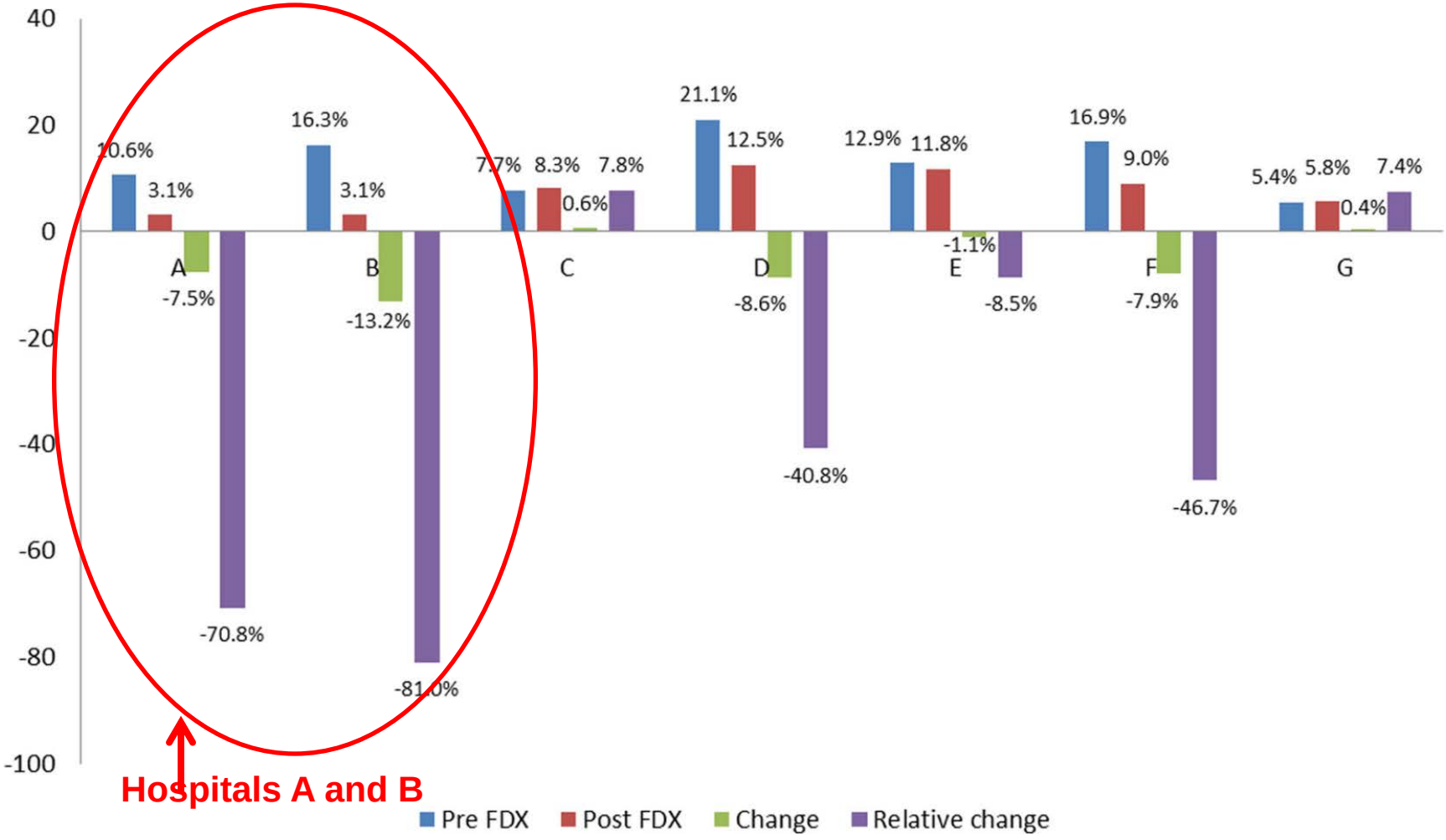
- Two-step
  - GDH EIA->C difficile toxin EIA
  - GDH EIA-> C difficile cytotoxin assay
  - And repeat >24h later if GDH+/Cdt-
- Three-step
  - GDH EIA-> C difficile toxin EIA , ->toxin PCR if GDH+/Cdt-

Fidaxomicin treatment (Hospital)

- first line in all episodes (A,B)
- Recurrences and selected primary episodes (C)
- First line for recurrences only (D)
- All lab-confirmed CDI episodes unless patient already recovered, discharged or relative contraindications (E)
- All CDI cases>75 years old, <75 if relapse, co-morbidities, concurrent antibiotics (F)
- Recurrences and primary episodes if considered high risk for recurrence (G)

Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259

CDI recurrence rates in the pre- and post- fidaxomcin periods



Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259

Fidaxomicin and 28-day mortality

- Centres A and B: fidaxomicin used for all primary episodes of CDI , D: first line for recurrences only

Centre	Pre-FDX 28-day mortality (%)	Post-FDX 28-day mortality (%)	P-value
A	18.2	3.1	<0.05
B	17.3	6.3	<0.05
C	20.8	16.7	
D	28.6	9.1	<0.05
E	22.9	20.0	
F	14.6	22.5	
G	30.4	18.8	

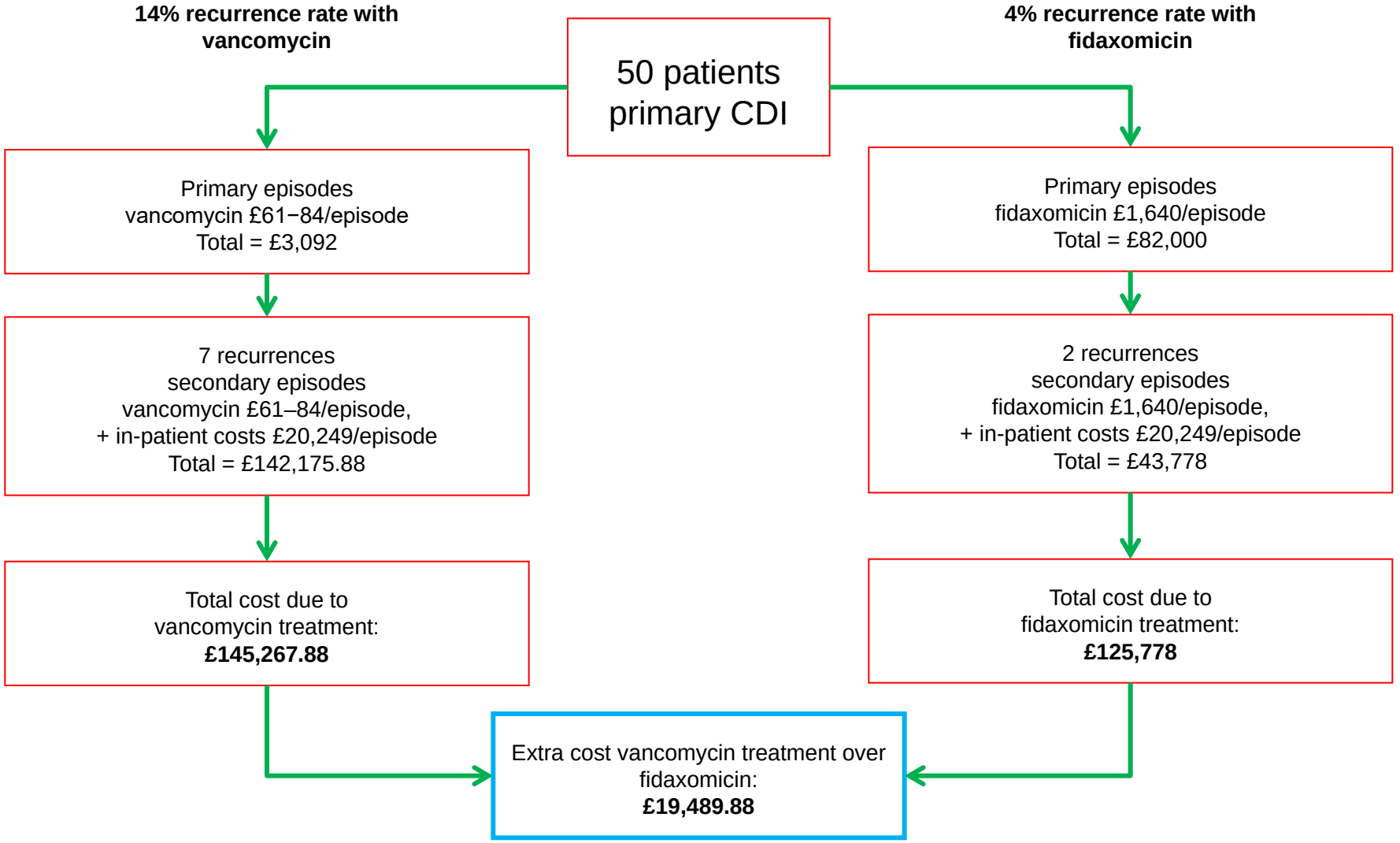
Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259

Summary of local service evaluation

- Variation between centres in diagnosis of CDI
- Wide variation in use of fidaxomicin
- Greatest relative reduction in two centres where fidaxomicin used first line in all CDI patients
- Significant reduction in 28-day all-cause mortality in both centres using fidaxomicin first line in all episodes (but also centre D)

Goldenberg SD et al. Eur J Clin Microbiol Infect Dis 2016;35:251-259

Cost comparison: fidaxomicin vs vancomycin



Based on: Nesnas J et al. Cost-effectiveness of fidaxomicin as first-line treatment for Clostridium difficile infection. Oral presentation, ECCMID 2014

Conclusions

- CDI numbers in England have fallen from a peak in 2007 but further reduction has stalled
- Good quality RCT evidence shows non-inferiority of fidaxomicin versus vancomycin for treatment of primary CDI episodes, and significant superiority for prevention of recurrence
- Local service evaluation results indicate the real-world potential for fidaxomicin to deliver better care by improving outcomes in this vulnerable group of patients
- Fidaxomicin can be a cost-effective treatment option when used first-line in a real-world setting