The Scottish *Clostridium difficile* Reference Service – the story so far

Professor John E Coia
Typing studies are useful to investigate outbreaks & to elucidate the epidemiology of infections

“This showed that a single strain …. was isolated from all six patients at some time during their episodes of diarrhoea”

“Relapse was caused by the acquisition of a new strain in two patients, and by re-emergence or reacquisition of the original strain in two patients”
Why did we need the service?

- Mandatory surveillance of CDAD introduced in October 2006
- Three of the objectives of that programme dependent on availability of typing
  - Identify outbreaks
  - Identify new emerging strains
  - Characterise the epidemiology of *C. difficile* in Scotland
- During first year of the programme isolates could be submitted to ARL, Cardiff for PCR ribotyping
  - Outbreak investigation
  - Detection of “hypervirulent” ribotype 027
- Due to workload requirement for further capacity apparent
  - CDRNE for England & Wales
  - Existing Scottish enteric reference services invited to tender
Where is the service?

- Service currently hosted within the Scottish *Salmonella* Reference Laboratory, Stobhill Hospital, Glasgow
- To relocate with all the Glasgow Reference Laboratories and Diagnostic Microbiology at Glasgow Royal Infirmary (2010)
What services do we provide?

- Confirmation of identity
- Antimicrobial sensitivity testing (E-test)
- PCR ribotyping

Not funded for isolation of organisms from stool or to provide an anaerobic reference service
Molecular typing of *C difficile*

- PFGE
- REA/RFLP
- RAPD
- VNTR (MLVA)
- PCR ribotyping
PCR Ribotype analysis of *C. difficile*

1. Variable length intragenic spacer regions of rRNA complex amplified by PCR and separated by gel electrophoresis

   O’Neill GL et al Anaerobe 1996; 2; 205-209

2. Image analysis

3. Comparison with BioNumerics® database
Which isolates?

- Service commissioned by HPS
- Referral criteria set by commissioners as part of tender
- Designed to:
  - Support mandatory national surveillance
  - Support outbreak investigation
  - Monitor emergence of “virulent” subtypes (esp ribotype 027)
  - Support AMR surveillance
Referral Criteria 1

Severe cases

- Admission for treatment of community associated CDAD
- Admission to ITU for treatment of CDAD or its complications
- Endoscopic diagnosis of PMC
- Surgery for complications of CDAD
- Death within 30 days following diagnosis of CDAD where it is either the primary or a major contributory factor.
- Persisting CDAD where patient remains symptomatic and toxin positive despite 2 courses of appropriate therapy
Referral Criteria 2

Suspected outbreaks
• When an outbreak is suspected and stools are positive for *Clostridium difficile* toxin. An outbreak of CDAD occurs when more cases of CDAD than would normally be expected occur in a clinical unit, ward or hospital.

Suspected infections and/or outbreaks with ribotype 027
• When infection with the hypervirulent strain 027 is suspected the *C. difficile* reference service must be contacted. This is required when:
  – Isolates of ribotype 027 have been identified
  – Patients have been recently hospitalised in England or abroad
Work to date

- Contract awarded August 2007
- Lab went “live” on 19/11/2007
- As of 31/08/2008
  - 652 isolates examined
  - 530 PCR ribotyped confirmed clinical isolates
PCR ribotypes in Scotland

Data from Scottish C. difficile Reference Service 20/11/07-31/08/08 n=530

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Molecular characterization and antimicrobial susceptibility patterns of *Clostridium difficile* strains isolated from hospitals in south-east Scotland

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*Clostridium difficile* isolates (n=149) collected in south-east Scotland between August and October 2005 were typed by four different methods and their susceptibility to seven different antibiotics was determined. The aims were to define the types of strain occurring in this region and to determine whether there were any clonal relationships among them with respect to genotypic and antibiotic resistance patterns. Ribotyping revealed that 001 was the most common type (n=113, 75.8%), followed by ribotype 106 (12 isolates, 8.1%). The majority of the isolates (96.6%, n=144) were of toxigenic 0, with two toxigenic V isolates and single isolates of toxigenotypes I, IV and XII. PCR and restriction analysis of the *tcd* genes from 147 isolates gave two restriction patterns: 145 of pattern VII and two of pattern I. Binary toxin genes were detected in only three isolates: two of ribotype 126, toxigenic type V, and one isolate of ribotype 023.

Toxigenic V types showed more variation, with 64.5% (n=40) of the common S-type (4939) and 21% (n=13) of S-type 4741, with six other S-types (one to three isolates each). All ribotype 001 isolates were of the same S-type (4939), with three isolates of other ribotypes being this S-type. No resistance was found to metronidazole or vancomycin, with resistance to tetracycline only found in 4.3% of the isolates. A high proportion of isolates were resistant to clindamycin (62.9%), moxifloxacin, ceftriaxone (both 87.1%) and erythromycin (94.8%). Resistance to three antibiotics (erythromycin, clindamycin and ceftriaxone) was seen in 86 isolates, with erythromycin, ceftriaxone and moxifloxacin resistance seen in 96 isolates. Resistance to all four of these antibiotics was found in 62 isolates and resistance to five (the above plus tetracycline) in one isolate: a ribotype 001, toxigenic type 0 strain. Whilst ribotype 001 was the most commonly encountered type, there was no evidence of clonal relationships when all other typing and antibiotic resistance patterns were taken into account.

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Distribution of Clostridium difficile ribotypes in consecutive isolates from Glasgow (n = 52) and Dundee (n = 45)

- Preponderance of Type 106
- Similar distribution East and West
Ribotype 027 in Europe

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* Not all countries have performed surveillance studies to C. difficile type 027 and this figure may underestimate the number of affected countries.
Ribotype 027 in Scotland
Other emerging ribotypes

- Importantly other strains of *C. difficile* (e.g. 106 and 078) with potential for hypervirulence and/or high transmissibility are present.
- CDAD caused by any strain (of any ribotype) should therefore be dealt with in the same manner, and all recommended infection prevention and control measures should be in place.
PCR ribotypes in Scotland

Data from Scottish C. difficile Reference Service 20/11/07-31/08/08 n=530

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Reference Service and surveillance objectives

• Identify new emerging strains
  • Yes (106, 027, 078)
• Characterise the epidemiology of *C. difficile* in Scotland
  • Yes for severe cases & outbreaks
  • Don’t know the underlying picture
• Supporting AMR programme
  • Yes
• Identify outbreaks
  • Yes. Helping to define episodes e.g. VOL
  • Need finer discrimination for local investigations
Reference Laboratory developments

• “Snapshot” programme
  – Joint development with HPS
• Molecular subtyping (MLVA)
  – CDRNE
  – ESCMID C diff study group
• Co-ordination & standardisation
  – EQA with CDRNE
  – ESCMID C diff study group
Research opportunities

• Extensive and expanding repository of Scottish C. difficile isolates
• Existing collaborations
• Keen to develop other partnerships
• Particular interest in typing & epidemiology
• SSRL has a proven record of working with other groups in UK and beyond
Further info

C. diff Reference Service Web Site
http://www.ssrl.scot.nhs.uk/cdiffhome.asp

First annual report on mandatory surveillance of *C. difficile* in Scotland

Quarterly report on mandatory surveillance of *C. difficile* in Scotland (Oct 07-Dec 07)

Quarterly report on mandatory surveillance of *C. difficile* in Scotland (Jan 08 -Mar 08)

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