Emergence of *Clostridium difficile* Ribotype 078 in Scotland

A-Lan Banks[1], D. Brown[2], H. Mather[2], J. Coia[2], A. Leanord[1], C. Wiuff[1]

1. Health Protection Scotland (HPS), Glasgow, Scotland, UK; 2. Scottish *Salmonella*, *Shigella* and *Clostridium difficile* (SSSCDRL) Reference Laboratory, Glasgow, Scotland, UK

INTRODUCTION

Clostridium difficile ribotype 078 has been reported as an emerging ribotype and has been associated with hypervirulence.[1] Following a significant increase in ribotype 078 isolates reported during the first three months of 2012[2], ribotype 078 data from samples sent to the Scottish *Salmonella Shigella* and *Clostridium difficile* Reference Laboratory (SSSCDRL) for PCR ribotyping between November 2007 and June 2012 were analysed.

METHODS

PCR ribotyping is routinely carried out on samples sent to SSSCDRL from severe cases and outbreaks according to standardised criteria (November 2007 to present)[3]. In addition, a fixed proportion of all cases including mild, moderate and severe disease are typed under a 'Snapshot Programme' which has been running from 2009 to the present.[4]

A severe case is defined as:
(1) admission to a healthcare facility for treatment of community associated CDI;
(2) admission to ITU for treatment of CDI or its complications;
(3) endoscopic diagnosis of pseudomembranous colitis (with or without toxin confirmation);
(4) surgery for the complications of CDI (toxic megacolon, perforation or refractory colitis);
(5) death within 30 days following a diagnosis of CDI where it is either the primary or a major contributory factor; and
(6) persisting CDI where the patient has remained symptomatic and toxin positive despite 2 courses of appropriate therapy.[3]

All isolates from samples from severe cases and outbreaks were susceptibility tested against a range of antibiotics including cefotaxime, clindamycin, erythromycin, levofloxacin, meropenem, moxifloxacin, and piperacillin-tazobactam. All samples regardless of referral criteria were susceptibility tested against metronidazole and vancomycin.

Information provided on the request forms for typing allow collection of data relating to the submitting laboratory/NHS administration area, date of birth, sex, community or hospital setting, and the reason for ribotyping request (including severity of disease, death and/or suspected outbreak).

Comparisons of the epidemiology of ribotype 078 isolates (and characteristics of cases) were made before and after the 1st January 2012 (following which ribotype 078 became the predominant type in Scotland).

All proportions were calculated for categorical variables using the χ^2 test.

RESULTS

From November 2007 to June 2012, a total of 179 (out of 3093) isolates of ribotype 078 were reported from severe cases and outbreaks (59% female, age range 1-98 years; median 77 years).

From January 2009 to June 2012, 118 (out of 1862) isolates of ribotype 078 were reported from the Snapshot Programme (62% female, age range 18-97 years: median 73 years).

The proportion of ribotype 078 increased year on year: 2.5% (2008), 3.2% (2009), 4.3% (2010) and 7.8% (2011) among isolates from severe cases/outbreaks; and 3.6% (2009), 5.6% (2010) and 6.4% (2011) among isolates from the Snapshot Programme.

From the beginning of 2012 there was a sudden increase in ribotype 078 among submissions to both programmes (Figures 1 and 2). In the first two quarters of 2012, ribotype 078 was the most commonly observed ribotype, accounting for 22% of severe cases/outbreaks and 17% of Snapshot isolates. This is the first time that ribotype 078 has been the predominant ribotype in either surveillance typing schemes.

FIGURE 1: Ribotype 078 isolates from severe cases/ outbreaks by quarter for the period November 2007 to June 2012

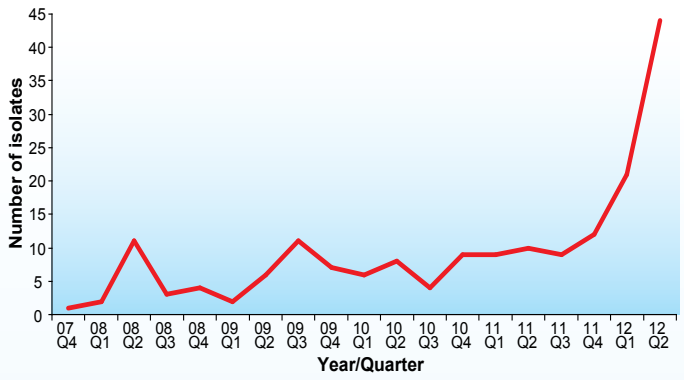
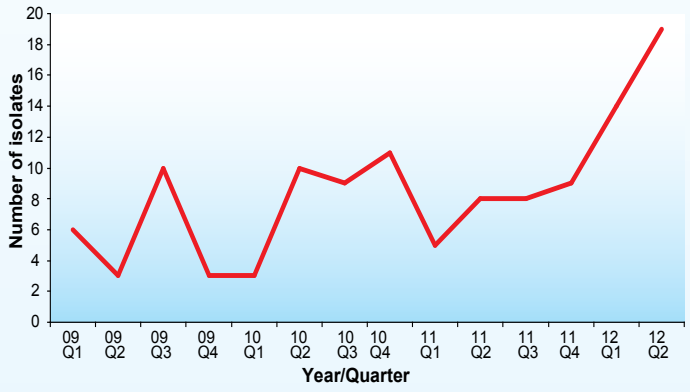
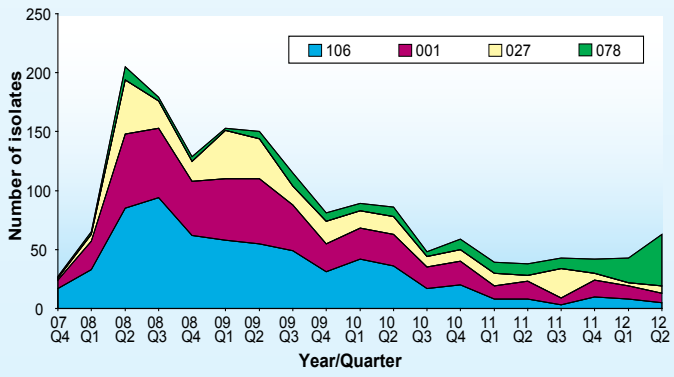


FIGURE 2: Ribotype 078 Snapshot isolates by quarter for the period January 2009 to June 2012



In comparison, the previously dominant ribotypes in Scotland (106, 001 and 027) have decreased significantly since 2008 and have remained at low levels during the first half of 2012 (Figure 3). A similar pattern is observed in the Snapshot isolates (data not shown).

FIGURE 3: Ribotype 106, 001, 027 and 078isolates from severe cases and outbreaks by quarter for the period November 2007 to June 2012



Among severe cases/outbreaks, the number of cases that were female, aged ≥65 years and part of a suspected outbreak was higher in ribotype 078 isolates typed after the 1st of January 2012. After 1st of January 2012 a smaller porportion of cases were categorised as community cases (4.8% vs. 13.8%). None of the changes were statistically significant at the $p<0.05$ level (Table 1). No comparisons were made using the Snapshot request forms due to a lack of clinical information.

From data provided by the SSSCDRL, there is strong evidence ($p<0.001$) to suggest that resistance to cefotaxime in ribotype 078 isolates typed after the 1st January 2012 increased significantly from 52.6% to 90.8% (Table 1). There were no significant changes to resistance proportions before and after the 1st January 2012 in the remaining antibiotics in Table 1.

TABLE 1: Characteristics of ribotype 078 isolates from severe cases and outbreaks before and after the 1st January 2012

	Before 01/01/12 (n=114)	After 01/01/12 (n=65)	Difference (95% CI)	P
	%	%		
Request form data				
Female	55.3	64.6	-9.4 (-24.1, 5.4)	0.2
≥65	77.2	84.6	-7.4 (-19.1, 4.3)	0.2
Community*	13.8	4.8	9.0 (0.7, 17.3)	0.06
Severe**	47.4	37.8	-9.7 (-8.3, 27.6)	0.3
Fatal**	20.5	20	0.5 (-14.2, 15.2)	0.9
Suspected outbreak**	20.5	22.2	-1.7 (-16.8, 13.4)	0.8
SSSCDRL data				
Cefotaxime resistance	52.6	90.8	-38.1 (-49.7, -26.6)	<0.001
Clindamycin resistance	97.4	98.5	-1.1 (-5.3, 3.1)	0.6
Erythromycin resistance	18.4	7.7	10.7 (1.1, 20.4)	0.05
Levofloxacin resistance	12.3	13.8	-1.6 (-11.9, 8.8)	0.7
Moxifloxacin resistance	7.9	4.6	3.3 (-3.8, 10.4)	0.4

* Based on patient category field on request form (n=109, 63, respectively)
** Based on clinical data field on request form (n=78, 45, respectively)

All isolates typed were sensitive to vancomycin and metronidazole.

Ribotype 078 was reported from twelve of the fourteen NHS health administrations (NHS boards) in Scotland. Two NHS boards reported outbreaks due to ribotype 078 (two separate outbreaks in the past 12 months).

CONCLUSIONS

C. difficile ribotype 078 has been reported as an emerging type across Europe[1,5] and has been associated with more severe disease (as a result of increased toxin production)[1] and reported high levels of recurrence in one outbreak in the Republic of Ireland.[6] Transmission to humans from animals and food has been postulated but this remains speculative.[1,7,8]

Since 2008, Scottish CDI incidence rates have decreased significantly in patients aged ≥65 years from 123 per 100 000 bed days in 2008 to 30 per 100 000 bed days in 2011 (similar decreases have occurred in patients aged 15-64 years since 2009).[9] During this period, ribotype 078 has increased steadily but it is only since the beginning of 2012 that this ribotype has become predominant in Scotland.

Ribotype 078 appears to be spread across most of the Scottish NHS boards. Two outbreaks due to ribotype 078 have been reported recently but these do not appear to explain the general increase observed since the beginning of 2012. In the rest of the UK, ribotype 078 is also increasing and outbreaks have been reported in both the Republic of Ireland and Northern Ireland (where ribotype 078 is also the predominant type).[6, 10, 11]

The limited data available provides few clues to the emergence of ribotype 078 in Scotland. There is a lack of evidence to suggest that there has been a change in the severity, number of deaths or suspected outbreaks associated with ribotype 078 before and after the 1st January 2012.

Previous reports have suggested an association with community patients[1,7] but the data provided here do not support this as most were categorised as in-patients. Similar findings have been reported in the Republic of Ireland where the majority of ribotype 078 cases had recent contact with hospitals.[6] This suggests that strain replacement may have occurred in Scottish hospitals with ribotype 078 replacing ribotypes 001, 106 and 027 which were previously the most common hospital ribotypes. Why ribotype 078 has increased while these three ribotypes have remained at relatively low levels compared to previous years is not clear.

The increase in the resistance to cephalosporins in Scottish isolates after 1st January 2012 cannot alone explain the sudden rise in ribotype 078 cases in Scotland. Primary and secondary care data from Scotland suggests that cephalosporin prescribing has decreased substantially in recent years. The majority of ribotypes 001, 106 and 027 remain resistant to the cephalosporins (as well as clindamycin, erythromycin and the fluoroquinolones)[9] suggesting the presence of other factors which are driving the emergence and increase of ribotype 078 in Scotland.

This study is limited by the lack of follow up of patients and availability of clinical data, and from the relatively smaller number of patients in the group after 1st January 2012. Caution is required in the interpretation of results from data obtained from referral forms for typing as the data is not validated and is incomplete. Further studies will be required to assess and evaluate risk factors for acquiring ribotype 078 in Scottish hospitals and associated severity of disease, recurrences and mortality.

References

1. Goorhuis A, Bakker D, et al. Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. Clin Infect Dis. 2008 Nov 1;47:1162-1170.
2. Health Protection Scotland. Quarterly report on the surveillance of *Clostridium difficile* infection (CDI) in Scotland, January-March 2012. Health Protection Scotland 2012; Available from: URL: http://www.hps.scot.nhs.uk/ewr/article.aspx
3. Health Protection Scotland. Protocol for the Scottish Surveillance Programme for *Clostridium difficile* Associated Disease. User Manual. Health Protection Scotland 2009; Available from: URL: http://www.hps.scot.nhs.uk/haiic/sshaip/guidelinedetail.aspx?id=40899
4. Health Protection Scotland. Protocol for the *Clostridium difficile* snapshot programme. Health Protection Scotland 2010; Available from: URL: http://www.hps.scot.nhs.uk/haiic/sshaip/guidelinedetail.aspx?id=46879
5. Bauer MP, Notermans DW, van Benthem BH, Brazier JS, Wilcox MH, Rupnic M, et al. *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet 2011 Jan 1;377(9759):63-73.
6. Burns K, Morris-Downes M, et al. Infection due to *C. difficile* ribotype 078: first report of cases in the Republic of Ireland. J Hosp Infect. 2010 June;75:287-291.
7. Jhung MA, Thompson AD, et al. Toxinotype V *Clostridium difficile* in humans and food animals. Emerg Infect Dis 2008;14:1039-1044.
8. Rupnik M, Widmer A, et al. *Clostridium difficile* toxinotype V, ribotype 078 in animals and humans. J Clin Microbiol 2008;46:2146.
9. Health Protection Scotland. The Annual Surveillance of Healthcare Associated Infection Report January - December 2011. Health Protection Scotland 2011; Available from: URL: http://www.documents.hps.scot.nhs.uk/hai/annual-report/annual-surveillance-hai-report-2011.pdf
10. Health Protection Agency. *Clostridium difficile* Ribotyping Network (CDRN) for England and Northern Ireland 2010-2011 annual report. Health Protection Agency 2012.
11. Health and Social Care Public Health Agency. *C. difficile* Surveillance Report quarter ending March 2012.

Poster produced by the Graphics Section, Health Protection Scotland