HHS Public Access

Author manuscript

J Hosp Infect. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

J Hosp Infect. 2021 March ; 109: 96–100. doi:10.1016/j.jhin.2020.10.028.

Genotypic correlation between post discharge *Clostridiodes difficile* infection (CDI) and previous unit-based contacts

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Abstract

Objective: Cases of *Clostridiodes difficile* infection (CDI) diagnosed after hospital discharge account for a substantial proportion of new infections. It is unclear if post discharge infections originate from hospital-based transmission.

Design: Retrospective cohort study.

Setting: Tertiary care cancer center. Non outbreak setting.

Methods: For all laboratory-identified cases of CDI in 2015– 2016, patients with post-discharge (PD) CDI within 8 weeks of their hospital stay were included in the study. Isolates from PD- CDI cases and their CDI positive unit-based contacts were first genotyped by MLST. Common strains were further examined by core genome sequencing (CGS) to evaluate transmission links.

Results: Of 173 cases examined by MLST, 50 % of PD cases matched previous unit contacts. Next, 34 isolates, including 16 PD cases and their 18-unit contacts were examined by CGS. None were ≤3 SNVs apart. Seventy percent of PD cases had in-hospital antibiotic exposure before CDI onset in the community.

Conclusion: Our study results suggest that symptomatic CDI cases are not a substantial source of transmission to PD cases. Frequent antibiotic exposure in post-discharge CDI cases is an important target for surveillance and stewardship efforts.

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This work has been presented in part at the poster session of ID week on October 6, 2017.

No conflict of interest (all authors)

INTRODUCTION

Clostridiodes difficle (*C. difficile*) infection (CDI) is a leading cause of health-care associated (HA) infection in the United States(1).The incubation period of *C. difficile* can be highly variable, with infections diagnosed days to weeks after the initial exposure to *C. difficile* spores(2, 3). Surveillance studies estimate that 3 out of every 4 HA- CDIs have onset in the community(4); and up to 15 % occur within 4 weeks after a hospital stay (post-discharge cases)(5). Due to the latency between the initial acquisition and onset of diarrheal symptoms, the source of infection may remain obscure in the majority of HA- CDI cases.

The combined approach of temporospatial links and genetic relatedness has elucidated several aspects of hospital-based *C. difficile* transmission(3, 6). Amongst the various *C. difficile* genotyping techniques, whole or core genome sequencing (WGS or CGS) are highly discriminatory methods. Multilocus sequence typing (MLST) is a low-resolution method but offers the distinct advantage of low cost, simplified analysis, and high agreement with CGS for unrelated strains(7).

In a previous study by Eyre et al(8), 19 % of the CDI cases that were genetically related to a previous infection had evidence of hospital contact with the donor, including 13 % with ward-based contact and less than 1 % acquired infection indirectly from ward-based contamination (defined as possible environmental contamination persisting for four weeks after the first infectious patient had been discharged). Although the study linked post discharge cases with their previous hospital contacts, the number of exposures with all other CD cases and their time from discharge was not characterized in detail.

The National Healthcare Safety Network (NHSN) requires US hospitals to report post-discharge (PD) CDI events even though the contribution of hospital versus community-based transmission in PD cases is not known. We seek to determine if symptomatic cases of CDI serve as a source of infection to the same unit occupants who later develop CDI after hospital discharge. In this study, we apply a joint approach of MLST and CGS to isolates from PD-CDI cases and their previous unit based contacts.

METHODS

Study setting:

This study was performed at Memorial Sloan Kettering Cancer Center (MSK), a tertiary care cancer specialty hospital with 475 beds and approximately 25,000 annual admissions. For all laboratory-identified CDI’s in 2015 and 2016, patients with PD-CDI within eight weeks of hospital discharge were included in the study. CDI is nosocomial or community-based acquisition of infection; past and future CDI events among study participants were obtained from the Infection Control database (CKM, Canada). At our institution, clinical diagnostic testing for CDI is performed using the Cepheid GeneXpert PCR platform (one-step testing). A clinical case of CDI was defined by positive PCR result on unformed stool specimen tested by the Cepheid GeneXpert assay [Cepheid Xpert C. difficile Epi assayXpert®,

Sunnyvale CA]. Screening of asymptomtic individuals for *C. difficile* was not done routinely in any patient population.

Community-acquired CDI cases were defined by onset in the community and without preceding hospitalization in 8 weeks. Hospital onset cases are defined as CDI diagnosed past 72 hours of inpatient admission. Putative donors were identified from the Infection control database using the following criteria:

- Direct contact: *C. difficile* positive unit mates (overlapping stays) of post discharge cases.
- Indirect contact: Previously discharged occupants from the same unit in the 12 weeks before admission of PD case.

For study purposes, the six most frequent strains at MSK are included: ST 1, 2, 3, 8, 11, and 42. First, MLST types of PD cases and their direct or indirect contacts were compared. For indirect contacts, the time interval was determined by admission date of PD case and, any CDI case on the same unit within 4 weeks, 4–8 weeks, 8–12 weeks of this date. Next, confirmatory genetic analysis with core genome sequencing (CGS) was conducted on a subset of MLST identical PD cases and their donors. Based on a plausibly higher likelihood of transmission, the analysis was restricted to unit mates with direct overlap or most proximal hospitalization to the PD case (≤ 4 weeks). Pearson Chi-Square tests are applied to assess differences in proportions between groups.

Laboratory methods:

Stools were thawed and ethanol shocked with a 1:4 dilution in 100% ethanol for at least 1 hour. After incubation and centrifugation, samples were inoculated on selective media for the detection of CD and incubated anaerobically. Growth confirmation of a single colony by PRO disk was performed with the remaining portion of the colony subbed to a blood agar plate for isolation. After a 48-hour anaerobic incubation, samples were submitted for core genome sequencing.

MLST was done as previously described(7). CGS was performed using established methods. Briefly, genomic DNA (gDNA) was extracted from *C. difficile* isolates using the QIAmp DNA Mini-Kit bacterial suspension protocol with some modifications as previously described(9). Libraries were prepared using Nextera XT reagents (Illumina, San Diego, CA) per manufacturers' instructions. Sequencing was performed on the Illumina MiSeq platform to generate 150 base paired-end reads. Bioinformatic analysis was performed by an in-house pipeline using publicly available tools. FASTQ files were demultiplexed and adaptor trimmed using the in-house pipeline. Quality of the sequences was evaluated and reads with a Q30 score of less than 30 for more than 50% of the bases were filtered out using FASTX. A range of kmer and coverage values was used with Velvet assembler to generate multiple assemblies for each isolate. Each assembly was evaluated, and the best assembly was used based on the highest N50 value. Genes were predicted on draft assemblies using prodigal (10). Genes were assigned functions using RPS-BLAST (11) and CDD database (12). PGAP pipeline was used for pan-genome analysis and building an SNP-based phylogeny tree. PGAP pipeline can perform five analytic functions, including

cluster analysis of functional genes, pan-genome profile analysis, genetic variation analysis of functional genes, species evolution analysis, and function enrichment analysis of gene clusters (13).

Isolates were considered isogenic if they differed by ≤2 core genome SNVs (isolates collected <124 days apart) or ≤3 core genome SNVs (isolates collected 124–364 days apart), based on analyses of *C. difficile* evolutionary rate established by previous studies (8, 14).

This study was reviewed and appoved be instiutional IRB and granted HIPAA waiver of authorization.

RESULTS

During the two-year study period, 1,365 new CDI cases were diagnosed, 542 community-acquired (40%), 440 hospital-onset (32%), and 383 (28%) post-discharge cases. Among these, 1,112 (82%) were successfully genotyped by MLST. Five hundred and twenty-nine (47.6%) met incusion criteria based on the strain type.

For the 383 PD cases, the median age was 58 years, 180 (47%) were females. The median time to CDI diagnosis from discharge was 19 days, with 162 PD cases diagnosed within 48 hours of readmission. Seventy percent (n=267) of patients received antibiotics during the index hospitalization. The most common antibiotic was beta-lactam- lactamase inhibitor in 135 (51%) patients, fluoroquinolones in 69 (26%), and 3rd or 4th generation cephalosporins in 87 (36%) patients. The median length of antibiotic therapy was four days.

Relatedness among PD cases and prior unit contacts by low resolution MLST

Based on the study inclusion criteria, 147/383 (38.4%) cases were due to selected endemic strains (Figure1). The breakdown by sequence type (ST) is as follows: ST2=46; ST42=39; ST8 =26; ST11=15; ST1=12; ST3=9. Among the 147 PD cases, 69 (47%) had contact with an isogenic MLST case [43 indirect; 8 direct, and 18 cases with both] (Figure 2). Table 1 shows the genotypic relationship by type of contact between patients.Only 8.3 % (125/1507) of the PD cases and their unit contacts had similar MLST strains. No differences were found when examined by the type of contact (direct vs. indirect; p= 0.574) or by the time interval for those with indirect contact (p= 0.343) (Table 1).

Core genome sequence (CGS) comparison of PD cases and same unit contacts

CGS was done to compare further the PD cases and their putative donors with similar MLST types. Fifty-one PD cases were eligible to be included, 16 (31%) could be successfully sequenced and analyzed due to various reasons (lost PD or donor sample, no growth in culture, sequencing failure). The analyzable cohort of 34 cases included the 16 PD infections (designated recipients “R” in Figure 3), and their 18 unit-based contacts (designated donors “D” in Figure 3). Each PD case had at least one matched donor, and two had one additional donor each. For these 18 donors, 10 were overlapping stays with the PD case, and eight were on the same unit within four weeks before admission of the PD case. Pairwise SNV comparison color-coded by PD case [R] and the same unit donor [D] is shown in Figure 3.

None of these 18 contacts had ≤ 3 SNV differences from PD cases. None of the common ST types examined by CGS had ≤2 SNP differences regardless of the epidemiologic link.

DISCUSSION

Our study results suggest that symptomatic CDI cases and environmental contamination from these cases are not the source of infection for unit mates who develop CDI after discharge from the hospital. Half of the PD cases in our study had a putative source by low resolution genotyping (MLST). However, no transmission was detected when CGS examined a subset of the cases with the closest epidemiological link. Antibiotic exposure during the index hospitalization was common.

Several recent population studies suggest a rise in community-onset CDI rates. According to a population-based report in Olmstead county, Minnesota two third of CDI cases have onset in the community. Approximately half of these cases were hospitalized within 12 weeks prior to CDI diagnosis(15). Pinzon et al's study from the VHA found that 9.1% of ~ 20,000 CDI episodes between 2011–2014 occurred within 4 weeks of discharge from a hospital(16). Further, antibiotic use was highest in this group (50 %) compared to an overall 40% exposure among all other CDI cases. Despite this shift in epidemiology, genotyping has not been applied to examine the role of hospital-based acquisition in PD CDI cases.

The lack of any transmission by CGS and high antibiotic use in PD-CDI cases suggests that *C. difficile* infections may start outside the hospital, and emphasis on antibiotic stewardship efforts is more likely to be effective in preventing PD-CDI.

There are several limitations in our study: isolates examined are restricted to unit-based contacts, not hospital-wide or outpatient contacts. Despite a robust two-step approach, our conclusions are based on successful core genome sequencing of ~ a third of the eligible cohort, including 10 pairs with direct overlap and the highest spatial probability of transmission. Recent studies applying WGS show that hospital-based CDI transmission is more likely to originate from cases then carriers(6). The role of environmental reservoir is not ascertained – only contamination that could have occurred from symptomatic cases in a predefined time interval. ST-1 cases were not isolated among the donor- recipient pairs examined by CGS (17)(Figure 3). Cases were defined based on symptoms of diarrhea and positive PCR. In a cancer population, *C. difficile* carriage rates are high, and diarrhea due to non-infectious causes is frequently encountered. This is a well recognized limitation of current assays and introduces the possibility of overestimating carriers as CDI cases. Recent studies applying WGS show that hospital-based CDI transmission is more likely to originate from cases then carriers(6)

In summary, our study results suggest that symptomatic CDI cases are not a substantial source of transmission to PD cases. Frequent antibiotic exposure in post-discharge CDI cases is an important target for surveillance and stewardship efforts.

Acknowledgements and funding source :

The authors acknowledge support from the MSK Cancer Center Support Grant/Core Grant (P30 CA008748).

The authors wish to acknowledge Natalie Chow for assistance with sequencing.

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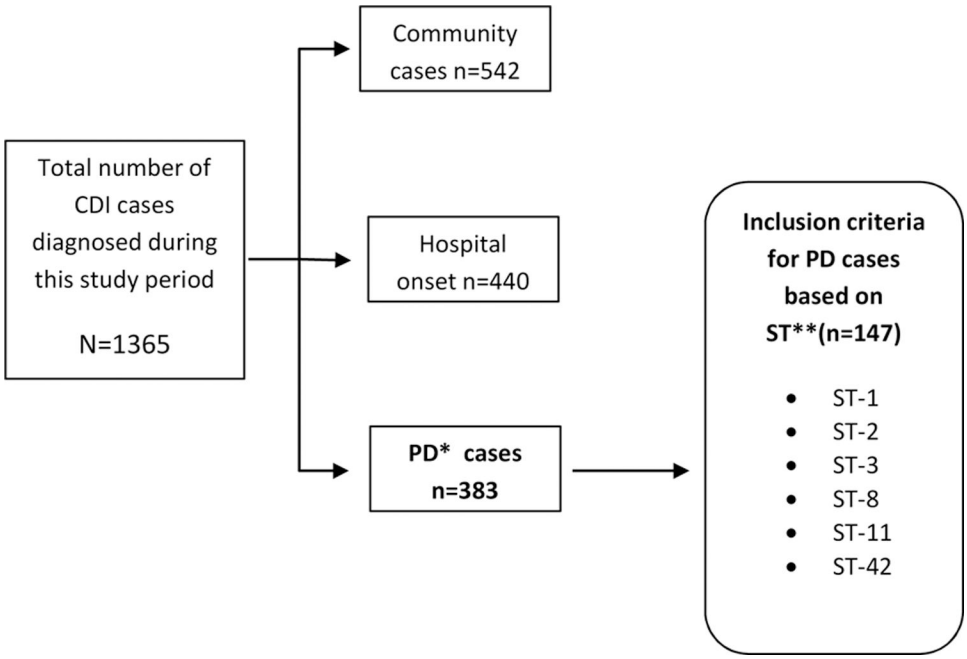


Figure 1.

Inclusion citeria for Postdischarge (PD) *C. difficile* cases during the two year study period.

*PD, post discharge cases

**ST; sequence types

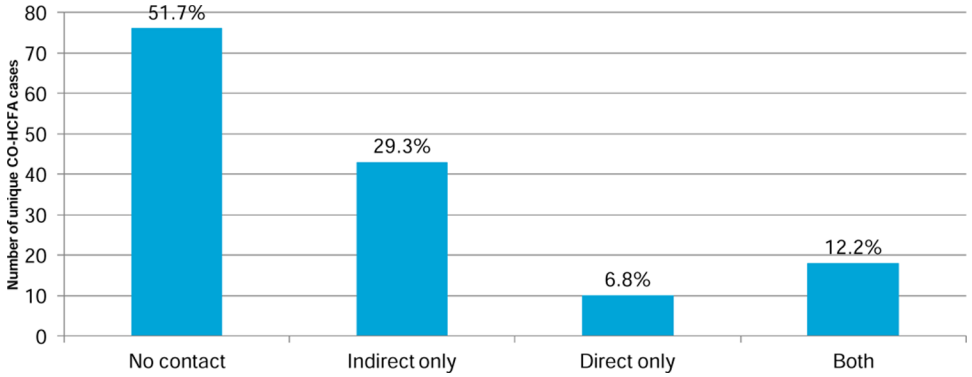
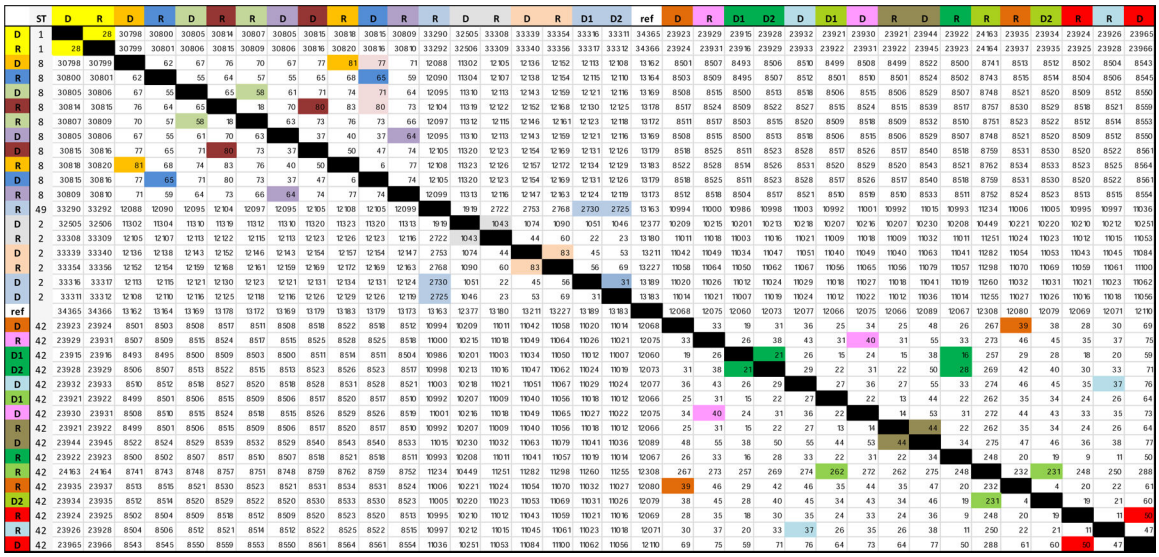


Figure 2.

Type of exposure for 147 PD cases and previous CDI cases on the same unit with shared MLST strain type



	ST	D	R	D	R	D	R	R	D	D	R	D	R	R	D	R	D	R	D1	D2	ref	D	R	D1	D2	D	D1	D	R	D	R	R	R	D2	R	R	D
D	1		28	30798	30800	30805	30814	30807	30805	30815	30818	30815	30809	33290	32505	33308	33339	33354	33316	33311	34365	23923	23929	23915	23928	23932	23921	23930	23921	23944	23922	24163	23935	23934	23924	23926	23965
R	1	28		30799	30801	30806	30815	30809	30806	30816	30820	30816	30810	33292	32506	33309	33340	33356	33317	33312	34366	23924	23931	23916	23929	23933	23922	23931	23922	23945	23923	24164	23937	23935	23925	23928	23966
D	8	30798	30799		62	67	76	70	67	77	81	77	71	12088	11302	12105	12136	12152	12113	12108	13162	8501	8507	8493	8506	8510	8499	8508	8499	8522	8500	8741	8513	8512	8502	8504	8543
R	8	30800	30801	62		55	64	57	55	65	68	65	59	12090	11304	12107	12138	12154	12115	12110	13164	8503	8509	8495	8507	8512	8501	8510	8501	8524	8502	8743	8515	8514	8504	8506	8545
D	8	30805	30806	67	55		65	58	61	71	74	71	64	12095	11310	12113	12143	12159	12121	12116	13169	8508	8515	8500	8513	8518	8506	8515	8506	8529	8507	8748	8521	8520	8509	8512	8550
R	8	30814	30815	76	64	65		18	70	80	83	80	73	12104	11319	12122	12152	12168	12130	12125	13178	8517	8524	8509	8522	8527	8515	8524	8515	8539	8517	8757	8530	8529	8518	8521	8559
R	8	30807	30809	70	57	58	18		63	73	76	73	66	12097	11312	12115	12146	12161	12123	12118	13172	8511	8517	8503	8515	8520	8509	8518	8509	8532	8510	8751	8523	8522	8512	8514	8553
D	8	30805	30806	67	55	61	70	63		37	40	37	64	12095	11310	12113	12143	12159	12121	12116	13169	8508	8515	8500	8513	8518	8506	8515	8506	8529	8507	8748	8521	8520	8509	8512	8550
D	8	30815	30816	77	65	71	80	73	37		50	47	74	12105	11320	12123	12154	12169	12131	12126	13179	8518	8525	8511	8523	8528	8517	8526	8517	8540	8518	8759	8531	8530	8520	8522	8561
R	8	30818	30820	81	68	74	83	76	40	50		6	77	12108	11323	12126	12157	12172	12134	12129	13183	8522	8528	8514	8526	8531	8520	8529	8520	8543	8521	8762	8534	8533	8523	8525	8564
D	8	30815	30816	77	65	71	80	73	37	47	6		74	12105	11320	12123	12154	12169	12131	12126	13179	8518	8525	8511	8523	8528	8517	8526	8517	8540	8518	8759	8531	8530	8520	8522	8561
R	8	30809	30810	71	59	64	73	66	64	74	77	74		12099	11313	12116	12147	12163	12124	12119	13173	8512	8518	8504	8517	8521	8510	8519	8510	8533	8511	8752	8524	8523	8513	8515	8554
R	49	33290	33292	12088	12090	12095	12104	12097	12095	12105	12108	12105	12099		1919	2722	2753	2768	2730	2725	13163	10994	11000	10986	10998	11003	10992	11001	10992	11015	10993	11234	11006	11005	10995	10997	11036
D	2	32505	32506	11302	11304	11310	11319	11312	11310	11320	11323	11320	11313	1919		1043	1074	1090	1051	1046	12377	10209	10215	10201	10213	10218	10207	10216	10207	10230	10208	10449	10221	10220	10210	10212	10251
R	2	33308	33309	12105	12107	12113	12122	12115	12113	12123	12126	12123	12116	2722	1043		44	60	22	23	13180	11011	11018	11003	11016	11021	11009	11018	11009	11032	11011	11251	11024	11023	11012	11015	11053
D	2	33339	33340	12136	12138	12143	12152	12146	12143	12154	12157	12154	12147	2753	1074	44		83	45	53	13211	11042	11049	11034	11047	11051	11040	11049	11040	11063	11041	11282	11054	11053	11043	11045	11084
R	2	33354	33356	12152	12154	12159	12168	12161	12159	12169	12172	12169	12163	2768	1090	60	83		56	69	13227	11058	11064	11050	11062	11067	11056	11065	11056	11079	11057	11298	11070	11069	11059	11061	11100
D	2	33316	33317	12113	12115	12121	12130	12123	12121	12131	12134	12131	12124	2730	1051	22	45	56		31	13189	11020	11026	11012	11024	11029	11018	11027	11018	11041	11019	12260	11032	11031	11021	11023	11062
D	2	33311	33312	12108	12110	12116	12125	12118	12116	12126	12129	12126	12119	2725	1046	23	53	69	31		13183	11014	11021	11007	11019	11024	11012	11022	11012	11036	11014	11255	11027	11026	11016	11018	11056
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D	42	23923	23924	8501	8503	8508	8517	8511	8508	8518	8522	8518	8512	10994	10209	11011	11042	11058	11020	11014	12068		33	19	31	36	25	34	25	48	26	267	39	38	28	30	69
R	42	23929	23931	8507	8509	8515	8524	8517	8515	8525	8528	8525	8518	11000	10215	11018	11049	11064	11026	11021	12075	33		26	38	43	31	40	31	55	33	273	46	45	35	37	75
D1	42	23915	23916	8493	8495	8500	8509	8503	8500	8511	8514	8511	8504	10986	10201	11003	11034	11050	11012	11007	12060	19	26		21	26	15	24	15	38	16	257	29	28	18	20	59
D2	42	23928	23929	8506	8507	8513	8522	8515	8513	8523	8526	8523	8517	10998	10213	11016	11047	11062	11024	11019	12073	31	38	21		29	22	31	22	50	28	269	42	40	30	33	71
D	42	23932	23933	8510	8512	8518	8527	8520	8518	8528	8531	8528	8521	11003	10218	11021	11051	11067	11029	11024	12077	36	43	26	29		27	36	27	55	33	274	46	45	35	37	76
D1	42	23921	23922	8499	8501	8506	8515	8509	8506	8517	8520	8517	8510	10992	10207	11009	11040	11056	11018	11012	12066	25	31	15	22	27		22	13	44	22	262	35	34	24	26	64
D	42	23930	23931	8508	8510	8515	8524	8518	8515	8526	8529	8526	8519	11001	10216	11018	11049	11065	11027	11022	12075	34	40	24	31	36	22		14	53	31	272	44	43	33	35	73
R	42	23921	23922	8499	8501	8506	8515	8509	8506	8517	8520	8517	8510	10992	10207	11009	11040	11056	11018	11012	12066	25	31	15	22	27	13	14		44	22	262	35	34	24	26	64
D	42	23944	23945	8522	8524	8529	8539	8532	8529	8540	8543	8540	8533	11015	10230	11032	11063	11079	11041	11036	12089	48	55	38	50	55	44	53	44		34	275	47	46	36	38	77
R	42	23922	23923	8500	8502	8507	8517	8510	8507	8518	8521	8518	8511	10993	10208	11011	11041	11057	11019	11014	12067	26	33	16	28	33	22	31	22	34		248	20	19	9	11	50
R	42	24163	24164	8741	8743	8748	8757	8751	8748	8759	8762	8759	8752	11234	10449	11251	11282	11298	11260	11255	12308	267	273	257	269	274	262	272	262	275	248		232	231	248	250	288
R	42	23935	23937	8513	8515	8521	8530	8523	8521	8531	8534	8531	8524	11006	10221	11024	11054	11070	11032	11027	12080	39	46	29	42	46	35	44	35	47	20	232		4	20	22	61
D2	42	23934	23935	8512	8514	8520	8529	8522	8520	8530	8533	8530	8523	11005	10220	11023	11053	11069	11031	11026	12079	38	45	28	40	45	34	43	34	46	19	231	4		19	21	60
R	42	23924	23925	8502	8504	8509	8518	8512	8509	8520	8523	8520	8513	10995	10210	11012	11043	11059	11021	11016	12069	28	35	18	30	35	24	33	24	36	9	248	20	19		11	50
R	42	23926	23928	8504	8506	8512	8521	8514	8512	8522	8525	8522	8515	10997	10212	11015	11045	11061	11023	11018	12071	30	37	20	33	37	26	35	26	38	11	250	22	21	11		47
D	42	23965	23966	8543	8545	8550	8559	8553	8550	8561	8564	8561	8554	11036	10251	11053	11084	11100	11062	11056	12110	69	75	59	71	76	64	73	64	77	50	288	61	60	50	47	

Figure 3.

Pairwise SNV comparison between spatially linked MLST concordant PD cases and putative donors. Pairs are color coded for comparison. PD cases labelled as recipients and previous contacts as donors.

Table 1.

Total number of CDI positive unit contacts by time and MLST concordant status for all PD cases (n=147)

Exposure	PD cases with prior CDI contact ^	Total previous contacts with CDI	Contacts with same ST type (Presumed transmission)	95% CI	Overall PD cases with same ST contact ¶
Indirect overlap *					
<4 weeks	121	389	30, 7.7%	(5.2–10.8%)	27
4–8 weeks	115	324	32, 9.8%	(6.9–13.7%)	20
8–12 weeks	103	340	30, 8.8%	(6.0–12.4%)	20
Direct Overlap	117	454	33, 7.2%	(5.1–10.1%)	26
Total		1507	125, 8.3%	(7.0–9.8%)	

* Interval between discharge of previous unit contact that is CDI positive and date of admission of CO-HCFA case.

^ Represents 147 PD cases - not mutually exclusive by exposure categories

¶ Represents 69 PD cases with concordant contact- not mutually exclusive by exposure categories