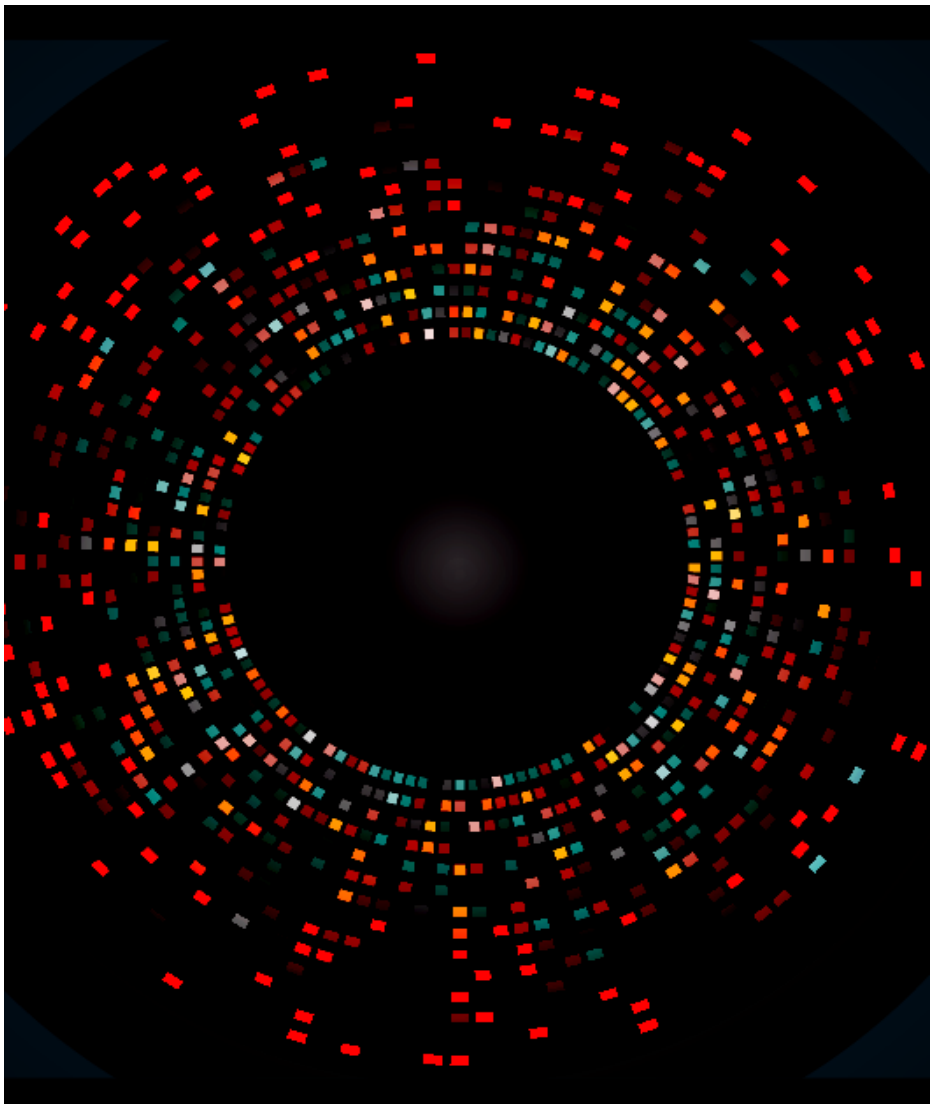
UK Health Security Agency

Clostridioides difficile ribotyping network (CDRN) for England and Northern Ireland

2018 to 2023



Contents

Introduction

Since the introduction of the *Clostridioides difficile* Ribotyping Network (CDRN) for England and Northern Ireland, coincident with the peak incidence of *C. difficile* infection (CDI) in England (and the UK), rates have fallen markedly (1). However, a subsequent period of relatively stability of CDI rates in England ended during the COVID-19 pandemic; compared with pre-pandemic rates, CDI incidence has increased in England by approximately 25%, particularly (but non-exclusively) driven by hospital onset cases (2). CDRN continues to respond to a major public health need, by providing a molecular epidemiological service that enhances our understanding of *C. difficile*, which is recognised as a global threat (3). CDI case fatality rates have also declined, notably in line with control of the epidemic ribotype *C. difficile* 027 (4 to 6). It is not possible to determine which interventions have been particularly responsible for the decreased incidence of CDI and associated deaths. However, it is plausible that access to the ribotyping and enhanced fingerprinting results provided by CDRN have facilitated improved local investigation and control of CDI cases, clusters and outbreaks. CDRN has certainly contributed to a much improved understanding of the epidemiology of CDI, and its scope or coverage is unrivalled worldwide.

Samples are submitted to CDRN according to local clinical need. We aim to provide results within 2 weeks of sample receipt. We believe that the timely data provided by CDRN has enabled healthcare institutions to respond to changes in CDI presentation and/or incidence. We encourage all hospitals to consider submitting samples according to the CDRN criteria so that they can be best placed to continue to prevent and control CDI.

Historically the CDRN has operated from a combination of the following participating laboratories:

- Leeds (Leeds General Infirmary) [Yorkshire and Humber]; CDRN Reference Laboratory
- Birmingham (Heartlands Hospital) [West and East Midlands Regions]
- Bristol [South West Region]
- Cambridge (Addenbrooke's Hospital) [East of England Region]
- Manchester (Manchester Royal Infirmary) [North West Region]
- Southampton (Southampton General Hospital) [South East Region]
- Belfast (Royal Victoria Hospital) [Northern Ireland Region]

Due to centralisation efforts in Spring 2021, a full national CDRN service is now delivered from UKHSA CDRN Reference Laboratory at Leeds. The Royal Victoria Hospital Belfast has continued to support locations in Northern Ireland.

Accessing the service

The CDRN laboratories provide access to *C. difficile* culture and ribotyping according to standardised criteria for submission of faecal samples. The number of samples to be submitted to the CDRN per scenario should be agreed prospectively with respective regional microbiologists, or a microbiologist from the CDRN laboratory, according to the extent and severity of CDI cases. The CDRN aims to provide timely information to help optimise the management of *C. difficile* at a local level, with a turnaround time of less than 2 weeks (this includes the time to culture *C. difficile*). It is recommended that the CDRN service is used by hospitals or infection control teams in England to investigate:

- increased frequency of cases or high baseline rates of CDI
- increased severity or complications of cases of CDI
- increased mortality associated with CDI
- increased recurrence rate of CDI

We believe that the CDRN service can help local teams to meet targets that have been set for reducing the incidence of CDI. Additionally, we collect, via a mandatory request form, antibiotic risk and outcome data that can be used to provide more detailed information about CDI at a national level. Some requests provide little such data, which hinders this aim, and we therefore encourage all users of the CDRN service to submit the data requested.

Enhanced DNA fingerprinting

Since late 2008, CDRN has offered an enhanced DNA fingerprinting (multi-locus variable repeat analysis (MLVA)) service. This can be used to characterise and improve the understanding of the transmission of epidemic *C. difficile* strains within healthcare institutions. Importantly, the method can provide a high level of discrimination among epidemic *C. difficile* ribotypes. For example, MLVA can distinguish more than 20 sub-types of *C. difficile* ribotype 027 (7). MLVA is far superior to most other fingerprinting methods, including pulsed field gel electrophoresis, for analysing closely related *C. difficile* strains (8). MLVA has similar discriminatory power, as a typing/fingerprinting method, to whole genome sequencing, although the latter method provides considerable additional genetic information (9).

Institutions should consider the use of the CDRN MLVA Enhanced Fingerprinting service to optimise the control and prevention of CDI. There is currently no charge for the enhanced fingerprinting service for NHS hospitals in England. Access to the service is controlled, in the first instance by regional microbiologists, given its high cost and need to balance availability with the scale of CDI challenge. MLVA is available via the Leeds laboratory.

The criteria used to access the enhanced fingerprinting service are:

- a hospital or trust with a high rate of CDI as identified with local commissioners

or:

- a hospital or trusts that is failing to meet its *C. difficile* target trajectory despite implementation and audit of control measures

or:

- a declared outbreak of CDI as agreed with the local Health Protection Unit

In addition:

- ribotyping carried out by CDRN must have confirmed the presence of a dominant *C. difficile* ribotype
- a plan should be in place of how results of *C. difficile* enhanced fingerprinting will contribute to the control of CDI
- infection control teams or consultant microbiologists will first need to agree with the regional microbiologist that use of the *C. difficile* enhanced fingerprinting service is merited
- numbers of samples or isolates to be examined will be agreed with the MLVA laboratory on a case-by-case basis, taking account of the scale of CDI challenge

Antibiotic susceptibility testing

In order to determine the epidemiology of the susceptibility to metronidazole, vancomycin and fidaxomicin of *C. difficile* isolates from CDI cases, periodic prospective surveillance is performed on strains received by the CDRN Reference Laboratory in Leeds. It is planned that new susceptibility surveillance data will be available later in 2023. Further such data is available via publications on a long-term European antibiotic susceptibility study (10 to 12).

Electronic requesting and reporting system

A dedicated electronic requesting and reporting system continues to be available for NHS trusts to complete electronic request forms and receive test results electronically, as well as access archived historical results. The service is accessible via the NHS N3 secure network and users must securely register on the site before making requests.

The service can be accessed online.

Historical data and user guides are available on the Public Health England (PHE) webpages.

The electronic requesting and reporting system has been fully operational in all regions for several years and this service is completely electronic. The system employs heightened user notification via email, enabling faster reporting of results to assist outbreak investigation, and enhance data analysis capabilities.

We are collaborating with the UKHSA healthcare-associated infection surveillance team to streamline data collection. The aim is to enable different electronic data collection systems to communicate, and so minimise the duplication of data input by users of the different surveillance schemes.

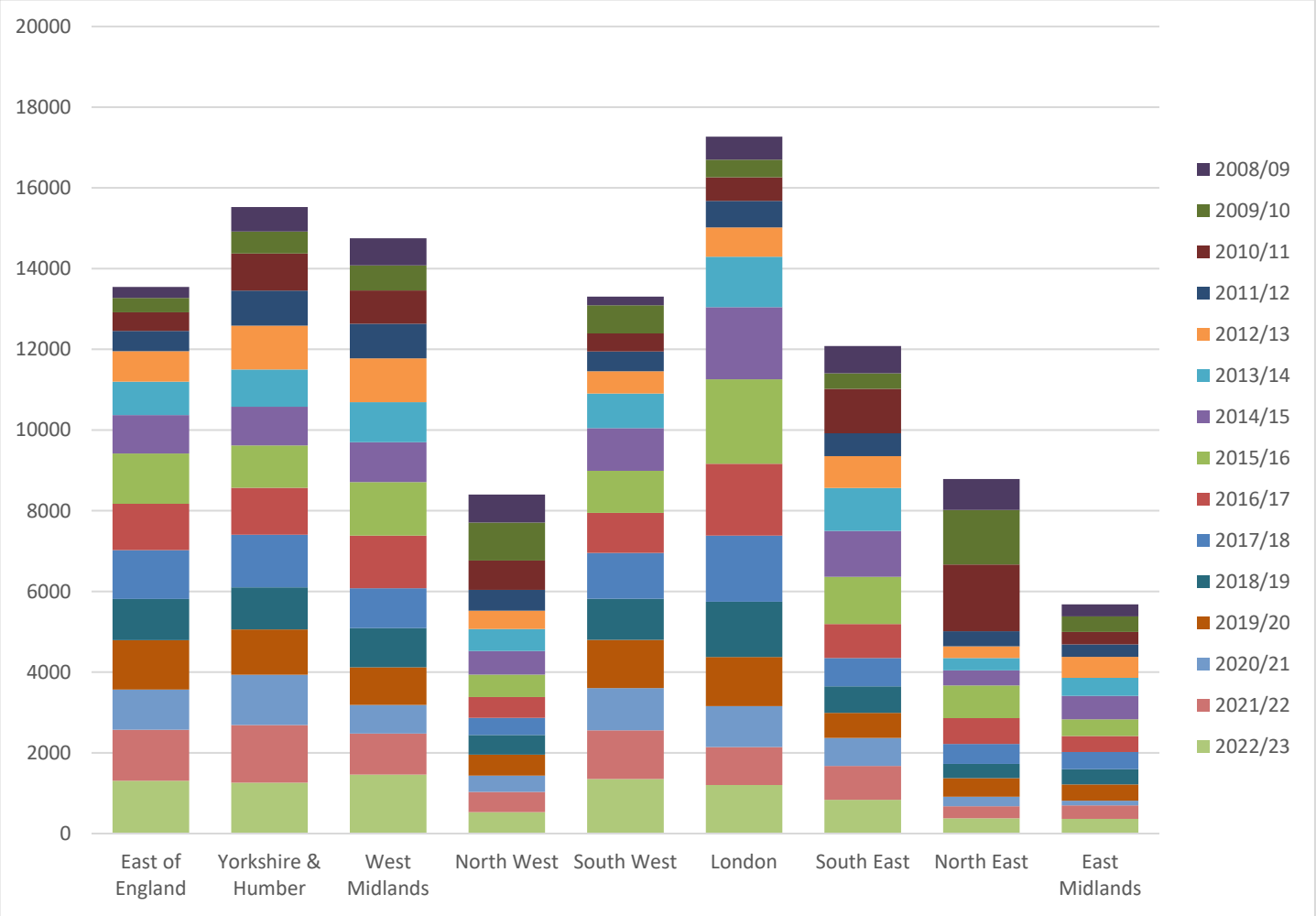
Results for 2018 to 2019, 2019 to 2020, 2020 to 2021, 2021 to 2022 and 2022 to 2023

In 2018 to 2019, 2019 to 2020, 2020 to 2021, 2021 to 2022 and 2022 to 2023, CDRN processed 7,296 faecal samples from 131 healthcare facilities, 7,698 faecal samples from 130 healthcare facilities, 6,462 faecal samples from 126 healthcare facilities, 7,829 faecal samples from 128 healthcare facilities and 8,688 faecal samples from 122 healthcare facilities, respectively.

Data available during this period shows only minor regional differences in the number of samples submitted to the service, relative to those submitted in previous periods (Figure 1). Submissions from the East Midlands, North East and North West regions have been proportionally lower than from other regions.

On average, 56, 59, 51, 61 and 71 samples were submitted to CDRN by each participating hospital in 2018 to 2019, 2019 to 2020, 2020 to 2021, 2021 to 2022 and 2022 to 2023, respectively.

Figure 1. Distribution of CDRN samples submitted to the service (2008/2009 to 2022/2023)



	East of England	Yorkshire and Humber	West Midlands	North West	South West	London	South East	North East	East Midlands
2008/09	274	609	669	693	215	571	676	770	297
2009/10	356	542	623	942	699	435	385	1350	388
2010/11	459	922	824	726	447	586	1103	1652	307
2011/12	504	867	860	517	491	657	566	374	308
2012/13	755	1086	1086	454	551	728	787	292	522
2013/14	827	924	989	547	857	1247	1066	307	444
2014/15	955	958	990	583	1057	1790	1136	371	582
2015/16	1243	1052	1325	555	1043	2092	1172	810	414
2016/17	1149	1163	1304	517	992	1780	843	642	397
2017/18	1210	1304	991	427	1137	1640	699	494	424
2018/19	1022	1041	970	485	1019	1368	660	353	378
2019/20	1224	1122	933	521	1196	1216	622	459	405
2020/21	995	1249	709	403	1046	1014	692	238	116
2021/22	1265	1428	1018	500	1204	944	839	297	334
2022/23	1308	1259	1459	531	1353	1201	836	378	363

It should be noted that an epidemiological study took place in the North East region during 2009 to 2011, which accounts for the larger numbers of samples processed here in these years.

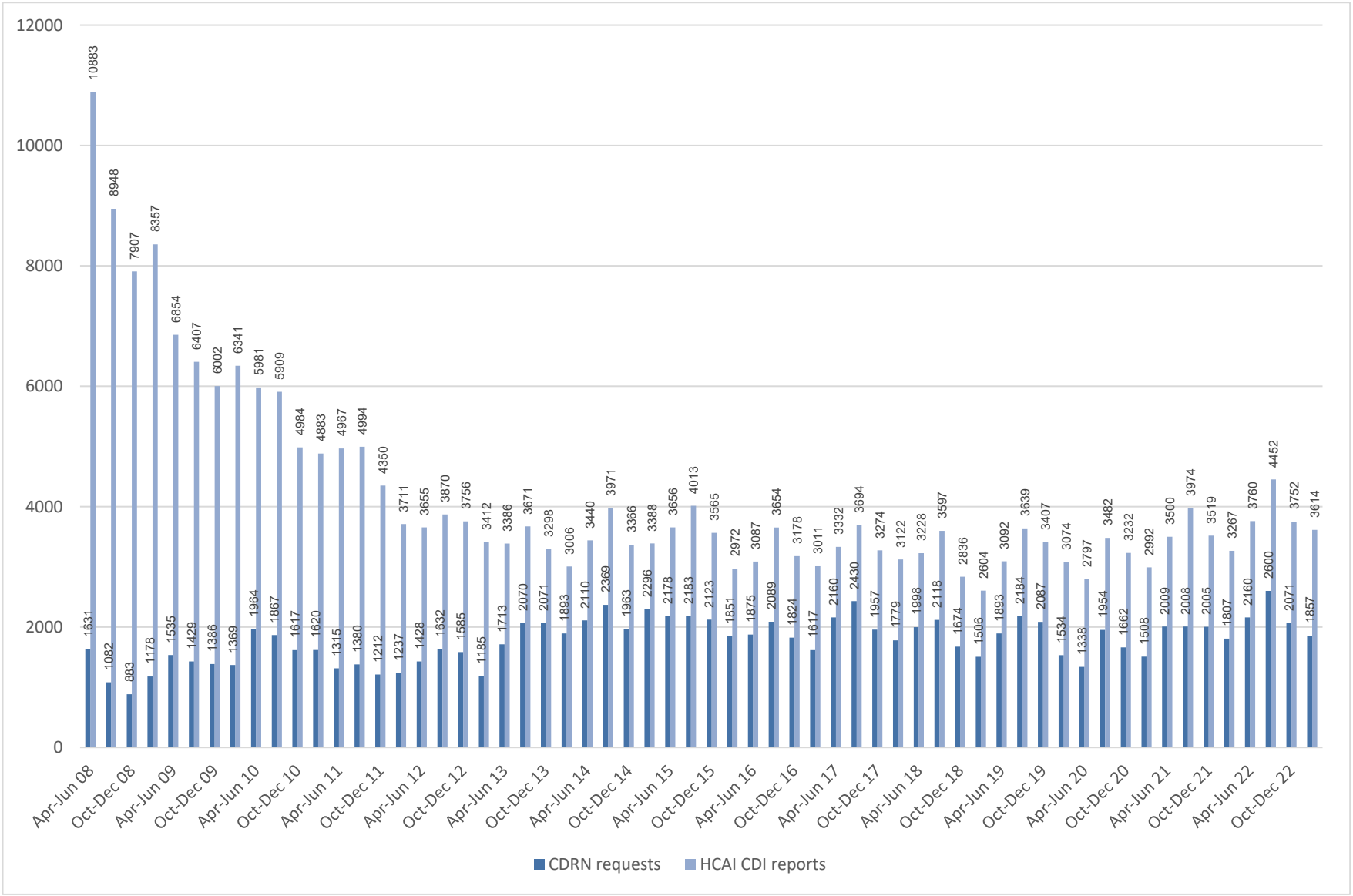
Proportion of mandatory CDI reported cases ribotyped

Figure 2 below shows the ribotyping sample submission to CDRN by quarter, expressed as the proportion of mandatory *C. difficile* (all reported cases) on the Mandatory HCAI Data Capture System (DCS) in England from April 2008 to March 2023.

The overall average annual proportion of *C. difficile* reported cases from whom samples were sent for ribotyping over the whole analysis period 2008 to 2023 was 47.6% (43.3% over the historical data period 2008/2009 to 2017/2018 and 55.9% over the last 5 years (2018/2019 to 2022/2023).

Usage of CDRN, expressed both in crude numbers and in terms of the proportion of all reported cases that are referred, has increased markedly since the service was launched. This data indicates that currently approximately one in every 2 reported cases of CDI are referred to CDRN for typing.

Figure 2. Proportion of HCAI CDI cases submitted for ribotyping to all reported cases of CDI to public health (2008/09 to 2022/23)



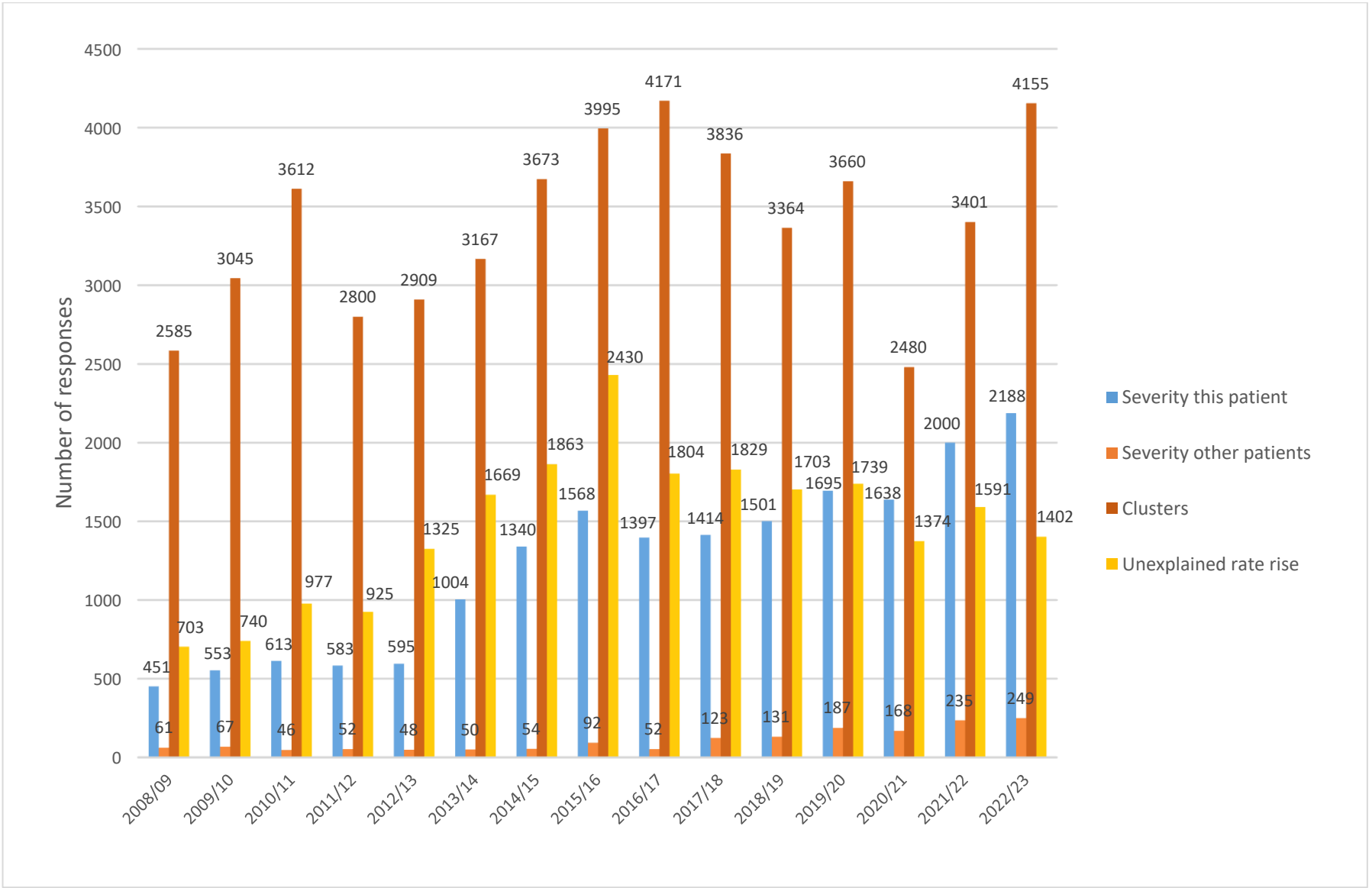
Reasons for sample submission to CDRN service

Samples submitted to CDRN are in response to clinical need. The reasons provided for sample submission are shown in Figure 3.

The most common reason cited for sample submission during the last 5 years (2018/2019 to 2022/2023) and during the historical period (2008/2009 to 2017/2018) was clustering of cases (44.9% and 47.4% of all samples cited this as a reason, respectively). Unexplained increase in CDI rate was cited as a reason for submission in 20.6% of cases during the last 5 years and in 20.0% during the historical period.

Notably, submissions associated with severity of symptoms of CDI in the affected patient and in other patients increased to 26.3% during the last 5 years (13.3% historically).

Figure 3. Reason for sample submission to CDRN (2008/09 to 2017/18)



C. difficile recovery rate

Figure 4 shows *C. difficile* recovery rates for samples submitted to the service since 2008/09. This data excludes samples not processed or rejected (not enough sample, duplicates and so on). There was a 29% increase between 2007/2008 and 2008/2009 in the proportion of faecal samples submitted to CDRN that were *C. difficile* culture-negative (that is, from 9.6% to 12.4%). This change may have reflected more false-positive samples (CDRN examines samples presumed to have tested toxin-positive at the source laboratory).

Notably, the *C. difficile* recovery rate progressively increased in the early CDRN years, and has remained stably high (at more than 91% since 2011/2012). This data is consistent with improved and then relatively effective laboratory diagnosis of CDI. Guidelines for the diagnosis of CDI were issued in 2012 (13).

Figure 4. *C. difficile* recovery rate (2008/2009 to 2022/2023)

Year	Total samples	*C. difficile* growth	Recovery rate
2008/2009	4,774	4,175	87.45%
2009/2010	5,720	4,995	87.33%
2010/2011	7,026	6,202	88.27%
2011/2012	5,144	4,761	92.55%
2012/2013	5,830	5,523	94.73%
2013/2014	7,208	6,781	94.08%
2014/2015	8,124	7,609	93.66%
2015/2016	8,931	8,335	93.33%
2016/2017	7,880	7,405	93.97%
2017/2018	7,585	7,079	93.33%
2018/2019	6,717	6,272	93.38%
2019/2020	6,995	6,514	93.12%
2020/2021	5,664	5,198	91.77%
2021/2022	6,934	6,335	91.36%
2022/2023	7,686	7,116	92.58%

Ribotype distribution

Changes in ribotype prevalence

Figure 5A demonstrates the marked shifts nationally in ribotype prevalences in the 40 quarters of historical CDRN operation (April 2008 to March 2018). The most prevalent ribotypes are shown, that is, those with an overall minimum of more than 2% prevalence in all regions for all years. The isolates designated ‘sporadic’ represent those ribotypes not commonly recognised across the original CDRN network of regional laboratories, during that period.

Figure 5B indicates ribotype prevalence nationally in the 20 quarters of CDRN operation during the past 5 years (April 2018 to March 2023). Ribotypes with a more than 5% prevalence are shown separately (prevalence less than 5% are shown together in grey). Figure 5C indicates the most prevalent ribotypes (5%) associated with severe CDI symptoms (that is, those samples where severity of symptoms of CDI in the affected patient was cited as the reason for submission). This data is displayed regionally in Figure 6.

Historically, there has been a striking decrease in the prevalence of *C. difficile* ribotype 027, and also in ribotypes 001 and 106, with ‘compensatory’ increases in the other types. Data presented here would suggest that in some regions, ribotype 027 has almost completely disappeared (some persistence observed in the North West, Figure 6B). With increased sample submission to CDRN, such an effect may be expected to accompany an increase in the relative contribution of other ‘emergent’ *C. difficile* ribotypes to overall disease burden. Notably, the pattern of ribotypes in England has become markedly more heterogeneous (507 distinct ribotypes reported within last 5 years).

The relative prevalence rates for individual ribotypes have remained reasonably stable nationally and within regions between April 2018 and March 2023. Thus the recent increase in CDI incidence does not appear to be related to a change in relative ribotype prevalences (2). Overall, ribotypes 015, 002. 014, 005, 020, 023 and 078 have become, and remain the most prevalent types in England (14.0%, 13.1%, 12.2%, 10.8%, 9.4%, 7.8% and 7.3%, respectively) during this period. Notably, these ribotypes are also those most commonly identified in patients with severe CDI symptoms.

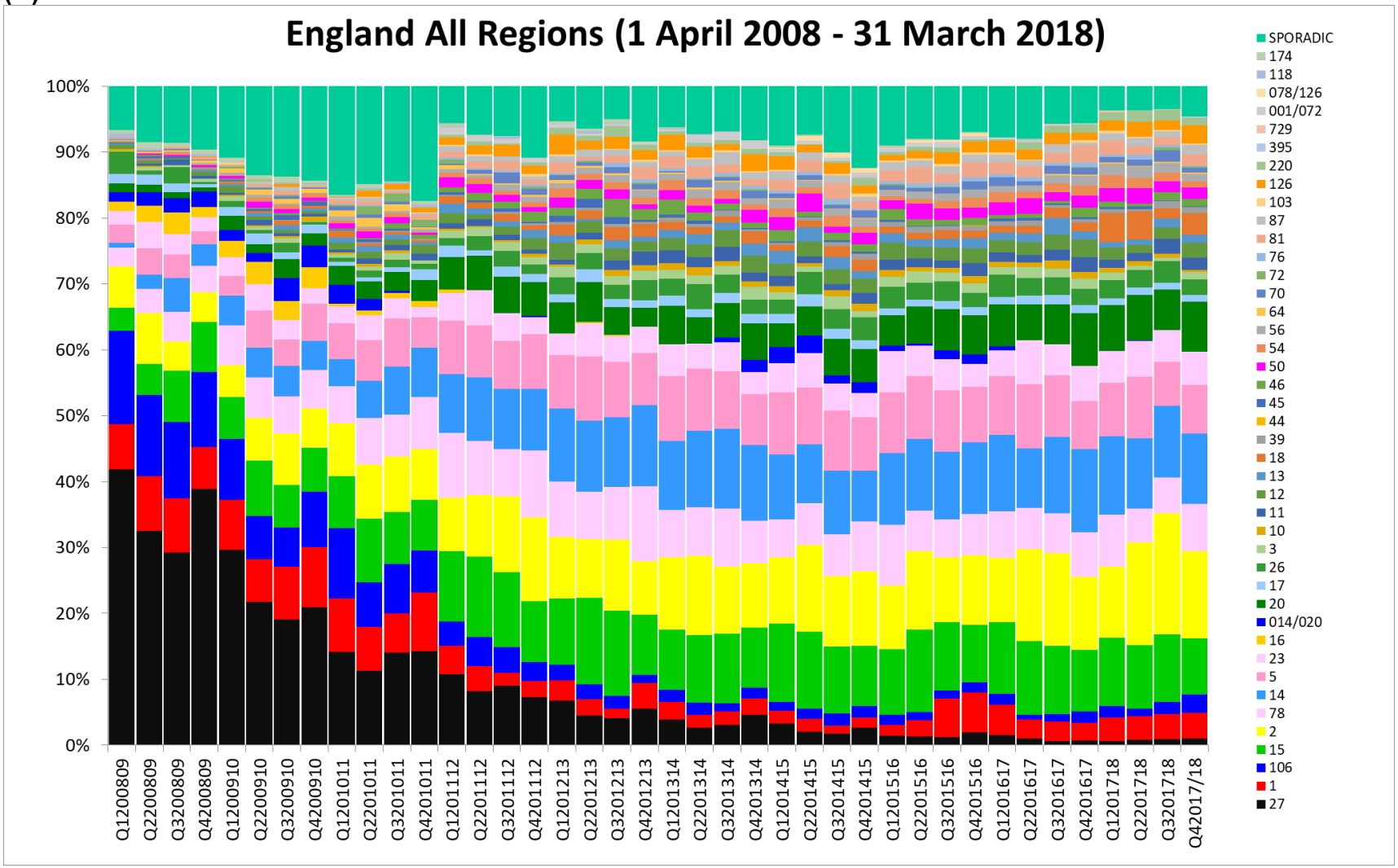
As part of the European, multicentre, prospective, biannual, point-prevalence study of *C. difficile* infection in hospitalised patients with diarrhoea (EUCLID), the largest *C. difficile* epidemiological study of its type, PCR ribotype distribution of *C. difficile* isolates in Europe was determined on 1,196 *C. difficile* isolates from diarrhoeal samples sent to the European coordinating laboratory in 2012 to 2013 and 2013 (from 2 sampling days) by 482 participating hospitals from 19 European countries (14). 125 distinct ribotypes were identified, with considerable intercountry variation in ribotype distribution. Ribotypes 027 (19%), 001/072 (11%) and 014/020 (10%) were the most prevalent, followed by ribotypes 002, 140, 010, 078, 176 and 018 (each less than 5%).

The prevalence of ribotypes 027 and 176, but not other epidemic strains, was inversely proportional to overall ribotype diversity (R2 = 0.717).

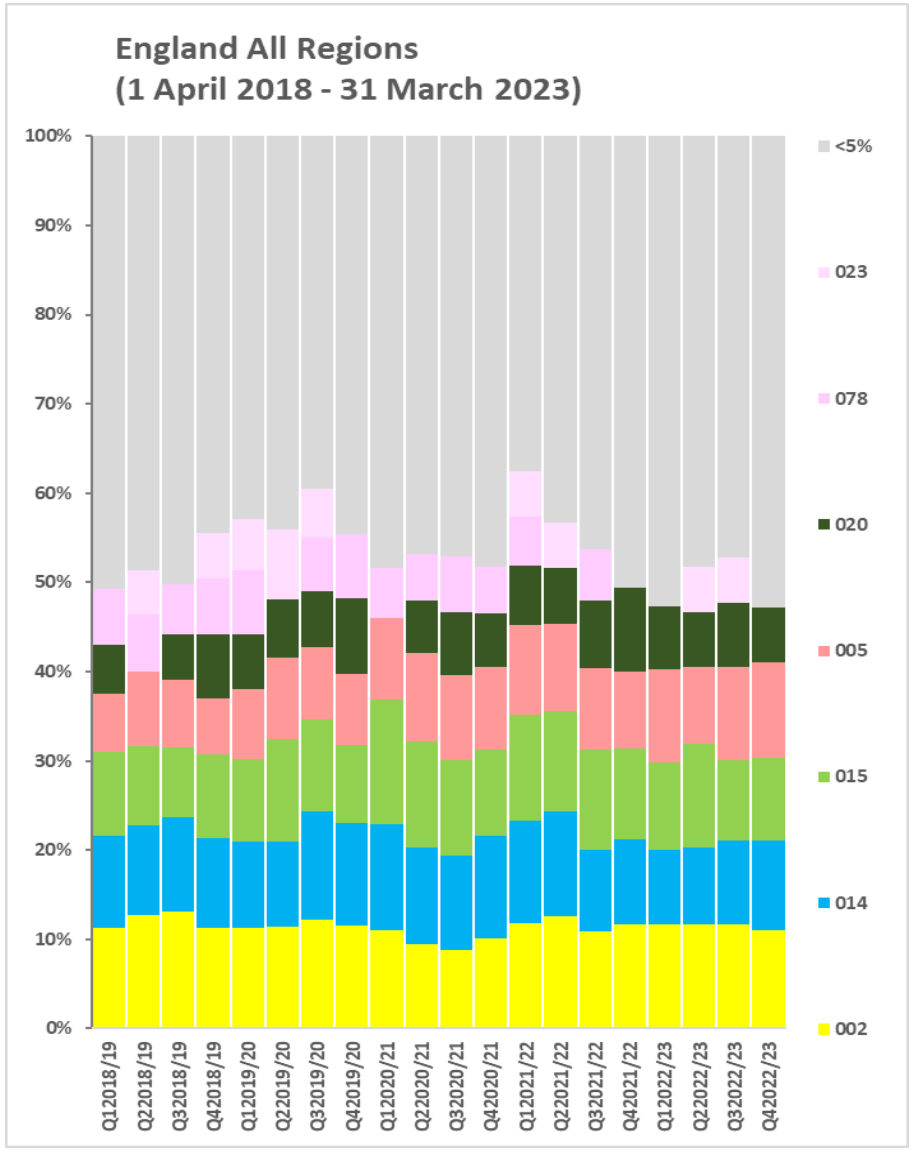
Importantly, there is increasing evidence that there are 2 distinct patterns of *C. difficile* ribotype spread (see Enhanced fingerprinting section).

Figure 5. Prevalence of *C. difficile* ribotypes in England (all regions) by quarter (April 2008 to March 2023): (A) April 2008 to March 2018 (more than 2% prevalence), (B) April 2018 to March 2023 (more than 5% prevalence), (C) April 2018 to March 2023 (more than 5% prevalence in patients with severe CDI)

(A)



(B)


England All Regions
(1 April 2018 - 31 March 2023)
100%
90%
80%
70%
60%
50%
40%
30%
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0%
<5%
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Q22018/19
Q32018/19
Q42018/19
Q12019/20
Q22019/20
Q32019/20
Q42019/20
Q12020/21
Q22020/21
Q32020/21
Q42020/21
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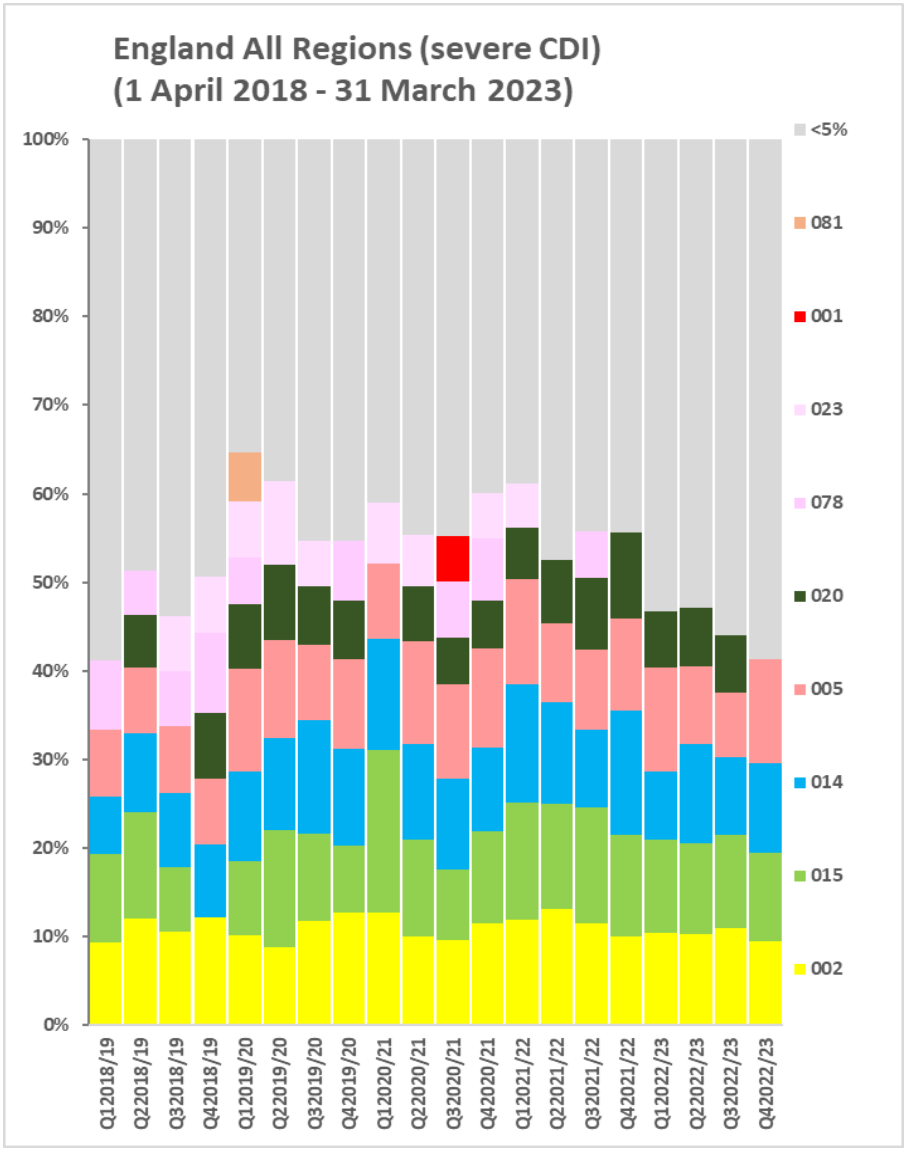
(C)


England All Regions (severe CDI)
(1 April 2018 - 31 March 2023)
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Q12019/20
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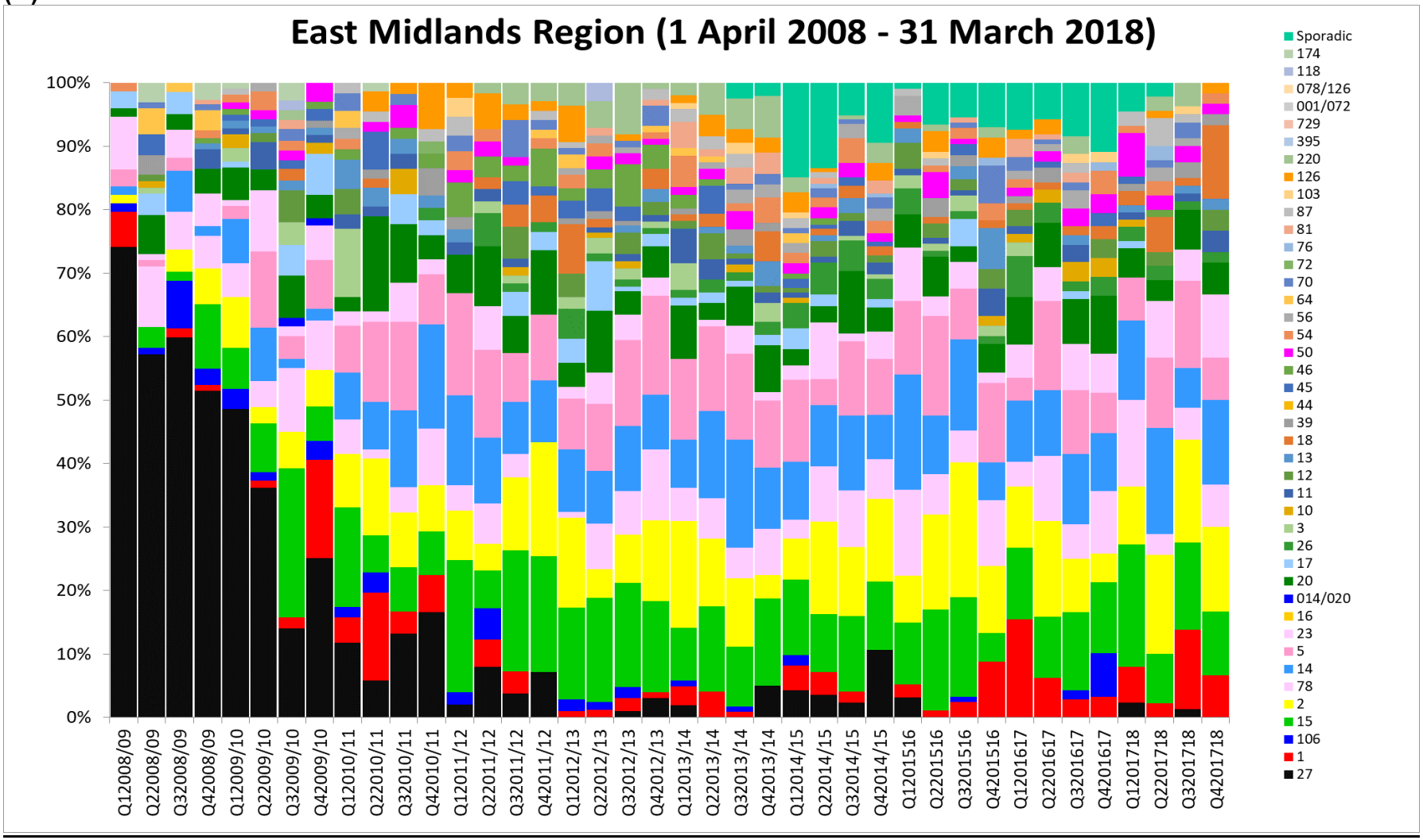
Q12022/23
Q22022/23
Q32022/23
Q42022/23

Figure 6. Distribution of PCR-ribotypes according to England region (April 2008 to March 2023): (A) April 2008 to March 2018 (more than 2% prevalence), (B) April 2018 to March 2023 (more than 5% prevalence), (C) April 2018 to March 2023 (more than 5% prevalence in patients with severe CDI)

(A)



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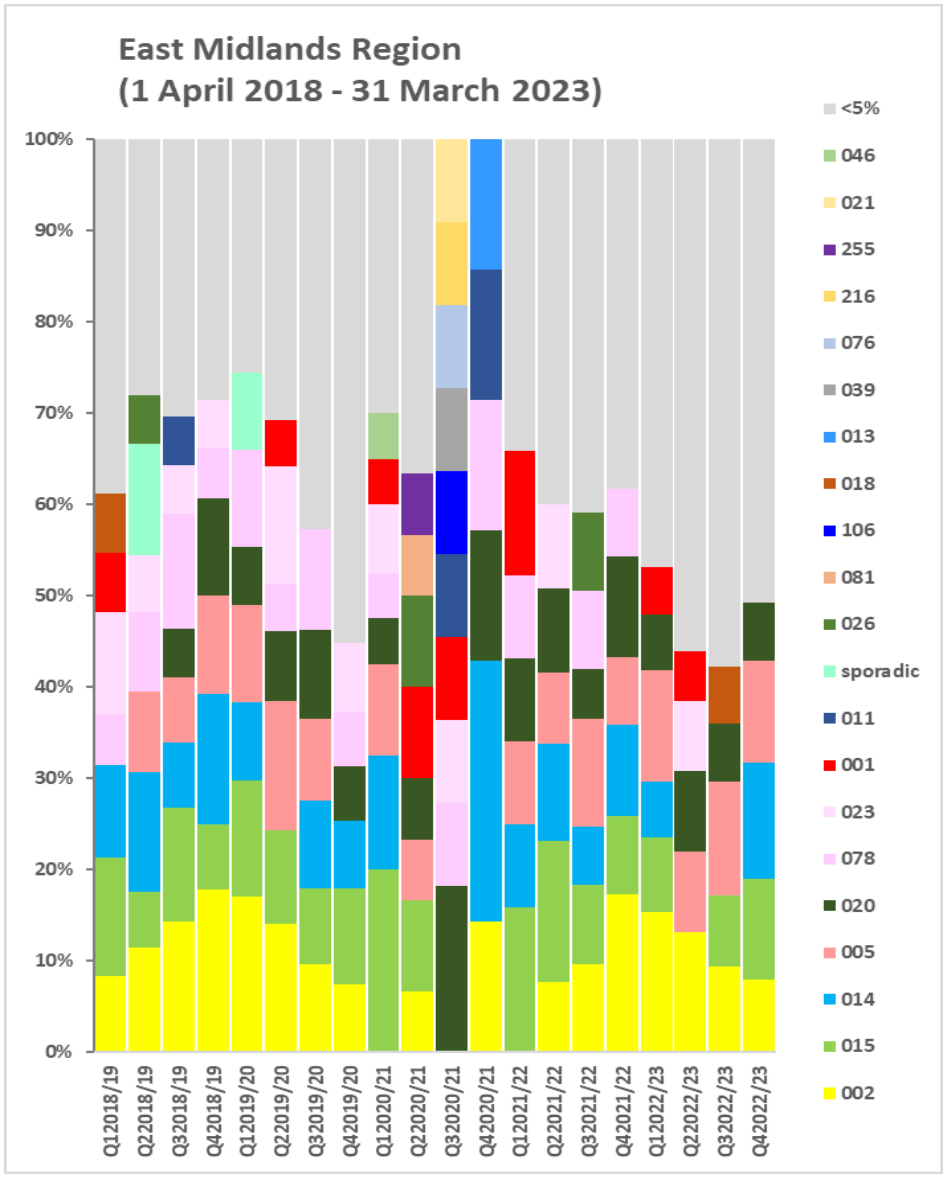
East Midlands Region
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Q12018/19
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Q32019/20
Q42019/20
Q12020/21
Q22020/21
Q32020/21
Q42020/21
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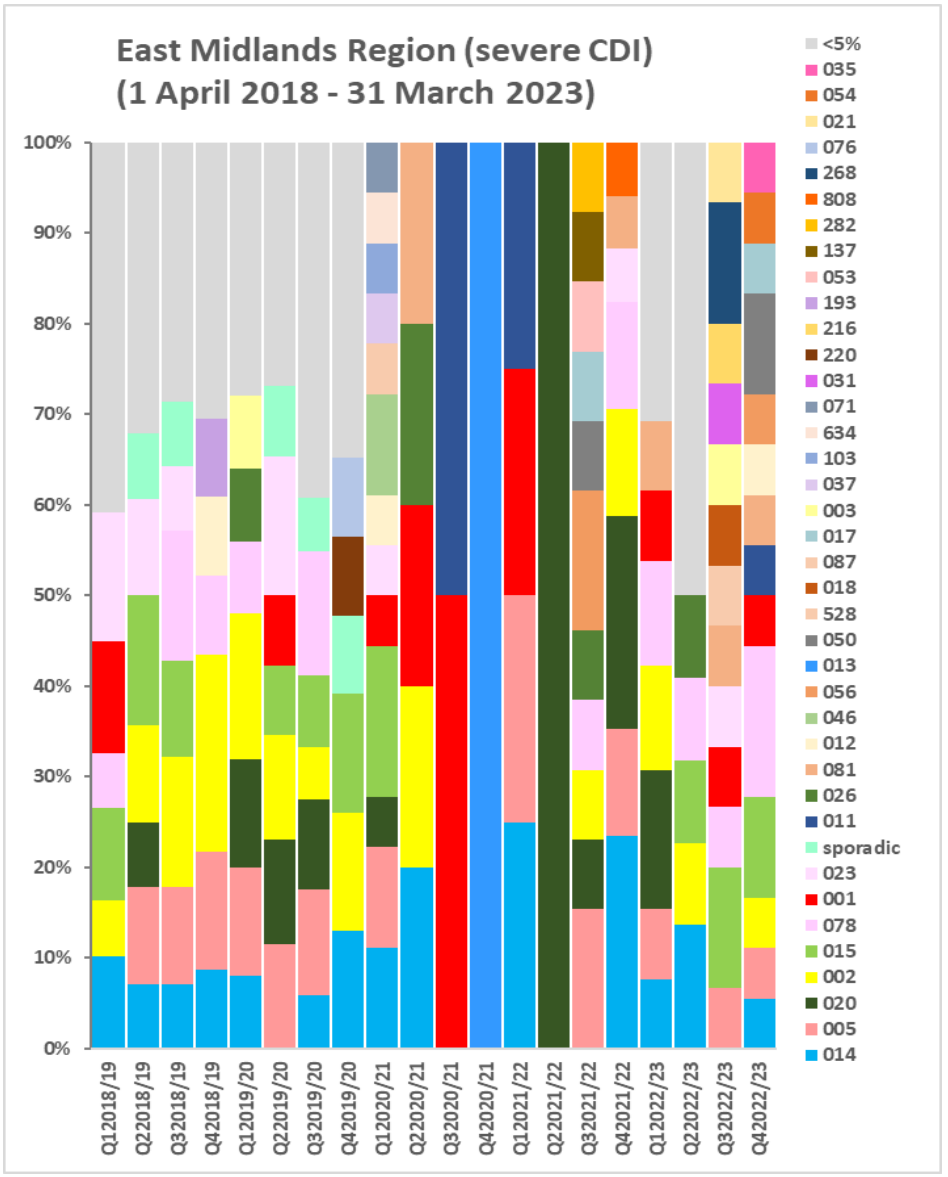
East Midlands Region (severe CDI)
(1 April 2018 - 31 March 2023)
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Q12020/21
Q22020/21
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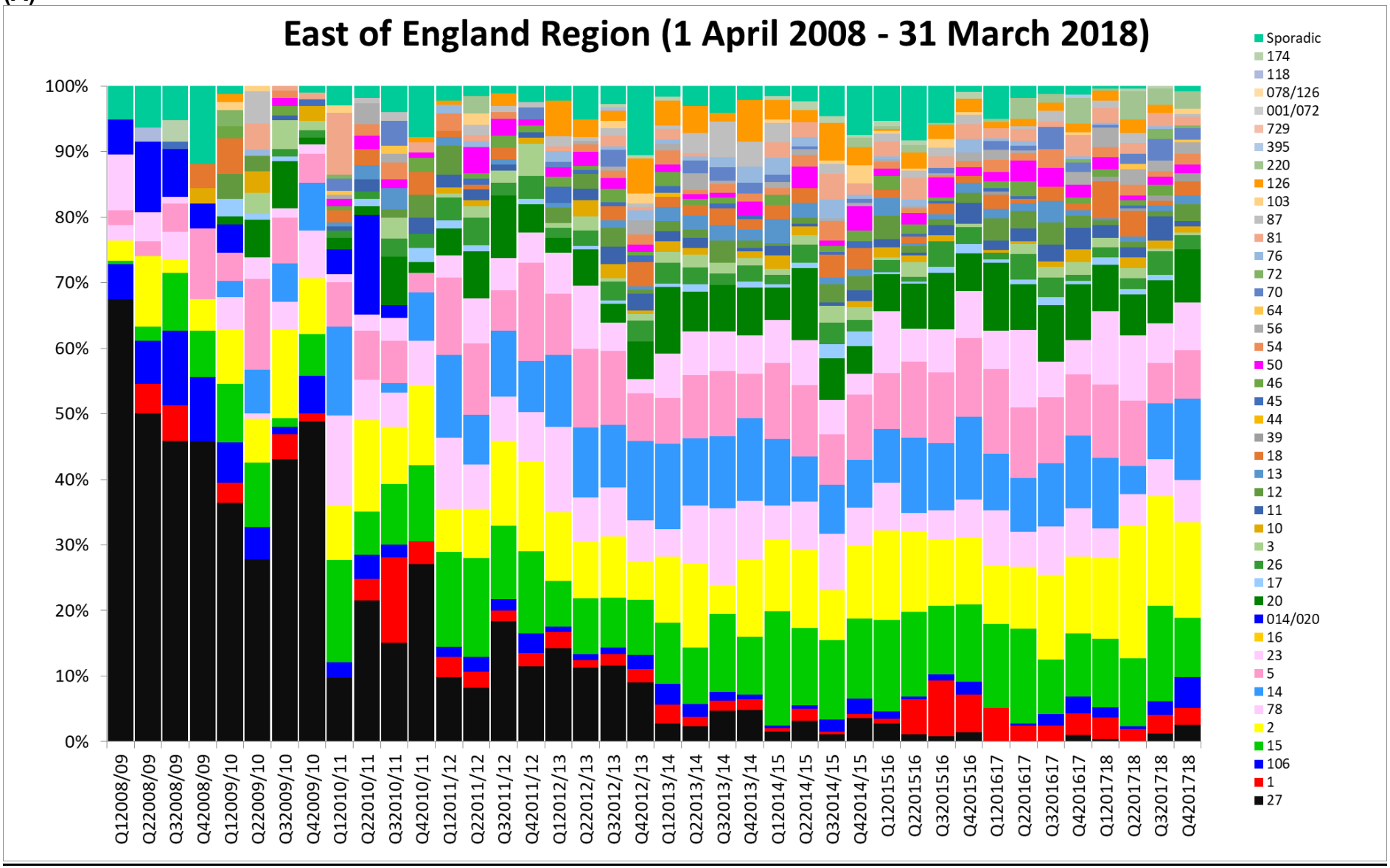
(A)


East of England Region (1 April 2008 - 31 March 2018)
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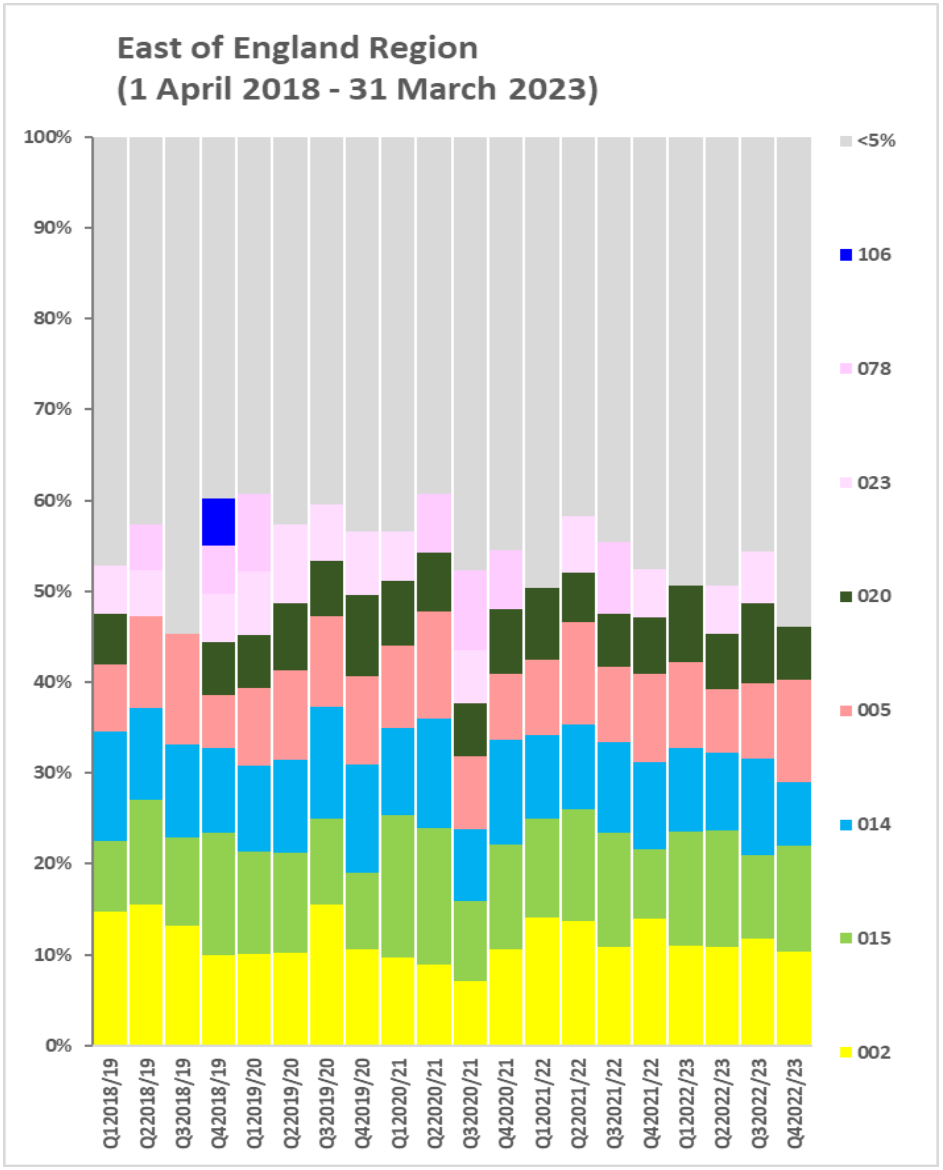
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Q12018/19
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Q32018/19
Q42018/19
Q12019/20
Q22019/20
Q32019/20
Q42019/20
Q12020/21
Q22020/21
Q32020/21
Q42020/21
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Q32021/22
Q42021/22
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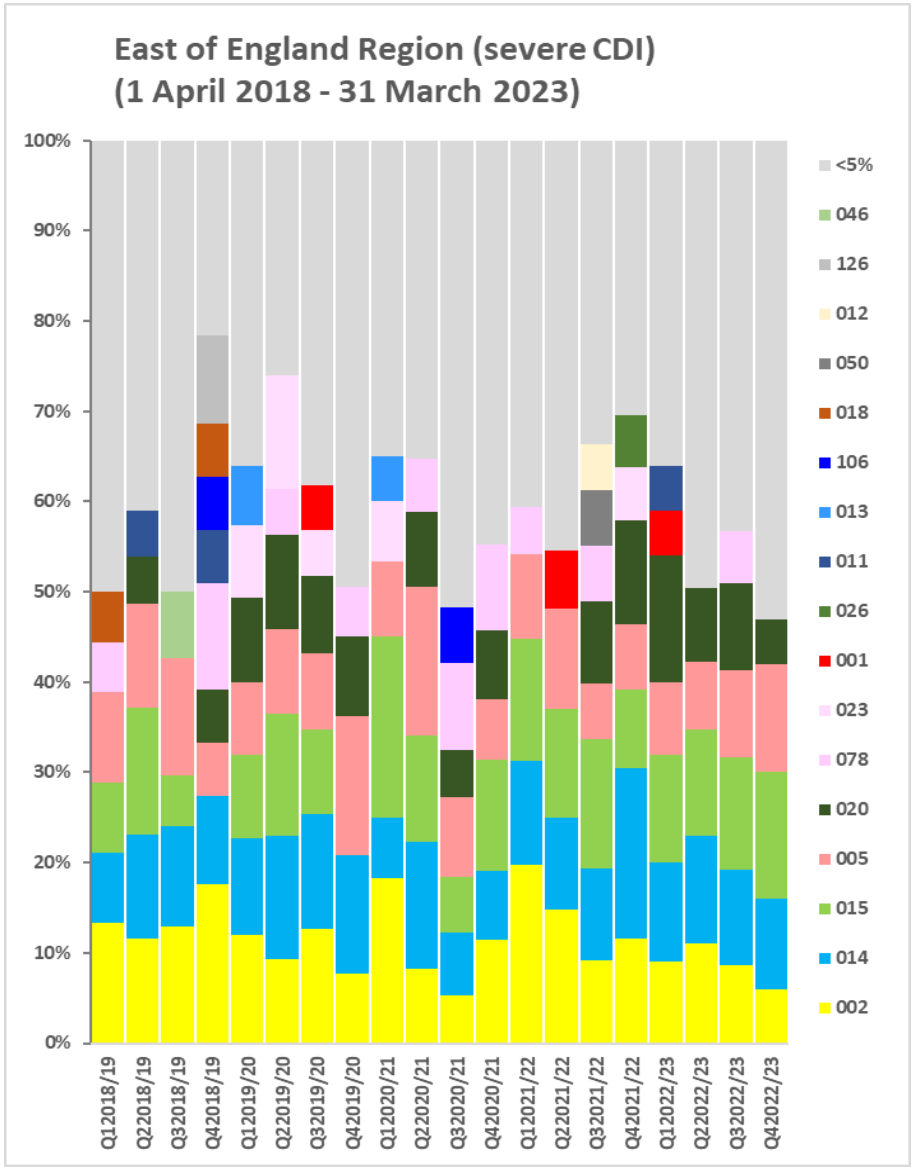
East of England Region (severe CDI)
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100%
90%
80%
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60%
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30%
20%
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Q22018/19
Q32018/19
Q42018/19
Q12019/20
Q22019/20
Q32019/20
Q42019/20
Q12020/21
Q22020/21
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Q22022/23
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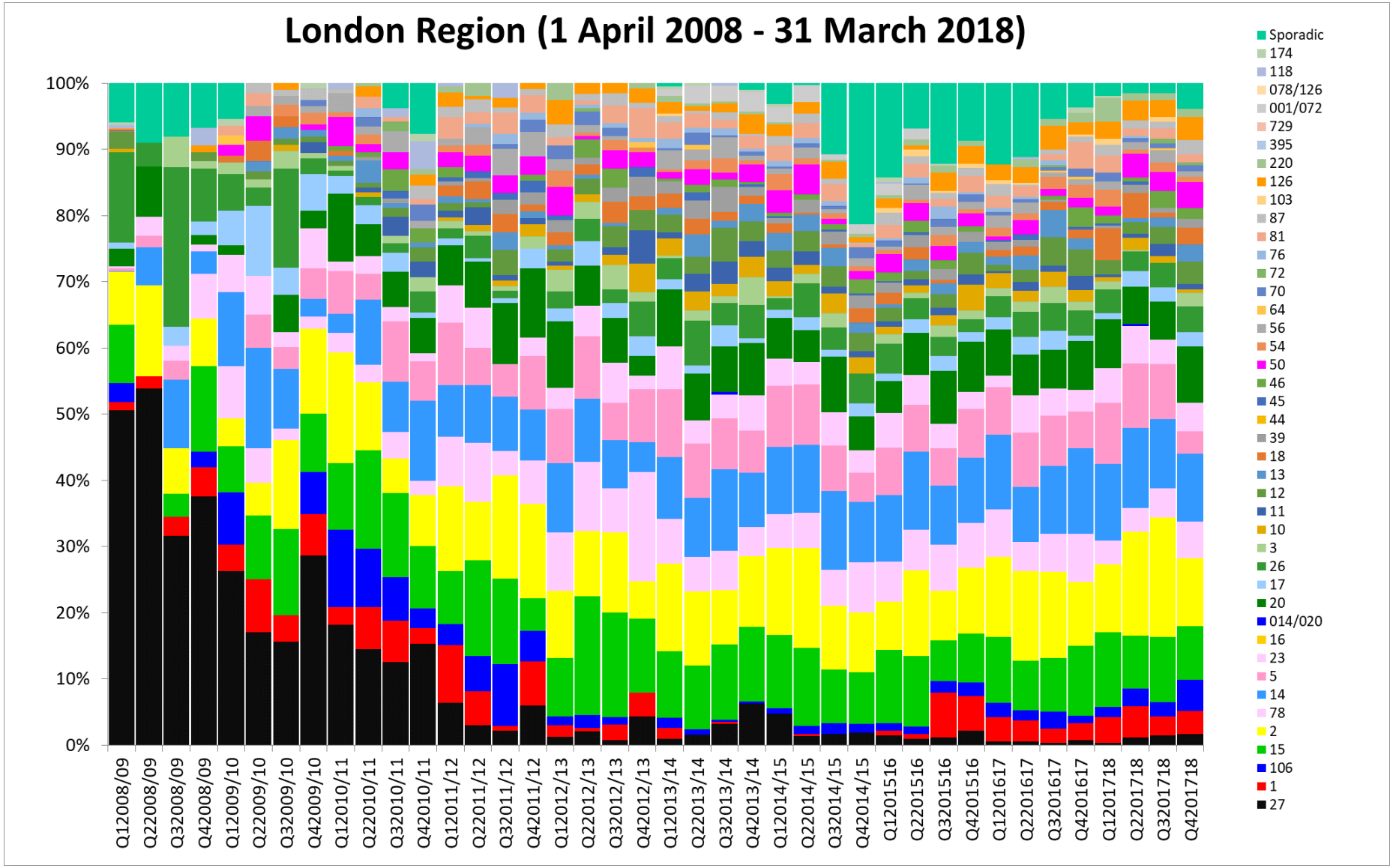
London Region (1 April 2008 - 31 March 2018)
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Sporadic
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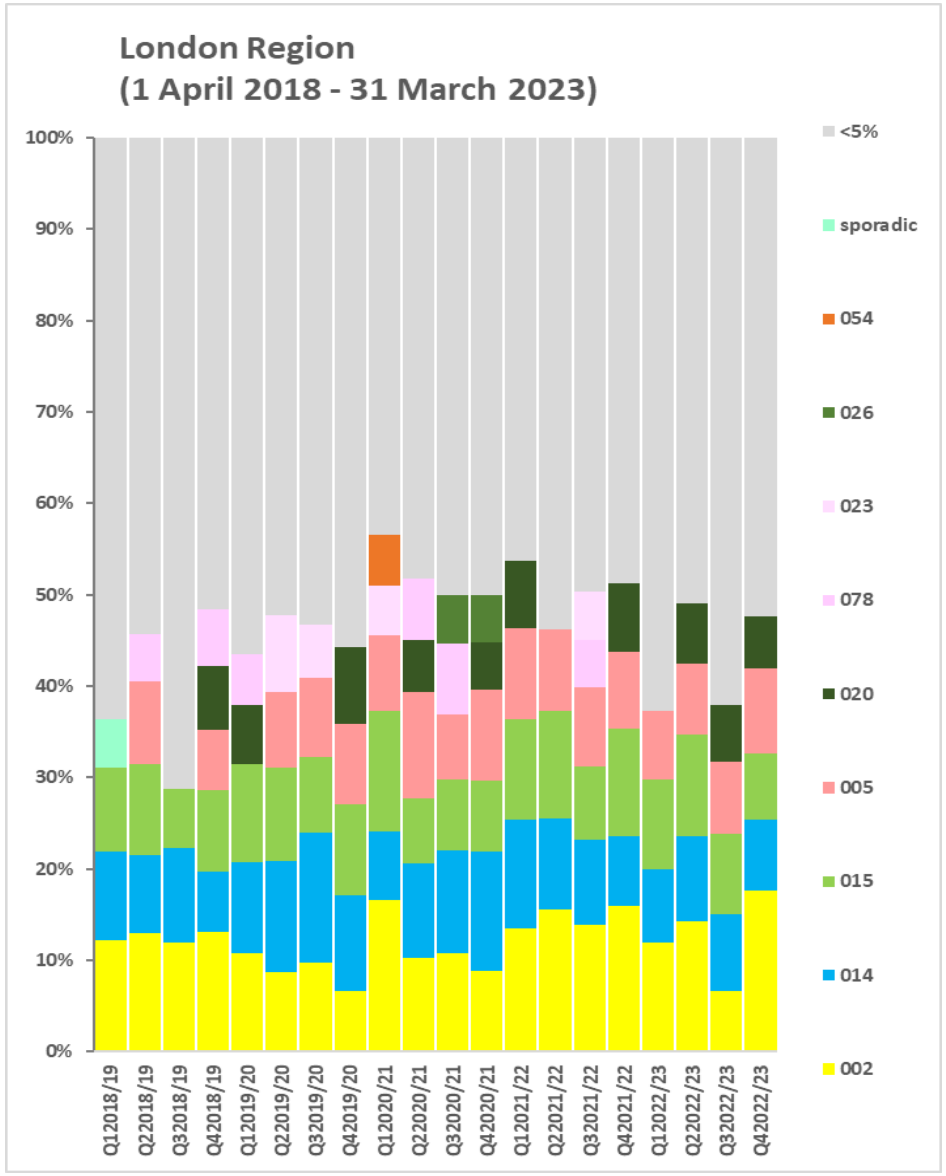
London Region
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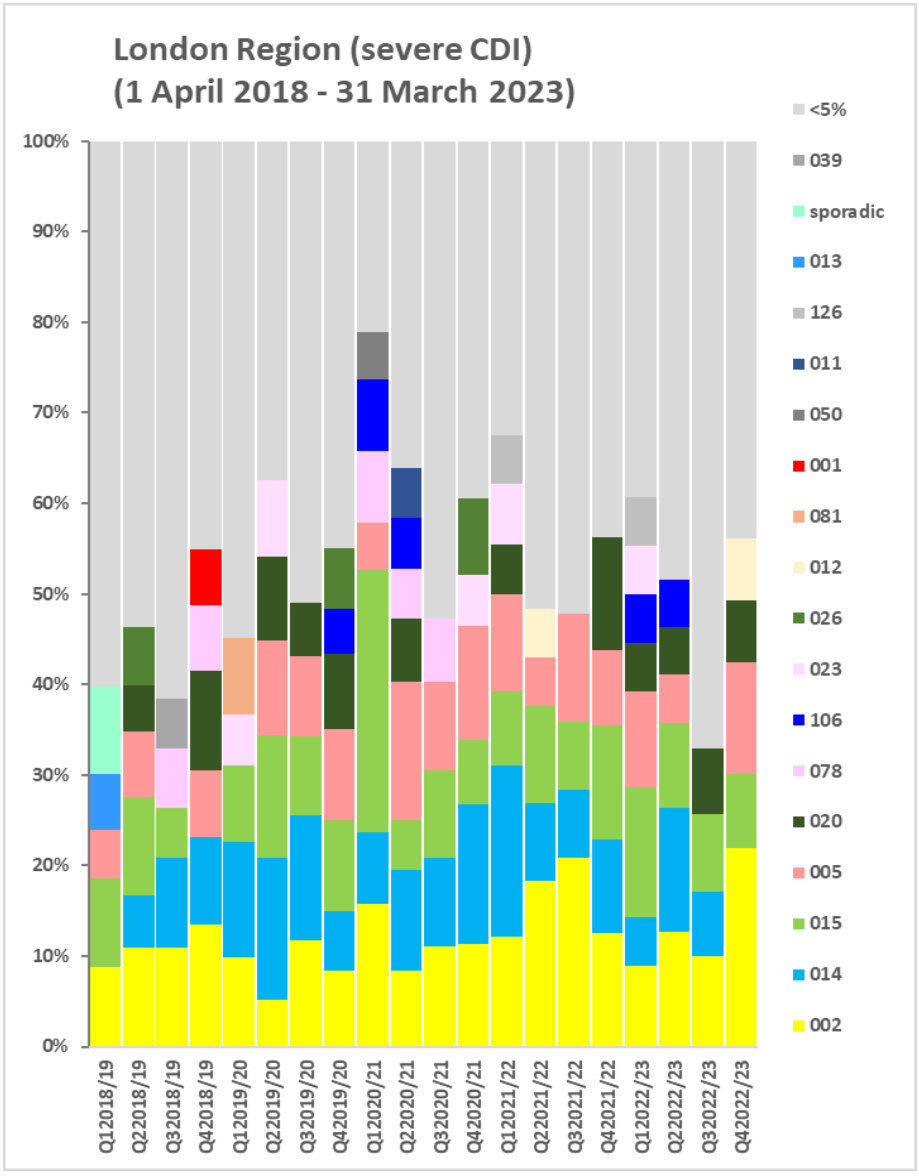
(C)


London Region (severe CDI)
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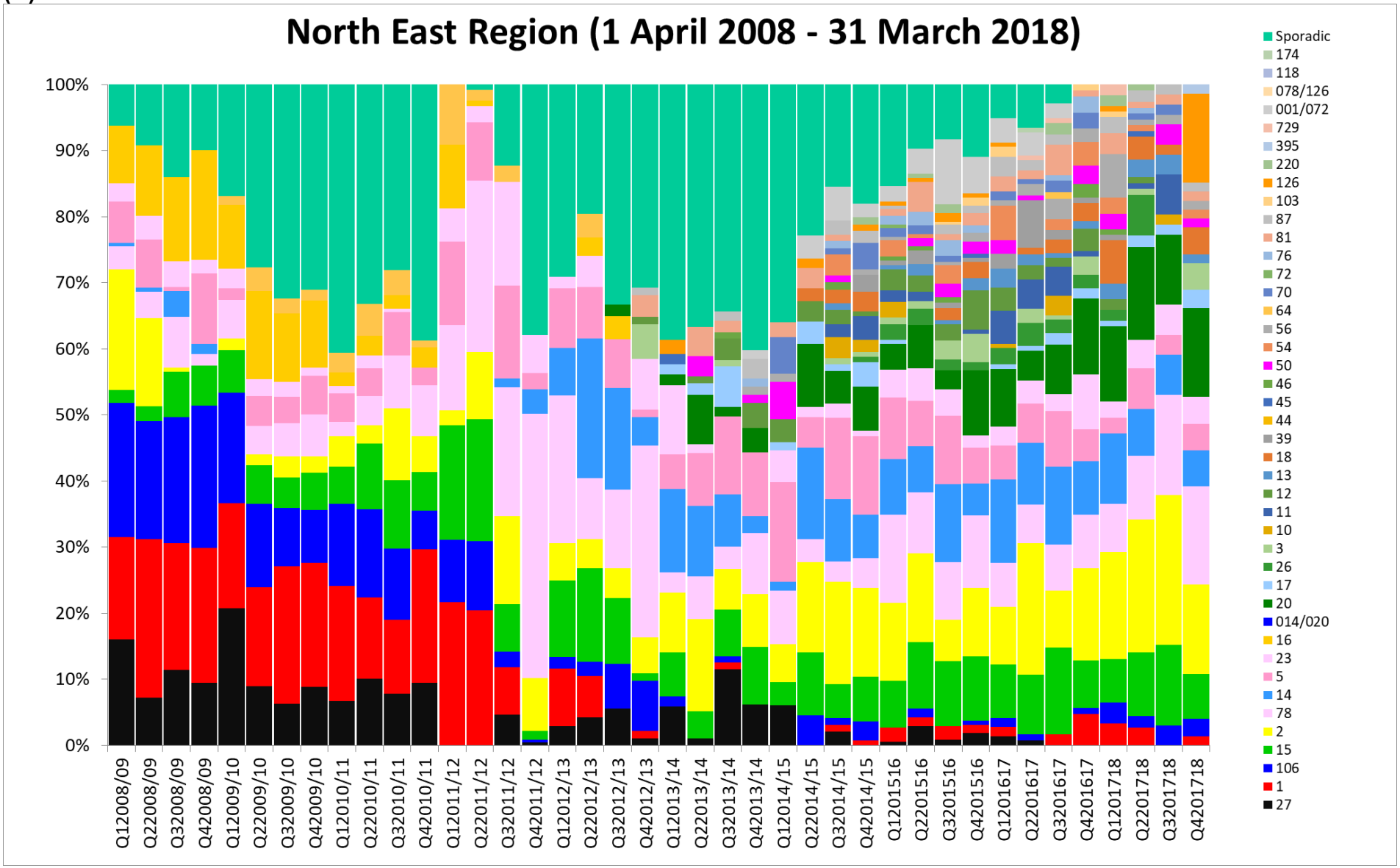
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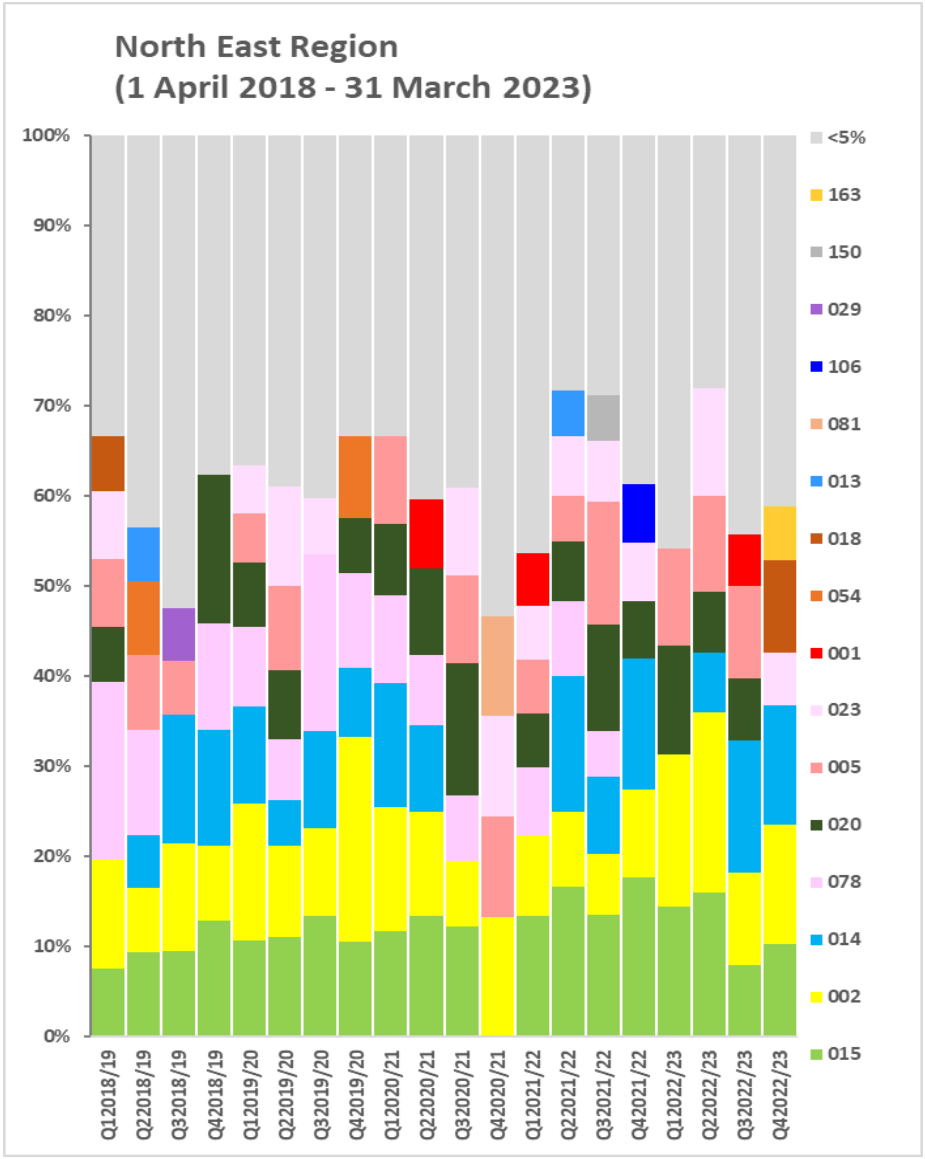
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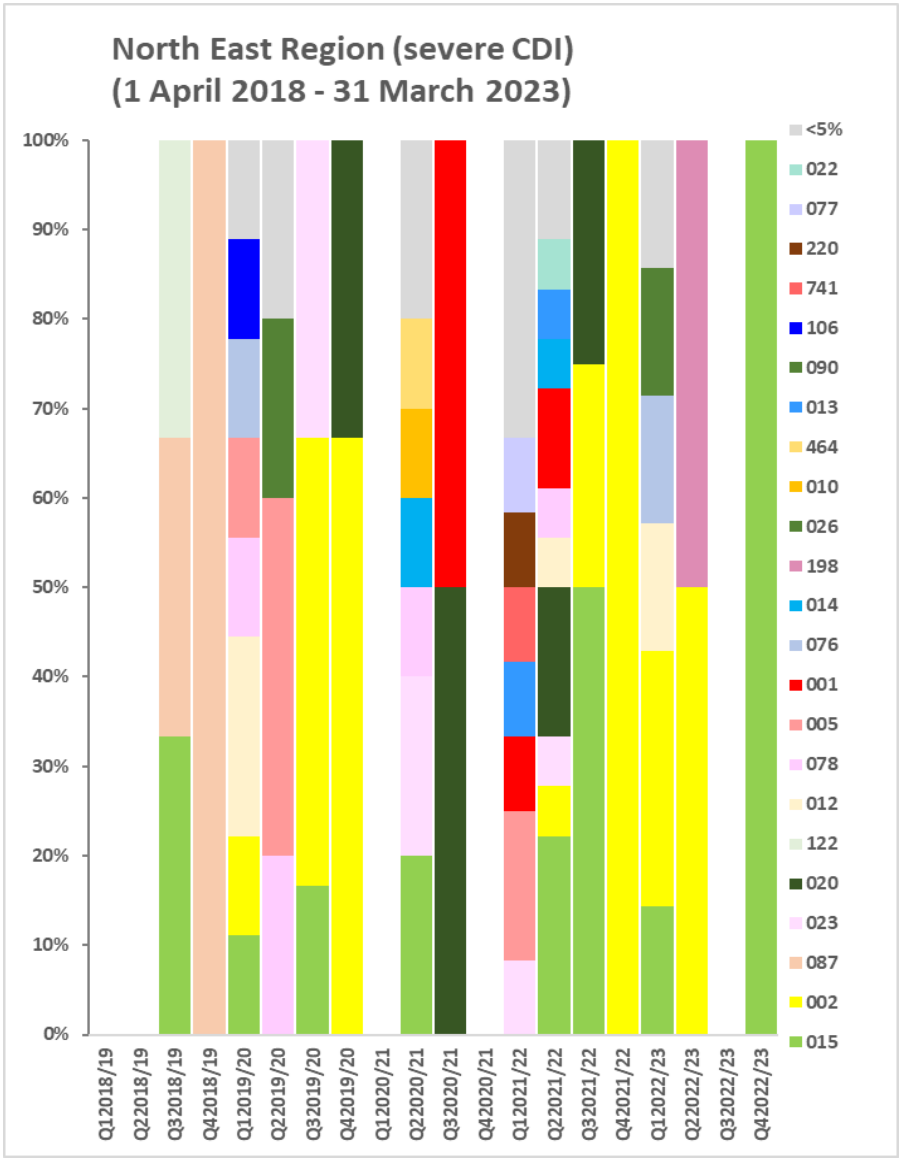
North East Region (severe CDI)
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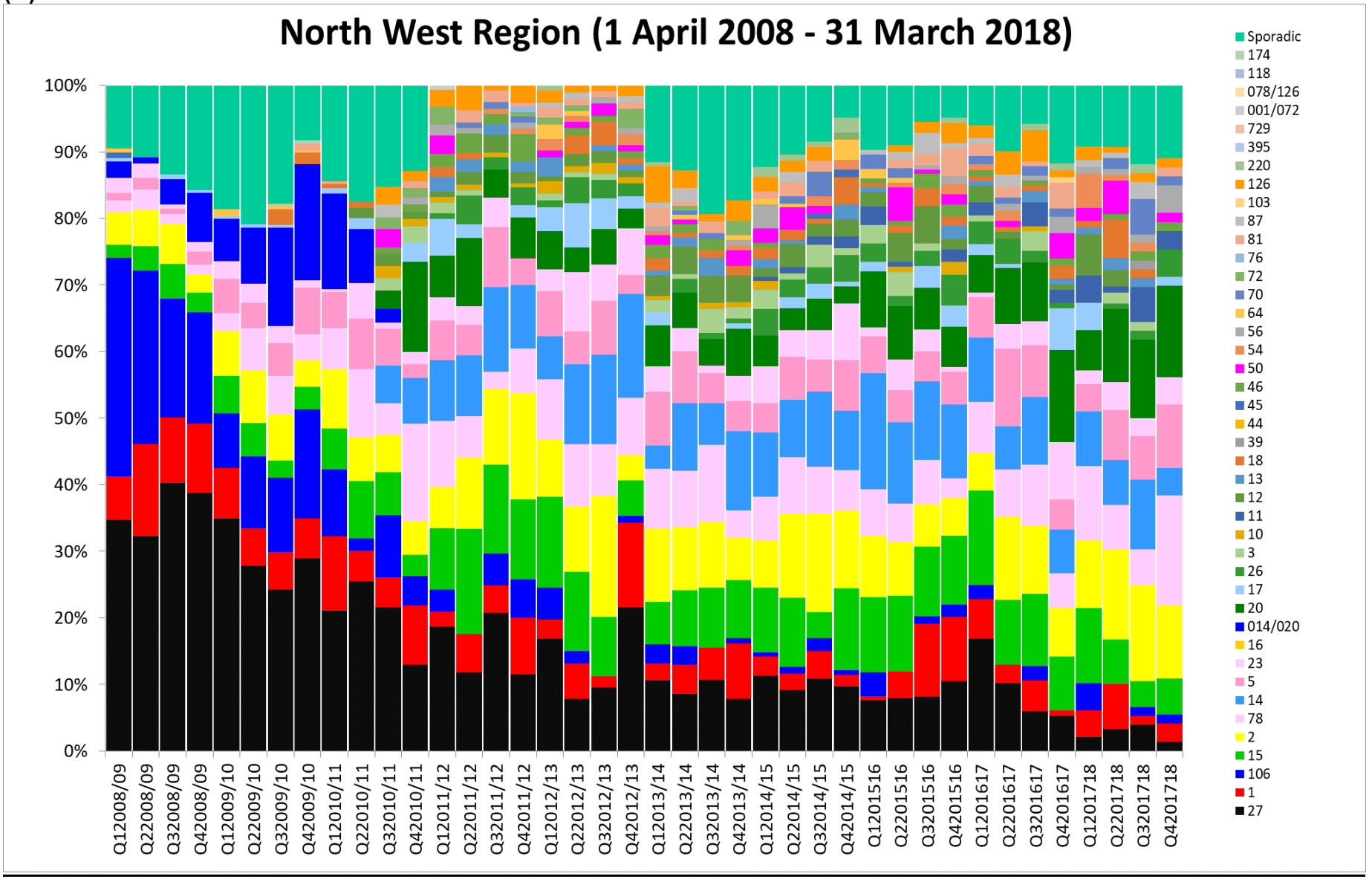
North West Region (1 April 2008 - 31 March 2018)
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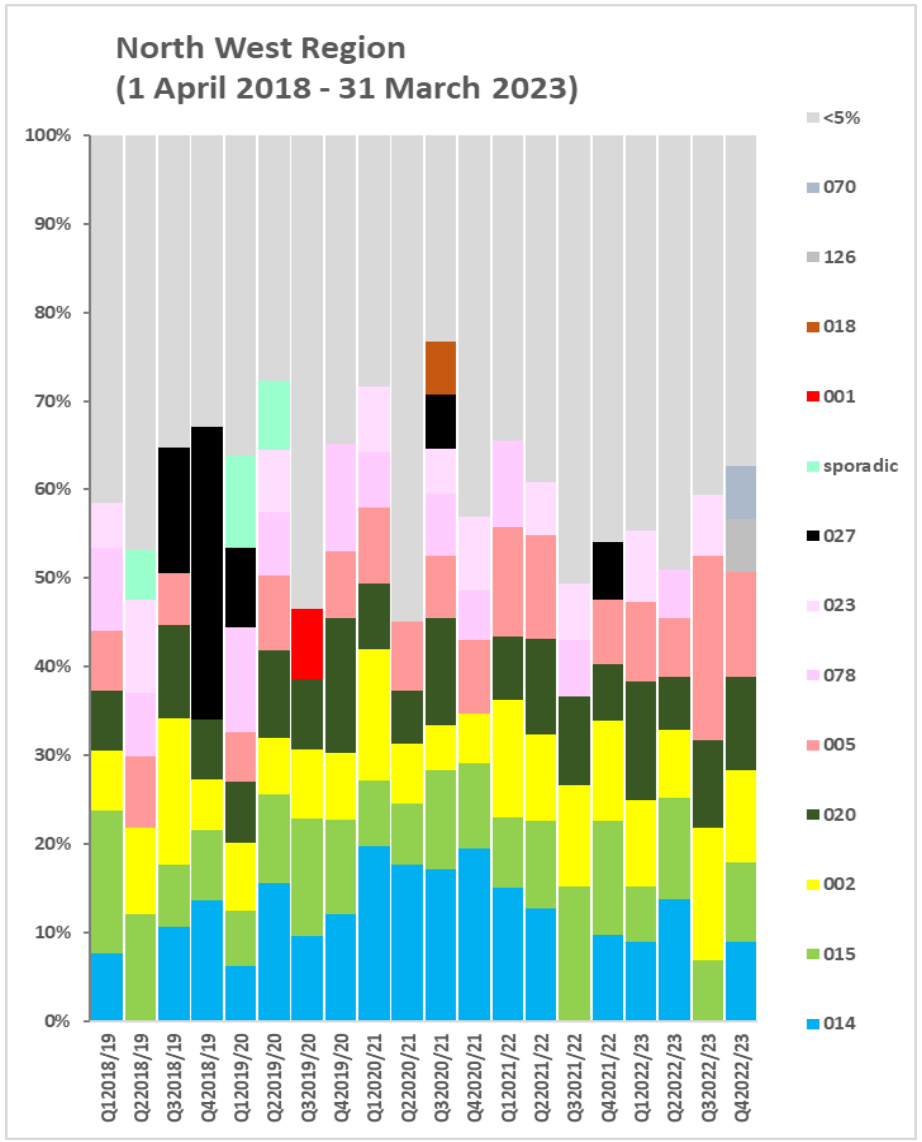
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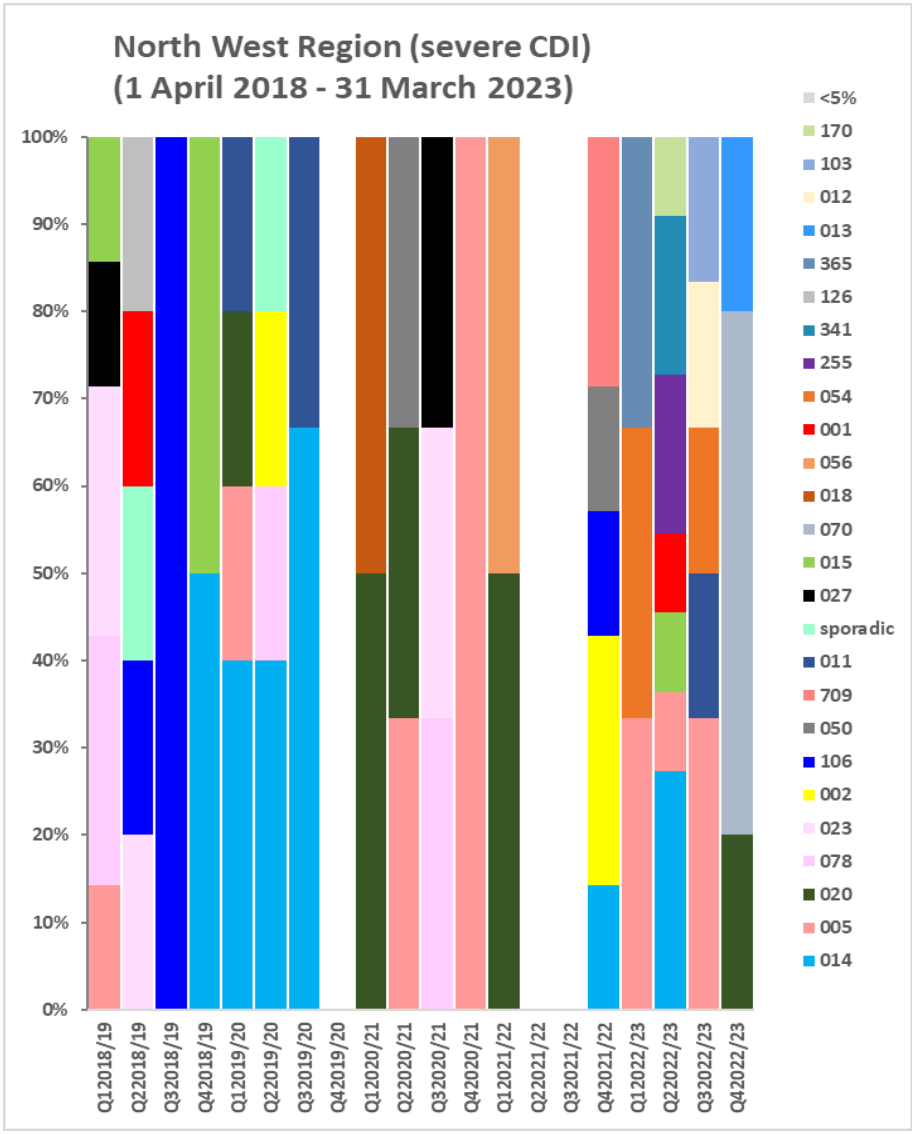
North West Region (severe CDI)
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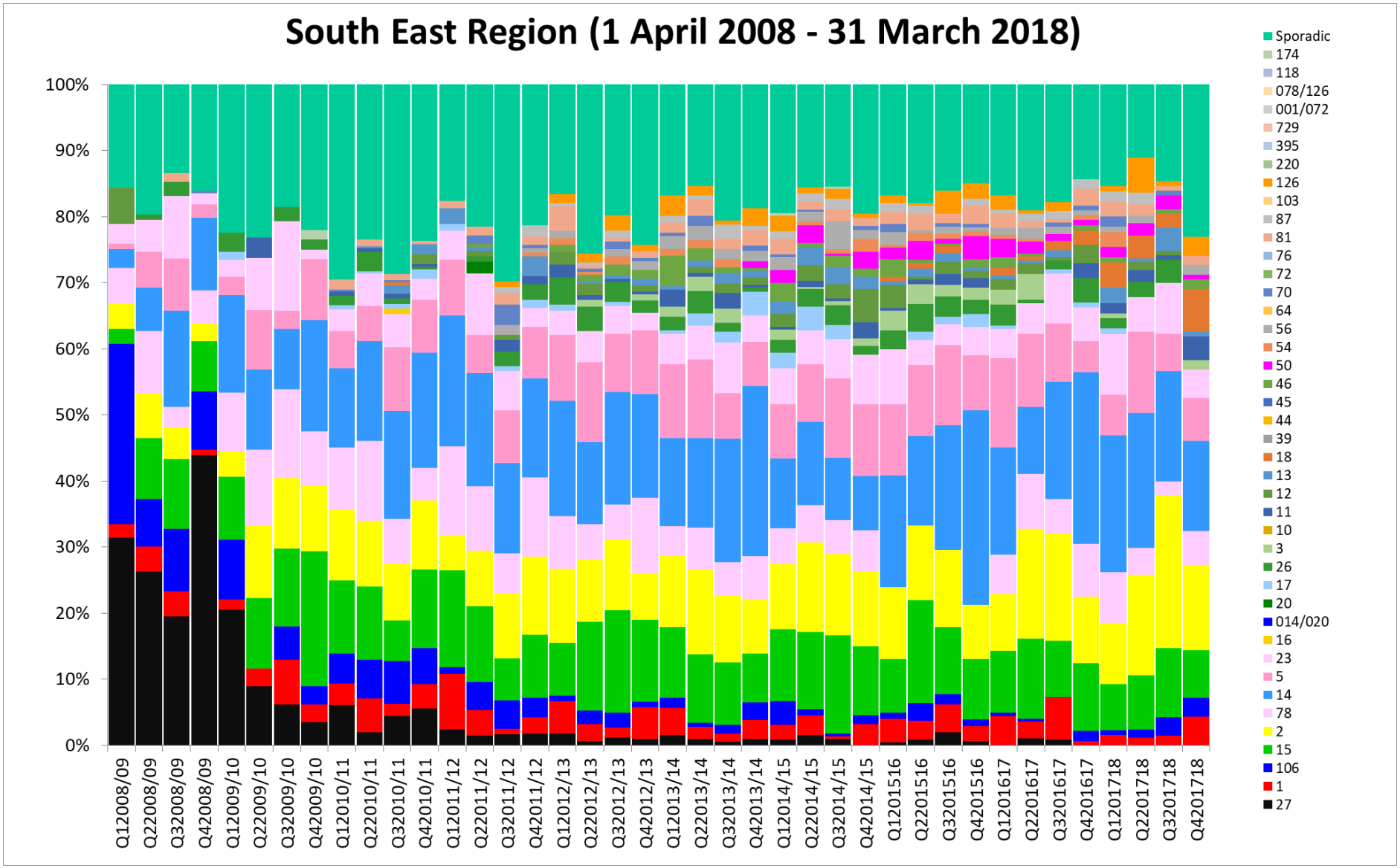
South East Region (1 April 2008 - 31 March 2018)
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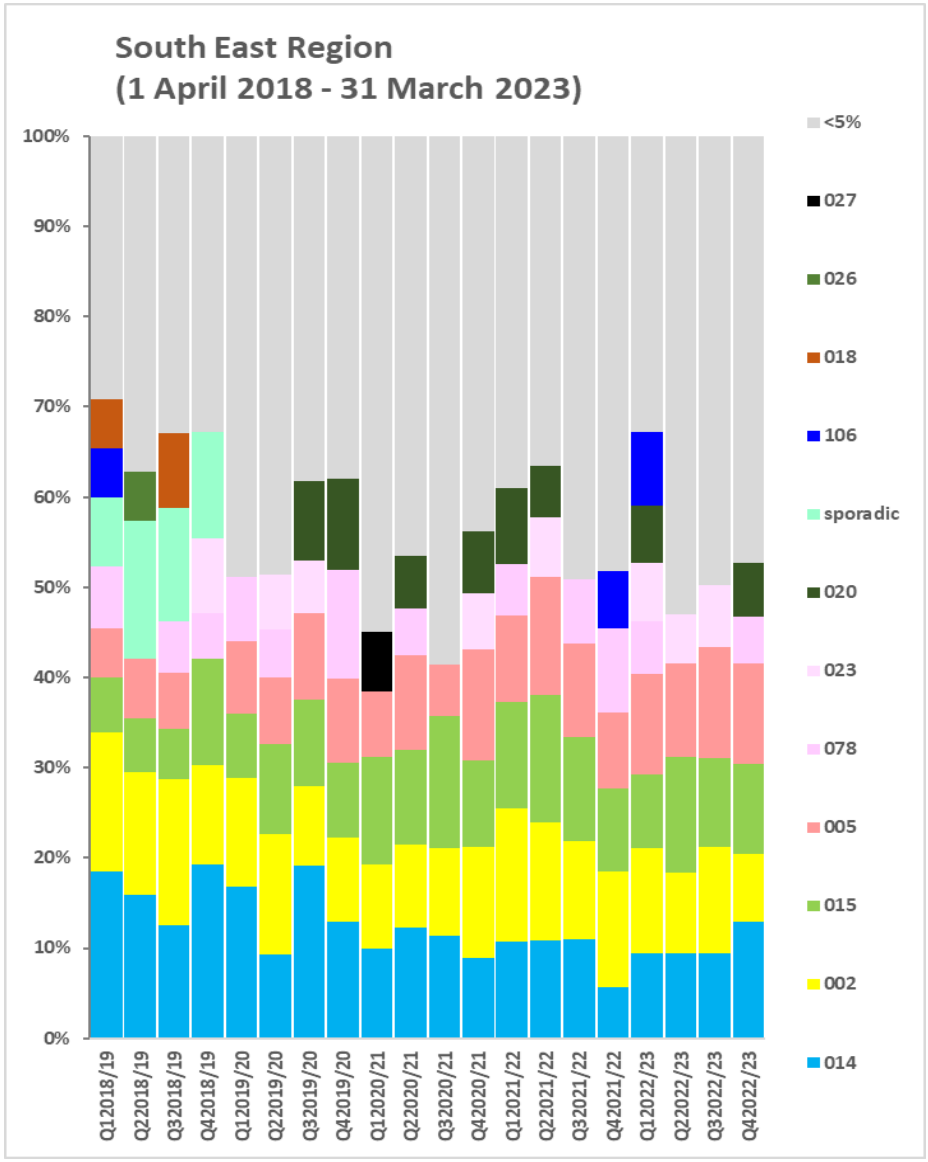
South East Region
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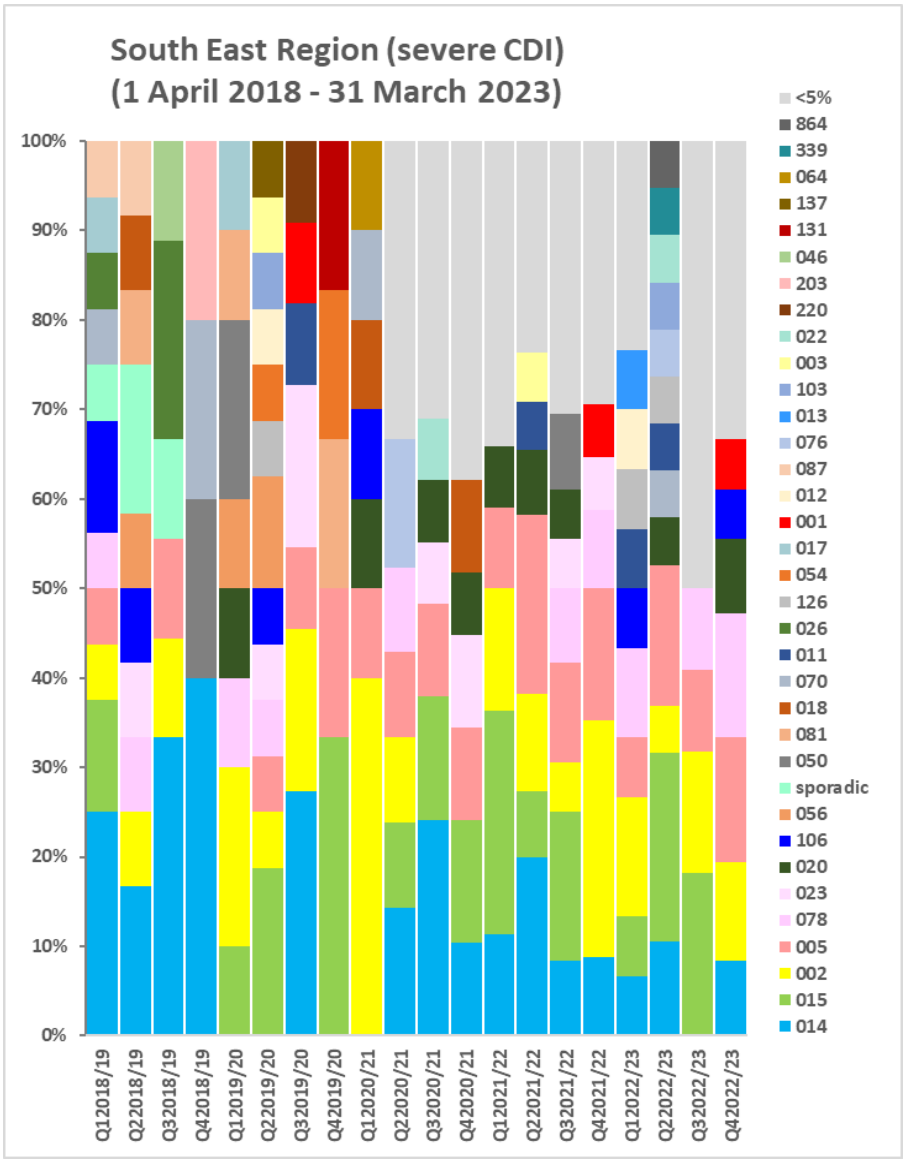
South East Region (severe CDI)
(1 April 2018 - 31 March 2023)
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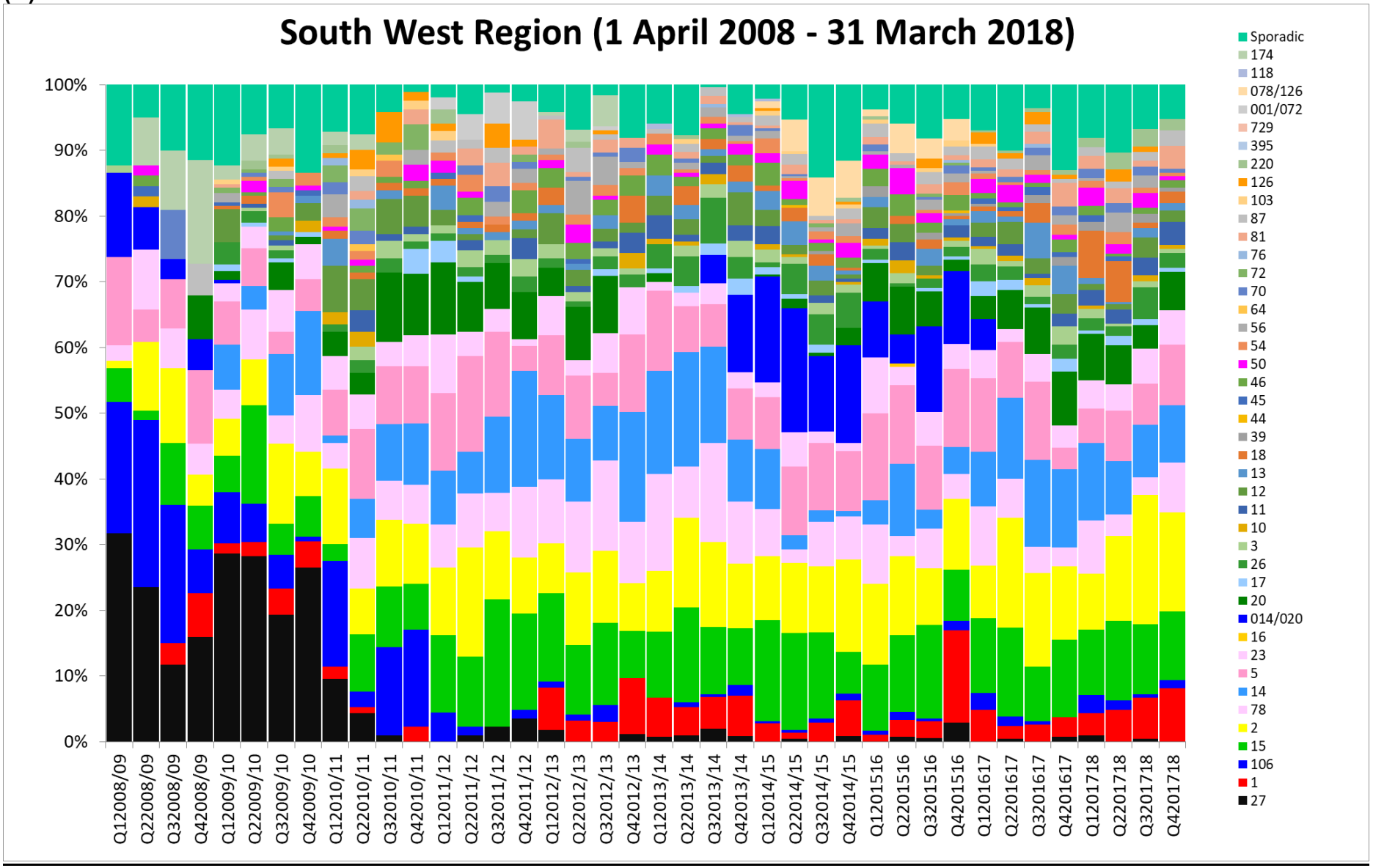
South West Region (1 April 2008 - 31 March 2018)
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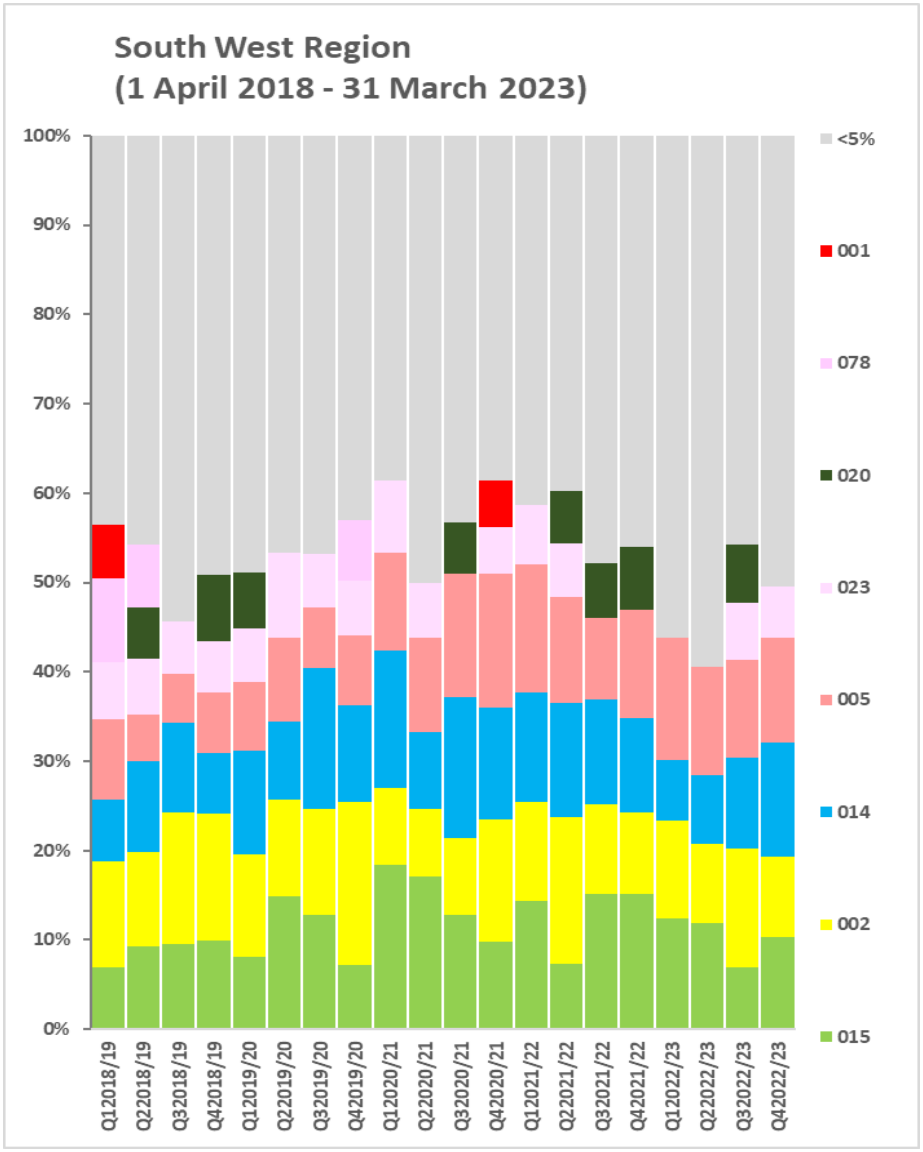
South West Region
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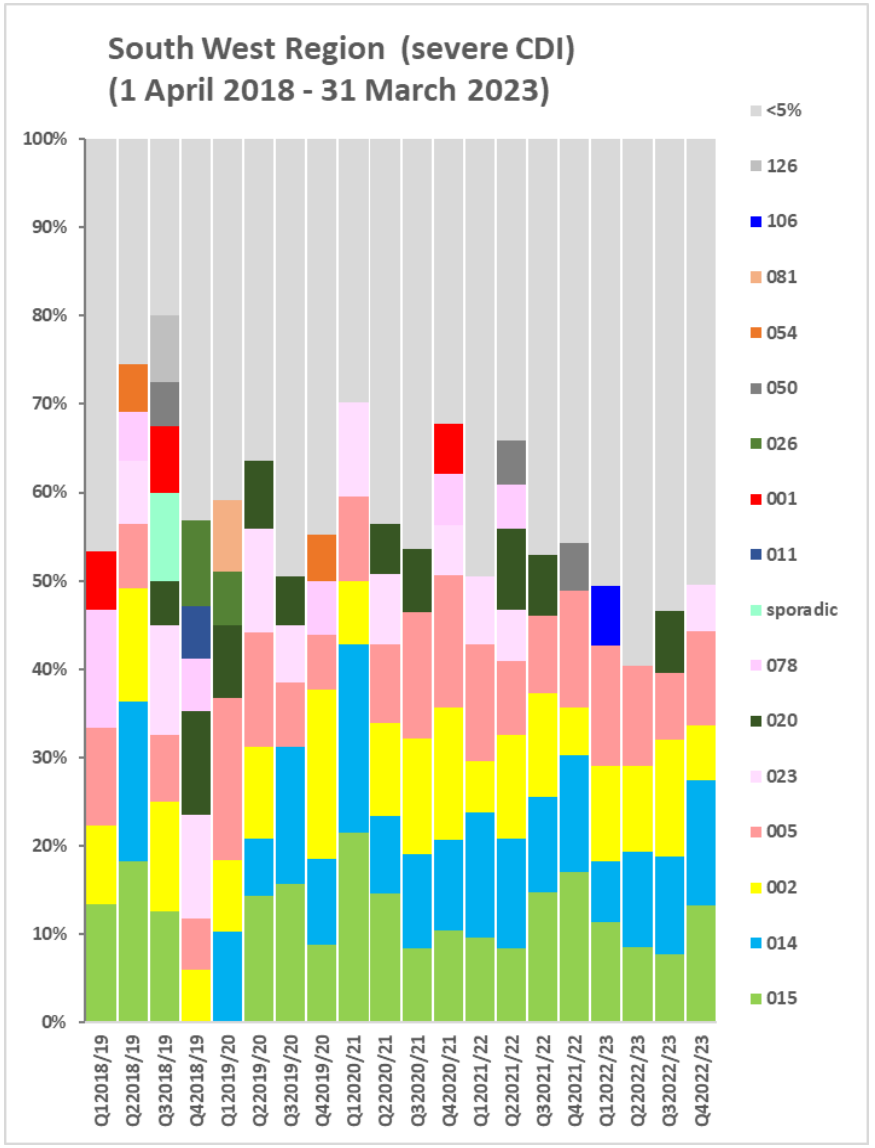
South West Region (severe CDI)
(1 April 2018 - 31 March 2023)
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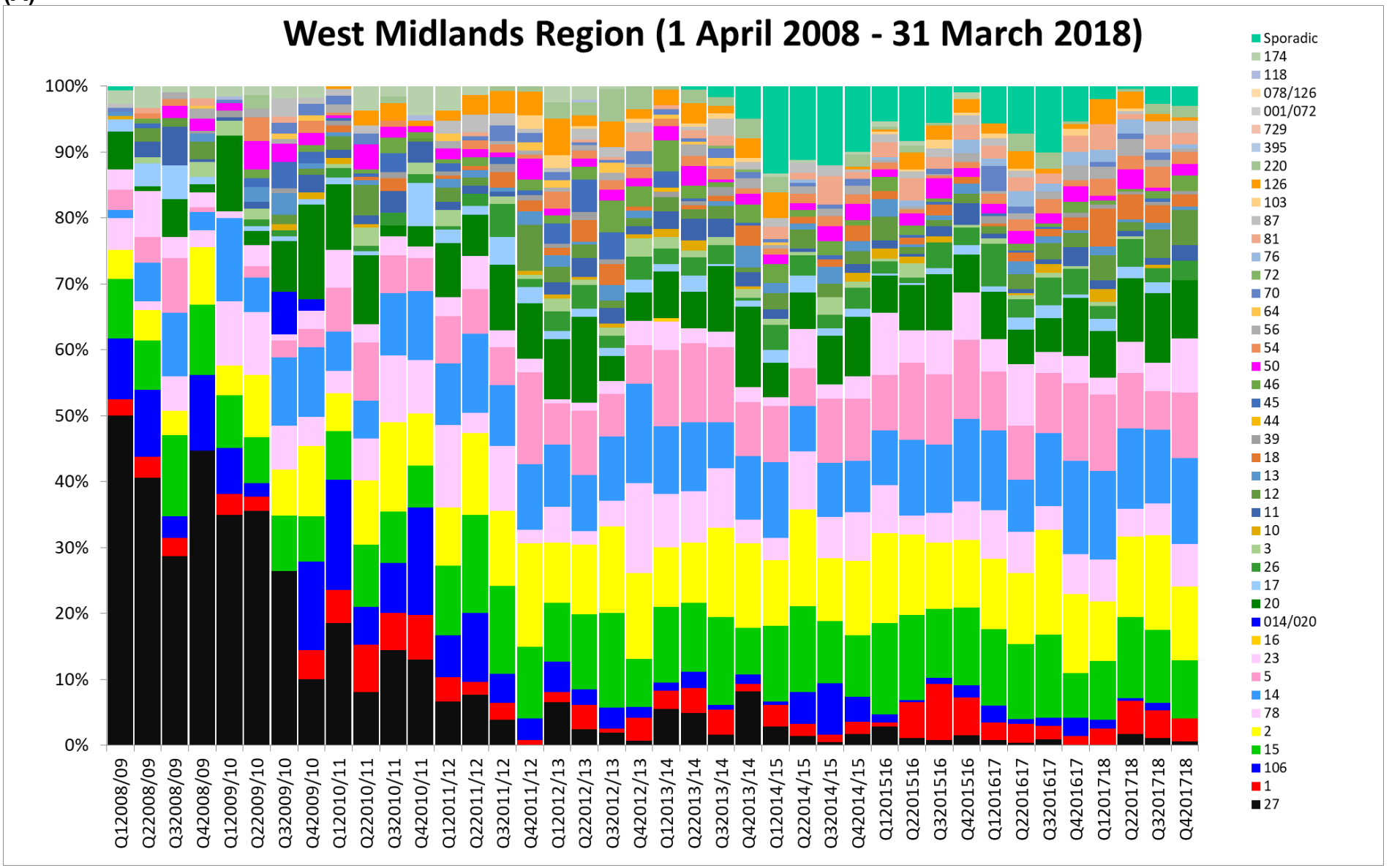
West Midlands Region (1 April 2008 - 31 March 2018)
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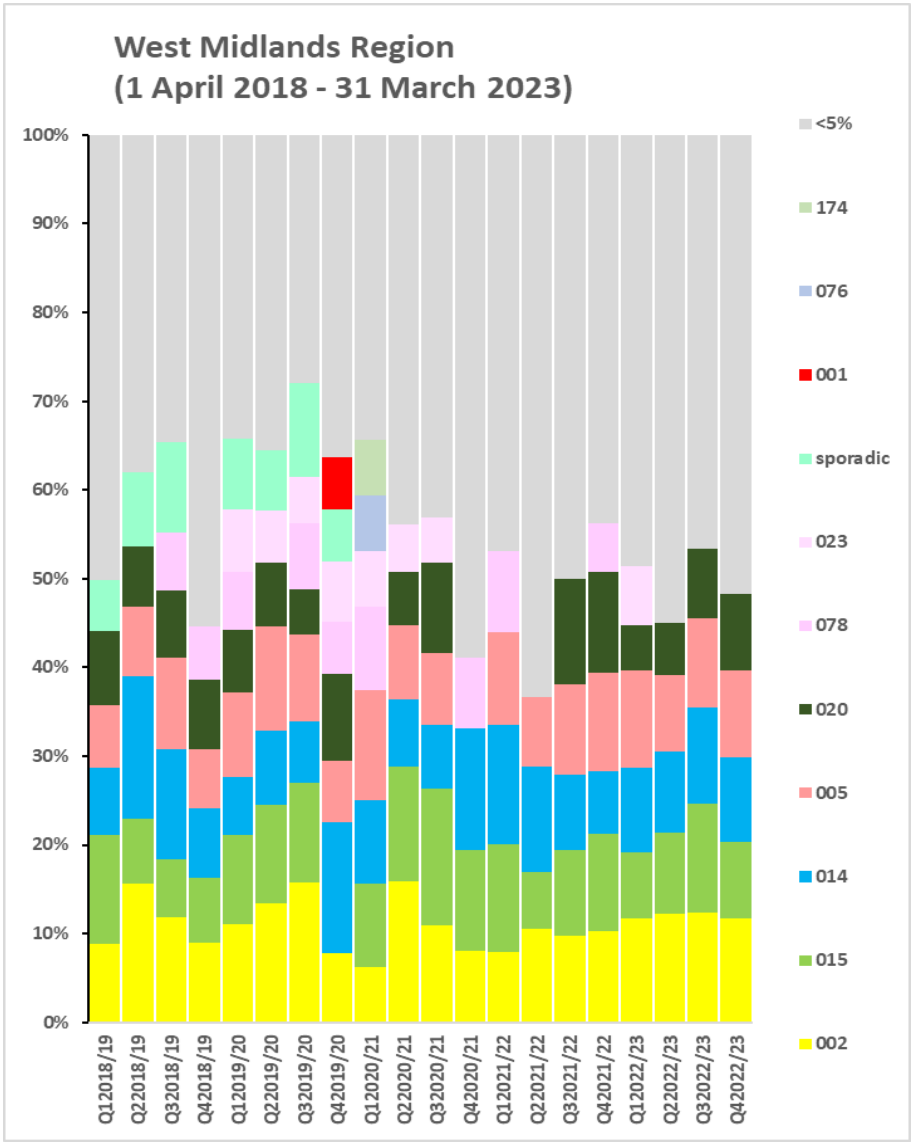
West Midlands Region
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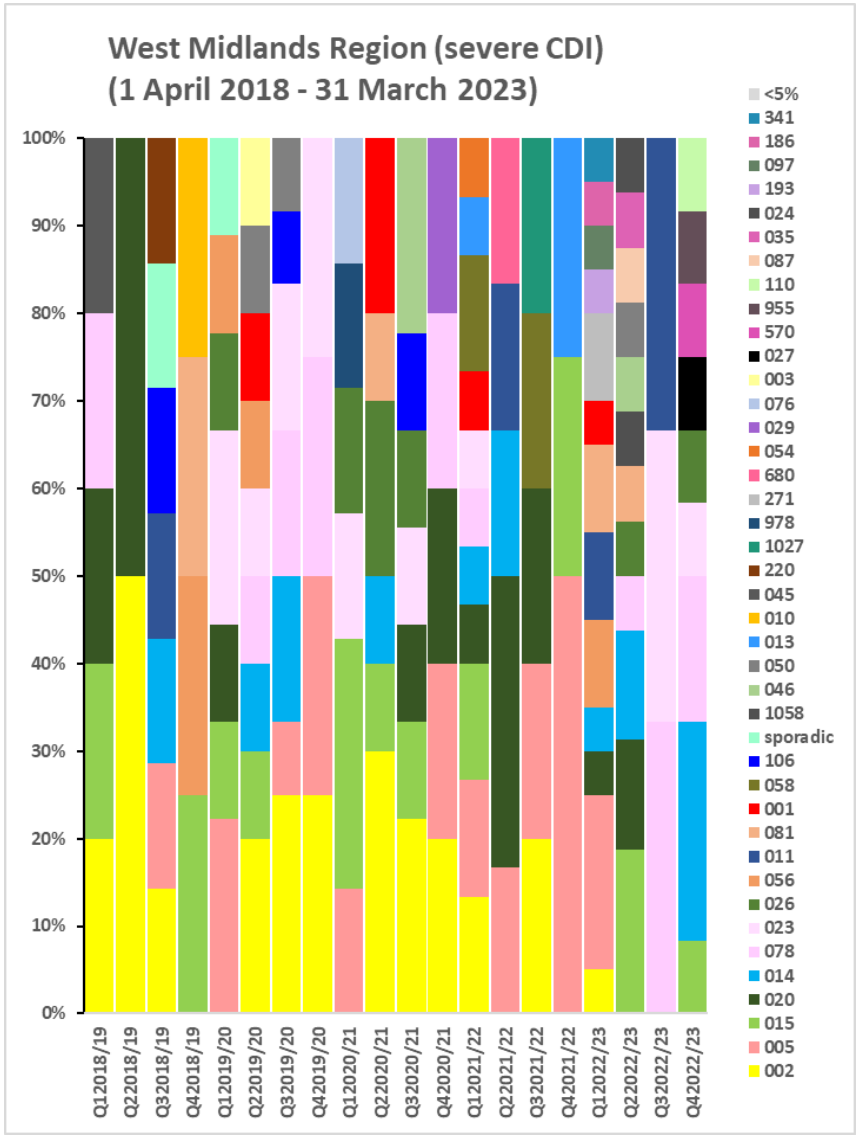
West Midlands Region (severe CDI)
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110
955
570
027
003
076
029
054
680
271
978
1027
220
045
010
013
050
046
1058
sporadic
106
058
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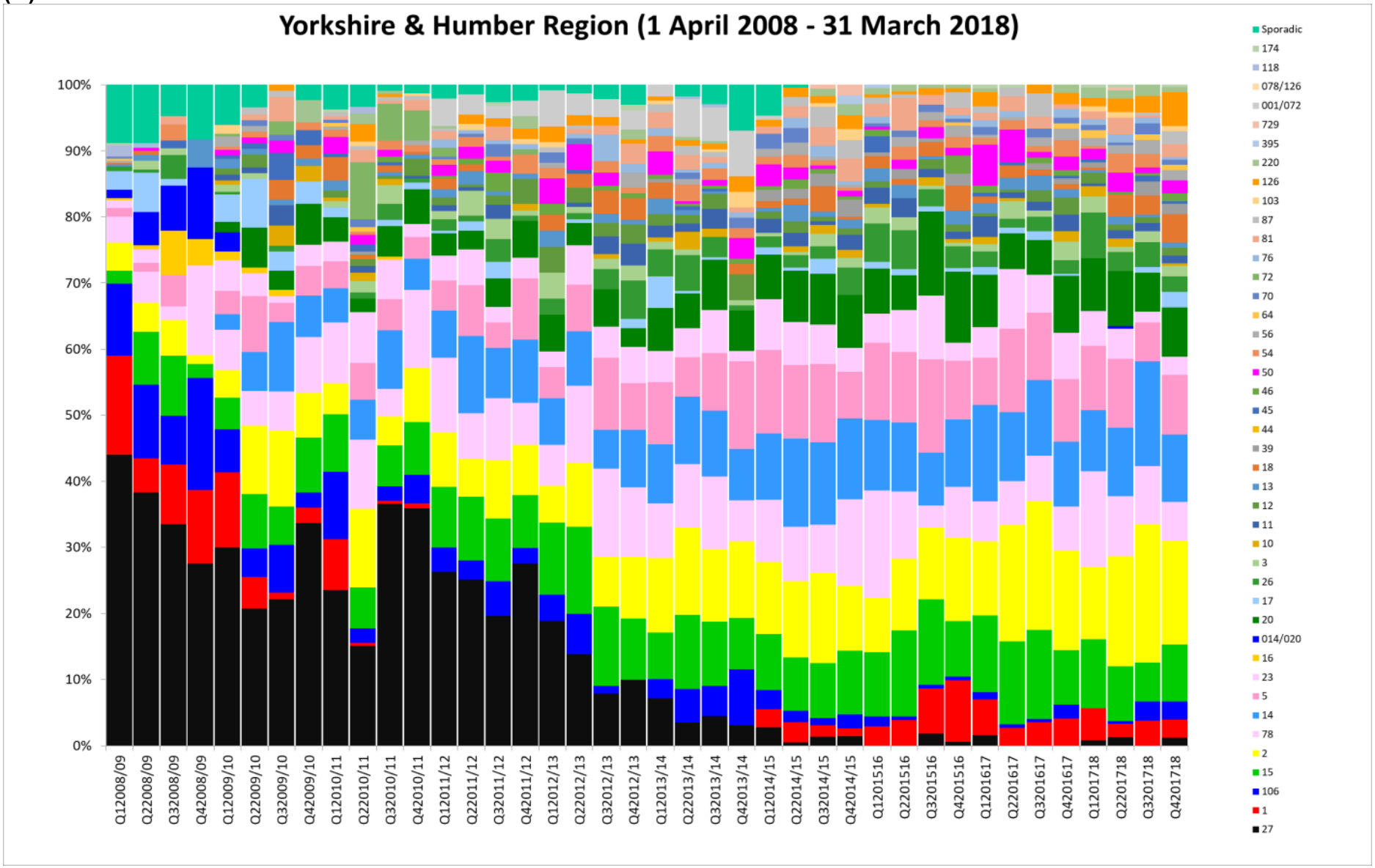
002

(A)


Yorkshire & Humber Region (1 April 2008 - 31 March 2018)
100%
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80%
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60%
50%
40%
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Q12008/09
Q22008/09
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Q42008/09
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Q22009/10
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Q42009/10
Q12010/11
Q22010/11
Q32010/11
Q42010/11
Q12011/12
Q22011/12
Q32011/12
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Q4201718
Sporadic
174
118
078/126
001/072
729
395
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126
103
87
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70
64
56
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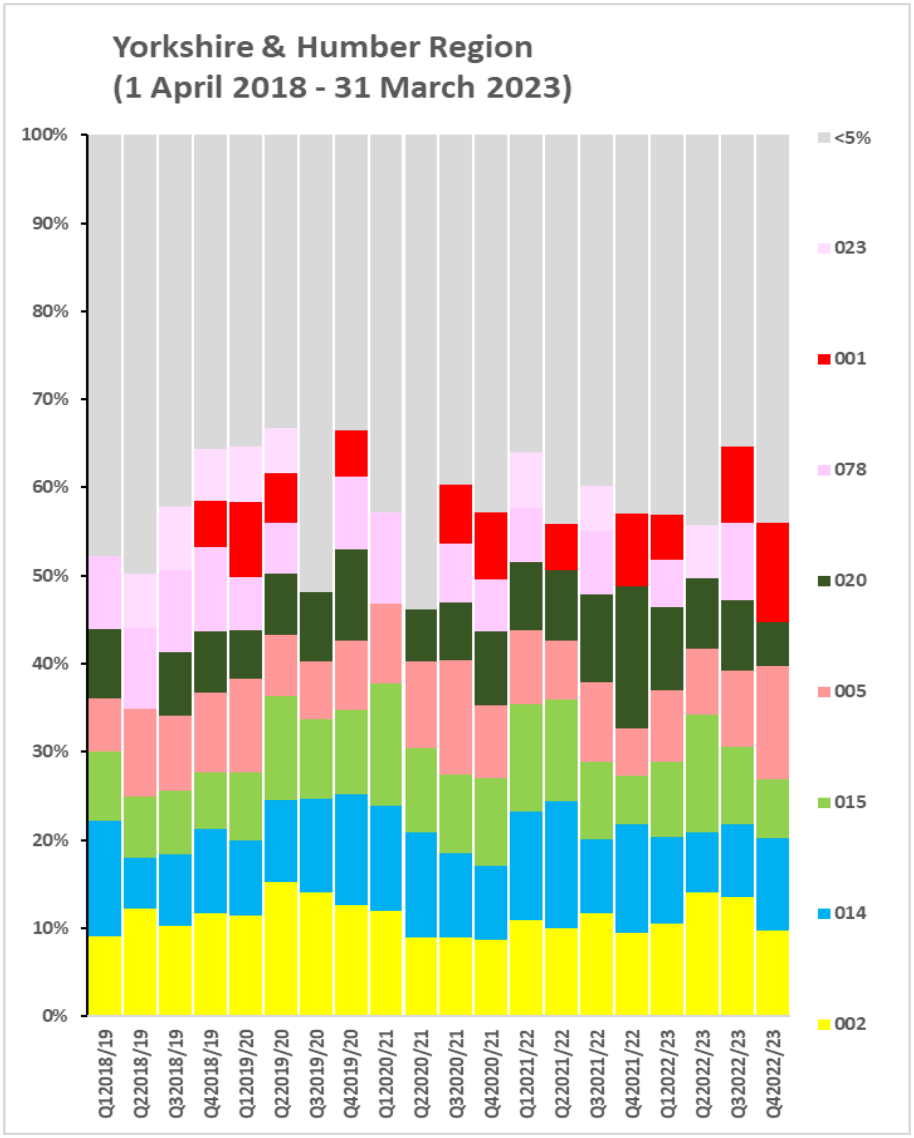
27

(B)


Yorkshire & Humber Region
(1 April 2018 - 31 March 2023)
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90%
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Q12018/19
Q22018/19
Q32018/19
Q42018/19
Q12019/20
Q22019/20
Q32019/20
Q42019/20
Q12020/21
Q22020/21
Q32020/21
Q42020/21
Q12021/22
Q22021/22
Q32021/22
Q42021/22
Q12022/23
Q22022/23
Q32022/23
Q42022/23
<5%
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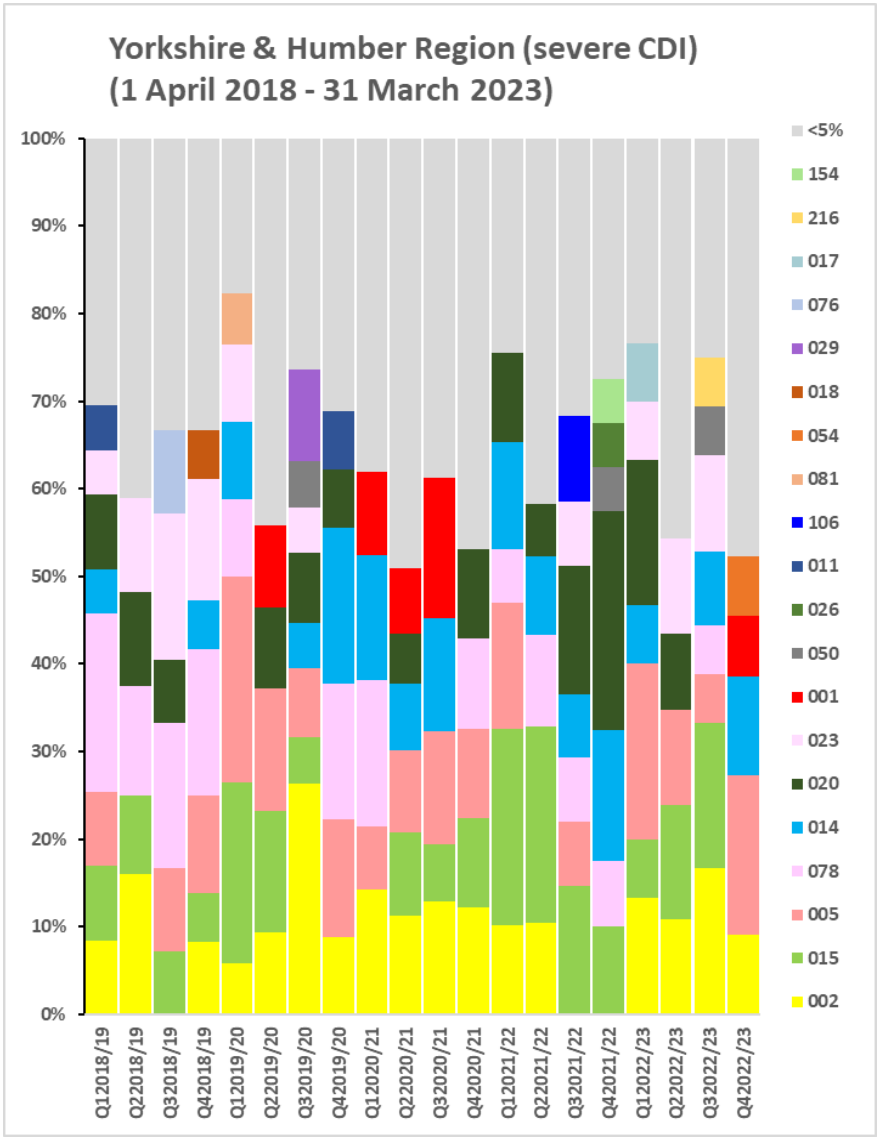
020
005
015
014
002

(C)


Yorkshire & Humber Region (severe CDI)
(1 April 2018 - 31 March 2023)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Q12018/19
Q22018/19
Q32018/19
Q42018/19
Q12019/20
Q22019/20
Q32019/20
Q42019/20
Q12020/21
Q22020/21
Q32020/21
Q42020/21
Q12021/22
Q22021/22
Q32021/22
Q42021/22
Q12022/23
Q22022/23
Q32022/23
Q42022/23
<5%
154
216
017
076
029
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106
011
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001
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078
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Enhanced fingerprinting

CDRN has continued to provide access to enhanced fingerprinting (MLVA) to support investigations into potential CDI case clusters or outbreaks in hospitals, when PCR-ribotyping data alone is insufficient. Since our last report, a total of 278 outbreak investigations were processed by MLVA involving 41 separate PCR-ribotypes (718 isolates; range 2 to 10 per investigation).

In 2018 to 2019, 2019 to 2020, 2020 to 2021, 2021 to 2022 and 2022 to 2023, Leeds performed 81 (206 isolates), 70 (204 isolates), 30 (85 isolates), 41 (92 isolates) and 56 (131 isolates) MLVA investigations, respectively. The most common ribotypes were 002, 014, 015, 078, 005 and 020 (featuring in 61, 37, 30, 29, 17 and 15 investigations, respectively).

CDRN originally published an analysis of enhanced fingerprinting (MLVA) investigations for potential CDI case clusters or outbreaks in hospitals in England (15). Notably, despite sharing a common ribotype, 19% of these potential CDI case clusters or outbreaks comprised unrelated isolates, and 34% contained a mixture of highly related and distinct isolates. These findings emphasise the value of enhanced fingerprinting to confirm or refute suspected CDI case clusters.

We have continued to examine the utility of whole genome sequencing in comparison with MLVA for the examination of case clusters. These efforts were part of a UK-wide consortium, funded by the Wellcome Trust and MRC, between the University of Oxford, UKHSA (then PHE) and the Wellcome Trust Sanger Institute, to establish how revolutionary new technologies can be optimally integrated into medical microbiology (16). We examined *C. difficile* isolates from 61 suspected outbreaks affecting 2 to 41 patients in 31 UK hospitals (300 samples) using both 7-locus MLVA and WGS. Conclusions on whether potential outbreaks were confirmed were concordant in 58 out of 61(95%) of investigations (9). We completed a front-line service performance comparison of MLVA and WGS techniques. All isolates from MLVA-based cluster/outbreak investigations received by our testing laboratory over a period of 12 months were also subjected to WGS, in real time (17). 103 investigations (285 isolates (range 2 to 11 per investigation)) from 42 hospitals were examined. Outcome data generated by MLVA and WGS was concordant in 95 out of 103 (92%) investigations. Using current strain relatedness criteria, all investigations of discordant outcome involved instances where WGS discriminated further than MLVA. Results for investigations using MLVA and WGS were available in 2 and 5 days, respectively.

More recently, 624 *C. difficile* isolates from 19 countries underwent WGS, which demonstrated that 5 ribotypes had within-country clustering: ribotype 356, only in Italy; ribotype 018, predominantly in Italy; ribotype 176, with distinct Czech and German clades; ribotype 001/072, including distinct German, Slovakian, and Spanish clades; and ribotype 027, with multiple predominantly country-specific clades including in Hungary, Italy, Germany, Romania, and Poland.

By contrast, no within-country clustering was observed for ribotypes 078, 015, 002, 014, and 020, which is consistent with a Europe-wide distribution (18). This and other data supports the existence of 2 distinct patterns of *C. difficile* ribotype spread, which are consistent with either predominantly healthcare-associated acquisition or Europe-wide dissemination via other routes or sources (for example, possibly via the food chain) (19, 20). Of interest, a recent large pan-European study identified a high *C. difficile* contamination of potatoes obtained from retail outlets in several countries, suggesting a possible source that could be agnostic of borders (21).

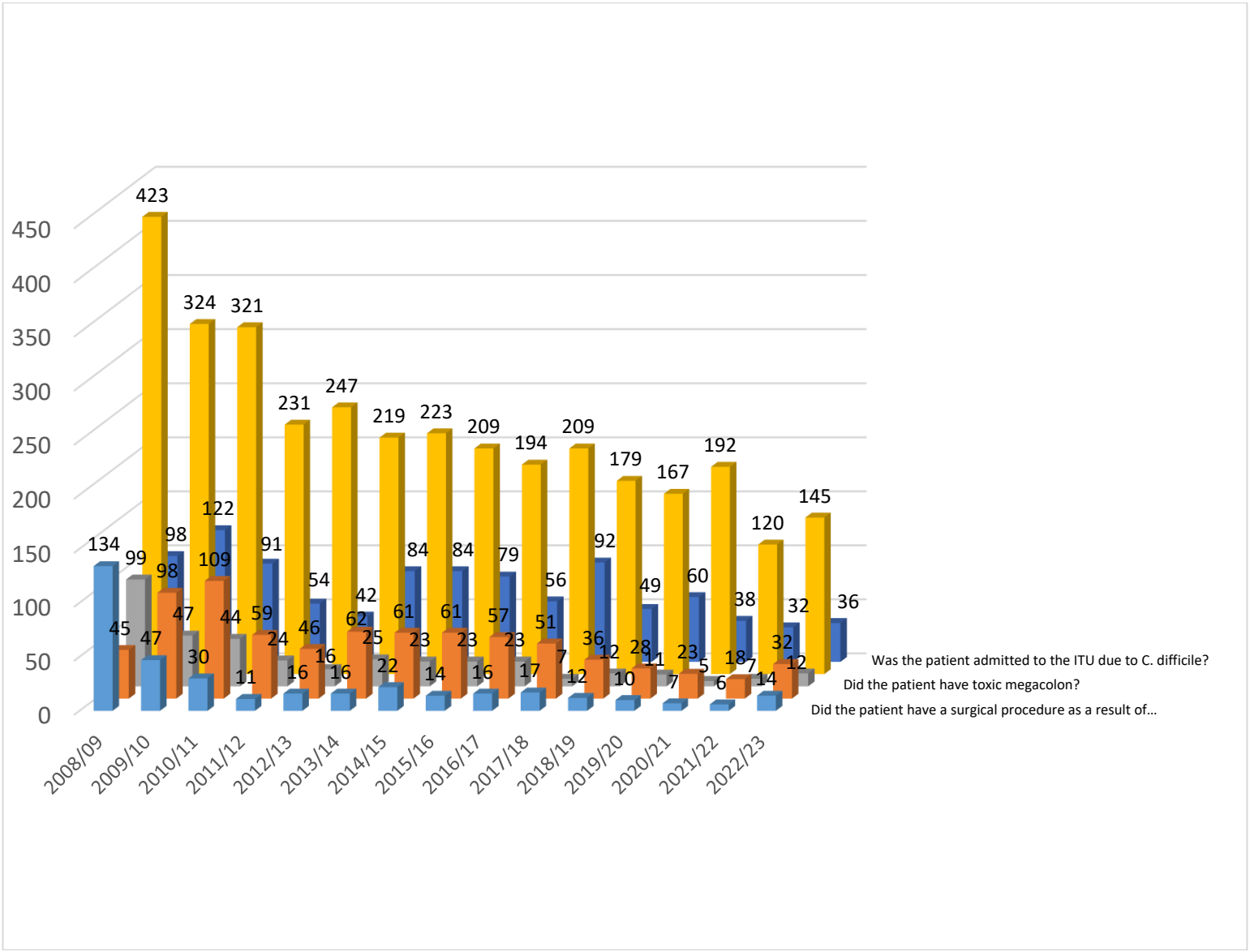
Overall, when applied to outbreak investigation of CDI, findings using MLVA and WGS are very similar, despite these techniques analysing different parts of the bacterial genome. WGS offers marginally higher levels of discrimination than MLVA. Although WGS analyses take longer than MLVA, processing times associated with both techniques remain relevant for hospital outbreak investigations. Notably, WGS provides additional data, such as antimicrobial susceptibility genotype and the presence or absence of virulence genes. WGS has also been successfully utilised as a novel surveillance tool to establish rates of *C. difficile* transmission between healthcare institutions, to facilitate targeted efforts in the reduction of CDI incidence (22). It is planned for CDRN to transition (in 2023 to 2024) to using WGS instead of MLVA for the enhanced fingerprinting or investigation of *C. difficile*.

Outcome data

In 2018 to 2019, 2019 to 2020, 2020 to 2021, 2021 to 2022, and 2022 to 2023, clinical follow-up data was available for approximately 53%, approximately 55%, approximately 49%, approximately 52% and approximately 49% of cases, respectively, although some follow-up data (for example mortality and admission to ITU) was provided more commonly (40% and 47% of cases, respectively).

Clinical follow-up data is shown in Figure 7 (this is for all referred cases, regardless of culture result); the data should be interpreted with caution given the partial response rate. Numbers of deaths and cases associated with either toxic megacolon or requiring surgery declined between 2008 to 2009 and 2011 to 2012 and have remained approximately stable thereafter. These observations are consistent with control and declining incidence of ribotype 027 CDIs.

Figure 7. Outcome data provided at the time of CDRN request submission (2008/2009 to 2022/2023)



A detailed analysis of risk factors associated with CDI, outcomes and specific ribotypes was presented in the 2009 to 2010 CDRN report. Further detailed information can also be found in 2 peer-reviewed reports (23, 24).

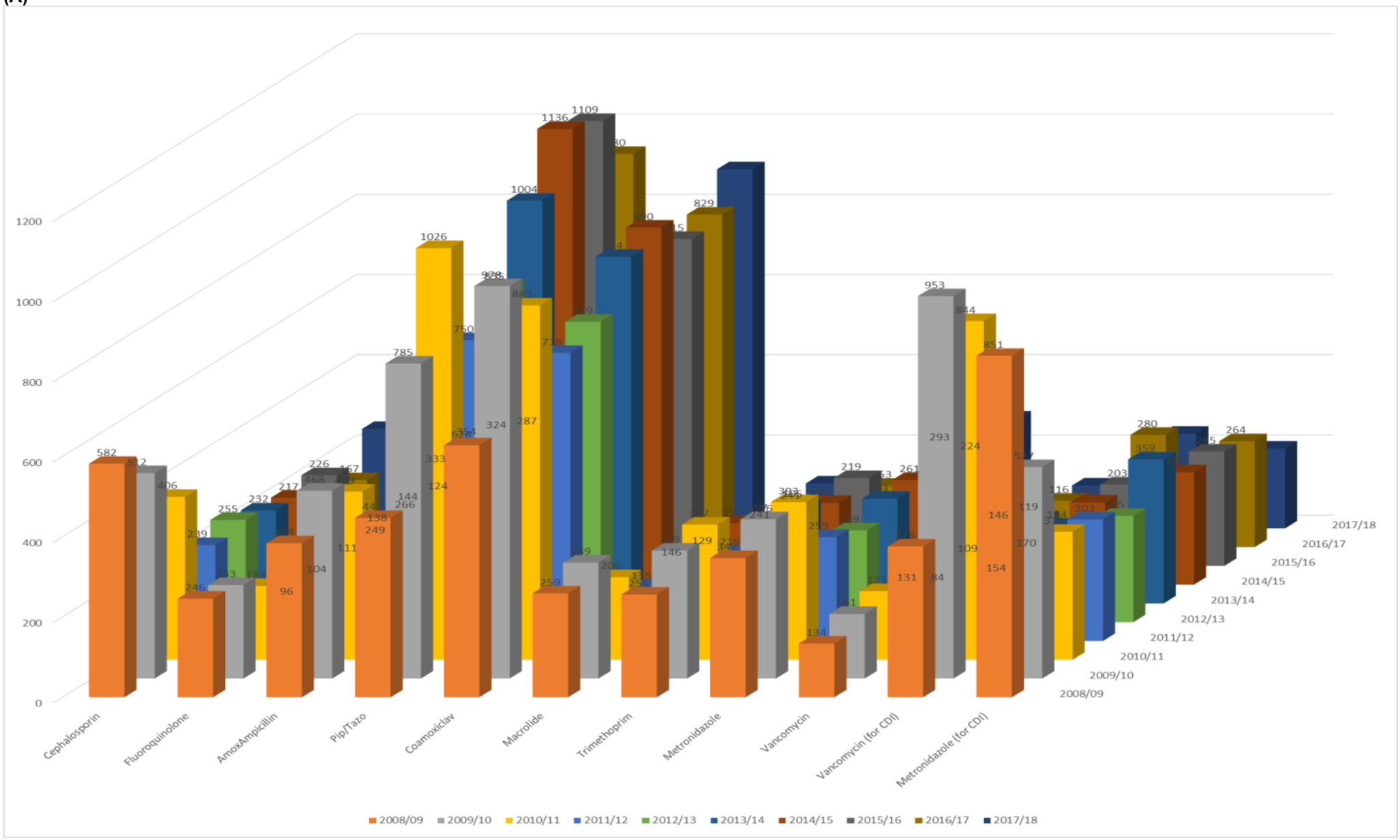
Antibiotic exposure

The interpretation of data on CDI risk associated with individual antibiotics is extremely difficult as commonly used agents may be reported as being associated with CDI more often than rarely prescribed antimicrobials, data often does not take into account duration of exposure or polypharmacy, and similarly may be confounded by other risks (patient age, co-morbidities and so on). Thus, the data in the following paragraphs needs to be interpreted with caution; notably, the data should not be considered to be indicative of which agents actually caused CDI.

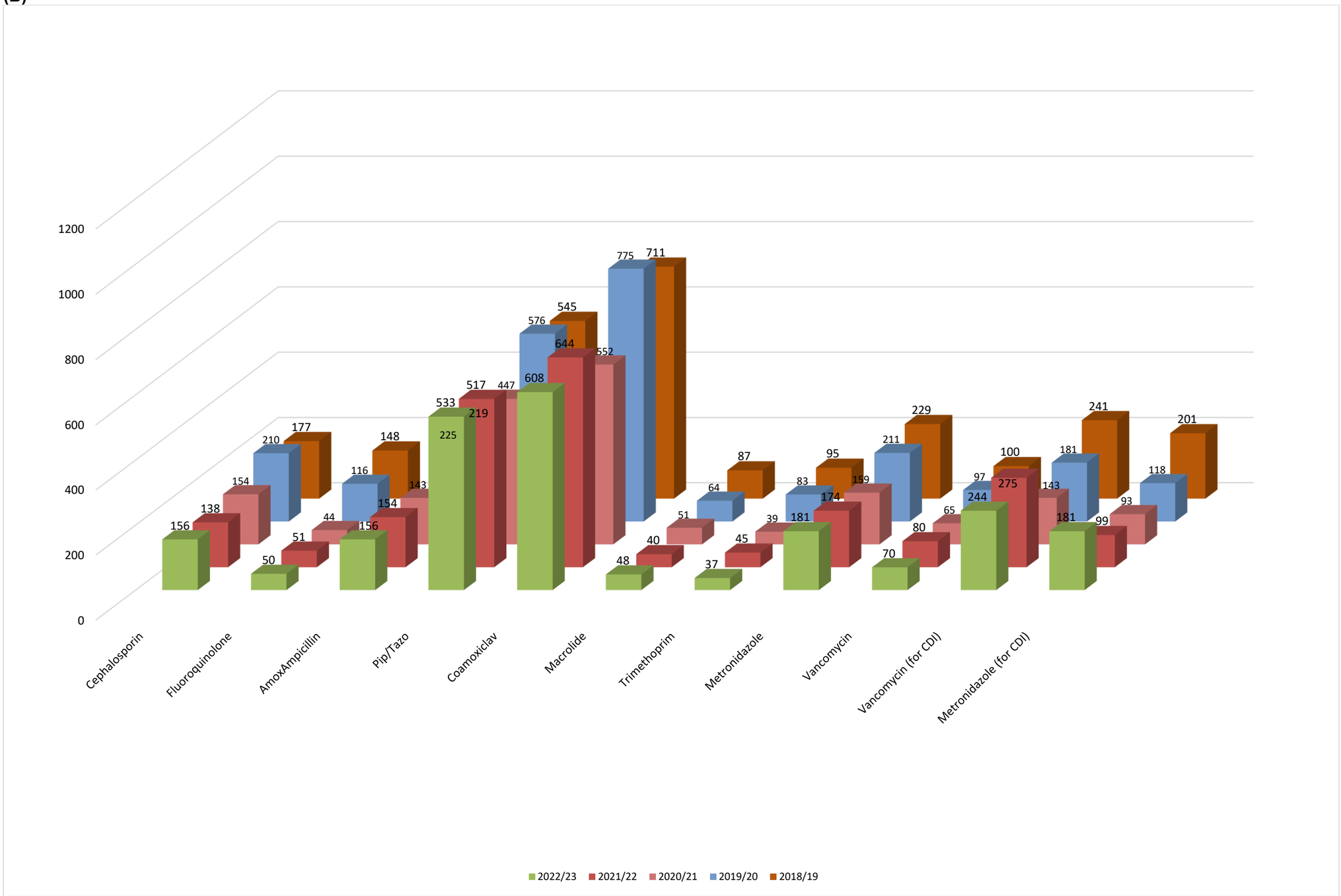
As in recent years, the most commonly reported antibiotics in 2018 to 2019, 2019 to 2020, 2020 to 2021, 2021 to 2022 and 2022 to 2023 were piperacillin-tazobactam (n=545, 576, 447,517,533) and co-amoxiclav (n=711, 775, 552, 644,608) (Figure 8). It is noticeable that the most commonly recorded antibiotics have changed markedly over the 15-year period that CDRN has been in existence. In 2007 to 2008, cephalosporins were the most commonly cited agents, whereas these were uncommonly cited in subsequent reporting periods, and indeed have been numerically superseded by co-amoxiclav and piperacillin-tazobactam from 2008 to 2009 onwards. This data likely reflects real changes in prescribing of systemic antibiotics as one of the control measures for CDI.

It is also noteworthy that in recent years there appears to have been a stable shift in the prescribing of CDI treatment antibiotics from metronidazole in favour of vancomycin (Figure 8). Such data is consistent with possible greater adherence to guidelines. Indeed, more recent evidence shows that vancomycin is superior to metronidazole for CDI treatment (25).

Figure 8. Reported antibiotics associated with CDI episodes (2008/2009 to 2022/2023): (A) April 2008 to March 2018; (B) April 2019 to March 2023
(A)



(B)


1200
1000
800
600
400
200
0
Cephalosporin
Fluoroquinolone
AmoxAmpicillin
Pip/Tazo
Coamoxiclav
Macrolide
Trimethoprim
Metronidazole
Vancomycin
Vancomycin (for CDI)
Metronidazole (for CDI)
156 138 154 210 177
50 51 44 156 154 116 148 143
225 533 219 517 447
608 576 644 552 545
775 711
48 40 51 64 87
37 45 39 181 174 83 95 159
70 80 65 244 275 97 100
181 99 93 143 181 118 241 201
2022/23
2021/22
2020/21
2019/20
2018/19

Metronidazole, vancomycin and fidaxomicin susceptibility

Previously, targeted surveillance, based on investigation of cases suspected to represent cross-infection, has identified reduced metronidazole and vancomycin susceptibility amongst epidemic ribotypes (26). Epidemic ribotypes with reduced metronidazole or vancomycin susceptibility were associated with location clusters, as determined by MLVA. This may indicate expansion or selection of strains with reduced susceptibility within epidemic ribotypes.

A panel of 75 UK *C. difficile* isolates, collected between 2014 to 2016, were uniformly susceptible to metronidazole, vancomycin and fidaxomicin (breakpoints less than 2mg/L for metronidazole and vancomycin, and less than 1mg/L for fidaxomicin). Geometric mean metronidazole, vancomycin and fidaxomicin MICs were 0.14, 0.65 and 0.02 mg/L, respectively, which were very similar to those found during 2014 to 2016 in a recent pan-European surveillance study of approximately 3,500 *C. difficile* isolates (0.21, 0.59, 0.02mg/L respectively) (1).

The most recent pan-European *C. difficile* antibiotic susceptibility surveillance publication noted that fidaxomicin susceptibility was maintained post-introduction of this agent; only one fidaxomicin resistant isolate (MIC more than 4mg/L) was detected (12). Interestingly, reduced ribotype diversity in individual countries was associated with increased antimicrobial resistance (across 9 antibiotics). Only occasional studies have described very small numbers of fidaxomicin resistant clinical *C difficile* isolates, but none of these was from the UK (27 to 31).

Further surveillance of *C. difficile* antibiotic susceptibility in England is planned for 2023 to 2024.

Summary

The *Clostridioides difficile* Ribotyping Network (CDRN) for England and Northern Ireland has for 15 years responded to a major public health need by providing a molecular epidemiological service that enhances our understanding of this pathogen. Since the introduction of CDRN the reports of *C. difficile* in England have fallen markedly, but have increased during the COVID-19 pandemic. Reports of deaths associated with CDI also started to decrease the year after CDRN commenced, which is likely due to enhanced control of the epidemic ribotype *C. difficile* 027. It is plausible that timely data provision by CDRN has enhanced the capacity of healthcare institutions and infection control and prevention teams to control CDI incidence.

Continued referral to CDRN will afford the greatest chance of identifying emergent *C. difficile* ribotypes. However, despite the approximately 75% decline in CDIs in England since 2007, the number of cases in England for which samples are submitted to CDRN has continued to increase (Figure 2), and now accounts for approximately half of all reported episodes. All NHS

hospitals in England have been encouraged to submit samples, according to set CDRN criteria. However, the high proportion of all CDIs that are currently referred to CDRN for ribotyping indicates a high likelihood that these criteria are not being followed consistently.

It is appropriate that the function of CDRN is continually reviewed to ensure that the service is cost effective. We emphasise that all hospitals should submit samples according to the CDRN criteria (see page 3). Use of enhanced fingerprinted (and in due course WGS) is recommended to optimise the control and prevention of CDI following discussion with CDRN or UKHSA personnel (see page 4).

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Acknowledgements

We thank everyone across the original CDRN who contributed to the successful development and consolidation of the service.

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Published: January 2024
Publishing reference: GOV-15543

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