Difficile indeed

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It has always lived up to its ominous species name: *Clostridium difficile*. It is difficult to culture, for example, and for this reason had for decades almost exclusively occupied hard-core devotees of anaerobic bacteria. In the 2000s, it also proved difficult to handle: outbreaks in hospitals began to be reported with increasing frequency in Europe and North America. Hypervirulent strains belonging to ribotype 027, and to a lesser extent 078, emerged that caused high morbidity and mortality among those infected, reviewed in [1,2]. Awareness rapidly increased and typing methods were fine-tuned. Investigations into risk factors for infection eventually led to identification of promising control measures, such as prudent antimicrobial drug stewardship, especially for those in risk groups.

The fact that the increase in frequency and severity of *C. difficile* infections was international led to discussions on the need to harmonise – and, if possible, standardise – methods and approaches for surveillance, diagnosis and strain typing. Two previous European reports provide the background to the work presented in the six papers forming this special issue of *Eurosurveillance*. These Europe-wide surveillance studies reported an increase in the mean incidence of *C. difficile* infections from 2.45 cases per 10,000 patient-days per hospital in 2005 to 4.1 in 2008 per 10,000 patient-days per hospital [3,4].

The special issue now at hand presents a mosaic of approaches, from an updated mapping of ‘the European territory’ to focused country-specific studies. What follows in this editorial is primarily a critical reading of the data, concentrating more on points that this author deems worthy of improvement or further attention.

Two European surveys look at available *C. difficile* infection (CDI) surveillance systems, and at laboratory capacity to diagnose CDI and type the responsible isolates [5,6]. While both identify several positive aspects, they also highlight room for improvement: the first, by Kola et al. based on data from 2011, shows that less than half of the responding 31 countries had a comprehensive, nationwide, ongoing CDI surveillance

system, while in three of them, only severe cases were being notified [5]. The documented use of different definitions, including the distinction between health-care- and community-associated (HA and CA) infections, poses an evident challenge for data comparison between countries. Perhaps even more critically, laboratory confirmation was included in 10 of the 18 analysed surveillance systems, and outcome only in five. Microbiological data, e.g. antimicrobial drug resistance phenotypes or molecular types, were regularly integrated with epidemiological data only in four countries, thus hampering immediate attempts to accurately identify potential outbreaks and dissemination routes. It will now be interesting to see to what extent these drawbacks will be overcome by the European Union (EU)/European Economic Area (EEA)-wide hospital-based CDI surveillance launched by the European Centre for Disease Prevention (ECDC): the surveillance protocol was published in 2015 [7], with data collection beginning in 2016.

The second survey, by van Dorp et al., compared European laboratory capacity to diagnose CDI and type the responsible isolates, in 2011 and in 2014, through the European *C. difficile* Infection Surveillance Network (ECDIS-Net) [6]. As already mentioned, laboratory capacity is crucial to detect and monitor the epidemiology of CDI and to detect the emergence of new strains. A total of 83 laboratories – that, unfortunately, could only be selected by convenience sampling – responded to the survey. The authors observed improvements in different aspects of the diagnostic approach between 2011 and 2014 in up to five laboratories per each improved aspect*. Comparison within a short span of three years may not have allowed a more promising extent of improvement. Nevertheless, some improvements could be seen when considering the use of diagnostic algorithms – classified as ‘optimal’, ‘acceptable’ or ‘incomplete’, although this classification was challenged by several participants. Here, a significant overall improvement, up to 31% or 46%, depending on bias assumptions, was observed. Identified barriers to improvements were, unsurprisingly, cost and lack of trained personnel. The existence of such barriers

in some European countries invites decisive European initiatives to overcome them. It should not be unreasonable to hope that European public health may also benefit from approaches (e.g. in funding) that have so clearly improved opportunities for European citizens in other areas of life, such as through strengthening Infrastructure for transport.

Harmonisation and standardisation of laboratory approaches and methods were another challenge. Building trust and capacity through persistent collaboration and proof-of-principle studies, e.g. in the form of ring trials that are as inclusive as possible, have been shown to help in similar contexts, as in [8].

Building on the two European surveys opening this issue [5,6], three CDI surveillance options were developed and piloted over a short period of three months in 37 acute care hospitals in 14 European countries: 'minimal' CDI surveillance (aggregated data); 'light' (including patient data for CDI); and 'enhanced' (with microbiological data for the first 10 CDI episodes for each hospital). In their paper, van Dorp et al. report a workload increasing, respectively, from 1.1 to 2.0 to 3.0 person-days per 10,000 hospital discharges, and that most responding hospitals found the light and enhanced options 'not difficult' [9].

Of the 14 European countries analysed, nine had already implemented CDI surveillance programmes, while five had not, and only two of the latter category declared that they would pursue it past the study's endpoint. The majority of hospitals were tertiary care hospitals: only five primary care hospitals participated. Unfortunately, only nine of the 14 participating countries took advantage of the offer for external quality assessment of strain typing, for reasons that are unclear. Of the 1,152 CDI episodes recorded by 'minimal' surveillance, only 23% included microbiological data in the 'enhanced' surveillance. This highlights once again laboratory data as a bottleneck towards a complete and high-value epidemiological picture necessary for timely control measures. The 'infamous' ribotype 027, though dominant (30% of all isolates), was identified in eight of the 14 participating countries, and with a widely varying frequency, ranging from 4% to 85% [9].

In the fourth European-wide report by Davies et al., a point-prevalence study that took place at two time-points, in 2012 and 2013, investigators bypassed the problem of interlaboratory harmonisation and standardisation by relying on a single reference laboratory [10]. They ribotyped 1,196 isolates from 482 hospitals in 19 European countries and identified 125 different ribotypes. Ribotype 027 represented 19% of the total. In areas where 027 (or 176, but not other strains) was dominant, overall ribotype diversity was low. This finding illustrates the ability of these two epidemic strains to very successfully occupy their species' ecological niche. On the other hand, increased ribotype diversity was seen in a specific patient age-group: those over 80

years' old. While in 2008, the most prevalent European ribotype was 078, in the 2012–13 study, it had dropped to only 3% – an almost threefold decrease, counter-mirroring the over threefold increase of 027. Interestingly, no distinct associations of specific ribotypes with either colonisation or infection were seen.

One final point from this study merits clinical and epidemiological attention: over 7% of isolates from infected patients belonged to ribotypes known to be non-toxinogenic. The authors therefore hypothesise multistrain infections, as indeed previously shown by others. The study also showed that, in addition to the presence of 'pan-European' ribotypes, some ribotypes did exhibit country- or region-specificity, emphasising the importance of adequate knowledge of local epidemiology for taking appropriate measures. Two papers in this issue, originating from different countries, complete the picture.

Fawley et al. present results from enhanced surveillance, comparing CA- and HA-CDI in England, from 2011 to 2013 [11]. They found ribotype 027 and recent antibiotic treatment significantly higher in the HA group, while ribotypes 002, 020 and 056 and no recent antibiotic treatment were more frequent among CA isolates. In contrast to the European-wide study by Davies et al., which, however, did not differentiate between HA- and CA- CDI, ribotype diversity decreased with increasing age among HA- as opposed to CA-CDI isolates. Of course, as the authors acknowledge, these comparisons rest on the assumption that the majority of elderly patients living in care homes did not routinely receive healthcare and thus will have rightly been categorised as CA cases. Finally, in patient groups with recent hospital contact, ribotype diversity was reduced – as might be expected from exposure to a more outbreak-prone environment, where one or a few epidemic strains would predominate.

Data from enhanced surveillance in the Czech Republic in 2014 are presented by Krutova et al. [12]. Voluntary participation of 18 hospitals, covering 30% of the country's hospital bed capacity, yielded an incidence of 6.1 cases per 10,000 patient bed-days for both CA- and HA- CDI, and 774 isolates that were ribotyped. Among 33 known and 37 novel ribotypes observed, ribotypes 176 and 001 predominated (24% and 29%, respectively). Further subtyping among these two ribotypes, by the more discriminatory multilocus variable-number tandem-repeat analysis (MLVA), revealed clonal clusters of 176 and 001 that were common in 11 and seven hospitals, respectively. This could indicate patient-to-patient spread, though this was not specifically investigated. Frequent use of 'suboptimal' diagnostic algorithms, and low testing frequency when funds were limited, were identified weaknesses. However, an encouraging aspect of this report was the steadily increasing participation of Czech hospitals in such studies: from three in 2008, to 10 in 2012–13 and 18 in 2014. Such increasing engagement confirms

that time, persistence, positive experience, as well as intracountry concerted efforts, can lead to a positive outcome.

Taken together, the studies presented in this issue, in concert with those that had prepared the ground for them and those that doubtless will follow, are praiseworthy as they contribute to both a raised awareness and a more solid documentation of a field fraught with difficulties. From the perspective of a benefit to public health, however, it will be useful to see to what degree such extensive, harmonised and/or standardised surveillance and typing will lead to better control of CDI and further reduction of outbreaks as well as sporadic cases.

* Author's correction

The sentence was modified on 26 July 2016 at the request of the author, to reflect more accurately the data the sentence summarises.

Conflict of interest

None declared.

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