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Employees of Swiss veterinary clinics colonized with epidemic clones of carbapenemase-producing *Escherichia coli*

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Sir,

The global spread of carbapenemase-producing Enterobacterales (CPE) represents an alarming public health issue. Infections due to these difficult to treat bacteria are associated with high morbidity and mortality rates. Moreover, subjects infected and/or colonized at the intestinal level can transmit their CPE to other people and may contribute to their diffusion in non-human settings.[1] Nowadays, the threat of CPE has also been increasingly observed among pets hospitalized at veterinary clinics. Frequently, the CPE isolated from these animals share the same carbapenemase genes and/or lineage of those found in humans.[2,3] However, data regarding the possible transmission of CPE from hospitalized animals to veterinary staff in contact with them, or vice versa, are lacking.

In Switzerland, the prevalence of CPE in both human and animal settings is still low (www.anresis.ch). Nevertheless, we recently described 21 cases of hospital-acquired gut colonization due to a common ST410 $bla_{OXA-181}$-harbouring *Escherichia coli* (ST410-OXA-181-*Ec*) in dogs and cats; such cases occurred during May–August 2018 at a large Swiss companion animal hospital (clinic A).[4] Moreover, at another veterinary hospital (clinic B), a case of wound infection due to an ST167 bla_{NDM-5}-possessing *E. coli* (ST167-NDM-5-*Ec*) occurred in a dog in February 2018 (strain 51008369SK1).[5] In this institution (June–July 2018), we also identified this type of CPE in rectal swabs of two other hospitalized dogs (strains AR202.2 and AR216.2b; GenBank: CP043946–CP043949 and CP043942–CP043945, respectively). Based on these alarming data, we decided to explore the presence of CPE in the intestinal tract of veterinary employees.

Between June and October 2018, a total of 108 employees of three Swiss veterinary clinics (A, *n*=46; B, *n*=37; and C, *n*=21) and one private practice (*n*=4) voluntarily self-collected their stools. Written informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of the Canton of Bern (KEK-BE No: 2018–00866).

Samples were enriched overnight in LB broth supplemented with cefuroxime and then plated on ChromID Carba (bioMérieux).[6] Colonies were identified at the species level using MALDI-TOF MS (Bruker). MICs were determined using the microdilution Sensititre™ GNX2F plate (Trek Diagnostic) and interpreted using the 2019 EUCAST criteria (www.eucast.org). Strains suspected of carbapenemase production (MICs of meropenem and/or ertapenem >0.125 mg/L and BlueCarba test positive) underwent WGS using both NovaSeq 6000 (Illumina) and MinION (Oxford Nanopore). The final assembly was annotated using the NCBI Prokaryotic Genome Annotation Pipeline.[6] Contigs were analysed using the tools of the Center for Genomic Epidemiology (www.genomicepidemiology.org/). Core genome MLST (cgMLST) analysis was also performed to compare the recovered CPE with those available in the NCBI.[4]

Two employees (1.9%) were shown to be colonized at the gut level with CPE (Table S1, available as Supplementary data at *JAC* Online); one subject at clinic A carried ST410-OXA-181-*Ec* (strain *Ec*-042; GenBank: CP042934–CP042936) and one subject at clinic B carried ST167-NDM-5-*Ec* (strain *Ec*-050; GenBank: CP043227–CP043230). Based on these worrying results, hospital environment swabs were taken from clinic A (*n*=182) and B (*n*=200) during July–August 2018 and processed.[6] Five carbapenemase-producing *E. coli* (two ST410-OXA-181-*Ec* and three OXA-48 producers of ST155, ST641 and ST4038) were detected at clinic A (data not shown).

Ec-042 carried $bla_{OXA-181}$ and *qnrS1* in a 51 kb IncX3 plasmid, while bla_{CMY-42} was in a 47 kb IncI1 element. The $bla_{OXA-181}$-carrying plasmid was indistinguishable from those previously found in the ST410-OXA-181-*Ec* strains isolated from the 21 colonized dogs and cats at clinic A (e.g. pAN-OXA-181)[4] and almost identical (identity ≥99.9%) to others described worldwide (Figure S1). Moreover, cgMLST analysis showed that *Ec*-042 shared a very high genetic relatedness to clinic A's ST410-OXA-181-*Ec* strains (e.g. strain AR24.2b),[4] but was also closely related to ST410 strains from gulls in the USA (Figure 1a).

Ec-050 possessed three main plasmids: a 99 kb IncFII/FIA/FIB plasmid harbouring bla_{NDM-5}, *aac(3)-IIa*, *aadA2*, *dfrA12*, *mph*(A), *sul1* and *tet*(A); a 71 kb IncFII plasmid with bla_{CMY-2} and *erm*(B); and a 115 kb IncI1 plasmid possessing bla_{TEM-30}, *aadA1*, *floR*, *sul1/2* and *dfrA1* resistance genes. The bla_{NDM-5}-harbouring

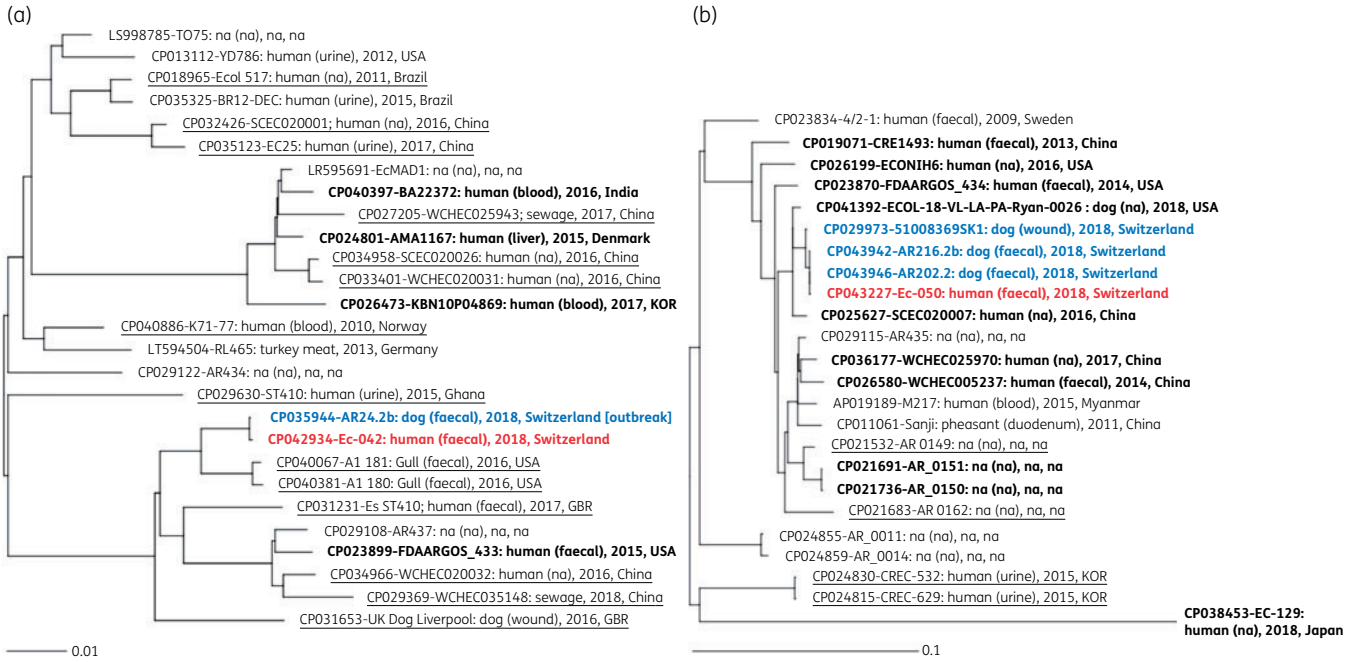

Figure 1. Phylogenetic Neighbor–Joining trees of representative *E. coli* complete chromosomes available in GenBank (accessed on 5 August 2019) together with the strains recovered in this study. Trees were generated and drawn using SeqSphere+ (v. 6.0.2, Rindom GmbH) comparing the genes of the core genome (cgMLST) of all included strains using the parameters 'pairwise ignoring missing values and % columns difference'. For each strain, we show the GenBank accession number, strain name, host (sample), year and country of detection. (a) Comparison of 3281 genes for 27 ST410 *E. coli* strains (strains possessing $bla_{OXA-181}$ are indicated in bold, whereas those possessing other carbapenemases are underlined). In red we show the $bla_{OXA-181}$-harbouring strain (*Ec*-042) recovered from the employee at clinic A, while in blue we show a representative strain (AR24.2b) responsible for the outbreak involving 21 pets at the same institution. (b) Comparison of 3595 genes for 24 ST167 *E. coli* strains (strains possessing bla_{NDM-5} are indicated in bold, whereas those possessing other carbapenemases are underlined). In red we show the bla_{NDM-5}-harbouring strain (*Ec*-050) recovered from the employee at clinic B, while in blue we show the strains detected in three dogs at the same institution. na, not available; GBR, Great Britain; KOR, South Korea. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

plasmid showed an identity >99.9% with those found in the ST167-NDM-5-*Ec* detected from the three dogs hospitalized at clinic B (strains 51008369SK1,[5] AR202.2 and AR216.2b) and one found in Italy in a human strain (Figure S2). Furthermore, cgMLST analysis showed that *Ec*-050 was highly related to the above NDM-5-producing dog strains, but also clustered with others detected in different countries and hosts (Figure 1b).

To the best of our knowledge, this is the first time that veterinary hospital staff have been found to be colonized with CPE. Worryingly, the recovered strains shared high genetic relatedness to those detected among dogs and cats hospitalized in the same employees' institutions. We also note that in our previous survey conducted at clinic A during 2013–16, gut CPE carriers among the staff were not identified.[7] This might indicate that acquisition of CPE among the personnel is relatively recent. However, whether the veterinarians introduced the CPE into the hospitals or became colonized while working with the colonized pets remains unknown.

In conclusion, this study revealed that the diffusion of very successful international epidemic CPE clones (e.g. ST410-OXA-181-*Ec* and ST167-NDM-5-*Ec*)[4,8,9] in companion animal veterinary clinics not only compromised the outcome of infected animals, but emphasized that people working with pets can be colonized. These subjects might also contribute to the transmission and further expansion of these life-threatening bacteria to healthy people in the community. Therefore, as practised in human hospitals, veterinary institutions must urgently implement optimal infection control practices (e.g. efficient cleaning and disinfection procedures) to face this concerning public health phenomenon.[10] Moreover, detection of CPE in companion animals should become notifiable as it is for people.

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Transparency declarations

None to declare.

Supplementary data

Table S1 and Figures S1 and S2 are available as Supplementary data at *JAC* Online.

References

1 Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. *J Infect Dis* 2017; **215** Suppl 1: S28–36.

2 Pomba C, Rantala M, Greko C *et al*. Public health risk of antimicrobial resistance transfer from companion animals. *J Antimicrob Chemother* 2017; **72**: 957–68.

3 Madec JY, Haenni M, Nordmann P *et al*. Extended-spectrum β-lactamase/AmpC- and carbapenemase-producing Enterobacteriaceae in animals: a threat for humans? *Clin Microbiol Infect* 2017; **23**: 826–33.

4 Nigg A, Brilhante M, Dazio V *et al*. Shedding of OXA-181 carbapenemase-producing *Escherichia coli* from companion animals after hospitalisation in Switzerland: an outbreak in 2018. *Euro Surveill* 2019; **24**: pii=1900071.

5 Peterhans S, Stevens MJA, Nuesch-Inderbinen M *et al*. First report of a bla_{NDM-5}-harbouring *Escherichia coli* ST167 isolated from a wound infection in a dog in Switzerland. *J Glob Antimicrob Resist* 2018; **15**: 226–7.

6 Budel T, Kuenzli E, Clement M *et al*. Polyclonal gut colonization with extended-spectrum cephalosporin- and/or colistin-resistant Enterobacteriaceae: a normal status for hotel employees on the island of Zanzibar, Tanzania. *J Antimicrob Chemother* 2019; **74**: 2880–90.

7 Pires J, Kuenzli E, Hauser C *et al*. Intestinal colonisation with extended-spectrum cephalosporin-resistant Enterobacteriaceae in different populations in Switzerland: prevalence, risk factors and molecular features. *J Glob Antimicrob Resist* 2018; **12**: 17–9.

8 Mataseje LF, Boyd DA, Fuller J *et al*. Characterization of OXA-48-like carbapenemase producers in Canada, 2011–14. *J Antimicrob Chemother* 2018; **73**: 626–33.

9 Giufre M, Errico G, Accogli M *et al*. Emergence of NDM-5-producing *Escherichia coli* sequence type 167 clone in Italy. *Int J Antimicrob Agents* 2018; **52**: 76–81.

10 Walther B, Tedin K, Lübke-Becker A. Multidrug-resistant opportunistic pathogens challenging veterinary infection control. *Vet Microbiol* 2017; **200**: 71–8.