13 One-Health spotlight on carbapenemase-producing Enterobacterales (CPE)

13.1 Introduction

Carbapenems are highly effective broad-spectrum antibiotics, used for severe infections with some multidrug-resistant microorganisms, in particular extended-spectrum beta-lactamase-producing Enterobacterales [1]. Their use is restricted mainly to humans. In farm animals, the use of carbapenems is not allowed; in small animals (dogs and cats), it is restricted to very specific cases when certain criteria are fulfilled [2].

Surveillance of carbapenem-resistant Enterobacterales is complex and cannot be based on resistance testing only, as it can be mediated via different mechanisms such as permeability defects, efflux pumps or by the production of carbapenemase enzymes. Therefore, to understand the spread of these microorganisms, genetic analyses are needed. Carbapenemase-producing Enterobacterales (CPE) are of special concern due to their multiresistance and their ability to rapidly spread vertically and horizontally, enabled by resistance genes on transmissible genetic elements such as plasmids.

In contrast to several regions in Asia, America and Europe where CPE are endemic, only sporadic cases have been reported in Switzerland in the past. However, aggravations of the epidemiological situations in neighboring European countries and increased reporting of individual CPE cases in Switzerland are worrisome and have led to an increased surveillance activity in this regard.

13.2 Human medicine

In humans, the increased use of carbapenems has led to an increasing number of CPE cases worldwide. As a consequence, other reserve antibiotics with a greater propensity for adverse effects, such as colistin, have to be administrated more frequently, leading to increased mortality, morbidity and healthcare costs. As stated previously, in Enterobacterales the non-susceptibility to carbapenems is often mediated by the production of carbapenemase enzymes. CPE are classified according to their amino acid sequences, i. e. as KPC, VIM, IMP, NDM or OXA genotypes. Within Europe, different genotypes are heterogeneously distributed: KPC and VIM have extensively been reported in southern Europe, interregional NDM spread has been observed in eastern and northern Europe, and OXA-48 is widespread in some western European countries (e. g. France) [3].

In Switzerland, several individual CPE cases and local outbreaks have been reported since 2009, and CPE were defined as notifiable pathogens by the Swiss Federal Office of Public Health in 2016. However, no systematically collected epidemiological Swiss data has been published so far. Recently, Michael Gasser and Alban Ramette systematically analysed CPE data collected by the Swiss Antibiogram Committee (SAC, 2013–2015) and the Federal Office of Public Health (FOPH, 2016–2018) in order i) to describe CPE distributions and trends of different genera and genotypes on a national, regional and hospital level and ii) to identify epidemiological factors associated with changes in case incidence [4].

In this study, it was found that yearly detected CPE isolates have more than tripled, from 65 in 2013 to 212 in 2018 (Figure 13). This increase was observed in isolates from both infections and screenings of patients admitted to hospitals for other reasons, and was most pronounced in 2018.

The most frequently isolated CPE species were *Klebsiella* spp. (56%) and *Escherichia coli* (27%) (see Table 13). During the study period (2013–2018), relative proportions of *E. coli* increased from 20% to 34%, whereas *Klebsiella* spp. decreased from 59% to 44%. The most frequent genotypes were OXA-48-type (43%), KPC (25%), and NDM (21%). In different regions of Switzerland there were considerable differences in the frequency of CPE isolates per 100,000 inhabitants (Figure 13) and the distribution of CPE genotypes showed characteristic regional patterns: in contrast to the French-speaking parts (West, Geneva) where OXA-48-types were the predominant genotypes (around 60%), KPC was the most frequently detected genotype in Ticino (South) (63%). This distribution mirrors the situation in Western Europe, where high rates of OXA-48-types are observed in France, whereas KPC is the predominant genotype in Italy. According to the trends in neighboring European countries, we might also witness further spread of the OXA-48-type and NDM-producing *E. coli*, and a stabilization or decrease of KPC producers.

In addition to time (years) and region, the gender was identified as a significant risk factor in a multivariable analysis, as isolates were predominately (62%) from male patients. In order to detect regional clusters, a simulated cluster analysis by WHONET-SatScan was performed. In five out of eight

Figure 13: A. Total number of CPE isolates related to colonization and infection from 2013–2018 (data from SAC and FOPH). B. Number of CPE isolates per 100,000 inhabitants of different ANRESIS regions 2018 (data from FOPH). Visit www.anresis.ch for an interactive view of this graph, including absolute numbers of CPE isolates 2013–2019.

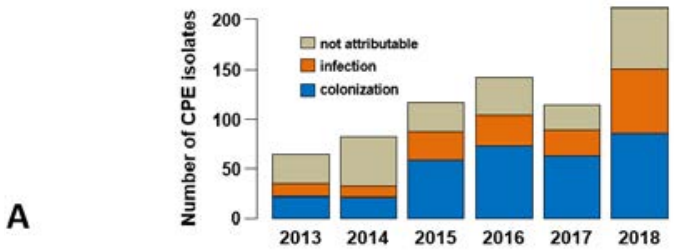

Table 13: Total number of CPE isolates per genus and genotype from 2013 to 2018. Adapted from Gasser, Ramette *et al.* [4].

		Klebsiella spp.	*Escherichia coli*	*Entero-bacter* spp.	*Citrobacter* spp.	*Proteus* spp.	*Providencia* spp.	Others	Total
IMP	**n**	1	0	0	0	0	0	0	1
	%	100; <1	0; 0	0; 0	0; 0	0; 0	0; 0	0; 0	0
KPC	**n**	153	9	5	1	0	1	2	171
	%	90; 40	5; 5	3; 9	<1; 3	0; 0	<1; 14	1; 17	25
NDM	**n**	66	41	21	9	3	5	1	146
	%	45; 17	28; 22	14; 40	6; 28	2; 33	3; 71	<1; 8	21
OXA-181	**n**	7	17	0	1	0	0	1	26
	%	27; 2	65; 9	0; 0	4; 3	0; 0	0; 0	4; 8	4
OXA-48-type	**n**	144	113	15	13	0	1	6	292
	%	50; 38	39; 61	5; 28	5; 41	0; 0	<1; 14	2; 50	43
OXA other	**n**	1	1	0	0	0	0	0	2
	%	50; <1	50; <1	0; 0	0; 0	0; 0	0; 0	0; 0	0
VIM	**n**	11	5	12	8	6	0	2	44
	%	25; 3	11; 3	27; 23	18; 25	14; 67	0; 0	5; 17	7
Total	**n**	383	186	53	32	9	7	12	682
	%	56	27	8	5	1	1	2	100

Marginal percentages respectively per row and column are shown. The category "Others" includes *Pluralibacter* spp., *Raoultella* spp., *Salmonella* spp., *Serratia* spp. and unknowns. The category "OXA other" includes the OXA-232 and OXA-244 genotypes.

Table 14: Monitoring program on carbapenem-resisant *E. coli* in livestock and meat thereof 2015–2019.

Year	Sample type	Number of samples (n)	Number of carbapenemase-producing *E. coli* (n)
2015	fattening pigs – cecum	300	0
	veal calves – cecum	298	0
	chicken meat	319	0
	pork meat	301	0
	beef meat	298	0
2016	broiler – pooled caecum	307	0
	chicken meat	302	0
2017	fattening pigs – cecum	296	0
	veal calves – cecum	304	0
	pork meat	302	0
	beef meat	299	0
2018	broiler – pooled caecum	307	0
	chicken meat	312	0
2019	fattening pigs – cecum	306	0
	veal calves – cecum	298	0
	pork meat	311	0
	beef meat	309	0

regions of Switzerland, significant clusters were identified, resulting in a total of seven clusters. Three of them were confirmed as local outbreaks by genetic analyses.

These analyses have shown the importance of a timely and detailed national surveillance for CPE. An important step was taken towards this goal in 2016, when the Federal Office of Public Health declared CPE reporting as mandatory. In addition, since 2019 all isolates suspected to contain CPE need to be sent to the Swiss national reference laboratory NARA (www.nara-antibiotic-resistance.ch) for in-depth genotyping and physical storage. Epidemiological data (e.g. travel history, invasiveness of disease or antibiotic pretreatments) are collected by the Federal Office of Public Health. In 2020, the Swiss Centre for Antibiotic Resistance ANRESIS, in close collaboration with NARA, established an up-to-date representation of Swiss CPE data, which is now accessible to the public (see www.anresis.ch).

13.3 Veterinary medicine (livestock and meat)

Since 2015, detection of carbapenemase-producing *E. coli* is included in the national antimicrobial resistance monitoring program for livestock and meat thereof (Table 14). The method is harmonized at the European level and is based on an enrichment step in non-selective buffered peptone water followed by plating out on two different selective agar plates for detection of carbapenemase-producing *Enterobacterales*, including OXA-48 phenotypes. From 2015 to 2018, only colonies suspected to contain *E. coli* were further analysed; since 2018, the presence of *Klebsiella* spp. has been included in the analysis of CPE. Moreover, all *Salmonella* strains isolated within the framework of the Swiss national surveillance program on *Salmonella* in chicken or from clinical cases of various animal species are analysed for their antimicrobial resistance pattern by micro broth dilution. Meropenem is included as a screening substance for CPE.

No carbapenemase-producing *E. coli* or *Salmonella* spp. were detected, whether in samples from the primary production level or in fresh meat. These results are in accordance with results reported by the European food safety authority (EFSA). In the period from 2017 to 2018, 18 European member states as well as Norway and Switzerland analyzed more than 30,000 samples from livestock and meat for the presence of carbapenemase-producing *E. coli* on a voluntary basis, with negative results [5]. Only in one case in 2017, one isolate with a carbapenemase phenotype from a cecal sample collected at slaughter from a pig in Germany was detected within the ESBL/pAmpC-monitoring program. The isolate was confirmed to produce VIM-1. In the previous period (2015–2016), approximately 17,000 samples were tested within Europe. In 2016, three *E. coli* from broilers and chicken meat, respectively, were isolated in Romania and have been confirmed as $bla_{\text{OXA-162}}$ carriers [5].

13.4 Veterinary medicine (small animals)

Unlike in human medicine, the use of carbapenems in veterinary medicine is controversially discussed. Carbapenems are not allowed for use in farm animals, and only exceptionally used in companion animals. While beta-lactam antibiotics are the most commonly used antimicrobials in cats and dogs, critically important antimicrobials such as fluoroquinolones and higher generation cephalosporins are also routinely used. Until very recently, reports of carbapenem resistance have been very rare in veterinary medicine.

In 2018, a large prospective, longitudinal, observational study was funded by the Federal Food Safety and Veterinary Office to assess risk factors for prevalence, and acquisition and carriage of multidrug resistant organisms (MDRO) in dogs and cats presented to five veterinary clinics/hospitals in Switzerland. Nasal/oropharyngeal and rectal swabs were collected from 183 dogs and 88 cats presented to 5 veterinary hospitals/clinics. In addition, nasal swabs and stool samples were collected from 50 owners and 108 employees of three Swiss veterinary clinics and one private practice.

The admission prevalence of MDRO carriage in pets was 15.5% (95%CI 11.4–20.4%); at admission, MDR- (ESBL or *pAmpC*) *E. coli* predominated, accounting for 34.1% of all MDRO isolates. One *E. coli* isolate from a dog additionally displayed resistance to carbapenem, due to the presence of a plasmid-mediated carbapenemase gene ($bla_{OXA-181}$) [6,7].

Overall discharge prevalence of MDRO carriage in pets was 32.6% (95%CI 26–39.8%), but varied significantly among care facilities (range 17.2–42.7%). Predominant hospital-acquired isolates among the three largest clinics were: ESBL-*E. coli* (16.1%) and ESBL-producing *Klebsiella pneumoniae* (ESBL-*Kp*) (12.9%). At discharge, 71.4% (25/35) of all MDR *E. coli* displayed resistance to ertapenem. Carbapenem resistance was due to the presence of plasmidic $bla_{oxa-181}$ (22 isolates, clinic 1), bla_{oxa-48} (1 isolate, clinic 1) or bla_{NDM-5} (2 isolates, clinic 2). *K. pneumoniae* were isolated from 38.5% (25/82) of all animals, the large majority were of the CTX-M-1/-3/-15 ESBL and DHA-1 pAmpC subtypes, and only one isolate from clinic 1 displayed a carbapenemase-encoding gene (bla_{OXA-48}) [6,7].

Resistant bacteria were isolated from 9 out of 50 owners (5/9 ESBL-*E. coli*; 4/8 MRCoNS; 1/8 MRSA). Interspecies transfer of MDRO between owners and dogs was not documented. However, two employees of veterinary clinics (1.9%) were shown to be colonized at the gut level with CPE. One employee (clinic 1) carried ST410-OXA-181-*Ec* (strain *Ec*-042; GenBank: CP042934–CP042936) and one (clinic 2) carried ST167-NDM-5-*Ec* (strain *Ec*-050; GenBank: CP043227–CP043230). Five carbapenemase-producing *E. coli* (two ST410-OXA-181-*Ec* and three OXA-48 producers of ST155, ST641 and ST4038) were also present in the hospital environment of clinic 1 [8].

In conclusion, this study has revealed that despite the fact that carbapenems are not routinely used in companion animal medicine, international epidemic CPE clones (e.g. ST410-OXA-181-*Ec* and ST167-NDM-5-*Ec*) disseminate in companion animal veterinary clinics and may also colonize veterinary staff. While transmission of CPE to owners has not been documented, enteral carriage in pets contributes to the spread of CPE in the environment. Therefore, veterinary institutions must urgently implement optimal infection control practices (e.g. efficient cleaning and disinfection procedures).

13.5 Discussion

Carbapenems are mainly used in human medicine as reserve antibiotics. After a slight increase in prescription up to 2013, carbapenem use in Switzerland has stabilized over the last six years. On the other hand, CPE prevalence in human medicine more than tripled from 2013 to 2018. Although most cases were sporadic, some small local outbreaks were detected. Single reports and genotype distribution suggest that most CPE cases are imported. Although epidemiological parameters such as the travel history should be reported to the FOPH with each isolate, this is unfortunately not done frequently, making more detailed analyses of this important feature impossible.

In veterinary medicine, carbapenems are not used in farm animals and only rarely in small animals (cats and dogs). Until 2019, carbapenem resistance was not reported in animals. However, epidemic CPE clones have recently been detected in companion animal veterinary clinics and veterinary staff. It is not known whether the veterinary staff introduced the CPE in the clinic or the colonization happened in the animal clinic.

Nevertheless, these observations show that antibiotic resistance can be present in multiple settings and may be transmitted from one compartment to the other, and that this can only be tackled using a collaborative One-Health approach.

In human medicine, CPE reporting is mandatory; this should also be considered in the veterinary field. Moreover, CPE isolates from human, animal and environmental samples should be analysed together, to immediately detect inter-compartment spreading of this important resistance.

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Textbox

Antibiotic-resistant bacteria in dogs and cats: guidelines for risk reduction

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Small-animal clinics and practices too are facing patients carrying antibiotic-resistant bacteria. For risk reduction, guidelines needed to be developed.

A working group of human and veterinary medicine experts developed a guide for dog or cat owners with pets carrying antibiotic-resistant bacteria, namely *methicillin-resistant staphylococci*, and extended spectrum beta-lactamase (ESBL) and carbapenemase-producing Enterobacteriaceae. A review for veterinary practitioners provides background information on the most important antibiotic-resistant bacteria in dogs and cats and on their occurrence, and discusses risk factors in dogs, cats and humans. Measures to reduce the risk of transmission to humans are outlined.

To reduce the development and dissemination of resistant bacteria in small-animal clinics and practices, the Vetsuisse Faculty Zurich developed infection prevention and control guidelines. These contain detailed information on the role of hand hygiene, personal hygiene, cleaning and disinfection, quarantine measures and antimicrobial stewardship in companion animal medicine.

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