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High Prevalence of Extended-Spectrum β-Lactamase, Plasmid-Mediated AmpC, and Carbapenemase Genes in Pet Food

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We evaluated the pet food contained in 30 packages as a potential origin of extended-spectrum cephalosporin-resistant Gram-negative organisms and β-lactamase genes (*bla*). Live bacteria were not detected by selective culture. However, PCR investigations on food DNA extracts indicated that samples harbored the $bla_{CTX\text{-}M\text{-}15}$ (53.3%), $bla_{CMY\text{-}4}$ (20%), and $bla_{VEB\text{-}4\text{-}like}$ (6.7%) genes. Particularly worrisome was the presence of $bla_{OXA\text{-}48\text{-}like}$ carbapenemases (13.3%). The original pet food ingredients and/or the production processes were highly contaminated with bacteria carrying clinically relevant acquired *bla* genes.

Enterobacteriaceae possessing β-lactamase genes (*bla*) encoding extended-spectrum β-lactamase (ESBL) (e.g., CTX-Ms, VEBs), plasmid-mediated AmpC (pAmpC) (e.g., CMYs), and carbapenemase (e.g., *Klebsiella pneumoniae* carbapenemases [KPCs], OXA-48-like, NDMs) enzymes have become a major threat to public health (1–4). Pets and food-producing animals may be colonized or even infected with these drug-resistant bacteria, possibly acting as a potential reservoir for their spread to humans (5–9).

In line with analyses performed on food products for humans (e.g., retail meat, vegetables) (9–12), this study investigated pet food as a potential source of genes conferring resistance to extended-spectrum cephalosporins (ESCs). For this purpose, we analyzed the presence of ESC-resistant *Enterobacteriaceae* (ESC-R-*Ent*), *bla* genes, and plasmid-specific markers in retail pet food.

In September 2013, 30 pet food (for cats and dogs) packages containing 50 g to 1 kg of mixed wet food with different flavors were purchased from three stores in Bern, Switzerland. The advertised ingredients (content declaration), the brands, and the manufacturers, as indicated on the package labels, are listed in Table 1. For most of the packages, only a minor proportion of the component(s) constituting the overall product was declared in detail. For 73% of the food samples, meat from chicken, duck, and/or turkey was advertised on the label, but this component contributed just 4% to 18% of the final composition. Declarations of the remaining compounds (72% to 96%) were missing. Furthermore, a large proportion of the food mixtures also contained an additional compound(s), like grains, plant-derived products, and fish by-products, that were "not promoted" but listed in the declaration of the composition (data not shown).

A portion of the food content (about 10 g each) was enriched in Luria-Bertani broth plus 20 μg/ml ampicillin (Sigma-Aldrich) at 37°C overnight. From there, an aliquot of 50 μl was streaked out on MacConkey, Drigalski plus cefotaxime (1.5 μg/ml), and MacConkey plus ceftazidime (2 μg/ml) agar plates (bioMérieux). ESC-R-*Ent* or other cephalosporin-resistant bacteria were not detected by selective cultivation in any of the 30 samples.

DNA isolation was performed with the QIAamp DNA minikit (Qiagen) using about 10 g of food from each package. Each sample was examined as previously described by standard PCR and DNA sequencing for the presence of *bla* genes (bla_{TEM}, bla_{SHV}, $bla_{CTX\text{-}M\text{-}1\ group}$, $bla_{CTX\text{-}M\text{-}9\ group}$, bla_{VEB}, bla_{CMY}, $bla_{OXA\text{-}48\text{-}like}$, bla_{IMP}, bla_{VIM}, bla_{NDM}), insertion sequence IS*Ecp1*, and plasmid types (IncA/C, IncN, IncI1, IncF, and IncL/M and the genes *parA*, *repA*, and *traU*) (1, 13–16).

As shown in Table 1, 16 samples were positive for bla_{ESBL} genes: 14 samples harbored $bla_{CTX\text{-}M\text{-}1\ group}$, one was positive for $bla_{CTX\text{-}M\text{-}1\ group}$ and bla_{VEB}, and one had only bla_{VEB}. In seven samples, the DNA sequence of the $bla_{CTX\text{-}M\text{-}1\ group}$ amplicon led us to suspect the presence of both the $bla_{CTX\text{-}M\text{-}3}$ and the $bla_{CTX\text{-}M\text{-}15}$ genes. This was due to the observation of a double peak in the DNA sequence corresponding to amino acid position 242, discriminating between the CTX-M-3 (Asp242) and CTX-M-15 (Gly242) variants.

It was not possible to determine the complete genetic environments of the amplified genes because the pet food processing and heat treatment steps used to sterilize the food likely caused a partial fragmentation of the bacterial DNA, and it was therefore not possible to amplify targets larger than 800 to 1,000 bp. However, for many samples, a positive amplification was detected for the IS*Ecp1*-$bla_{CTX\text{-}M}$ intergenic region (Table 1), with the expected distance of 48 bp from the start codon of the $bla_{CTX\text{-}M\text{-}15}$ gene (17). This result demonstrates that $bla_{CTX\text{-}M\text{-}15}$ was an acquired, presumably plasmid-located resistance gene. Conversely, the $bla_{CTX\text{-}M\text{-}3}$ gene may be presumably derived from pet food contaminated with *Kluyvera* species progenitors, where it is intrinsic (18).

The two bla_{VEB}-positive amplicons were $bla_{VEB\text{-}4\text{-}like}$ and were very likely acquired resistance genes, since this gene has never been described in a progenitor species. We recently identified $bla_{VEB\text{-}6}$, a $bla_{VEB\text{-}4\text{-}like}$ variant, in a *Proteus mirabilis* isolate from poultry meat in Switzerland (10).

Six samples (20%) were positive for $bla_{CMY\text{-}4}$ (Table 1). Sequencing analyses indicate that $bla_{CMY\text{-}4}$ cannot be attributed to the chromosomal gene found in the ancestral species (*Citrobacter freundii*) generating this family of pAmpCs (i.e., no 100% DNA

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TABLE 1 Epidemiological characteristics and DNA amplicons of relevant antibiotic resistance and plasmid traits from 30 pet food samples

Sample no.	Pet type	Food component(s) (% declared on label)	Country[a]	Store	Brand[b]	Manufacturer[b]	*bla* gene(s) found						IncL/M plasmid typing[f]			IncF, repFII plasmid typing[f]
							OXA-48[c]	CTX-M-1 group[d]	CMY[e]	VEB	TEM[f]	SHV[f]	TraU	ParA	RepA	
101	Cat	Beef (4), chicken (4)	GER	A	1	I	−	IS*Ecp1*-CTX-M-15, CTX-M-3	−	VEB-4-like	+	+	−	−	+	+
102	Cat	Veal (4), poultry (4)	GER	A	1	I	−	IS*Ecp1*-CTX-M-15, CTX-M-3	CMY-4	−	+	+	−	−	+	+
103	Cat	Salmon (4), trout (4)	GER	A	1	I	−	−	−	−	−	−	+	+	+	+
104	Cat	Poultry (4), liver (4)	GER	A	1	I	−	IS*Ecp1*-CTX-M-15, CTX-M-3	−	−	+	+	−	−	+	+
106	Cat	Turkey (14), rabbit (8)	GER/NED	A	2	I, II	−	IS*Ecp1*-CTX-M-15, CTX-M-3	−	−	+	+	−	−	+	−
107	Cat	Beef (14), turkey hearts (8)	GER/NED	A	2	I, II	−	−	−	−	−	−	+	−	+	+
109	Cat	Salmon (4), chicken (4)	EU	A	3	III	−	IS*Ecp1*-CTX-M-15, CTX-M-3	−	−	+	−	+	−	+	+
1010	Cat	Beef (4)	EU	A	3	III	−	IS*Ecp1*-CTX-M-15	−	−	+	−	−	−	+	+
1011	Cat	Turkey (4), duck (4)	EU	A	3	III	−	−	CMY-4	−	+	−	+	+	+	+
1013	Dog	Beef (4)	EU	A	4	IV	−	IS*Ecp1*-CTX-M-15, CTX-M-3	−	−	+	+	+	−	+	+
1014	Dog	Lamb (4)	EU	A	4	IV	−	−	−	−	+	+	+	+	+	+
1015	Dog	Rabbit (4)	EU	A	4	IV	OXA-48	−	−	VEB-4-like	+	+	−	−	+	+
1016	Dog	Turkey (4), peas (2)/carrots (2)	LIE	A	5	V	−	−	−	−	+	+	+	+	+	+
1017	Cat	Poultry (4)	DEN	B	6	VI	−	−	−	−	−	−	+	−	+	+
1018	Cat	Chicken (8), green beans (5)	EU	B	7	VII	−	−	−	−	+	+	+	+	+	+
1020	Cat	Turkey (4)	EU	B	8	VIII	−	−	−	−	+	+	+	−	+	+
1021	Cat	Poultry (4)	EU	B	8	VIII	−	IS*Ecp1*-CTX-M-15	−	−	+	+	+	−	−	−
1023	Dog	Beef (4), chicken (4)	NED	B	9	IX	OXA-48	IS*Ecp1*-CTX-M-15	−	−	+	−	−	−	+	+
1024	Dog	Turkey (4), chicken (4)	EU	B	10	IV	−	IS*Ecp1*-CTX-M-15	CMY-4	−	+	+	+	−	+	+
1025	Dog	Beef (4), liver (4)	EU	B	10	IV	−	IS*Ecp1*-CTX-M-15, CTX-M-3	CMY-4	−	+	+	+	−	+	+
1026	Dog	Poultry (4)	FRA	B	11	X	−	IS*Ecp1*-CTX-M-15	CMY-4	−	+	+	-	−	+	+
1027	Cat	Chicken (4)	EU	C	12	VIII	−	IS*Ecp1*-CTX-M-15	−	−	+	+	+	−	+	+
1028	Cat	Poultry (4)	EU	C	12	VIII	−	IS*Ecp1*-CTX-M-15	−	−	+	+	+	−	+	+
1029	Cat	Chicken (4), turkey (4)	LIE	C	13	V	−	−	−	−	+	+	−	−	+	+
1030	Cat	Beef (4)	LIE	C	14	V	−	−	−	−	+	+	−	−	+	+
1031	Cat	Poultry (4)	LIE	C	14	V	OXA-48-like[c]	CTX-M-15	CMY-4	−	+	−	−	−	+	+
1032	Cat	Poultry (4)	EU	C	15	NA	−	CTX-M-15	−	−	+	+	+	−	+	+
1033	Dog	Beef (4)	NED	C	16	XI	−	−	−	−	+	−	−	−	+	+
1034	Dog	Chicken (14), rice (4)	GER/NED	C	17	I, II	−	−	−	−	+	−	+	−	+	+
1035	Dog	Turkey (14), rice (4)	GER/NED	C	17	I, II	OXA-48	−	−	−	+	+	−	−	+	+

[a] GER, Germany; NED, The Netherlands; FRA, France; LIE, Liechtenstein; DEN, Denmark; EU, European Union (the specific country was not declared).

[b] Brands and manufacturers are coded with 1 through 17 and I through VIII, respectively. These data are given as an indication of brands produced at the same factory (i.e., manufacturer VIII produces for brands 8 and 12) or brands receiving products from more than one manufacturer (i.e., brand 2 has manufacturers I and II). NA, not available due to unreadable labeling.

[c] OXA-48-like sequence contains the following amino acid changes compared to OXA-48 (Trp25Leu, Gln41Leu, Thr99Met, Glu168Gln, and Ser171Ala) or OXA-181 (Trp25Leu, Gln41Leu, Thr99Met, Ala104Thr, and Asp110Asn).

[d] The copresence of CTX-M-3 and CTX-M-15 is suggested by a double pick in the DNA sequence of the CTX-M-1 group amplicon, corresponding to amino acid position 242, discriminating between the CTX-M-3 and CTX-M-15 variants (Asp242 in CTX-M-3 and Gly242 in CTX-M-15 [GenBank accession no. Y10278 and AY044436, respectively]). By PCR analysis, most of the $bla_{\text{CTX-M-15}}$ genes were associated with IS*Ecp1*.

[e] By PCR analysis, no $bla_{\text{CMY-4}}$ genes were associated with an upstream IS*Ecp1* element.

[f] +, PCR-positive amplicon; −, PCR-negative amplicon. Amplicons were not sequenced.

homology) (19). Conversely, it has always been identified on plasmids and is usually found in *Enterobacteriaceae* isolates of human origin (3) and in retailed chicken meat (20, 21).

Three food samples were contaminated with bla_{OXA-48} (Table 1). In particular, DNA sequences of the amplicons revealed that they were 100% identical to the plasmid-mediated bla_{OXA-48} genes usually identified on IncL/M plasmids circulating in *Enterobacteriaceae* (13). These sequences showed three nucleotides of difference with the intrinsic $bla_{OXA-48-like}$ genes identified in *Shewanella* species progenitors. Therefore, the genes found in the food samples were likely acquired resistance genes. Conversely, in a fourth sample, a novel $bla_{OXA-48-like}$ variant was identified (see Table 1 footnotes), and this might have derived from an unknown progenitor contaminating the food. Unfortunately, because of the fragmentation of the bacterial DNA, it was not possible to determine the genetic environments (e.g., Tn*1999*-like) of the four $bla_{OXA-48-like}$ genes (13). In particular, no amplification was detected when a primer lending into the $bla_{OXA-48-like}$ gene (OXA-48RVout [5′-TCATACGTGCCTCGCCAATT-3′]) was combined with a primer specific for the genetic vicinity of its 5′ end (IS1999RVout [5′-GGATATTGGCTTCGCGCATC-3′]).

Investigation of the plasmid types showed that most of the samples were contaminated with IncL/M and IncF plasmids, while IncA/C, IncN, and IncI1 plasmids were not present. Remarkably, all the food samples were positive for one or more of the targets of the PCR-typing scheme proposed to detect the IncL/M plasmid pOXA48 (*repA*, *traU*, and *parA*; Table 1) (13, 16). All but two samples were positive for the repFII replicon, suggesting a high prevalence of IncF plasmids, which are widely diffused in *Enterobacteriaceae* and very often associated with the $bla_{CTX-M-15}$ gene (22).

Overall, our data indicate that a relevant contamination of *bla* genes was detected in the pet food, suggesting a reservoir of antibiotic resistance bacteria in the production chain preceding the final packaging. Hence, the source(s) from which the pet food acquired the resistance genes remains to be elucidated. Potential derivations may be the original food components themselves or other ingredients that were added to the mixture, as well as the various steps in the food production process. When looking at the designated ingredients, no clear correlations were detected at the level of the different *bla* genes to the respective food components. The comparison of the detected resistance genes to the respective countries of production and to the factories that produced the different brands gave no clear correlations. This is partially due to the fact that, for almost half of the packages, it was not stated from which country within the European Union the respective products were manufactured (Table 1).

It is particularly relevant that the resistance genes detected in this study (e.g., bla_{OXA-48}, $bla_{CTX-M-15}$, $bla_{VEB-4-like}$, and bla_{CMY-4}) are those typically found in human rather than in animal settings, while it would have been expected to find other gene variants such as $bla_{CTX-M-1}$ and bla_{CMY-2} (6). This observation is also supported by the fact that no plasmids demonstrated to be prevalent in food-producing animals and in food of animal origin (e.g., the IncN and IncI1 plasmids associated with $bla_{CTX-M-1}$ or the IncA/C and IncI1 plasmids associated with bla_{CMY-2}) were found in the food (6, 10, 12, 23, 24). However, we emphasize that the detection of bla_{OXA-48} is worrisome due to its epidemiological and clinical impact (25). The bla_{OXA-48} gene is usually detected in humans (3, 26), but bla_{OXA-48}-possessing *Enterobacteriaceae* isolates were found recently in pets (27).

In conclusion, our data point toward a likely environmental or human-made contamination source(s) that may have taken place during the various steps of the production process of the pet food. Since bacteria were killed during the preservation process (heat treatment step), and contaminating bacterial DNA was highly fragmented, it is unlikely that these resistance genes were transmitted among the bacterial flora in animals fed with this food. However, it is important to trace the source of the drug-resistant bacteria and to prevent the contamination of pet food. These results should raise awareness of the importance of identifying the contamination source(s) because it might be an original niche of clinically important multidrug-resistant bacteria and associated mobile genes.

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