

# Characterization of Extended-Spectrum $\beta$ -Lactamases Produced by *Escherichia coli* Isolated from Hospitalized and Nonhospitalized Patients: Emergence of CTX-M-15-Producing Strains Causing Urinary Tract Infections

Annemieke Smet,<sup>1,2</sup> An Martel,<sup>1</sup> Davy Persoons,<sup>3,4</sup> Jeroen Dewulf,<sup>3</sup> Marc Heyndrickx,<sup>4</sup> Geert Claeys,<sup>5</sup> Marc Lontie,<sup>6</sup> Britt Van Meensel,<sup>6</sup> Lieve Herman,<sup>4</sup> Freddy Haesebrouck,<sup>1,\*</sup> and Patrick Butaye<sup>1,2,\*</sup>

Extended-spectrum  $\beta$ -lactamase (ESBL)-producing *Escherichia coli* isolates were obtained from hospitalized and nonhospitalized patients in Belgium between August 2006 and November 2007. The antimicrobial susceptibility of these isolates was determined and their ESBL genes were characterized. Clonal relationships between the CTX-M-producing *E. coli* isolates causing urinary tract infections were also studied. A total of 90 hospital- and 45 community-acquired cephalosporin-resistant *E. coli* isolates were obtained. Tetracycline, enrofloxacin, gentamicin, and trimethoprim-sulfamethoxazole resistance rates were significantly different between the community-onset and hospital-acquired isolates. A high diversity of different ESBLs was observed among the hospital-acquired *E. coli* isolates, whereas CTX-M-15 was dominating among the community-acquired *E. coli* isolates ( $n = 28$ ). Thirteen different pulsed-field gel electrophoresis profiles were observed in the community-acquired CTX-M-15-producing *E. coli*, indicating that multiple clones have acquired the *bla*<sub>CTX-M-15</sub> gene. All community-acquired CTX-M-15-producing *E. coli* isolates of phylogroups B2 and D were assigned to the sequence type ST131. The hospital-acquired CTX-M-15-producing *E. coli* isolates of phylogroups B2, B1, A, and D corresponded to ST131, ST617, ST48, and ST405, respectively. In conclusion, CTX-M-type ESBLs have emerged as the predominant class of ESBLs produced by *E. coli* isolates in the hospital and community in Belgium. Of particular concern is the predominant presence of the CTX-M-15 enzyme in ST131 community-acquired *E. coli*.

## Introduction

**B**ETALACTAMS ARE EXTENSIVELY USED in human medicine.<sup>13</sup> Acquired resistance to these antibiotics in gram-negative bacteria is mainly mediated by bacterial  $\beta$ -lactamases and the emergence of extended-spectrum  $\beta$ -lactamases (ESBLs) is of great clinical importance. ESBLs have the ability to inactivate most  $\beta$ -lactam antibiotics, including oxyimino- $\beta$ -lactams such as ceftazidime, ceftiofur, and aztreonam. They do not hydrolyze cephamycins and carbapenems and they are inhibited by clavulanic acid.<sup>4</sup> ESBL-producing bacteria, especially bacteria producing CTX-M enzymes, are worldwide

detected in various medical institutions.<sup>13,21</sup> Originally, ESBLs were mainly demonstrated in bacteria isolated from patients hospitalized in intensive care units. Epidemics, caused by these bacteria, starting in the intensive care units and spreading to other parts of the hospital have been well documented.<sup>9</sup> Later on, CTX-M-producing *Escherichia coli* from humans with urinary tract infections (UTIs) in the community became more frequently described. Most of these isolates are not only resistant to ceftriaxone, but also to other commonly used first-line agents for UTIs, such as trimethoprim-sulfamethoxazole, ciprofloxacin, gentamicin, and nitrofurantoin.<sup>5,13,21</sup>

<sup>1</sup>Department of Pathology, Bacteriology, and Avian Diseases, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium.

<sup>2</sup>Department of Bacteriology and Immunology, CODA-CERVA-VAR, Brussels, Belgium.

<sup>3</sup>Veterinary Epidemiology Unit, Department of Reproduction, Obstetrics, and Herd Health, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium.

<sup>4</sup>Institute for Agricultural and Fisheries Research, Technology, and Food Science, Melle, Belgium.

<sup>5</sup>Department of Clinical Microbiology, Faculty of Medicine, Ghent University, Ghent, Belgium.

<sup>6</sup>Medisch Centrum voor Huisartsen ("medical center serving only general practitioners"), Leuven, Belgium.

\*These authors share senior authorship.

Because of the increasing importance of multiresistant ESBL-producing *E. coli*, clinicians should be aware of the possibility of treatment failures of serious infections caused by these bacteria. Therefore, monitoring the prevalence of ESBL-producing isolates and their antimicrobial susceptibility profile at local, regional, or global level is required to develop optimal ways to adapt clinical practices and to determine the most effective agents and strategies for the treatment of infections caused by these bacteria.<sup>13</sup>

The objectives of this study were to characterize the ESBLs produced by nosocomial- and community-acquired *E. coli* and to compare their antimicrobial susceptibility pattern. The clonal relationships between CTX-M-producing *E. coli* isolates causing UTIs were also studied.

## Materials and Methods

### Sampling

Between August 2006 and November 2007, 2266 *E. coli* strains were consecutively isolated from samples of hospitalized and nonhospitalized patients in Belgium. *E. coli* from hospitalized patients were isolated on tryptone soy agar plates supplemented with ceftazidime (2 mg/ml). The *E. coli* from the community-onset UTI were isolated using the standard procedure for urine cultures. Clinical data collected with each referred isolate included whether the isolate was considered to be hospital or community acquired. Hospital-acquired isolates, collected at the Faculty of Medicine, Ghent University, were defined as isolates from patients who had been admitted >48 hr earlier. Community-acquired isolates were defined as isolates from specimens referred from a medical center serving only general practitioners in Leuven.

### Antimicrobial susceptibility testing and analysis of $\beta$ -lactamases

The antimicrobial susceptibility of the *E. coli* isolates was determined by the Kirby Bauer disk diffusion test using 21

antibiotic disks (Neo-sensitabs; Rosco Diagnostica, Taastrup, Denmark) as described previously.<sup>18</sup> Of these 21 tested antimicrobial agents, seven were  $\beta$ -lactams. Clinical Laboratory Standards Institute (CLSI) guidelines (document M100-S17) were followed for inoculum standardization, medium and incubation conditions, and internal quality control organisms (*E. coli* ATCC 25922). The presence of an ESBL was established on the basis of the CLSI guidelines.<sup>7</sup> Isoelectric focusing was performed on crude enzyme extracts to determine the  $\beta$ -lactamases present in each isolate. The ESBL gene was characterized by polymerase chain reaction and sequencing as described previously.<sup>18</sup>

### Genetic background of CTX-M-producing strains

Clonal relatedness of *E. coli* carrying the predominant CTX-M enzyme was established by pulsed-field gel electrophoresis (PFGE).<sup>1</sup> The assignment of *E. coli* phylogenetic groups was carried out by a multiplex polymerase chain reaction assay as described previously.<sup>6</sup> Multilocus sequence typing (MLST) was performed using seven conserved housekeeping genes (*adh*, *fumC*, *gyrB*, *icd*, *mdh*, *purA*, and *recA*) (www.mlst.ucc.ie).<sup>20</sup> All *fumC* sequences from *E. coli* isolates belonging to phylogroup D were analyzed for a C288T single-nucleotide polymorphism.<sup>8</sup>

### Statistical analysis

The analysis of variance test was used for analysis of mean differences in antimicrobial resistance between community-onset and nosocomial isolates and between different CTX-M-producing strains. All analyses were performed using SPSS, version 16 (SPSS, Chicago, IL).

## Results

Of the 2266 isolates that were screened, a total of 135 (6%) cephalosporin-resistant *E. coli* isolates were identified. All isolates were unduplicated consecutive ESBL-producing

TABLE 1. NUMBER AND PERCENTAGE OF RESISTANCES TO  $\beta$ -LACTAM AND NON- $\beta$ -LACTAM ANTIMICROBIALS OF CEPHALOSPORIN-RESISTANT *ESCHERICHIA COLI* ISOLATED FROM HOSPITALIZED AND NONHOSPITALIZED PATIENTS

Antimicrobial agents <sup>a</sup>	Number (%) of resistant strains			
	<i>E. coli</i> (n = 45) Hospital, nonurine samples	<i>E. coli</i> (n = 45) Hospital, urine samples	<i>E. coli</i> (n = 45) <sup>a</sup> Community, urine samples	CTX-M-15-positive strains (n = 43)
Amoxicillin-clavulanic acid	0 (0)	0 (0)	12 (26.7)	9 (21)
Ceftazidime	42 (93)	24 (53.3)	15 (33.3)	22 (51.2)
Cefepime	44 (97.6)	29 (64.4)	21 (46.7)	26 (60.5)
Ceftriaxone	45 (100)	41 (91)	39 (87)	39 (90.7)
Azteonam	31 (70)	29 (64)	21 (46.7)	27 (62.8)
Kanamycin	17 (38.1)	12 (26.7)	11 (24.4)	6 (14)
Gentamicin	10 (21.4)	2 (4.4)	13 (28.9)	13 (30.2)
Streptomycin	19 (42.9)	11 (24.4)	2 (4.4)	8 (18.6)
Neomycin	10 (23.8)	5 (11.1)	8 (17.8)	7 (16.27)
Tetracycline	33 (73.8)	35 (77.8)	25 (55.6)	26 (60.5)
Nalidixic acid	22 (48.8)	30 (66.7)	42 (93.3)	42 (97.2)
Enrofloxacin	20 (45)	25 (55.6)	37 (82)	36 (83.7)
Trimethoprim	32 (71.4)	36 (80)	20 (44.4)	18 (41.9)
Sulphonamides	34 (76.2)	41 (91)	25 (55.6)	22 (51.2)

<sup>a</sup>None of the 135 isolates showed resistance to imipenem and only 1 (2%) community-acquired *E. coli* isolate showed resistance to ceftoxitin.

TABLE 2. SIGNIFICANT DIFFERENCES ( $p < 0.05$ ) IN THE PREVALENCE OF ACQUIRED ANTIMICROBIAL RESISTANCES BETWEEN COMMUNITY- AND NOSOCOMIAL-ACQUIRED EXTENDED-SPECTRUM  $\beta$ -LACTAMASE-PRODUCING *ESCHERICHIA COLI*

Acquired antimicrobial resistance	No. (%) of <i>E. coli</i> isolates		
	Community acquired (n = 45)	Nosocomial acquired (n = 90)	p-Value
Tetracycline	25 (55.6)	68 (75.8)	0.018
Enrofloxacin	37 (82.2)	45 (50)	<0.0001
Gentamicin	13 (28.9)	8 (9)	0.002
Trimethoprim-sulfamethoxazole	28 (62)	79 (88)	0.001

*E. coli* collected from 90 hospitalized (hospital-acquired) and 45 nonhospitalized (community-acquired) patients. Of these hospital-acquired *E. coli*, 45 were from urine samples and 45 from nonurine samples. The latter originated from wounds ( $n = 17$ , 37.8%), sputum ( $n = 17$ , 37.8%), and blood cultures ( $n = 11$ , 24.4%). The 45 community-acquired isolates originated from urine samples from humans with UTIs.

A summary of results of disk diffusion tests of hospital-acquired and community-acquired *E. coli* is shown in Table 1. Resistance to enrofloxacin was present in 82 (60.7%), nalidixic acid resistance in 94 (69.6%), tetracycline resistance in 93 (69%), and trimethoprim-sulfamethoxazole resistance in 112 (83%) of the 135 isolates. Gentamicin, streptomycin, neomycin, and kanamycin resistances were present in 25 (18.5%), 32 (24%), 23 (17%), and 40 (29.6%) of the 135 isolates, respectively. Several differences in antimicrobial resistance profiles were seen between hospital-acquired and community-acquired *E. coli* as indicated in Table 2.

Of the 135 *E. coli* isolates, 123 isolates were multidrug resistant showing resistance to two or more non- $\beta$ -lactam

antimicrobial agents. Four percent of the isolates showed only resistance to  $\beta$ -lactams, 5% of the isolates were resistant to one additional antimicrobial agent, and the other 91% were resistant to at least two or more antimicrobials (data not shown).

The distribution of different ESBLs among nosocomial- (urine and nonurine samples) or community-acquired *E. coli* isolates from humans in Belgium is shown in detail in Table 3. Seventy two (53%) of 135 were positive for CTX-M-1-like  $\beta$ -lactamases (CTX-M-1, CTX-M-15), 10 (7.5%) were positive for CTX-M-2-like  $\beta$ -lactamases (CTX-M-2), 20 (15%) were positive for CTX-M-9-like  $\beta$ -lactamases (CTX-M-9 and CTX-M-14), and 32 (24%) were negative for CTX-M enzymes. These isolates carried  $\beta$ -lactamases from the TEM family or SHV family. Table 3 shows a high diversity of different ESBLs among the hospital-acquired *E. coli* isolates. However, among the community-acquired *E. coli* isolates, the CTX-M-15 enzyme belonging to the CTX-M-1-like  $\beta$ -lactamases was dominating ( $n = 28$ , 62%). It has to be noted that more than half of the CTX-M-15 producing *E. coli* (hospital- and community-acquired) isolates were resistant to tetracyclines, nalidixic acid, and enrofloxacin (Table 1).

PFGE was used to assess the diversity of the community-acquired *E. coli* isolates producing CTX-M-15, to determine if the community-acquired UTIs were caused by one single clone producing this enzyme. Similarity among profiles was determined by cluster analysis in a dendrogram using the cutoff of at least 80%. Thirteen different clusters were observed (Fig. 1). Some strains were clonally related because they differed only by one or few bands (Fig. 1).

To establish the clonal relationships between the nosocomial- ( $n = 14$ ) and community-acquired ( $n = 28$ ) CTX-M-15-producing *E. coli* isolates causing UTIs, phylogenetic groups were determined and MLST was performed. The community-acquired CTX-M-15-producing *E. coli* isolates belonged to phylogroups B2 (91%) and D (9%), whereas the nosocomial-acquired CTX-M-15-producing *E. coli* isolates belonged to

TABLE 3. DISTRIBUTION OF EXTENDED-SPECTRUM  $\beta$ -LACTAMASES AMONG 135 CEPHALOSPORIN-RESISTANT *ESCHERICHIA COLI* ISOLATED FROM HOSPITALIZED AND NONHOSPITALIZED PATIENTS

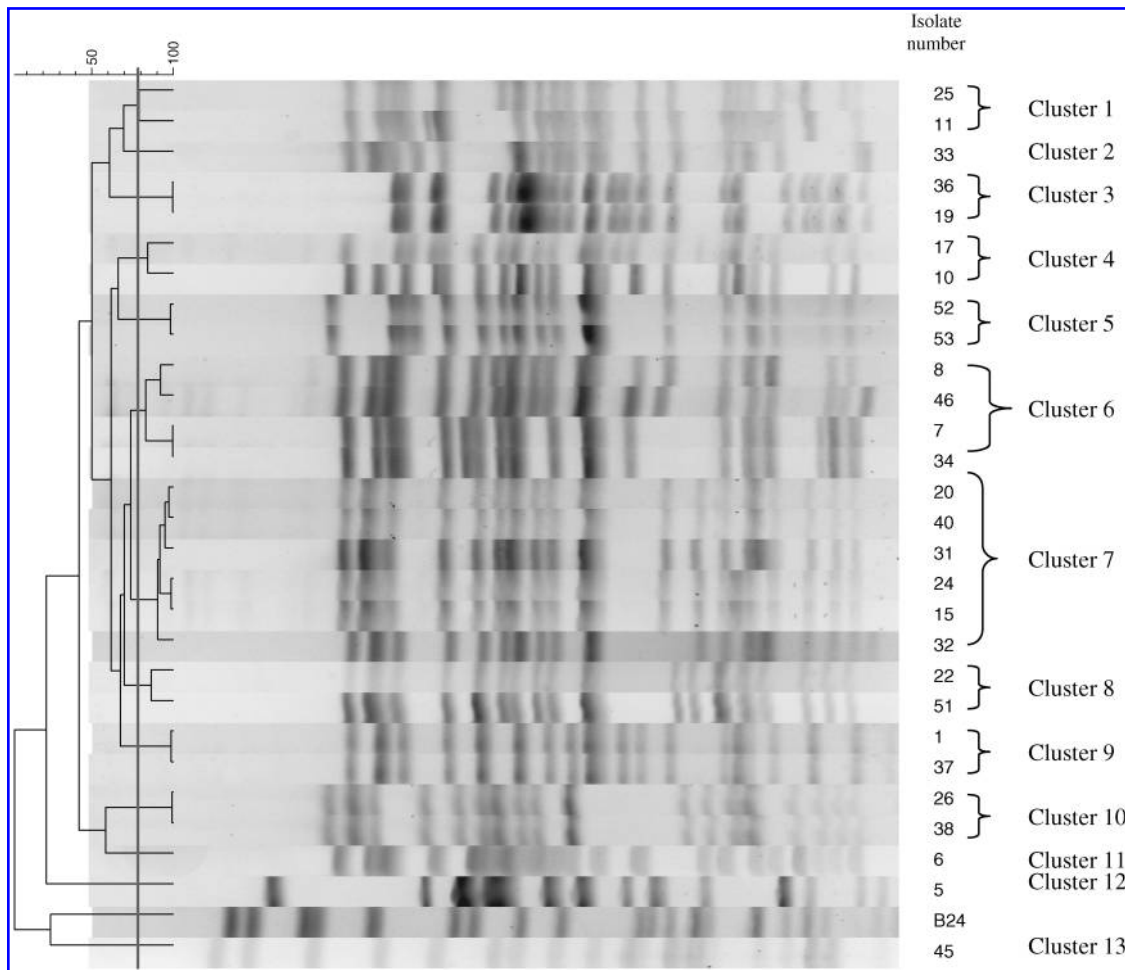
Enzyme	$\beta$ -Lactamase	Number (%) of isolates			Total (%)
		<i>E. coli</i> (n = 45) <sup>a</sup> Hospital, nonurine samples	<i>E. coli</i> (n = 45) <sup>b</sup> Hospital, urine samples	<i>E. coli</i> (n = 45) <sup>c</sup> Community, urine samples	
Narrow spectrum $\beta$ -lactamase	TEM-1	21 (46.7)	9 (20)	23 (51.1)	53 (39.3)
	OXA-1 <sup>d</sup>	0 (0)	5 (11.1)	15 (33.3)	20 (14.8)
ESBL	TEM-16	0 (0)	1 (2.2)	0 (0)	1 (1)
	TEM-24	6 (13)	4 (8.9)	0 (0)	10 (7.5)
	TEM-52	3 (6.7)	1 (2.2)	0 (0)	4 (3)
	SHV-12	13 (28.9)	1 (2.2)	3 (6.7)	17 (12.6)
	CTX-M-1	9 (20)	12 (26.7)	8 (17.8)	29 (21.5)
	CTX-M-2	6 (13.3)	4 (8.9)	0 (0)	10 (7.5)
	CTX-M-9	2 (4.4)	1 (2.2)	0 (0)	3 (2.3)
	CTX-M-14	4 (8.9)	7 (15)	6 (13)	17 (12.6)
CTX-M-15	1 (2.2)	14 (31.1)	28 (62.2)	43 (32)	

<sup>a</sup>Two *E. coli* isolates had both SHV-12 and CTX-M-15 and one had both SHV-12 and TEM-24.

<sup>b</sup>One *E. coli* isolate had both SHV-12 and CTX-M-1, and one had both SHV-12 and CTX-M-15.

<sup>c</sup>One *E. coli* isolate had both SHV-12 and CTX-M-14.

<sup>d</sup>*E. coli* isolates that had OXA-1 enzyme produced also CTX-M-15 enzyme. ESBL, extended-spectrum  $\beta$ -lactamase.



**FIG. 1.** Dendrogram generated by Bionumerics software (Applied Maths, Kortrijk, Belgium), showing the results of cluster analysis on the basis of pulsed-field gel electrophoresis fingerprinting (with *Xba*I). Similarity analysis was performed using Pearson coefficient (optimal 1%, tolerance 1%), and clustering was done by the unweighted-pair group method using average linkages. The gray line shows the delineation line of 80%. The different pulsed-field gel electrophoresis profiles and isolate numbers, carrying a CTX-M-15 enzyme, are indicated. All isolates were community acquired with the exception of B24, which was nosocomially acquired.

phylogroups B2 (22%), B1 (11%), A (44%), and D (23%). All community-acquired *E. coli* isolates of phylogroups B2 and D were assigned to the sequence type (ST) ST131. All nosocomial-acquired *E. coli* isolates of phylogroups B2, B1, A, and D corresponded to ST131, ST617, ST48, and ST405, respectively. The C288T single-nucleotide polymorphism in the *fumC* gene was absent in the strains belonging to phylogroup D.

Statistical analysis of the 135 isolates revealed that isolates containing a CTX-M-2 gene were less frequently resistant to tetracycline than isolates harboring a CTX-M-9-like gene (CTX-M-9, CTX-M-14) (12 [60%] of 20 vs. 10 [100%] of 10,  $p=0.02$ ). Enrofloxacin resistance was significantly higher in CTX-M-1-like (CTX-M-1, CTX-M-15) than in CTX-M-2-containing strains (48 [65%] of 73 vs. 3 [30%] of 10,  $p=0.04$ ).

## Discussion

More than half of the isolates included in this study were resistant to enrofloxacin, tetracycline, and trimethoprim-sulfamethoxazole. Acquired resistance to aminoglycosides

was also often present. These results confirm that ESBL-producing *E. coli* are often multiresistant, which may jeopardize clinical efficacy of antimicrobial treatment of infections caused by these microorganisms.

Our study included clinical *E. coli* isolates from both hospital and community sites. The percentage of acquired resistance to tetracycline and trimethoprim-sulfamethoxazole was significantly higher in hospital-acquired isolates, whereas community-acquired isolates were more often resistant to enrofloxacin and gentamicin. The reason for this finding is not clear. Epidemiological studies taking into account antimicrobial usage in the patient populations included in our study may help to explain these differences.

Several countries have reported the presence of different CTX-M enzymes among hospital-acquired *E. coli* isolates, including CTX-M-1, CTX-M-2, CTX-M-9, CTX-M-14, and CTX-M-15.<sup>2,5,8,11</sup> Similar findings were found among our hospital-acquired isolates.

In most studies worldwide, CTX-M-15 was the most common enzyme among clinical community-acquired *E. coli* isolates causing UTIs.<sup>3,9,10,12,13</sup> Also, in our study, CTX-M-15

was clearly the most prevalent enzyme among the community-acquired *E. coli* causing UTIs.

Distinct PFGE profiles were detected among the community-acquired CTX-M-15-positive strains, indicating that the predominant presence of enzyme in community-acquired *E. coli* causing UTIs is not due to the spread of a single *E. coli* clone. CTX-M-encoding genes have been shown to be located on a plasmid,<sup>19,22</sup> which may have been transmitted to different *E. coli* strains.

MLST revealed that all these isolates belonged to ST131. Clonal outbreaks of *E. coli* corresponding to the ST131 have already been reported in several countries.<sup>11,12,14–17</sup>

Several phylogroups and STs were found in our collection of nosocomial-acquired *E. coli* isolates causing UTIs. Phylogroups B2 and D are known to be associated with the hospital setting. The ST types ST131 and ST405 belonging to B2 and D, respectively, have already been described among CTX-M-15-producing *E. coli* isolated from hospitalized patients.<sup>2,8,14</sup> Nosocomial-acquired CTX-M-15-producing *E. coli* isolates corresponding to ST48 and ST617 have, to our knowledge, not yet been described.

An evolutionary convergent relationship among ST131 and the plasmids carrying the *bla*<sub>CTX-M-15</sub> gene could explain successful dissemination of CTX-M-15-carrying plasmids within this *E. coli* lineage as mentioned previously.<sup>8</sup> Molecular characterization of CTX-M-15-carrying plasmids is necessary to obtain better insights into the molecular epidemiology of the CTX-M-15 gene in *E. coli*.

More than half of the nosocomial-acquired isolates included in our study produced a CTX-M enzyme. This confirms that CTX-M enzymes, which can be seen as community ESBL producers, have also taken their entry into hospital-acquired<sup>11</sup> *E. coli*.

In conclusion, this is the first detailed documentation of the diversity of ESBLs among *E. coli* isolates obtained from hospitalized and nonhospitalized patients in Belgium. Of particular concern is the predominant presence of the CTX-M-15 enzyme in community-acquired *E. coli* corresponding to ST131.

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### Disclosure Statement

No competing financial interest exists.

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Address correspondence to:

Annemieke Smet

Department of Pathology, Bacteriology, and Avian Diseases

Faculty of Veterinary Medicine

Ghent University

Salisburylaan 133

Merelbeke 9820

Belgium

E-mail: annemieke.smet@ugent.be

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