Broad-spectrum β-lactamases among *Enterobacteriaceae* of animal origin: molecular aspects, mobility and impact on public health

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Abstract

Broad-spectrum β-lactamase genes (coding for extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases) have been frequently demonstrated in the microbiota of food-producing animals. This may pose a human health hazard since these genes may be present in zoonotic bacteria, which would cause a direct problem. They can also be present in commensals, which may act as a reservoir of resistance genes for pathogens causing disease both in humans and animals.

Broad-spectrum β-lactamase genes are frequently located on mobile genetic elements, such as plasmids, transposons and integrons, which often also carry additional resistance genes. This could limit treatment options for infections caused by broad-spectrum β-lactam-resistant microorganisms. This review addresses the growing burden of broad-spectrum β-lactam resistance among *Enterobacteriaceae* isolated from food, companion and wild animals worldwide. To explore the human health hazard, the diversity of broad-spectrum β-lactamases among *Enterobacteriaceae* derived from animals is compared with respect to their presence in human bacteria. Furthermore, the possibilities of the exchange of genes encoding broad-spectrum β-lactamases – including the exchange of the transposons and plasmids that serve as vehicles for these genes – between different ecosystems (human and animal) are discussed.

Introduction

Resistance to β-lactams in *Enterobacteriaceae* is mainly due to the production of β-lactamases which may be encoded either chromosomally or on plasmids (Bradford, 2005). Resistance to extended-spectrum β-lactams has been associated with the production of broad-spectrum β-lactamases such as extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases and metallo-β-lactamases (MBLs) (Batchelor *et al.*, 2005a). ESBLs confer resistance to most β-lactam antibiotics, but are not active against cephamycins and carbapenems and are inactivated by β-lactamase inhibitors such as clavulanic acid. This is in contrast to AmpC β-lactamases, which are not inhibited by clavulanic acid and usually confer resistance to all β-lactams, with the exception of dipolar ionic methoxy-imino-cephalosporins, such as cefepime and the carbapenems (Bradford, 2005). MBLs can hydrolize all clinical β-lactam substrates, with the exception of aztreonam.

Broad-spectrum β-lactamase-producing *Enterobacteriaceae* have increasingly been detected in humans since the early 1990s and in animals since 2000 (Arlet *et al.*, 2006; Bertrand *et al.*, 2006; Caratolli, 2008; Cloeckaert *et al.*, 2007; Jacoby, 2009; Li *et al.*, 2007; Paterson & Bonomo, 2005; Pitout & Laupland, 2008; Smet *et al.*, 2008; Smet *et al.*, 2009; Walsh, 2008). Resistance in bacteria of animals and its impact on human health have drawn much attention worldwide (Aarestrup, 2006; Phillips *et al.*, 2004). The first pathway of resistance transfer is the direct transfer of a pathogen from animals to humans. This is the case for zoonotic agents such as *Salmonella*, where resistance against β-lactams, including extended-spectrum cephalosporins, has been demonstrated (Bertrand *et al.*, 2006; Cloeckaert *et al.*, 2007). Animals may also harbour resistance genes in their residing commensal flora. Commensal *E. coli* isolates have been implicated in the transmission of genetic resistance traits (Kruse & Sorum, 1994) because their resistance genes may jump from one bacterium to another, mainly by means of mobile genetic elements such as transposons and plasmids.

The present review analyses the growing burden of β-lactam resistance among *Enterobacteriaceae* of animals, focussing on the use of β-lactams in veterinary medicine and food-animal production, and on the β-lactamase genes and their ability to be transferred. The diversity of broad-spectrum β-lactamases among *Enterobacteriaceae* from food-producing, companion and wild animals, as well as from humans, is compared and the possible movement across bacterial populations from different hosts is discussed.

Use of β-lactam antimicrobials in veterinary medicine and food animal production

One of the most important group of antimicrobial agents in veterinary medicine and food animal production are the β-lactams. These antimicrobial agents can be divided into different groups, three of which are used in veterinary medicine: the penicillins, the first- to fourth-generation cephalosporins, and the β-lactamase inhibitors. An overview of the antimicrobial activity of the different β-lactam groups and their use in veterinary and human medicine is given in Table 1. The recommended use of β-lactams for the treatment of disease in swine, cattle, horses, poultry, cats and dogs is presented in Table 2.

The different surveillance programs around the world have made it possible to obtain a good knowledge of β-lactam usage in food and non-food animals (Batchelor *et al.*, 2005; Guardibassi *et al.*, 2004; Hammerun & Heuer, 2009; Li *et al.*, 2005; Lloyd, 2007; McEwan & Fedorka-Cray, 2006; Schwarz *et al.*, 2001; Schwarz & Chaslus-Dancla, 2001; CIPARS, 2006; DANMAP, 2006; NARMS, 2004). By way of summary, ampicillin and amoxicillin are regarded as the drugs of choice in avian medicine in many continents. These drugs are used in most European countries, with the exception of Finland, Denmark and Sweden. In Spain, amoxicillin-clavulanic acid is also allowed for use (Schwarz & Chaslus-Dancla, 2001). Third-generation cephalosporins are rarely used in poultry and only under very limited conditions

for treatment of valuable poultry stocks (Guardibassi *et al.*, 2008). However, ceftiofur, licensed for veterinary use in the USA since 1988, has been given to one-day-old chickens to prevent early mortality in the USA (Batchelor *et al.*, 2005). In Europe, cephalosporins are not allowed for use in poultry (Schwarz & Chaslus-Dancla, 2001; Smet *et al*., 2008), although extra-label use occurs.

In cattle, pigs, horses, cats and dogs, aminopenicillins are often used. Third- and fourth-generation cephalosporins have been approved as second choice treatment of different disease conditions such as metritis, foot rot and mastitis in cattle, respiratory disease in ruminants, horses and swine, and skin diseases in cats and dogs (Batchelor *et al.*, 2005; Bradford *et al.*, 1999; Guardibassi *et al.*, 2008; Mason & Kietzmann, 1999; Watson & Rosin, 2000).

Besides their use in clinical therapy, β-lactams, especially penicillins, have been used as feed additives to improve growth. They were fazed out in Europe after the appearance of the "Swann Report" in 1975, in which concerns were raised that the use of antimicrobials for growth promotion could lead to increasing resistance in bacteria of human and animal origin (anonymous, 1968). However, in the USA penicillins are still used at subtherapeutic levels for growth promotion (Aarestrup, 2006).

β-lactam resistance mechanisms

All β-lactam agents have a four-membered β-lactam ring in their structure. A beta-lactam ring is a cyclic amide with a heteroatomic ring structure consisting of three carbon atoms and one nitrogen atom. These antimicrobial agents prevent the bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis through acting on penicillin binding proteins (PBPS). The number of PBPS varies between bacterial species and these PBPS are found as both membrane-bound and cytoplasmatic proteins. The peptidoglycan layer maintains the cell shape and protects the bacterium against osmotic forces. In Gram-positive

bacteria, peptidoglycan forms a thick layer on the cytoplasmic membrane, whereas in Gram-negative bacteria and mycobacteria, peptidoglycan is a thin layer sandwiched between the outer membrane and the cytoplasmic membrane (Giguère *et al.*, 2006; Greenwood, 2000; Poole, 2004).

Bacterial resistance to β-lactams can be due to at least three mechanisms. The first mechanism consists of mutations in genes encoding PBPS, the acquisition of alternative PPBS or the creation of mosaic PBPS. All these altered PBPS have a reduced affinity for β-lactams and as such can keep their function in maintaining the cell wall. The second mechanism consists of a change in the permeability of the cell wall. This may be due to alterations in the expression of porins or active efflux. The third mechanism, and by far the most common one, is the inactivation of the drug by β-lactamases (Batchelor *et al.*, 2005; Poole, 2004; Massova & Mobashery; 1998; Shah *et al.*, 2004). In this review the focus will be on the resistance mediated by β-lactamases, since this is the predominant mechanism of β-lactam resistance in Gram-negative bacteria, especially in *Enterobacteriaceae.* β-lactamases inactivate β-lactams by hydrolysing their four-membered β-lactam ring. They break a bond in the β-lactam ring to disable the molecule (Shah *et al.*, 2004).

β-lactamases: an overview

Until now, more than 400 β-lactamases have been reported and new β-lactamases continue to emerge worldwide (Bradford, 2005; Gupta, 2007; Jacoby, 1991; Waalsh, 2008; Jacoby, 2009). The main characteristics of the different families of β-lactamases, as presented in the brief overview below, are well documented on the following website: http://www.lahey.org/Studies/.

Extended-spectrum β-lactamases

TEM-type β-lactamases

More than 150 TEM-type β-lactamases have been found, and all of them are derivatives of TEM-1 or TEM-2 by point mutations. TEM-1 was first demonstrated in 1965 in an *Escherichia coli* isolate from a patient in Athens, Greece, named Temoneira (designation TEM) (Datta & Kontomichalou, 1965). In contrast to the majority of TEM β-lactamases, TEM-1, TEM-2 and TEM-13 are not ESBLs and are only able to hydrolyse penicillins. Some TEM derivatives have been found to have a reduced affinity for β-lactamase inhibitors and are called inhibitor resistant TEM (IRT). These enzymes have negligible activity against extended-spectrum cephalosporins and are not considered to be ESBLs (Chaibi et al., 1999). However, mutants of the TEM derivatives (called CMT-1, CMT-2, CMT-3 and CMT-4) have been identified that have the ability to hydrolyse both third-generation cephalosporins and β-lactamase inhibitors (Fiett *et al.*, 2000; Neuwirth *et al.*, 2001).

SHV-type β-lactamases

Another family of β-lactamases are the SHV (sulfydryl variable) enzymes. The progenitor of the SHV enzymes, SHV-1, was first described in *Klebsiella pneumoniae*. SHV-1 confers resistance to broad-spectrum penicillins. In 1983, a *Klebsiella ozaenae* strain was isolated in Germany possessing a SHV-2 enzyme which efficiently hydrolyzed cefotaxime and, to a lesser extent, ceftazidime. To date, more than 50 SHV derivatives are known, all being derivatives of SHV-1 or SHV-2. Like the TEM-type enzymes, the majority of the SHV enzymes are ESBLs (Gupta, 2007; Paterson & Bonomo, 2005).

CTX-M-type β-lactamases

A third family consists of the CTX-M enzymes, which are also ESBLs and were first isolated in Munich. The designation CTX-M reflects the hydrolytic activity of these β-lactamases against cefotaxime. It appears that the CTX-M-type β-lactamases are closely related to β-lactamases of *Kluyvera* spp. CTX-M enzymes have 40% or less identity with TEM and SHV-type ESBLs. So far, more than 70 CTX-M enzymes have been isolated. They are divided into 5 clusters on the basis of the amino acid sequence: CTX-M-1, CTX-M-2, CTX-M-8, CTX-M-9 and CTX-M-25 (Gupta, 2007; Paterson & Bonomo, 2005).

OXA-type β-lactamases

Most OXA-type β-lactamases, so named because of their oxacillin-hydrolizing capabilities, do not hydrolyse extended-spectrum cephalosporins and are not regarded as ESBLs. The exceptions to this rule are OXA-10 and OXA-13 to OXA-19 (Toleman *et al.*, 2003). The evolution of ESBL OXA-type β-lactamases from parent enzymes with narrow spectra has many parallels with the evolution of TEM- and SHV-type ESBLs.

Other examples of ESBLs

PER (Pseudomonas extended-resistant), VEB (Vietnam extended-spectrum β-lactamase), BES (Brazil extended-spectrum), GES (Guiana extended-spectrum), TLA (named after Tlahuicas Indians), SFO (*Serratia fonticola*) and IBC (integron-borne cephalosporinase) are other examples of ESBLs that have been discovered (Gupta, 2007; Jacoby, 2006; Paterson & Bonomo, 2005). These enzymes are not so common among *Enterobacteriaceae* as the ESBLs described above.

AmpC β-lactamases

Another large group of broad-spectrum β-lactamases are the AmpC enzymes, which are typically encoded on the chromosome of many Gram-negative bacteria, including *Citrobacter*, *Serratia* and *Enterobacter* species, where its expression is usually inducible (Jacoby, 2009). AmpC type β-lactamases may be carried on plasmids of bacterial species lacking the chromosomal *ampC* gene, such as *Klebsiella* spp. Plasmid-mediated AmpC enzymes have been found in *E. coli*, although this species can also increase production of its normally weakly expressed chromosomal AmpC enzyme by gene duplication or mutation in the *ampC* promoter or attenuator with consequent enhanced gene expression (Caroff *et al.*, 2000). Plasmid-mediated AmpC enzymes have been named – with inconsistency typical of β-lactamase nomenclature – according to the resistance produced to cephamycins (CMY, 43 varieties), cefoxitin (FOX, 7 varieties), moxalactam (MOX, 3 varieties) or latamoxef (LAT, 4 varieties), according to the type of enzyme (ACC (Ambler class C), 4 varieties or ACT (AmpC type), 3 varieties), or according to the site of discovery, such as the Miriam Hospital in Providence (MIR-1) or the Dhahran Hospital in Saudi Arabia (DHA, 2 varieties). BIL-1 was named after the patient (Bilal) who provided the original sample (Philippon *et al.*, 2002).

Metallo-β-lactamases

The metallo-β-lactamases (MBL) are a molecularly diverse group of broad-spectrum β-lactamases. They are widespread in *Pseudomonas aeruginosa*, *Acinetobacter* species (such as VIM (Verona integron-encoded metallo-β-lactamase) and OXA types) and have been more recently detected in *Enterobacteriaceae* (such as VIM, KPC (*K. pneumoniae* carbapenamases) and GES-types) (Jacoby, 2006; Walsh, 2008). So far, MBLs have not been detected in bacteria of animals, so this group of β-lactamases will not be reviewed further in this paper.

Classification of broad-spectrum β-lactamases: a source of confusion

Because of the diversity of the enzymatic characteristics of the β-lactamases, many attempts have been made to categorize these enzymes by using their biochemical attributes. Several different classification schemes for bacterial β-lactamases have been described. The two most often used of these systems will be discussed in this chapter.

The first classification system, devised by Bush *et al.* (1995), is based on the activity of the ß-lactamases against different ß-lactam antimicrobials (substrate specificity). It contains a wide variety of subgroups. Three major groups of enzymes can be defined: (1) cephalosporinases that are not greatly inhibited by clavulanic acid, (2) penicilinases, cephalosporinases and broad-spectrum β-lactamases that are inhibited by β-lactamase inhibitors, and (3) metallo-β-lactamases (carbapenamases) that hydrolyze penicillins, cephalosporins and carbapenems with the exception of aztreonam (Bush *et al.*, 1995).

Recently, Giske *et al.* (2009) enlarged the ESBL definition with a view to achieving a balance between scientific and clinical needs. Several points of the Bush classification system were reconsidered, as described below.

First, Bush *et al.* (1995) described ESBLs as enzymes that can be differentiated from their parental enzymes, which do not hydrolyse extended-spectrum β-lactams.

Secondly, several β-lactamases (e.g. GES-5) that possess carbapenamase activity are still reported in the literature as ESBL.

Third, the Bush classification system does not make a distinction between AmpC β-lactamases of chromosomal origin and those of plasmid origin. However, plasmid-mediated AmpC enzymes have greater clinical importance from an infection control perspective than do their chromosomal counterparts (i.e. the added risk of transferable resistance genes).

Finally, Bush *et al.* (1995) wrote that the classification scheme does not take into account the actual importance of phenotypic tests for β-lactamases.

So if scientific researchers adopt these points of the Bush classification system, there is little hope for the clinicians being properly informed about appropriate treatment. Thus, by broadening the ESBL definition, the communication with the clinicians and infection control practitioners will be largely enhanced (Giske *et al.*, 2009).

The second – and most widely used – classification scheme for β-lactamases is the Ambler system, which divides β-lactamases into four classes (A, B, C and D) on the basis of their amino acid sequences. At first, Ambler described two classes: class A β-lactamases (TEM, SHV and CTX-M enzymes), which have their active site at a serine residue, and class B enzymes (metallo-β-lactamases), which utilize a bivalent metal ion (zinc ion) to attack the β-lactam ring (Ambler, 1980). Later on, when new insights were acquired, a novel class of serine β-lactamases, class C (AmpC β-lactamases), was defined. These showed little sequence similarity to the class A enzymes. And finally, another new class of serine β-lactamases, known as the OXA β-lactamases (class D), was identified (Ambler, 1980).

A revision of the Ambler classification system by Hall & Barlow (2005) presupposed the existence of differences among the metallo-β-lactamases. They proposed to divide the class B enzymes into three subgroups: B1, B2 and B3. Members of subgroups B1 and B2 share many sequence similarities, but differ largely from the members of subgroup B3 (Hall & Barlow, 2005).

These different classification schemes have been and will continue to be updated according to the growing knowledge of the β-lactamases. It is better, however, not to abandon the existing classification systems, since they are widely used and well known, but rather to adapt them to the growing knowledge.

Mobility of broad-spectrum β-lactamase genes among *Enterobacteriaceae*

β-lactamase (*bla*) genes encoding broad-spectrum β-lactamases have mainly been reported in *Enterobacteriaceae* and are associated with mobile genetic elements (MGEs), such as insertion sequences (ISs), integrons, transposons, plasmids and phage-related elements. It has to be noted that insertion sequences and transposons can hop from the chromosome to a plasmid or between plasmids or back to the chomosome within a bacterial cell, but require a conjugative element (plasmid or conjugative transposon) or phage to be mobilized between bacterial cells. The diversity of these genetic vehicles enhances the spread of broad-spectrum β-lactamases. What follows is an overview of these genetic elements.

Mobile genetic elements described as carriers of ESBL genes

MGEs for bla_{TEM} genes

All bla_{TEM} genes are carried by three of the earliest described bacterial transposons, namely Tn*1*, Tn*2* and Tn*3*. These transposons contain the transposase and resolvase genes, *tnpA* and *tnpR*, as well as a *res* resolution site. They are about 99% identical to each other, with most of the differences confined to a region close to the *res* site (Partidge & Hall, 2005). Most of the structures surrounding the bla_{TEM} genes are Tn*3*-like transposons possessing 38 bp inverted repeats (IRs) (Heffron *et al.*, 1979; Partidge & Hall, 2005). Table 3 shows a summary of all known bla_{TEM} gene-transposon associations. Some examples of bla_{TEM} carrying transposons are given in Fig. 1A and 1B.

MGEs for bla_{SHV} genes

Few studies have investigated the genetic support of bla_{SHV}-like genes. These genes originate from the chromosome of *Klebsiella pneumoniae* and are spread together with other *K. pneumoniae* chromosomal DNA fragments from the chromosome to a plasmid within a

bacterial cell, following IS*26*-dependent mobilization (Fig. 1C). Their presence on a conjugative element makes them able to spread between Gram-negative bacteria (Carattoli *et al.*, 2005; Chiaretto *et al.*, 2008; Gangoué-Piéboji *et al.*, 2005 ; Jouini *et al.*, 2007 ; Miriagou *et al.*, 2005; Poirel *et al.*, 2008; Raskin *et al.*, 2005; Riaño *et al.*, 2006 ; Rodriguez-Baño *et al.*, 2008; Romero *et al.*, 2005; Teshager *et al.*, 2000; Tian *et al.*, 2009; Yu *et al.*, 2006). So far, the bla_{TEM} and bla_{SHV} genes have never been described in integron structures.

MGEs for $bla_{\text{CTX-M}}$ genes

Like the bla_{SHV} genes, $bla_{\text{CTX-M}}$ genes are also mobilized from the chromosome of a naturally resistant bacterium. In this case, *Kluyvera* species are involved (Olson *et al.*, 2005; Rodriguez *et al.*, 2004). Several genetic elements such as the insertion sequences (IS) IS*Ecp1* and IS*CR1* and phage-related elements, which have been found to be involved in the mobility of $bla_{\text{CTX-M}}$ genes, are discussed below (Bae *et al.*, 2007; Canton & Coque, 2006; Oliver *et al.*, 2005; Poirel *et al.*, 2008).

IS*Ecp1*-like elements belong to the IS*1380* family of insertion sequences and have been identified in association with genes belonging to the $bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-2}}$, $bla_{\text{CTX-M-25}}$ and $bla_{\text{CTX-M-9}}$ ESBL gene clusters (Bae *et al.*, 2006a; Bae *et al.*, 2006b; Eeckert *et al.*, 2006; Fernandez *et al.*, 2007; Liu *et al.*, 2007; Navon-Venezia *et al.*, 2008; Sheng *et al.*, 2008). Extensive analysis has shown that IS*Ecp1* is responsible for the mobility of a transposition unit including itself and a $bla_{\text{CTX-M}}$ gene. This insertion sequence element is located upstream of a $bla_{\text{CTX-M}}$ gene. A schematic representation of this IS*Ecp1*-like element in association with a $bla_{\text{CTX-M}}$ gene is given in Fig. 1D (Canton & Coque, 2006; Poirel *et al.*, 2005a).

Another, rather specific IS element found in association with $bla_{\text{CTX-M}}$ genes is the insertion sequence common region (IS*CR1*), formely known as *orf*513 (Partridge & Hall, 2003; Stokes *et al.*, 1993). The function of this IS element remained unknown until comparative analysis

linked these so-called common region elements to a group of IS*91*-like insertion sequences (Toleman *et al.*, 2006a). The IS*91*-like ISs are a family of unusual IS elements that differ from most other IS elements, both in structure and in mode of transposition. They can perform rolling-circle (RC) transposition, in which a single IS element can mobilize the sequences to which it is attached (del Pilar Garcillan-Barcia *et al.*, 2001; Garcillan-Barcia *et al.*, 2001; Tavakoli *et al.*, 2000). It has been proposed that IS*CR1* may mobilise the nearby sequence and a truncated 3'conserved sequence (CS) from one integron to the 3'CS of another integron through RC transposition, thus facilitating the formation of complex class 1 integrons associated with IS*CR1* (Toleman *et al.*, 2006a; Toleman *et al.*, 2006b), as shown in Fig. 1E (Bae *et al.*, 2007; Canton & Coque, 2006; Garcia *et al.*, 2005; Novais *et al.*, 2006; Riaño *et al.*, 2009).

A third type of genetic elements associated with $bla_{\text{CTX-M}}$ genes are the phage-related elements (Fig. 1F) (Oliver *et al.*, 2005). This highlights the fact that phages may serve as tools for natural genetic engineering processes that eventually lead to the evolution and spread of antimicrobial resistance (Muniesa *et al.*, 2004; Oliver *et al.*, 2005; Riaño *et al.*, 2009).

MGEs for other ESBL genes

In contrast to the $bla_{\text{CTX-M}}$ genes, the $bla_{\text{VEB-1}}$ gene was identified as a gene cassette in class 1 integrons (Fig. 1G) (Girlich *et al.*, 2001; Poirel *et al.*, 1999; Poirel *et al.*, 2005b). Moreover, the $bla_{\text{GES-1}}$ gene was also found to be a gene cassette in a class 1 integron structure (Fig. 1H) (Poirel *et al.*, 2000). Another study described the location of the $bla_{\text{GES-1}}$ gene cassette on a class 3 integron (Fig. 1I) (Correia *et al.*, 2003). These findings underlined the fact that integron-located ESBL genes are not only part of the Ambler class D (OXA-10) (Girlich *et al.*, 2001) or class B (IMP-1, active on imipenem) (Miriagou *et al.*, 2005), but may also be part of class A. This is of interest since most of the plasmid-mediated ESBL that are

spreading worldwide are of class A and their integron location may provide them additional potential for spreading.

Mobile genetic elements described as carriers of *ampC* β-lactamase genes

Many genetic elements have been found to be involved in the mobilization of *ampC* genes onto plasmids within a bacterium (D'Andrea *et al.*, 2006; Jacoby & Tran, 1999; Queenan *et al.*, 2001; Raskine *et al*., 2002; Winokur *et al.*, 2001), the most important of which are discussed below.

The insertion sequence IS*Ecp1* has been identified in association with many bla_{CMY} genes, including the bla_{CMY-2} gene (Fig. 2A) (D'Andrea *et al.*, 2006; Hopkins *et al.*, 2006b; Hossain *et al.*, 2004; Literacka *et al.*, 2004; Nakano *et al.*, 2007; Poirel *et al.*, 1999; Poirel *et al.*, 2000; Toleman et al., 2006b; Winokur *et al.*, 2001; Wu *et al.*, 1999) and the bla_{ACC-1} and bla_{ACC-4} genes (Papagiannitsis et al., 2007; Partridge, 2007). IS*Ecp1* plays a dual role. It is not only responsible for the mobility of a transposition unit including itself and a resistance determinant, as was also described for bla_{CTX-M} genes, but it can also supply an efficient promoter for the high level expression of neighbouring genes (Hossain *et al.*, 2004)

Other *ampC* genes, such as bla_{CMY-1}, bla_{CMY-8}, bla_{CMY-9}, bla_{CMY-10}, bla_{CMY-11}, bla_{CMY-19} bla_{MOX-1} and bla_{DHA-1}, have been found downstream of an ISCR1 involved in gene mobilisation in complex class 1 integrons (Toleman et al., 2006b). This mobile genetic element has also been associated with bla_{CTX-M} genes, as mentioned above. The schematic representation of bla_{DHA-1}, bla_{CMY-10} and bla_{CMY-11} genes in association with *IS*CR1 in a complex class 1 integron is given in Fig. 2B.

A *Citrobacter freundii*-derived sequence of 4,252 bp, which included a bla_{CMY-13} gene and was bound by two directly repeated IS*26* elements, was found on an Inc*N* plasmid from *Escherichia coli* (Fig. 2C), indicating that this gene may have spread, from the chromosome

to a plasmid within a bacterium, following IS*26*-dependent mobilization as was also described for bla_{SHV} genes (Miriagou et al., 2004).

Impact of mobile genetic elements as carriers of broad-spectrum β-lactamases on epidemiology and co-resistance selection

Genes encoding broad-spectrum β-lactamases can be carried by a variety of MGEs such as insertion sequences, transposons and plasmids. These mobile genetic elements may have different potentials in the dissemination of resistances, such as IS*Ecp1*, which seems to mobilise and transport genes onto plasmids quite easy and efficiently (Bae *et al.*, 2006a; Bae *et al.*, 2006b; Eeckert *et al.*, 2006; Fernandez *et al.*, 2007; Liu *et al.*, 2007; Navon-Venezia *et al.*, 2008; Sheng *et al.*, 2008).

The success of the spread of specific β-lactamases will thus be determined mainly by the MGEs in terms of the the selection and dispersion of these enzymes.

The most striking examples of the impact of mobile genetic elements on the epidemiology and co-resistance selection are discussed below.

MGE as a carrier for the bla_{TEM-52} gene

The bla_{TEM-52} gene is located on a Tn*3*-like transposon that is found on a large stable conjugative Inc*I1* plasmid. This plasmid is found mainly in *Enterobacteriaceae* isolated from poultry and humans (Cloeckaert *et al.*, 2007; Hasman *et al.*, 2005; Smet *et al.*, 2008; Smet *et al.*, 2009). Surprisingly, until now, no other resistance genes have been associated with this plasmid. This is most probably due to its broad host spectrum and the possibility of its spreading internationally, though until now it has spread mainly in Europe (Weill *et al.*, 2004; Cloeckaert *et al.*, 2007; Hasman *et al.*, 2005; Smet *et al.*, 2008).

MGE as a carrier for the bla$_{\text{CTX-M-15}}$ *gene*

Another plasmid-mediated gene is *bla*$_{\text{CTX-M-15}}$. This gene is associated with IS*Ecp1* and is mainly described in *Enterobacteriaceae* of human origin worldwide (Boyd *et al.*, 2004; Hopkins *et al.*, 2006c; Karisik *et al.*, 2006; Lavollay *et al.*, 2006; Nicolas-Chanoine *et al.*, 2008). This gene has been found on a multitude of plasmids of different sizes and with different incompatibility (Inc) groups, such as Inc*I1* and Inc*FII*. The latter Inc group is frequently co-associated with replication genes originating from Inc*FIA* or Inc*FIB* (Hopkins *et al.*, 2006c; Karisik *et al.*, 2006). This indicates that the association with IS*Ecp1* is important in the spread of this gene among different plasmids. Besides the horizontal spread of a *bla*$_{\text{CTX-M-15}}$-carrying plasmid from one bacterium to another, the worldwide clonal spread of certain CTX-M-15-positive *E. coli* isolates has also been shown to be important in the dissemination of this resistance gene (Lavollay *et al.*, 2006; Nicolas-Chanoine *et al.*, 2008).

MGE as a carrier for the bla$_{\text{CTX-M-2}}$ and *bla*$_{\text{CTX-M-9}}$ *genes*

Other *bla*$_{\text{CTX-M}}$ genes, such as the *bla*$_{\text{CTX-M-2}}$ and *bla*$_{\text{CTX-M-9}}$ genes, are located on plasmids, similarly to *bla*$_{\text{CTX-M-15}}$, though they are associated with different Inc groups and are associated with IS*CR1* as part of a complex class 1 integron, as already mentioned (Bae *et al.*, 2007; Canton & Coque, 2006; Garcia *et al.*, 2005; Novais *et al.*, 2006; Riaño *et al.*, 2009). The *bla*$_{\text{CTX-M-2}}$ and *bla*$_{\text{CTX-M-9}}$ genes are mainly found on Inc*HI2* plasmids and may also be located on Inc*P*, Inc*A/C* or Inc*FI* plasmids. The *bla*$_{\text{CTX-M-9}}$ gene is also found on the chromosome (Fernandez *et al.*, 2007; Hopkins *et al.*, 2006c; Novais *et al.*, 2006). These genes are found in *Enterobacteriaceae* from food-producing animals and humans. An important difference between *bla*$_{\text{CTX-M-9}}$ and *bla*$_{\text{CTX-M-15}}$ is the co-resistance caused by non-β-lactam resistance gene cassettes associated with these class 1 integrons. As such, these *bla*$_{\text{CTX-M-9}}$ genes may be easily selected by the use of other non-β-lactam antimicrobial agents

(Fernandez *et al.*, 2007; Novais *et al.*, 2006; Riaño *et al.*, 2009; Sabaté *et al.*, 2002). Similarly for $bla_{\text{CTX-M-2,}}$ however, a variety of non-β-lactam resistance gene cassettes have been found in these complex class 1 integrons, which makes them perfect discrimination tools (Arduino et al., 2002; Power et al., 2005; Valverde et al., 2006).

MGE as a carrier for the $bla_{\text{CMY-2}}$ gene

The $bla_{\text{CMY-2}}$ gene has been found to be located on an Inc*I1* or Inc*A/C* plasmid (Hopkins et al., 2006c). These plasmids seem to be very promiscuous, having been found all over the US, mainly associated with *Salmonella* (Winokur *et al.*, 2000; Zhao *et al.*, 2008). They are also emerging in other continents, though less in association with *Salmonella* (Briñas *et al.*, 2005; Li *et al.*, 2008; Pai *et al.*, 2004; Su *et al.*, 2005). This gene is like the $bla_{\text{CTX-M-15}}$ gene associated with an IS*Ecp1*-like element, which makes the spread of this bla gene between plasmids within a bacterium possible. Therfore, the dissemination of this gene could not be explained in terms of the clonal spread of CMY-2-producing bacteria, but rather in terms of different plasmids carrying a $bla_{\text{CMY-2}}$ gene (Naseer et al., 2009; Winokur *et al.*, 2001).

Broad-spectrum β-lactamases among *Enterobacteriaceae* from animals

Data on the presence of ESBL- and AmpC β-lactamase-producing *Enterobacteriaceae* isolated from healthy and sick animals are discussed in this section. Per group (food-producing animals, companion animals and wild animals), ESBL-producing bacteria are handled first, followed by the AmpC β-lactamase-producing bacteria.

Food-producing animals

Healthy animals

Between 2002 and 2009, the number of publications reporting commensal broad-spectrum cephalosporin resistant *Enterobacteriaceae* isolated from food-producing animals has increased dramatically. A summary of the published data of ESBL- or AmpC β-lactamase-producing bacteria isolated from food-producing animals is listed in Supplementary file 1. The diversity among the ESBL encoding genes in *Enterobacteriaceae* from food-producing animals is by far larger than what is seen for the AmpC encoding genes. So far, the presence of ESBLs among commensal *Enterobacteriaceae* has been found to range from 0.2 to 40.7% (Supplementary file 1). Some ESBLs seem to be confined to specific individual countries, such as TEM-106 in Belgium, CTX-M-8 and SHV-5 in Tunisia and several CTX-M enzymes in China (Duan *et al.*, 2006; Jouini *et al.*, 2007; Smet *et al.*, 2008; Tian *et al.*, 2009). Other ESBLs have been found to be more widely distributed. So far, TEM-52- and SHV-12-producing *Enterobacteriaceae*, isolated especially from poultry, have only been described on the European continent (Supplementary file 1) (Briñas *et al.*, 2003; Chiaretto *et al.*, 2008; Cloeckaert *et al.*, 2007; Costa *et al.*, 2009; Hasman *et al.*, 2005; Machado *et al.*, 2008; Smet *et al.*, 2008; Riaño *et al.*, 2006). ESBLs such as CTX-M-1, CTX-M-2 and CTX-M-14 have been found in many European countries, being associated with *E. coli* mainly from poultry (Supplementary file 1) (Briñas *et al.*, 2003; Costa *et al.*, 2009; Girlich *et al.*, 2007; Jouini *et al.*, 2007; Kojima *et al.*, 2005; Machado *et al.*, 2008; Shiraki *et al.*, 2004; Smet *et al.*, 2008). The CTX-M-15 enzyme, the most widely diffused enzyme among human *Enterobacteriaceae*, was only recently detected among *E. coli* from poultry and pigs (Smet *et al.*, 2008; Tian *et al.*, 2009).

The presence of AmpC β-lactamase mediated resistance in commensal *Enterobacteriaceae* ranged from 0.01 to 88.5% (Supplementary file 1). CMY-2 is the most common enzyme

identified among these isolates. On a dairy farm, the overwhelming presence of CMY-2-producing *E. coli* (88.5% of the isolated strains) could be linked to the use of ceftiofur to treat respiratory infections in calves (Donaldson *et al.*, 2006). There is a striking difference in the presence of CMY-2 between *E. coli* and *Salmonella* isolates from poultry, cattle and pigs in Japan and Canada (Supplementary file 1). This may indicate that there is somehow a different epidemiology of CMY-2-producing *Enterobacteriaceae* in those countries among different animal species.

Sick animals

To date, only a few studies have been published reporting ESBL or AmpC-producing *Enterobacteriaceae* isolated from sick pigs and cattle. The presence of ESBL- or AmpC-producing bacteria among diseased poultry has so far not been described. An overview is given in the second part of Supplementary file 1.

Data on the presence of ESBL-producing *Enterobacteriaceae* among diseased cattle and pigs have so far only been described in a Korean and a French report. TEM and SHV ESBLs have been described in Korea, whereas different members of the CTX-M family are predominantly present in France (Supplementary file 1) (Madec *et al.*, 2008; Rayamajhi *et al.*, 2008).

AmpC enzymes have been detected among clinical bovine and porcine *Enterobacteriaceae*. The prevalence of these AmpC-producing animal pathogens varied from 0.3 to 77%. In most reports, CMY-2 enzymes and mutations in the promoter and attenuator regions of the chromosomal AmpC enzyme were found, but in one report DHA-1 enzymes were also found (Supplementary file 1).

Companion animals

Healthy animals

A few studies describing the presence (7 to 20%) of ESBL- or AmpC β-lactamase-producing *E. coli* isolated from the faecal microflora of healthy pets have been published (Supplementary file 2).

ESBLs – predominantly CTX-M-1 – have not only found their way into commensal *E. coli* from dogs in Europe, but have also recently been found among commensal *E. coli* from cats and dogs in Latin America (Caratolli *et al.*, 2005; Costa *et al.*, 2004; Moreno *et al.*, 2008). So far, CMY-2-producing *E. coli* have only been isolated from the faeces of healthy dogs in Italy (Carattoli *et al.*, 2005).

Sick animals

Five recent prevalence studies are available on the presence of broad-spectrum β-lactamases in *Enterobacteriaceae* from sick companion animals with urinary tract infections. The presence of ESBL- or AmpC β-lactamase-producing *E. coli* from diseased dogs ranged from 1.4% to 19.4% (Supplementary file 2). ESBLs of the CTX-M-1 cluster were the most predominant enzymes found. In four reports, CMY enzymes – mainly CMY-2 – were found, though CMY-7 enzymes were found in one study (Supplementary file 2). This is a situation similar to what is found in food-producing animals. However, the limited data available on broad-spectrum β-lactamases in pet animals is not sufficient to provide a good idea as to which broad-spectrum β-lactamases are spreading. Further epidemiological surveillance in pet animals should be performed to estimate the burden of this resistance.

Wild animals

Healthy animals

In Portugal, national surveillance in birds of prey and seagulls shows the emergence of broad-spectrum β-lactamases among *Enterobacteriaceae* from wild animals (Costa *et al.*, 2006; Poeta *et al.*, 2008). To date, no AmpC β-lactamases have been identified. The occurrence of ESBLs was as high as 19% in *E. coli* isolates from faecal samples, mainly of birds of prey and seagulls, with a predominance of CTX-M-1, CTX-M-14 and TEM-52 enzymes (Supplementary file 3). A recent French study describes a 9.4% prevalence of commensal ESBL-producing *E. coli* from wild yellow-legged gulls. The most predominant ESBL was CTX-M-1 (Supplementary file 3). These enzymes were also found in the feacal flora of food-producing animals and companion animals (Ho *et al.*, 2008; Miro *et al.*, 2005). The animals may have been contaminated by eating the leftovers from human food (Costa *et al.*, 2006; Poeta *et al.*, 2008). More studies should be performed in order to trace the origins of this contamination, including analysis of the prevalence of this type of resistance in different ecosystems.

Broad-spectrum β-lactamases in animal-associated bacteria: significance for human health

Presence of broad-spectrum β-lactamase-producing *Enterobacteriaceae* from humans

In order to be able to compare differences and similarities between the situation in animal and human *Enterobacteriaceae*, the diversity of broad-spectrum β-lactamase-producing commensals and pathogens present in humans will first be discussed in this chapter. The ESBL-producing bacteria will first be discussed, followed by the AmpC β-lactamase-producing bacteria.

Healthy humans

Since 2000, the number of publications reporting the faecal carriage of broad-spectrum β-lactamase-producing commensal *Enterobacteriaceae* from humans has been rising (Ho *et al.*, 2008; Kader *et al.*, 2007; Kaneko *et al.*, 2007; Leflon-Guibot *et al.*, 2008; Miro *et al.*, 2005; Moubareck *et al.*, 2005; Pallechi *et al.*, 2007; Pongpech *et al.*, 2008; Rodriguez-Baño *et al.*, 2008; Valverde *et al.*, 2004; Vinué *et al.*, 2009). An overview of commensal broad-spectrum β-lactamase-producing bacteria, mainly *E. coli*, is given in Supplementary file 4. Most available publications describe the faecal carriage of ESBL-producing *Enterobacteriaceae* with a presence ranging from 0.6% as a lower limit in France (Leflon-Guibot *et al.*, 2008) to the upper limit of 68% in Spain (Rodriguez-Baño *et al.*, 2008) (Supplementary file 4). The most predominant family of ESBLs reported among commensal *E. coli* is the CTX-M family, with the CTX-M-9 cluster being the most common cluster worldwide (Supplementary file 4). This may indicate that commensal *E. coli* of humans may constitute a reservoir of $bla_{\text{CTX-M}}$ genes.

So far, information about the presence of AmpC β-lactamase producing strains from faecal samples of healthy humans remains limited. In Japan, a prevalence of commensal CMY-2-producing *E. coli* of 3.2% has been reported (Supplementary file 4).

Sick humans

Most studies dealing with the presence of broad-spectrum β-lactamases in bacteria from humans refer to pathogens. The occurrence of broad-spectrum β-lactamase-producing pathogens has already been extensively reviewed (Arlet *et al.*, 2006; Jacoby, 200~~8~~9; Livermore *et al.*, 2007; Paterson *et al.*, 2005; Pitout *et al.*, 2005). Infections caused by *Enterobacteriaceae* complicate therapy and limit treatment options. Population studies of

568 human pathogens producing ESBLs or AmpC β-lactamases in hospitals and the community
569 worldwide are summarized in Supplementary file 5.
570 ESBL-producing human pathogens have been reported worldwide, with a presence of 0.3 to
571 91% in Europe, 0.8 to 5.6% in North America and 12 to 31% in Africa and the Middle East.
572 In the Asia and Pacific region, the presence of ESBL-producing pathogens ranges from 11.3-
573 38.6% (Supplementary file 5).
574 ESBLs, such as TEM-52 and SHV-12, among human pathogens were first reported in Europe
575 (Arlet *et al.*, 1994; Arpin *et al.*, 2003; Babini *et al.*, 2000; De Gheldre *et al.*, 2001; Knothe *et*
576 *al.*, 1983; Livermore *et al.*, 2007; Politi *et al.*, 2005; Saladin *et al.*, 2002; Vahaboglu *et al.*,
577 2001; Weill *et al.*, 2004). Later on, TEM-type ESBLs were described in the United States
578 (Jacoby *et al.*, 1988; Rice *et al.*, 1996). Since then, CTX-M ESBLs have become dominant,
579 with a much greater penetration into *E. coli* strains worldwide.
580 There are considerable geographical differences in the occurrence of ESBLs, especially of the
581 CTX-M enzymes. Many different CTX-M enzymes are widely distributed, mostly among *E.*
582 *coli,* causing urinary tract infections (Brenwald *et al.*, 2003; Doi *et al.*, 2007; Livermore et al.,
583 2007; Paterson *et al.*, 2005; Pitout *et al.*, 2005). Some CTX-M enzymes seem to be dominant
584 in specific European countries, such as CTX-M-14 and CTX-M-9 in Spain and Portugal
585 (Garcia *et al.*, 2005; Mendonça *et al.*, 2007; Rodriguez-Baño *et al.*, 2009; Romero *et al.*,
586 2005), CTX-M-1 and CTX-M-15 in Italy and France (Brigante *et al.*, 2005; Carattoli et al.,
587 2008; Livermore et al., 2005) and CTX-M-15 in the United Kingdom (Livermore *et al.*,
588 2007). In the United States, the most common CTX-M-type ESBL is CTX-M-15, followed by
589 CTX-M-16, CTX-M-8, and CTX-M-14 (Hanson et al., 2008; Lewis et al., 2007; Sjölund *et*
590 *al.*, 2008). Different CTX-M enzymes, with the predominance of CTX-M-15 and CTX-M-14,
591 have also been reported among nosocomial and community acquired *E. coli* isolates causing
592 urinary tract infections on the African and Asian continents (Bae *et al.*, 2007; Cao *et al.*,

2002; Chmelnitsky *et al.*, 2005; Gangoué-Piéboji *et al.*, 2005; Ho *et al.*, 2005; Soge *et al.*, 2006; Song *et al.*, 2009).

AmpC β-lactamases have been found less frequently than ESBLs among *Enterobacteriaceae*. CMY-2 is the AmpC enzyme with the broadest geographic spread, being an important cause of β-lactam resistance in nontyphoid *Salmonella* strains in many countries. This type of resistance is increasing worldwide (Batchelor *et al.*, 2005b; Dunne *et al.*, 2000; Kruger *et al.*, 2004; Li *et al.*, 2005; Su *et al.*, 2005; Wichard *et al.*, 2005; Winokur *et al.*, 2000).

The AmpC phenotype in *E. coli* is more often due to increased production of the chromosomal AmpC β-lactamase, as reported in a few prevalence studies (Bergström & Normark, 1979; da Silva Dias *et al.*, 2008; Mammeri *et al.*, 2008; Mulvey *et al.*, 2005; Potz et al., 2006) (Table 8). However, CMY-producing *E. coli* strains, mainly CMY-2, have also been demonstrated (Supplementary file 5) (Adler *et al.*, 2008; Gazouili *et al.*, 1998; Hopkins *et al.*, 2006a,b; Li *et al.*, 2008; Moland *et al.*, 2002; Mulvey *et al.*, 2005; Pai *et al.*, 2008; Pitout *et al.*, 2007; Winokur *et al.*, 2001).

It seems that broad-spectrum β-lactamases have been evolving and spreading at a rapid rate among humans worldwide over the last 20 years.

Differences and similarities between the situation in animal and human *Enterobacteriaceae*

β-lactamases were first detected in the early 1980s in humans, and their presence and diversity have been increasing ever since. The first time cephalosporin resistance was noted in animals was in early 2000. Compared to what is known in humans, the knowledge of the epidemiology of broad-spectrum β-lactamase-producing bacteria in animals is rather limited. As the spread of these β-lactamases in animals only recently started to increase, it is possible that these genes may be of human origin (Hernadez *et al.*, 2005). However, β-lactamases in

humans can also be of animal origin, as has been shown for the zoonotic *Salmonella* Infantis and Virchow isolates (Bertrand *et al.*, 2006; Cloeckaert *et al.*, 2007), in which cases the infecting cephalosporin resistant bacterium was directly derived from the animal.

The diversity of broad-spectrum β-lactamases in human *Enterobacteriaceae* is much higher than the situation in animal bacteria (Fig. 3).

In animals, there is a predominance of TEM-52, CTX-M-1, CTX-M-14 and CMY-2-producing *Enterobacteriaceae*, with the predominance of CMY-2 in North-America, and of CTX-M-1, CTX-M-14 and TEM-52 enzymes in Europe (Allen & Poppe, 2002; Carattoli *et al.*, 2005; Cloeckaert *et al.*, 2007; Costa *et al.*, 2004; Costa *et al.*, 2006; Costa *et al.*, 2009; Donaldson *et al.*, 2006; Hasman *et al.*, 2005; Machado *et al.*, 2008; Smet *et al.*, 2008; Winokur *et al.*, 2000; Zhao *et al.*, 2008).

These enzymes, together with CTX-M-9 and CTX-M-15, are also predominantly present in human bacteria. Some enzymes in human bacteria are even limited to specific countries such as CTX-M-39 in Israël, CTX-M-13 in China, CTX-M-40 in Thailand, and TEM-63 and TEM-131 in South Africa (Chmelnitsky *et al.*, 2005; Ho *et al.*, 2005; Kiratisin *et al.*, 2008; Kruger *et al.*, 2004). These enzymes have not been detected in animal *Enterobacteriaceae*. However, it must be said that the presence of these broad-spectrum β-lactamases in animal *Enterobacteriaceae* has not yet been investigated in these countries.

The most prevalent enzymes in commensal and pathogenic *E. coli* from both humans and animals are CTX-M-9, SHV-12 and CTX-M-14 in Spain, CTX-M-14 and CTX-M-32 in Portugal, CTX-M-1 in France and Italy, CTX-M-2 in Japan and, finally, CMY-2 in Canada and the United States. This may indicate that there is somehow a similar epidemiology among animal and human bacteria. Comparison of the genetic relatedness of *Enterobacteriaceae* recovered from different countries and origins and harboring the same ESBL or AmpC enzyme may help to explain this hypothesis.

Impact on public health of animal-derived *Enterobacteriaceae* producing broad-spectrum β-lactamases

The presence of broad-spectrum β-lactamase-producing bacteria in animals is increasing, and it is not unrealistic to expect that this will have an impact on human health. Resistance may be transferred in two ways. Due to close contact or consumption of animal meat, a β-lactam resistant zoonotic strain, in most cases *Salmonella* spp., may be transferred directly from animal to human, thus possibly causing infection, as has been demonstrated in a number of reports (Bertrand *et al.*, 2006; Cloeckaert *et al.*, 2007; Espié *et al.*, 2005; Fey *et al.*, 2000; Riaño *et al.*, 2009). As for direct transfer of resistance, the use of antimicrobial agents, selecting resistant bacteria may be the most important factor. However, the exact role of different antimicrobials in resistance development or dissemination remains unknown, though it could possibly be assessed by means of the pharmacokinetics and phamacodynamics of these antimicrobials. In vivo studies may also likely provide insights into the role of antimicrobial agents.

Moreover, resistance may possibly be acquired indirectly, through the transfer of resistance genes from bacteria of animal origin to bacteria infecting humans. Studies pointing out the possibilities of indirect transfer of resistance genes remain limited.

Cloeckaert *et al.*, (2007) emphasised that TEM-52-producing *Salmonella* sp. are not only spreading between poultry and humans through direct transfer, but that the stable plasmid carrying this gene (Smet et al., 2009) may also be spreading between different *Salmonella* serotypes, thus indicating a possibility for indirect resistance transfer.

Another example of indirect transfer of resistance is the dispersion of CMY-2-producing *E. coli* from cattle and pigs to humans, or vice versa, due to the association of this gene with IS*Ecp1* (Naseer *et al.*, 2009; Hopkins *et al.*, 2006; Winokur *et al.*, 2001). Again, this highlights the importance of MGEs in the spread of resistance genes.

Therefore, both the selective effect of the antibiotics and the MGEs carrying these *bla* genes could be important factors in indirect resistance transfer. Little is known about the influence of these MGEs on the spread of the *bla* genes. This lack of knowledge could make it difficult to predict the possibilities of spread, thus underlining the need for further investigations.

Concluding remarks

The widespread use of extended-spectrum cephalosporins creates a reservoir of resistant bacteria and resistance genes that may add to the burden of β-lactam resistance in human medicine and shorten the time that these valuable antimicrobial compounds will be available for the effective treatment of infections. Moreover, multiresistance frequently associated with strains carrying ESBLs and AmpCs is worrisome since these strains can be selected by a manifold of different antimicrobial agents, which could dramatically reduce the treatment options.

Resistance against β-lactams is increasingly being reported and is on the rise in *Enterobacteriaceae* from both humans and animals. This coincides with the increasing numbers of β-lactamase variants. It is also interesting to note that there is no specific β-lactamase associated with animals since most enzymes are also predominantly present in bacteria found in humans.

Some ESBLs and AmpC β-lactamases seem to be dedicated to a specific geographical region, while others are more widely spread. This appears to be without obvious reason. However, the wordwide detection of certain broad-spectrum β-lactamases does not seem to be linked to the expansion of bacterial clones, but rather to plasmid-mediated horizontal gene transmission. Epidemiological studies dealing with the dissemination of β-lactam resistance may help to explain these findings.

The understanding of why some MGEs seem to be very successful in spreading is of essential importance. Moreover, these MGEs frequently carry other resistance genes that are co-transferred and cause co-resistance selection.

The clinical and commercial pressure to use β-lactams, as well as the global mobility of humans, animals and food products guarantee that the spread of β-lactamase genes will continue. β-lactam antibiotics may enter the environment, such as water sources, having been excreted in the faeces and/or urine of treated animals. Water may therefore also be a potential source of selective pressure.

More studies are needed to make a more accurate risk assessment concerning the spread of antimicrobial resistance, as well as on the mechanisms of linkage and transferability of β-lactam resistance determinants in natural environments. Therefore, the evaluation of the possible impact of this resistance in animals for human health studies should not be limited to pathogenic bacteria, but must also include commensals, since they may be a major reservoir of resistance genes, as has already been shown to be the case in poultry (Smet *et al.*, 2008).

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1446 **Table 1.** β-lactams used in veterinary and human medicine (Guardabassi *et al.*, 2008; Hammerum & Heuer, 2009; Hornish & Kotarski, 2002)

β-lactams	**Spectrum of activity**	**Veterinary medicine**	**Human medicine**
Penicillins	are mainly active against Gram-positive bacteria. Aminopenicillins are also active against Gram-negative bacteria.	ampicillin, amoxicillin, benzylpenicillin, cloxacillin, hetacillin	penicillin, ampicillin, amoxicillin
Penicillin-β-lactamase inhibitor combinations	exhibit negligible antimicrobial activity. Their sole purpose is to prevent the inactivation of β-lactam antibiotics and, as such, they are co-administrated mostly with penicillins	amoxicillin-clavulanate	amoxicillin-clavulanate, piperacillin-tazobactam
First generation cephalosporins	are moderate spectrum agents. They are effective alternatives for treating staphylococcal and streptococcal infections.	cepadroxil, cefapirin, cephalexin	Cefalozin
Second generation cephalosporins	have a greater Gram-negative spectrum while retaining some activity against Gram-positive bacteria.	cefaclor, cefamandole, cefonicid, ceforanide, cefuroxime	cefuroxime, cefoxitin
Third generation cephalosporins	have a broad spectrum of activity and further increased activity against Gram-negative organisms.	cefovecin, cefpodoxim, ceftiofur	ceftriaxone, cefotaxime, ceftazidime
Fourth generation cephalosporins	have the broadest activity both against Gram-negative and Gram-positive bacteria.	cefquinome	Cefepime
Monobactams	have a strong activity against susceptible Gram-negative bacteria, but no useful activity against Gram-positive bacteria or anaerobes.	not in use	Aztreonam
Carbapenems	have a broad spectrum of activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria.	imipenem, meropenem[a]	imipenem, meropenem

[a] Use only in the case of life-threatening infections and when susceptibility tests have shown resistance to all other antimicrobials except carbapenems.

Table 2. Use of β-lactams as the first or second choice for the treatment of diseases in swine, cattle, poultry, horses, and cats & dogs (modified from Guardabassi *et al.*, 2008)

Animal	Clinical indication	β-lactam use (first choice)	β-lactam use (second choice)
swine	necrotic enteritis	penicillins	
	respiratory/systemic disease	penicillins, ceftiofur	
cattle	neonatal septicemiae		third (ceftiofur) or fourth (cefquinome) generation cephalosporins
	salmonellosis	ceftriaxone	
	calf diarrhoea	ampicillin, amoxicillin, amoxicillin-clavulanic acid	
	septic arthritis	ampicillin, amoxicillin	third or fourth generation cephalosporins
	foot rot[b]	ampicillin	
	metritis[b]	ampicillin, penicillin	
	mastitis	penicillin	third or fourth generation cephalosporins
poultry	dysbacteriosis	benzylpenicillins	
	collibacilosis	ampicillin, amoxicillin	
	Ornithobacterium rhinotracheale infection	ampicillin, amoxicillin	
	fowl cholera	ampicillin, amoxicillin	
	Riemerella anatipestifer infections	ampicillin, amoxicillin	
	erysipelas	penicillins	
horses	clostridial myostitis	penicillins	

	pigeon fever	penicillins	
	osteomyelitis	penicillins	Ceftiofur
	septic arthritis	penicillin	Ceftiofur
	wounds	penicillin[a]	Ceftiofur
	cystitis	penicillin, ampicillin	ceftiofur
	pyelonephritis	ampicillin	Ceftiofur
	endocarditis, pericarditis	penicillin[a]	Ceftiofur
	bacterial meningitis	penicillin[a]	Ceftiofur
	listeriosis	penicillin, ampicillin	Ceftiofur
	cellulitis	ceftiofur	
	neonatal septicemiae	penicillin[a]	third generation cephalosporins
cats & dogs	reccurent pyoderma	amoxicillin-clavulanic acid, first generation cephalosporins	
	skin wounds	cefotaxime, cephalexin	
	cystitis	aminopenicillins	amoxicillin-clavulanic acid, cephalosporins
	acute peritonitis	cefoxitin, cefotetan	
	pneumoniae	amoxicillin-clavulanic acid, cephalosporins	
	osteomyelitis	amoxicillin-clavulanic acid, cephalosporins	
	leptospirosis	penicillin G, amoxicillin	

1464 [a] in combination with gentamicin; [b]ceftiofur is used as last choice

Table 3. Known *bla*$_{TEM}$ gene-transposon associations

***bla* gene**	**Transposon-like structure**	**Reference**
bla$_{TEM-1a}$	Tn*3*	Partidge & Hall, 2005
bla$_{TEM-1b}$	Tn*2*	Partridge & Hall, 2005
bla$_{TEM-2}$	Tn*1*	Partidge & Hall, 2005
bla$_{TEM-3}$	Tn*1*	Mabilat *et al.*, 1992
bla$_{TEM-10}$	Tn*2*	Bradford *et al.*, 1994
bla$_{TEM-12}$	Tn*2*	Bradford *et al.*, 1994
bla$_{TEM-15}$	Tn*801* (Tn*3*-like)	Chouchani *et al.*, 2007
bla$_{TEM-20}$	Tn*3*	Sunde *et al.*, 2009
bla$_{TEM-21}$	Tn*801* (Tn*3*-like)	Dubois *et al.*, 2005
bla$_{TEM-52}$	Tn*3*	Cloeckaert *et al.*, 2007
bla$_{TEM-67}$	Tn*1*	Naas *et al.*, 2003
bla$_{TEM-121}$	Tn*3*	Dubois *et al.*, 2002
bla$_{TEM-144}$	Tn*2*	Vignoli *et al.*, 2006

Supplementary file 1. Presence of *Enterobacteriaceae* producing broad-spectrum β-lactamases in food-producing animals (per animal group, ESBL-producing *Enterobacteriaceae* are listed first followed by the AmpC β-lactamase-producing *Enterobacteriaceae*)

Healthy animals

Animal	Percentage of samples in which β-lactamases were found to be present (Total number of samples tested)	Proportion (as %) of positive samples in which each type of β-lactamase was found	Species	Year of isolation	Country	Reference
poultry	17.5 (40)	TEM-52 (80), CTX-M-1 (7), SHV-2 (13)	*E. coli, K. pneumoniae*	1998-2004	Portugal	Machado *et al.*, 2008
	not specified	TEM-52	*Salmonella* spp.	2001-2005	Belgium	Cloeckaert *et al.*, 2007
	not specified	TEM-52	*Salmonella* spp.	2001-2002	The Netherlands	Hasman *et al.*, 2005
	40.1 (76)	TEM-52 (83), CTX-M-14 (9.5), CTX-M-32 (7.5)	*E. coli*	2004	Portugal	Costa *et al.*, 2009
	10.7 (489)	TEM-52 (14), TEM-106 (2), CTX-M-1 (20), CTX-M-2 (8), CTX-M-14 (6), CTX-M-15 (2)	*E. coli*	2007	Belgium	Smet *et al.*, 2008
	11 (112)	CTX-M-1	*E. coli*	2005	France	Girlich *et al.*, 2007
	6.4 (38)	CTX-M-8(10), CTX-M-14 (30), SHV-5 (10)	*E. coli*	Not specified	Tunesia	Jouini *et al.*, 2007
	0.2 (2747)	CTX-M-2 (17), CTX-M-14 (5.5)	*E. coli*	1999-2002	Japan	Kojima *et al.*, 2005
	0.7 (556)	CTX-M-9	*Salmonella* spp.	1999-2004	Spain	Riaño *et al.*, 2006
	1.6 (120)	CTX-M-14 (20), SHV-12 (20)	*E. coli*	2000-2001	Spain	Briñas *et al.*, 2003
	0.6 (2162)	SHV-12	*Salmonella* spp.	2005-2006	Italy	Chiaretto *et al.*, 2008
	0.8 (120)	CMY-2 (20)	*E. coli*	2000-2001	Spain	Briñas *et al.*, 2003
	0.1 (8426)	CMY-2	*Salmonella* spp.	1994-1999	Canada	Allen & Poppe, 2002

	0.3 (2747)	CMY-2 (44)	*E. coli*	1999-2002	Japan	Kojima *et al.*, 2005
	6.9 (83)	CMY-2	*Salmonella* sp.	2004-2005	Japan	Taguchi *et al.*, 2006
	10 (489)	CMY-2 (41)	*E. coli*	2007	Belgium	Smet *et al.*, 2008
	3.1 (32)	CMY-2	*E. coli*	Not specified	Taiwan	Yan *et al.*, 2004
	10 (10119)	CMY[a]	*Salmonella* sp.	2002-2006	United States	Zhao *et al.*, 2008
	1.6 (120)	Mutation promoter region AmpC (40)	*E. coli*	2000-2001	Spain	Briñas *et al.*, 2003
	0.3 (2747)	Mutation promoter region AmpC (44)	*E. coli*	1999-2002	Japan	Kojima *et al.*, 2005
	4 (76)	Mutation promoter region AmpC (9)	*E. coli*	2004	Portugal	Costa *et al.*, 2009
cattle	2.6 (607)	CTX-M-1(84), CTX-M-14 (8), SHV-12 (8)	*E. coli*	2006	France	Madec *et al.*, 2008
	6.4 (38)	CTX-M-1 (60)	*E. coli*	Not specified	Tunesia	Jouini *et al.*, 2007
	1.5 (270)	CTX-M-2	*E. coli*	2000-2001	Japan	Shiraki *et al.*, 2004
	37 (297)	CTX-M[a]	*E. coli*	2004	United Kingdom	Liebana *et al.*, 2006
	0.01 (8426)	CMY-2	*Salmonella* spp.	1994-1999	Canada	Allen & Poppe, 2002
	88.5 (122)	CMY-2	*E. coli*	2003	United States	Donaldson *et al.*, 2006
	27.7 (297)	Mutation promotor region AmpC	*E. coli*	2004	United Kingdom	Liebana *et al.*, 2006
pigs	6.6. (212)	CTX-M-15 (35), CTX-M-22 (57), SHV-2 (8)	*E. coli*	2002-2007	China	Tian *et al.*, 2009
	0.2 (436)	SHV-12	*Salmonella* spp.	1999-2004	Spain	Riaño *et al.*, 2006
	2.6 (35)	SHV-12	*Citrobacter Freundi*	1998-2004	Portugal	Machado *et al.*, 2008
	2.4 (86)	CMY-2	*E. coli*	Not specified	Canada	Kozak *et al.*, 2009
	7.4 (280)	CMY-2	*Salmonella* sp.	2000-2005	Mexico	Zaidi *et al.*, 2007
	30 (30)	CMY-2	*E. coli*	Not specified	Taiwan	Yan *et al.*, 2004
Sick animals						
cattle	2.4 (3984)	CMY-2	*Salmonella* spp.	2000-2004	United States	Freye *et al.*, 2008

	0.6 (2252)	AmpC[a]	*Salmonella* spp.	1999-2001	United States	Gupta *et al.*, 2003
	77 (32)	Mutation promoter region AmpC	*E. coli*	1996	United States	Bradford *et al.*, 1999
	0.03 (16200)	Mutation promoter region AmpC	*E. coli*	2002	United Kingdom	Liebana *et al.*, 2004
	6.2 (657)	CTX-M-1 (70), CTX-M-14 (18), CTX-M-15 (6), TEM-126 (6)	*E. coli*	2006	France	Madec *et al.*, 2008
pigs	5.3 (156)	TEM-20 (22), TEM-52 (11), SHV-28 (22), SHV-33 (22)	*E. coli, K. pneumoniae*	1999-2006	Korea	Rayamajhi *et al.*, 2008
	8.4 (156)	CMY-2 (11), DHA-1(33)	*K. pneumoniae*	1999-2006	Korea	Rayamajhi *et al.*, 2008
cattle & pigs	20.7 (535)	CMY-2	*E. coli, Salmonella*	1998-1999	United States	Winokur *et al.*, 2000

[a]not genotypically characterized

Supplemetary file 2. Presence of *Enterobacteriaceae* producing broad-spectrum β-lactamases in companion animals (per animal group, ESBL-producing *Enterobacteriaceae* are listed first followed by the AmpC β-lactamase-producing *Enterobacteriaceae*)

Healthy animals						
Animal	**Percentage of samples in which β-lactamases were found to be present (Total number of samples tested)**	**Proportion (as %) of positive samples in which each type of β-lactamase was found**	**Species**	**Year of isolation**	**Country**	**Reference**
dogs	10.4 (75)	TEM-52 (75), CTX-M-1 (25)	E. coli	Not specified	Portugal	Costa *et al.*, 2004
	20 (72)	CTX-M-1 (7.5)	*E. coli*	2001-2003	Italy	Carattoli *et al.*, 2005
	14.3 (70)	CTX-M-1 (40), CTX-M-14 (40), PER-2 (50)	*E. coli*	2006	Chile	Moreno *et al.*, 2007
	7 (72)	CMY-2 (5)	*E. coli*	2001-2003	Italy	Carattoli *et al.*, 2005
cats	5.7 (70)	CTX-M-1 (100), PER-2 (75)	*E. coli*	2006	Chile	Moreno *et al.*, 2007
Sick animals						
dogs	19.4 (72)	CTX-M-1 (52), SHV-12 (20)	*E. coli*	2001-2003	Italy	Carattoli *et al.*, 2005
	4.2 (72)	SHV[a]	*E. coli*	Not specified	Portugal	Feria *et al.*, 2002
	11 (72)	AmpC[a]	*E. coli*	Not specified	Portugal	Feria *et al.*, 2002
	1.6 (61)	CTX-M-15 (33)	*E. coli*	2004-2006	Portugal	Pomba *et al.*, 2008
	3.2 (61)	CMY-2 (66)	*E. coli*	2004-2006	Portugal	Pomba *et al.*, 2008
	1.4 (72)	CMY-2 (5)	*E. coli*	2001-2003	Italy	Carattoli *et al.*, 2005
	4.7 (780)	CMY-7	*E. coli*	2000-2001	Australia	Sidjabat *et al.*, 2006
cats	2.7 (72)	CTX-M-1 (10.5)	*E. coli*	2001-2003	Italy	Carattoli *et al.*, 2005

horses	0.3 (1347)	CTX-M-1 (45)	*E. coli, K. pneumoniae*	2003-2005	The Netherlands	Vo *et al.*, 2007
	0.4 (1347)	CMY-2 (55)	*E. coli, K. pneumoniae*	2003-2005	The Netherlands	Vo *et al.*, 2007

[a]not genotypically characterized

Supplementary file 3. Presence of *E. coli* producing broad-spectrum β-lactamases in wild animals in Portugal and France (Costa *et al.*, 2006; Poeta *et al.*, 2008; Bonnedahl *et al.*, 2009)

Animal	Percentage of samples in which β-lactamases were found to be present (Total number of samples tested)	Proportion (as %) of positive samples in which each type of β-lactamase was found	Year of isolation
deer, owl, birth of prey, fox	19.2 (72)	TEM-52 (44), CTX-M-1(11), SHV-12 (11), CTX-M-14 (34)	2003-2004
Seagulls	19.1 (57)	TEM-52 (72), CTX-M-1(9), CTX-M-14 (9), CTX-M-32 (9)	2007
yellow-legged gulls	9.4 (90)	CTX-M-1 (53), CTX-M-15 (6), TEM[a](29), SHV[b](12)	Not specified

[a]not genotypically characterized

1513 **Supplementary file 4.** Occurrence of faecal carriage of broad-spectrum β-lactamase-producing *Enterobacteriaceae in* healthy humans

1514 worldwide

Species	Percentage of healthy human subjects tested in which β-lactamase was found to be present (Total number of healthy human subjects tested)	Proportion (as %) of positive healhy humans tested in which each type of β-lactamase was found	Year of isolation	Location	Reference
E. coli, K. pneumoniae	22 (54)	CTX-M-9 (1.9), CTX-M-14 (13), CTX-M-24 (3.7), CTX-M-38 (3.7)	2002	China	Ho *et al.*, 2008
E. coli	3.3 (1321)[b]	CTX-M-3 (6.7), CTX-M-9 (60), CTX-M-14 (6.7), CTX-M-15 (6.7), SHV-12 (13.3), PER[a] (6.7)	2003	Spain	Miro *et al.*, 2005
E. coli, Klebsiella pneumoniae, Enterobacter cloaca Citrobacter freundii	30.8 (382)	CTX-M-15 (83), SHV-5 (17)	2003	Lebanon	Moubareck *et al.*, 2005
E. coli	0.3 in 1991 (849), 11.8 (400) in 2003 [b]	TEM-4 (7.1), TEM-52 (3.6), CTX-M-10 (3.6), SHV-2 (3.6), SHV-12 (25), CTX-M-9 (21.4), CTX-M-14 (32.1)	1991 and 2003	Spain	Valverde *et al.*, 2004
E. coli	0.7 in 1991 (849), 5.5 in 2003 (400) [c]	CTX-M-9 types (62.5), SHV-12 (31.2)	1991 and 2003	Spain	Valverde *et al.*, 2004
E. coli	31 (159)[d]	CTX-M (47.5), SHV (52.5)[a]	2005-2006	Spain	Rodriguez-Baño *et al.*, 2008
E. coli	68 (53)[b]	CTX-M (66.6), SHV (33.3)[a]	2005-2006	Spain	Rodriguez-Baño *et al.*, 2008
E. coli	0.1 in 2002 (3174), 1.7 in 2005 (54)	CTX-M-2 (32), CTX-M-14 (16), CTX-M-15 (28), CTX-M-24 (8), CTX-M-56 (4), SHV-2 (2), SHV-12 (2)	2002 and 2005	Latin- America	Pallechi *et al.*, 2007
E. coli, K. pneumoniae	13.1(426)	Not specified	Not specified	Saudi Arabia	Kader *et al.*, 2007
E. coli	7.0 (270)	CTX-M-14 (58), CTX-M-22 (15), CTX-M-79 (22), CTX-M-24 (5)	Not specified	China	Tian *et al.*, 2009
E. coli	0.6 (332)	CTX-M-15	2006	France	Leflon-Guibout *et al.*, 2008
E. coli	4.2 (120)	Not specified	Not specified	Thailand	Pompech *et al.*, 2008

E. coli	6.7 (105)	CTX-M-14 (28.5), CTX-M-1 (28.5), CTX-M-32 (14.3), CTX-M-8 (14.3), TEM-52 (14.3)	2007	Spain	Vinué *et al.*, 2009
E. coli	3.2 (63)	CMY-2	2003	Japan	Kaneko *et al.*, 2007

[a]not genotypically characterized, [b] hospitalized patients, [c] outpatients and [d] non-patients

1530 **Supplementary file 5.** Population studies of broad-spectrum β-lactamase-producing human pathogens worldwide

Species	Percentage of samples in which β-lactamase was found to be present (Total number of samples tested)	Proportion (as %) of positive samples in which each type of β-lactamase was found	Year of isolation	Type of infection	Location	Reference
ESBLs						
K. pneumoniae	6 in 1993, 28 in 1994 (not specified)	TEM-type[a]	1993-1994	Not specified	Hospital, USA	Rice *et al.*, 1996
E. aerogens	14 (260)	TEM-24 (86), TEM-3 (14)	1994-1997	Not specified	21 different hospitals in Belgium	De Gheldre *et al.*, 2001
Enterobacteriaceae	12 (259)	SHV-12	1995-1998	Urinary tract infections, bacteraemia	Hospital, Cameroon	Gangoué-Piéboji *et al.*, 2005
K. pneumoniae	36.1 (678)	Not specified	1998-1999	Urinary tract infections	Hospital, South Africa	Bell *et al.*, 2002
E. coli, K. pneumoniae, Proteus mirabilis, Enterobacter aerogens	1.5 (2599)	TEM-3 (2), TEM-15 (5), TEM-19 (2), TEM-21 (23), TEM-24 (64), CTX-M-1 (2), SHV-44 (2)	1999	Urinary tract infections, bacteraemia, wounds	Hospital, France	Arpin et al., 2003
E. coli	0.3 (not specified)	CTX-M-9	1996-1999	Bacteraemia, urinary tract infections, wounds	Hospital, Spain	Garcia *et al.*, 2005
E. coli	12 (not specified)	CTX-M-2 (80), CTX-M-39 (15), SHV-5 (5), SHV-12 (10), TEM-133 (10)	2000	Not specified	Hospital, Israel	Chmelnitsky *et al.*, 2005
P. mirabilis	13.1 (99)	SHV-5 (14), CTX-M-13 (57), CTX-M-14 (21), TEM-11 (7)	1999-2002	Bactaeremia	Hospital, China	Ho *et al.*, 2005
E. coli, K. pneumoniae	5.7 (563)	CTX-M-9 (1), CTX-M-14 (38), SHV-2 (1), SHV-4 (10), SHV-12 (43), TEM-4 (4), TEM-20 (8), TEM-53 (1)	1995-2003	Bacteraemia, urinary tract infections, respiratory tract infections	Not specified, Spain	Romero *et al.*, 2005

E. coli	0.3 (20258)	CTX-M-types[a]	1999-2003	Mainly urinary tract infections	Hospital and community, Italy	Brigante *et al.*, 2005
E. coli	1.4 (1700)	CTX-M-9 (12), CTX-M-14 (41), CTX-M-32 (3), TEM-52 (6), SHV-12 (9)	2002-2003	Mainly urinary tract infections	Hospital, Spain	Briñas *et al.*, 2005
E. coli	91 (122)	CTX-M-1 (1), CTX-M-3 (2), CTX-M-9 (36), CTX-M-14 (22), CTX-M-15 (2), CTX-M-32 (4), SHV-12 (31), SHV-2 (5), TEM-116 (4), TEM-52 (2), TEM-4 (1)	2002-2003	Urinary tract infections	Community, Spain	Rodriguez-Bano *et al.*,2009
K. pneumoniae	31.3 (96)	CTX-M-15	2002-2003	Urinary tract infections	Community, Nigeria	Soge *et al.*, 2006
E. coli, K. Pneumoniae	87.3 (362)	*E. coli:* CTX-M-14 (44), CTX-M-15 (37), CTX-M-27 (1), CTX-M-40 (0.5), CTX-M-55 (17.5) *K. pneumoniae*: CTX-M-3 (3), CTX-M-14 (52), CTX-M-15 (39), CTX-M-27 (1), CTX-M-55 (5)	2004-2005	Urinary tract infections	Hospital, Thailand	Kiratisin *et al.*, 2008
E. coli	17 (163)	CTX-M-15	2006	Urinary tract infections	Hospital, Italy	Carattoli *et al.*, 2008
K. pneumoniae, E. aerogenes	11.4 (6121, *K. Pneumoniae*) 47.7 (2353, *E. coli*)	Not specified	Not specified	Not specified	Hospital, France	Albertini *et al.*, 2002
Salmonella spp.	0.03 (3027)	CTX-M-14 (12.5)	1999-2002	Salmonellosis	Hospital, Taiwan	Li *et al.*, 2005
Salmonella spp.	15.6 (160)	TEM-63 (31), TEM-131 (38), SHV-12 (31)	2002-2003	Salmonellosis	13 different hospitals in South Africa	Kruger *et al.*, 2004
Salmonella spp.	5.6 (1864)	CTX-M-type[a]	2003	Not specified	U.S. public health laboratories	Sjölund *et al.*, 2008
Salmonella spp.	0.4 (1233)	CTX-M-9 (60), CTX-M-10 (20), SHV-2 (20)	2000-2004	Salmonellosis	2 hospitals, Spain	Riaño *et al.*, 2009
E. coli	66 (181)	CTX-M-14 (7.5), CTX-M-15 (91.5), CTX-M-32 (1)	2004-2006	Urinary tract infections, wounds, bacteraemia	Hospital and community, Portugal	Mendonça *et al.*, 2007
E. coli	0.8 (75)	CTX-M-14 (92), CTX-	Not specified	Urinary tract	Community, USA	Hanson *et al.*, 2008

		M-15 (8)		infections		
K. pneumoniae	0.9 (14)	CTX-M-14 (50), SHV-like (50)	Not specified	Urinary tract infections	Community, USA	Hanson *et al.*, 2008
E. coli	3.5 (536)	CTX-M-1 (5), CTX-M-2 (10), CTX-M-9 (5), CTX-M-14 (5), CTX-M-15 (75)	2005-2006	Respiratory tract infections, bacteraemia, urinary tract infections	Health Care Centers, Canada	Zhanel *et al.*, 2007
E. coli	14.2 (576)	CTX-M-3 (12), CTX-M-9 (2), CTX-M-12 (1), CTX-M-14 (39), CTX-M-15 (33), CTX-M-22 (2) CTX-M-27 (1), CTX-M-57(2)	2007	Urinary tract infections, wounds, bacteraemia	Hospital, Korea	Song *et al.*, 2009
AmpC β-lactamases						
E. coli	5.5 (109)	Mutations *ampC* promotor	Not specified	Urinary tract infections	Hospital, Sweden	Bergstörm & Normark, 1979
E. coli	0.7 (29323)	Mutations *ampC* promotor	2000	Not specified	Hospital, Canada	Mulvey *et al.*, 2005
E. coli	4.1 (109)	Mutations *ampC* promotor	2001	Mainly urinary tract infections	University Hospital, Rio de Janeiro, Brazil	Da Silva Dias *et al.*, 2008
E. coli	0.5 (1700)	Mutations *ampC* promotor (24)	2002-2003	Mainly urinary tract infections	Hospital, Spain	Briñas *et al.*, 2005
E. coli	7.1 (574)	Mutations *ampC* promotor	2004	Not specified	Hospitals in Londen and South East England	Potz *et al.*, 2006
E. coli	0.6 (2800)	Mutations *ampC* promotor	2006	Urinary tract infections, septicaemia	Hospital, France	Mammeri *et al.*, 2008
Salmonella spp.	0.1 (4093)	CMY-2	1996-1998	Salmonellosis	U.S. community health departments	Dunne *et al.*, 2000
Salmonella spp.	0.6 (320)	CMY-2	1998	Salmonellosis	Iowa State Hygienic Laboratory (U.S.)	Winokur *et al.*, 2000
Non-typhi *Salmonella* spp.	3.2 (1378)	CMY	2000	Salmonellosis	U.S. state and local public health laboratories	Whichard *et al.*, 2005
Non-typhi *Salmonella* spp.	0.2 (3027)	CMY-2 (87.5)	1999-2002	Salmonellosis	Mackay Memorial Hospital, Taiwan	Li *et al.*, 2005
Non-typhi *Salmonella* spp.	1.9 (160)	CMY-2	2002-2003	Salmonellosis	13 different hospitals in South Africa	Kruger *et al.*, 2004

Salmonella spp.	8.4 (106)	CMY-2 (67), CMY-4 (11), DHA-1 (22)	1999-2003	Salmonellosis	Health Protection Agency, United Kingdom	Batchelor *et al.*, 2005
Salmonella spp.	0.6 (3635)	CMY-2	1999-2003	Salmonellosis	Hospital, Taiwan	Su *et al.*, 2005
E. coli	2.6 (2133)	LAT-3, LAT-4	1996	Active infection	Hospital, Greece	Gazouili *et al.*, 1998
E. coli	0.6 (1017)	CMY-2	1998-2000	Urinary tract infections, bacteraemia	Hospital, USA	Winokur *et al.*, 2001
K. pneumoniae	13.2 (408)	ACT-1, DHA-1, FOX-5, CMY-2	1996-2000	Not sp<ecified	24 different hospitals in 18 states of the USA	Moland *et al.*, 2002
E. coli	0.09 (29323)	CMY-2	1999-2000	Not specified	12 different hospitals in Canada	Mulvey *et al.*, 2005
K. pneumoniae	7.2 (389)	DHA-1 (50), CMY-1-like (50)	1998-2002	Bacteraemia	Seoul National University Hospital, Seoul, South Korea	Pai *et al.*, 2004
E. coli	0.1 (1700)	CMY-2 (6)	2002-2003	Mainly urinary tract infection	Hospital, Spain	Briñas *et al.*, 2005
E. coli	24 (103)	CMY-2 (80), CMY-7 (16), CMY-21 (4)	1995-2003	Not specified	Health Protection Agency, London, United Kingdom	Hopkins *et al.*, 2006a
E. coli	0.16 (369)	CMY-2	2000-2003	Not specified	Calgary Health Region, Canada	Pitout *et al.*, 2007
E. coli, *K. pneumoniae*	2.8 (1935)	DHA-1 (76), CMY-2 (24)	2003-2005	Not specified	Hospital, Shangai, China	Li *et al.*, 2008
E. coli, *Klebsiella* spp.	49 in *E. coli* and 55 in *Klebsiella* (173)	CIT-type (89), ACC-types (21), FOX (16), DHA (4)[a]	Not specified	Not specified	Hospital, UK and Ireland	Woodford et al., 2007
Enterobacteriaceae	4.9 (3217)	Not specified	2006-2007	Not specifeid	University Hospital, Basel, Switzerland	Adler *et al.*, 2008

[a]not genotypically characterized

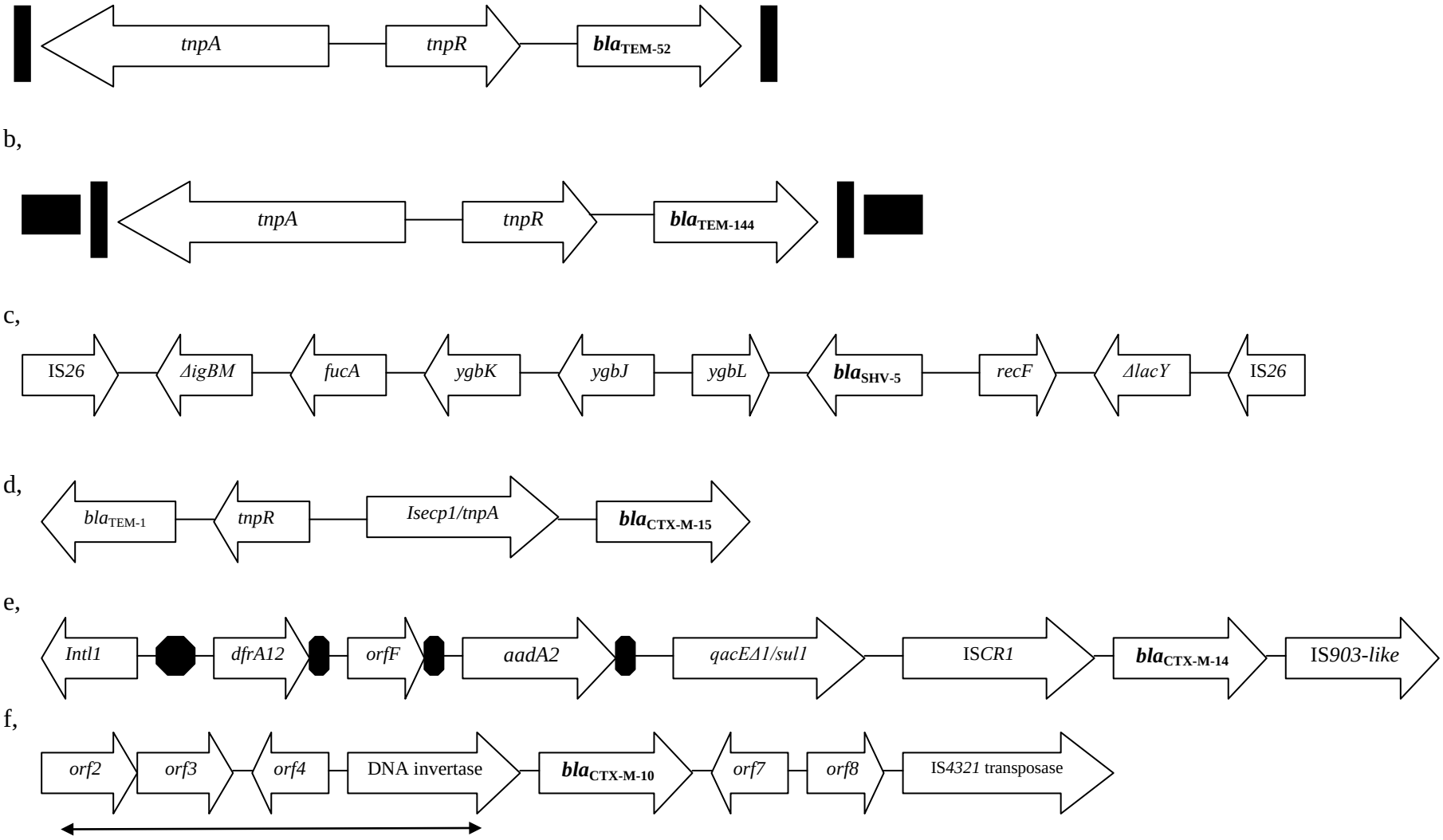
Figure legends

Fig. 1: Modular schematic structure of the backbones of mobile genetic elements containing ESBL genes. (a) A *bla*$_{\text{TEM-52}}$-carrying Tn*3*-like transposon (inverted repeats, vertical black rectangles) (Cloeckaert *et al.*, 2007). (b) A Tn*2*-like transposon harbouring the *bla*$_{\text{TEM-144}}$ gene (Rom protein gene, horizontal black rectangles) (Vignoli *et al.*, 2006). (c) A *bla*$_{\text{shv-5}}$ gene, which was found together with seven other co-lineair genes (*ΔigBM*, *fucA*, *ygbK*, *ygbJ* and *ygbL*) originating from *K. pneumoniae* and flanked by two IS*26* elements inserted in the same orientation (Miriagou *et al.*, 2005). (d) An IS*Ecp1*-like element in association with the *bla*$_{\text{CTX-M-15}}$ gene and the Tn3-like transposon harbouring a *bla*$_{\text{TEM-1}}$ gene (Canton & Coque, 2006). (e) A complex class 1 integron, comprising the class 1 integron and its gene cassettes (*dfrA12*, *orfF* and *aadA12*) with 59-be (black ovals), *intI1* (integrase gene) and *attI* (recombination site, black circle), the *bla*$_{\text{CTX-M-14}}$ gene associated with the IS*CR1* element and a duplication of the *qacEΔ1/sul1* tandem (Bae *et al.*, 2007). (f) The *bla*$_{\text{CTX-M-10}}$ gene located downstream of phage-related elements (*orf2*, *orf3*, *orf4* and DNA invertase) (Oliver *et al.*, 2005; Riaño *et al.*, 2009). (g) A class 1 integron harbouring the gene cassettes (*bla*$_{\text{VEB-1}}$ *bla*$_{\text{OXA-10}}$-like and *arr-2*-like gene cassettes) with 59-be (black ovals), *intI1* (integrase gene) and *attI* (recombination site, black circle)) (Riaño *et al.*, 2009; Girlich *et al.*, 2001). (h) An In52 class 1 integron structure harbouring the *bla*$_{\text{GES-1}}$, *aac(6')lb'*, *dfrXVB*, *clmA4*, *aadA2* gene cassettes (59-be (black ovals), *intI1* (integrase gene) and *attI* (recombination site, black circle)) (Poirel *et al.*, 2000). (i) A class 3 integron harbouring the gene cassettes (*bla*$_{\text{GES-1}}$ gene cassette and a fusion event between *bla*$_{\text{OXA-10}}$-type and *aac(6')-lb* gene cassettes) with 59-be (black ovals), *intI3* (integrase gene) and *attI* (recombination site, black circle) (Correia *et al.*, 2003).

Fig. 2: Modular schematic structure of the backbones of mobile genetic elements containing plasmidic *ampC* genes. (a) An IS*Ecp1*-like element in association with the $bla_{\text{CMY-2/5}}$ gene. The $bla_{\text{CMY-2}}$ gene is the most common *ampC* β-lactamase gene among *Enterobacteriaceae* worldwide, being related to the *ampC* genes of *Citrobacter freundii* (Giles *et al.*, 2004; Winokur *et al.*, 2001). The *blc* and *sugE* genes showed 96% sequence identity with the two genes just found downstream of the *Citrobacter freundii* chromosomal *ampC* gene (Giles *et al.*, 2004). (b) $bla_{\text{DHA-1}}$, $bla_{\text{CMY-10}}$ and $bla_{\text{CMY-11}}$ in association with *IS*CR1 in a complex class 1 integron (59-be: black ovals and *attI* recombination site: black circle) with *aadA2* as gene cassette (Lee *et al.*, 2004; Verdet *et al.*, 2000). The $bla_{\text{CMY-10}}$ and $bla_{\text{CMY-11}}$ genes, related to chromosomally *ampC* genes of *Aeromonas* spp., are evolved from the $bla_{\text{CMY-1}}$ gene. A sequence identical to the ISCR1 was found upstream from the $bla_{\text{CMY-10}}$ and $bla_{\text{CMY-11}}$ genes (Jacoby, 2009; Lee *et al.*, 2004). The genetic organization of the gene coding for DHA-1 was mobilized from the Morganella morganii chromosome and inserted into a *sulI*-type integron (Verdet *et al.*, 2000). (c) schematic representation of the 4252 bp *C. freundii*-derived sequence containing the $bla_{\text{CMY-13}}$ gene (Miriagou *et al.*, 2004). The $bla_{\text{CMY-13}}$-*ampR* region was bound by two directly repeated IS*26* elements.

Fig. 3: Schematic representation of the number of studies reporting the presence of the most predominant ESBLs among *Enterobacteriaceae* isolated from healthy (a) and sick animals (b) and healthy (c) and sick humans (d) (modified from Tables 4, 5, 6, 7 and 8).

Fig. 1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b,
tnpA
tnpR
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c,
IS26
ΔigBM
fucA
ygbK
ygbJ
ygbL
blaSHV-5
recF
ΔlacY
IS26
d,
blaTEM-1
tnpR
Isecp1/tnpA
blaCTX-M-15
e,
Intl1
dfrA12
orfF
aadA2
qacEΔ1/sul1
ISCR1
blaCTX-M-14
IS903-like
f,
orf2
orf3
orf4
DNA invertase
blaCTX-M-10
orf7
orf8
IS4321 transposase
Phage related region

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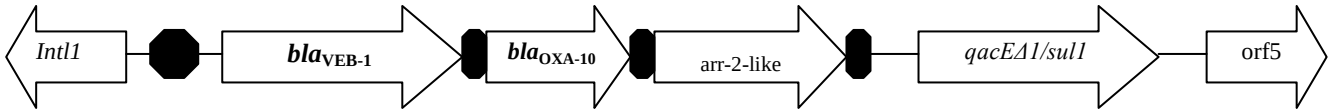
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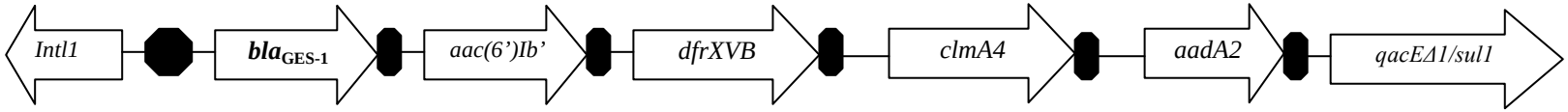
blaOXA-10
arr-2-like
qacEΔ1/sul1
orf5

h,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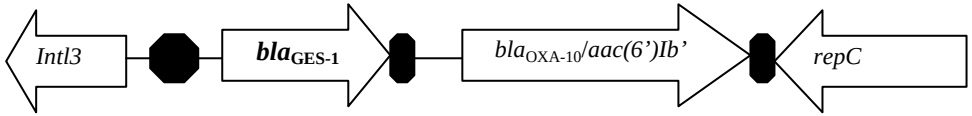
aac(6')Ib'
dfrXVB
clmA4
aadA2
qacEΔ1/sul1

i,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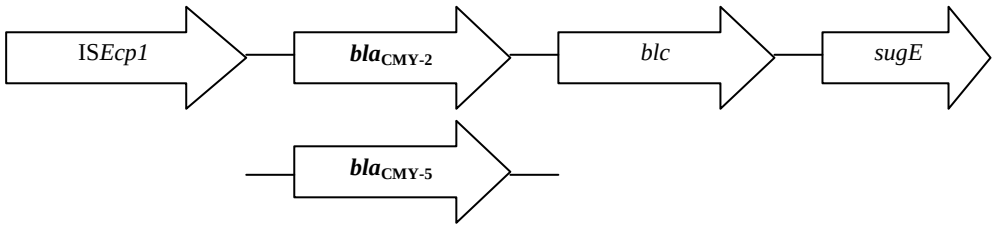
blaGES-1
blaOXA-10/aac(6')Ib'
repC

Fig. 2

a,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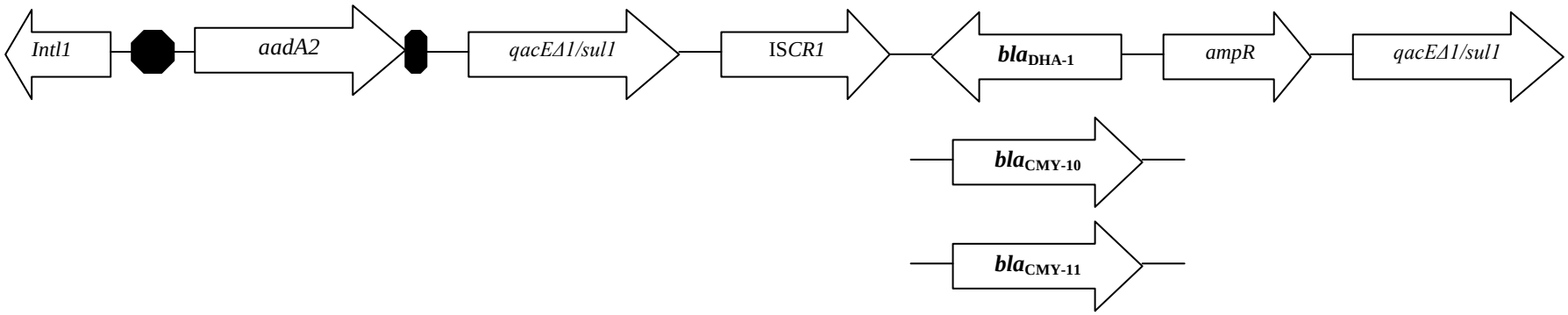
blaCMY-2
blc
sugE
blaCMY-5

b,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ISCR1
blaDHA-1
ampR
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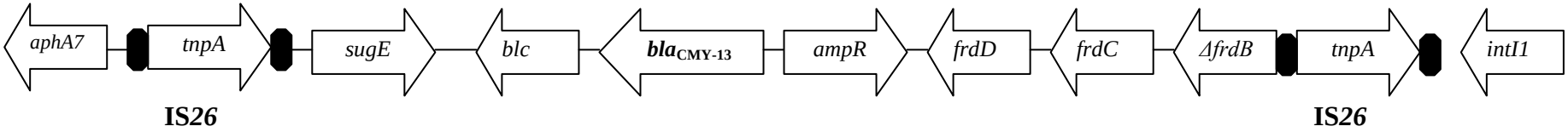
blaCMY-10
blaCMY-11

c,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sugE
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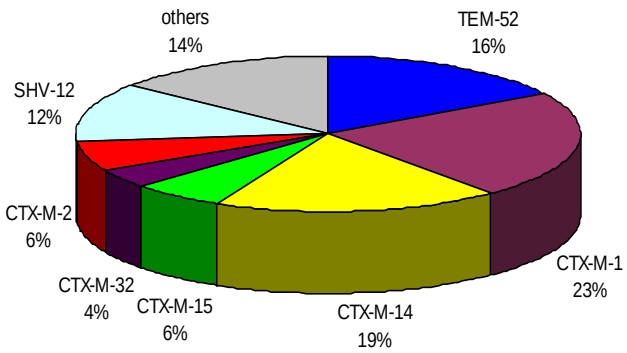
frdC
ΔfrdB
tnpA
intI1
IS26
IS26

1625 **Fig. 3**

a



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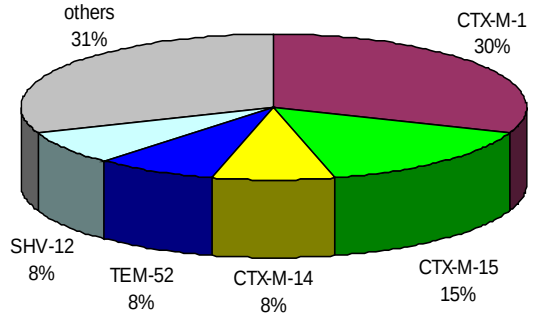
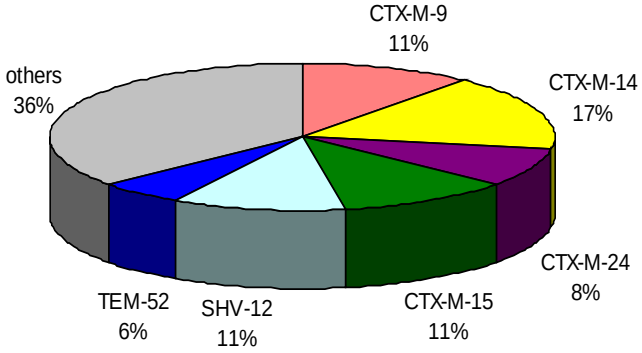


1626

c



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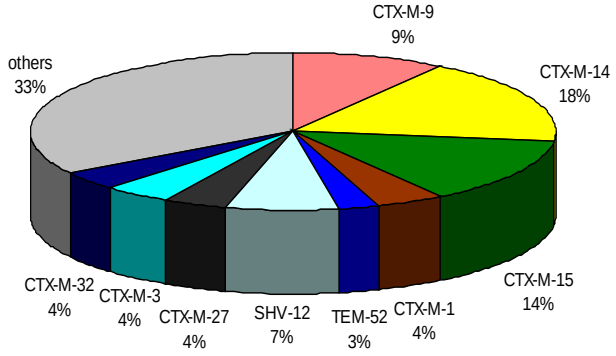

1627