Transmission of Antibiotic Resistant Enterobacteriaceae between Animals and Humans Gastrointestinal Tract with the Evidence of *in vivo* Plasmid Transfer

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Abstract: Recently, the main point of discussion is being undertaken whether the resistance of bacteria and plasmids could have been transmitted to humans from animals. Using antimicrobials in livestock production was previously shown to be followed by the occurrence of the resistant bacteria in the treated animals as well as in humans (caretakers, their family members etc.). Evidences exist that the transmission of resistance might have taken place from animals to humans. Many of these evidences were not direct and were based on the similarities between the resistance profiles of bacteria (among others indicatory *E. coli*) isolated from animals (poultry, pigs, cattle) and from humans having contact with these animals (farm workers, animal caretakers, their family members). Direct evidences have been based on the molecular methods allowing the detection of either clonally related, resistant zoonotic bacteria in humans and animals or related to resistance of plasmids isolated from humans and animals.
Key words: *Enterobacteriaceae*, β-lactamase, *E. coli*, CTX-M

Antibiyotik Dirençli Enterobacteriaceae'lerin Hayvan ve İnsan Sindirim Sistemi Arasında *in vivo* Plazmit Transferinden Kaynaklı Geçişi

Özet: Esas tartışma konusu olan nokta, bakteri ve plazmit kaynaklı bakteri direncinin hayvanlardan insanlara nasıl geçebileceğidir. Antibiyotiklerin çiftlik hayvanlarında kullanımı daha önceleri dirençli bakterilerin tedavi görmüş hayvanlarda ve insanlarda varlığını göstermiştir (hayvan bakıcıları ve çiftlik çalışanları). Direncin geçişinin hayvanlardan insanlara doğru olabileceği şeklinde kanıtlar bulunmaktadır. Bu kanıtların çoğu, direkt olmamakla birlikte hayvanlardan (çiftlik hayvanları) ve bunlarla temas halindeki insanlardan (hayvan bakıcıları ve çiftlik çalışanları) izole edilen bakteriler arasındaki direnç profillerinin benzerliklerine dayanmaktadır. Direkt kanıtlar, birbirleriyle klonal ilişkili insan ve hayvan kaynaklı dirençli zoonotik bakterilerin veya yine bunlardaki dirençle ilgili plazmitlerin moleküler metotlara dayalı olarak saptanması ile olmuştur.
Anahtar kelimeler: *Enterobacteriaceae*, β-laktamaz, *E. coli*, CTX-M

INTRODUCTION

The studies reported several resistant *Enterobacteriaceae* transmissions with the following cases: transmission of the same resistant *E. coli* (harbouring a plasmid known currently as IncFII) was demonstrated from chickens to farm workers and their family members (Levy et al., 1976). The similar plasmids conferring resistance to ampicillin and tetracycline were also described by Holmberg et al. (1984) in diverse *S. enterica* from beef and from infected humans with diagnosed salmonellosis. The similar plasmids encoding resistance to aminoglycoside-streptothricin were detected in different *E. coli* from pigs fed with this antimicrobial and also in farm workers and their families in the study of (Hummel et al., 1986). In 1990s, a range of similar plasmids conferring resistance to gentamycin and apramycin was detected in *E. coli* and *S. enterica* from cattle and *E. coli* from diseased humans in Belgium (Chaslus-Dancla et al., 1991).

Cloeckaert et al. (2007) described an epidemic IncI1 *bla*TEM-52 plasmid (now known to be ST5/CC571; 100) in various serovars of *S. enterica* from human (France) and poultry (Belgium). Recently, a range of *E. coli* isolates from humans and poultry harboring the same IncI1 *bla*CTX-M-1 (mainly ST7/CC5) and IncI1 *bla*TEM-52 (ST10, ST36/ CC5) plasmids were reported in the Netherlands by (Leverstein-van Hall et al., 2011). Madec at al. (2012) demonstrated that the IncFII (F31:A4:B1205 /IncFII and F2:A:B-/IncFII) plasmids harbouring the *bla*CTX-M-15 genes and IncI1 (CC31) circulated between diverse clones of *E. coli* from humans and animals in France.

Transmission of Resistance

Transmission of the resistance may occur either via direct contact with the animal harboring the resistant bacteria or via food chain (consumption of contaminated food or drinking water) (Marshall and Levy, 2011). It has been suggested that the resistant bacteria may reside on

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the particles suspended in the air which may then be deposited on the skin of or inhaled by the exposed individuals (Heuer et al., 2011). Contamination of agricultural products, in particular sprouts, with coliform bacteria resistant to multiple antimicrobials was also reported (Boehme et al., 2004). Shiga-toxin producing *E. coli* causing an outbreak in Germany in May 2011 resulting in fifty reported deaths was shown to harbor a large *bla*CTX-M-15 plasmid (Rasko et al., 2011). The probable source of this bacterium was sprouts likely contaminated with faces (Buchholz et al., 2011). Contamination of meat products was described among others by (Wu et al., 2008; Wu et al., 2009) tetracycline and sulphonamide resistant *E. coli* were detected in pig carcasses in Denmark. Zhao et al. (2012) also reported that *E. coli* resistant to antimicrobials were detected in retail meat in USA.

Bortolaia et al. (2010) isolated CTX-M producing *E. coli* from chicken egg in Denmark, in this case interestingly the sample originated from organic farm with no history of antimicrobial usage. Resistant bacteria transmitted from animals to humans or *vice versa* may either cause infections (zoonoses) or the resistance genes may transfer to bacteria colonizing the gut of the recipient host organism. There exist experimental evidences that the transmission of plasmids between diverse *Enterobacteriaceae* may take place *in vivo* in the gut of animals and humans. Resistant bacteria originating from animal feces may contaminate fruits (Khan et al., 2005), vegetables (possibly via faecals-containing fertilizers), soils and the surface waters and these sources may be picked up by other animals transmitting the resistance (likely on plasmids) genes further (Ardiles-Villegas et al., 2011; Bahl et al., 2009).

Epidemiology of broad-spectrum β-lactamases among *Enterobacteriaceae* from animals

ESBL- and AmpC β-lactamase-producing *Enterobacteriaceae* isolated from healthy and sick animals including food-producing animals, companion animals and wild animals. ESBL-producing bacteria are handled first, followed by the AmpC β lactamase-producing bacteria. Several studies reported that commensal broad spectrum cephalosporin resistant *Enterobacteriaceae* isolated from food producing animals has increased dramatically. 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%. 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 (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 (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 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%. 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. This may indicate that there is somehow a different epidemiology of CMY-2-producing *Enterobacteriaceae* in those countries among different animal species.

Up to date, only a few studies have been published reporting ESBL or AmpC-producing *Enterobacteriaceae* isolated from diseased pigs and cattle. The presence of ESBL- or AmpC-producing bacteria among diseased poultry has so far not been described. Data on the presence of ESBL-producing *Enterobacteriaceae* among diseased cattle and pigs have so far only been described in Korean and French reports. TEM and SHV ESBLs have been described in Korea, whereas different members of the CTX-M family are predominantly present in France (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.

Differences and similarities between different β-lactamases of *Enterobacteriaceae* in animal and human

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 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 the cases infecting cephalosporin resistant bacterium was directly derived from the animal. The diversity of broad-spectrum β-lactamases in human *Enterobacteriaceae* is much higher than in animal bacteria.

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 and 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.

Resistance of intestinal *E. coli*

Jonathan (2001) has made an experimental attempt to prove that *E. coli* has the ability to become resistant to the antibiotics when having exposure to antimicrobial agents. The development of drug resistance in intestinal bacteria is very different *in vitro* and *in vivo* conditions (Yan and Gilbert, 2004). Antimicrobial resistance can be transferred rapidly through a susceptible bacterial population *in vitro*. The possibility of transfer in the normal gut (*in vivo*), however, can be detected only at a very low rate (Freter et al., 1983; Licht et al., 1999). Evidence obtained from laboratory and epidemiological studies indicated that the persistence of resistant bacteria was related to the persistence of antimicrobial drug use (Andersson, 2003). If an antimicrobial drug is used continuously, the persistence of resistant organisms will go on. Thus, *E. coli* has often higher degrees of antimicrobials which have a long history of use (Alhaj et al., 2007). Series of studies on the resistance of *E. coli* which were isolated from animals and humans have strongly suggested that those bacteria which are resistant to antimicrobials used in animals would also be resistant to antimicrobials used in humans (VSPA, 2006; Miles et al., 2006; Umolu et al., 2006).

Mayrhofer et al. (2006) showed a direct relationship between the degree of antimicrobial use and resistance in *E. coli* isolates. *E. coli* isolated from different animal species was different concerning the degree of resistance (Burch, 2005). *E. coli* isolates from domestic species was resistant to the largest number of antimicrobial agents tested (neomycin, gentamicin, sulphonamides, chloramphenicol, orfloxacin, tetracycline, ampicillin, cephalothin, trimethoprim-sulfamethoxazole, nalidixic acid, nitrofurantoin, and sulfisoxazole) compared with isolates from human excretions, wildlife and surface water (Sayah et al., 2005). Pigs of different ages exhibit different resistance patterns of bacteria because older aged pigs use more antimicrobials which are affected more by the resistance of fecal *E. coli (*Mathew et al., 1999). The prevalence of resistance to one or more of the antimicrobial agents tested in pigs (98.3 %) was much higher than that in cattle (31.1 %) (Lim et al., 2007).

Antimicrobial resistance trend in bacteria has increased (Schröder, 2004; Burch, 2005). Resistant *E. coli* isolated from medical hospitals between 1998 and 2003 in Germany has increased significantly over the time (Schröder, 2004). Porcine *E. coli* isolated in the United Kingdom (UK) has had an increase in resistance to tetracycline, trimethoprim, sulphonamide and the fluoroquinolones (Burch, 2005). Further, some intestinal *E. coli* had the ability to resist to some antimicrobials, such as sulphonamides, chloramphenicol, ampicillin and cephalothin although these *E. coli* strains had never been in contact with such substances (Bettelheim and Thomas, 1997). Multi-resistance to clinically useful antimicrobial drugs has been found in *E. coli* (Lim et al., 2007). It was observed in a variety of sources (humans, wildlife, domestic animals and surface water) (Sayah et al., 2005). Intestinal bacteria plasmids can contribute to exchanging genes encoding antibiotic resistance (Nirdnoy, 2005; Petridis et al., 2005; Schjørring et al., 2005). *E. coli* often carries multi-resistant plasmids (Umolu et al., 2006) and it is considered as a reservoir of resistant genes to transfer those plasmids to other species as well as pathogens in humans and animals (Balis et al., 1996; Sunde and Sorum, 2001). Boerlin et al. (2005) suggested a possibility of transferability of resistance and virulence genes on plasmids of pathogenic *E. coli* isolated from diarrhea and healthy pigs. Further studies of resistance in *E. coli* have been already found such mechanisms of quinolone resistance by chromosomal mutation and plasmid medicated resistance (Mammeri et al., 2005).

CONCLUSION

Bacterial isolates with the same resistance patterns (confirmed to be clonally related) were reported in humans and animals, typically following the introduction of an antimicrobial to the livestock production. Moreover, the same resistance plasmids were found in the diverse isolates from animals and humans; some of these plasmids were self-transmissible. Transmission of plasmids between enteric bacteria in human and animal guts was also demonstrated. Considering these mentioned data, it seems likely that resistance plasmids found in humans may originate from animal sources.

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