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«prudent use» als eine Anwendung, die den therapeutischen Effekt maximiert unter gleichzeitiger Minimierung der Resistenzentwicklung. Die Weltorganisation für Tiergesundheit, OIE fügt hinzu, dass dabei nicht nur eine einzelne Massnahme, sondern eine Reihe davon zum Einsatz kommen soll. Einige Massnahmen zur Förderung des «prudent use» sind:

- die Ausbildung der Studierenden zu einem frühen Zeitpunkt im Studium. Eine Vertiefung der Kenntnisse zu Antibiotika und deren restriktiver Anwendung im 4. und/oder 5. Jahr ist in Planung.
- die Erarbeitung von allgemeinen Leitlinien zum Vorgehen und Anwendung von Antibiotika.
- die Erarbeitung von spezifischen Leitlinien pro Organklasse und/oder Erreger (Unterteilung der Wirkstoffe in «first line» und Reserve).

Auf Grund der notwendigen Abklärungen zur Gewährung der Lebensmittelsicherheit, sind die Einsatzmöglichkeiten bei Nutztieren viel eingeschränkter als für Heimtiere (inklusive Pferde mit einem solchen Status). Der Einsatz neuerer Antibiotika der Humanmedizin ist aufgrund mangelnder Definition der Höchstkonzentrationen in Fleisch und Milch der Nutztiere gar verboten. Hingegen werden Wirkstoffe wie Fluorchinolone und Cephalosporine der 3. und 4. Generation regelmässig bei diesen Tiergruppen eingesetzt. Diese Wirkstoffe sind aus Sicht der WHO kritisch und dürften nicht zur Prophylaxe eingesetzt werden sondern müssen der Behandlung klinischer Erkrankungen vorbehalten bleiben, die auf eine Erstlinientherapie unzureichend angesprochen haben (Tierarzneimittelkompendium der Schweiz).

Ein Verbot der als kritisch bezeichneten Wirkstoffe wird immer wieder diskutiert (zum Bsp. in Grossbritannien) oder wurde sogar gesetzlich verankert (Finnland, Schweden, teilweise auch in den Niederlanden). In einigen Ländern haben gewisse Produktionssektoren auf die kritischen Wirkstoffe freiwillig verzichtet (Die Niederlande, Frankreich, Dänemark).

4. Schlussfolgerung

Abschliessend tragen Tierärzte und Tierärztinnen eine grosse Verantwortung, da sie aktiv den Antibiotikaeinsatz mitbestimmen. Eine exzellente Ausbildung von Seiten der Pharmakologie, der Bakteriologie, der Lebensmittelsicherheit sowie den Kliniken kann massgeblich dazu beitragen die jungen Tierärztinnen und Tierärzte über Antibiotikaeinsatz und Resistenzproblematik zu informieren und ihnen Leitlinien für eine praxisnahe Umsetzung an die Hand zu geben. Die WHO sprach schon vor einigen Jahren von einer Krise wegen zunehmenden Resistenzen. Sicher sind neben nationalen Massnahmen auch international koordinierte Vorgehen sinnvoll. In der Veterinärmedizin ist bereits ein Rückgang der Antibiotikaverkäufe zu verzeichnen. In dem vorliegenden Vorschlag zur Revision der TAMV (Tierarzneimittelverordnung) werden zusätzliche Massnahmen zur Einschränkung der Abgabe von Antibiotika vorgesehen. ■

Antibiotic resistance - a global concern: transfer of ESBL producing *Enterobacteriaceae* at the livestock-human-environment interface, a One-Health perspective

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Antibitotic resistance (AR) is a growing problem, threatening to compromise the achievements of modern medicine. Many experts warn that humankind might soon be faced with the beginning of a post-antibiotic era characterized by untreatable bacterial infections. The situation is such that (i) the World Health Organization (WHO) called AR «a serious worldwide threat to public health» (*http://www.who.int/mediacentre/news/releases/2014/amr-report/en/*), and (ii) reinsurers as well as the World Economic Forum (WEF) ranked AR as the 5th most serious among the global societal risks in 2014 (*http://www.swissre.com/about_us/managing_risks/Global_Risks_Report_2014.html*).

Antibiotic resistance impairs the therapeutic efficiency of antimicrobials. Microbial pathogens have four general strategies to become resistant. The resistance factors usually have a genetic basis. The resistance genes may be inherent properties of defined microorganisms or may be located on mobile genetic elements that are transferable. Transferability greatly promotes the global dissemination of resistance under the selective pressure exerted by the use, overuse and misuse of large amounts of antibiotics.

Extended-spectrum b-lactamases (ESBL) are the resistance determinants most appropriate to serve as a model to show the dissemination of antibiotic resistance among human and the non-human environments. This, for a number of reasons: (i) b-lactams are the earliest antibiotics, and are in clinical use since the 1940-ies, (ii) they are the most popular anti-

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biotics being administered in nearly two thirds of all human antimicrobial treatments worldwide, (iii) different derivatives of b-lactams, including five generations of cephalosporins have been developed (iv) thus, enormous selective pressure has been exerted by b-lactams, prompting bacteria to adapt.

The first b-lactamase (resistance determinant against b-lactam antibiotics) was discovered in 1940, almost simultaneously to the introduction of the first penicillin into clinical practice. The first plasmid-mediated b-lactamase (resistance determinant against b-lactam antibiotics which can be transferred) in *Escherichia coli* – TEM-1 – was described in 1962 and inactivated penicillins and first generation cephalosporins (1G-Ceph). During the 1970-ies and early 80-ies, 2nd and 3rd-generation cephalosporins (2G-Ceph and 3G-Ceph) came into market, followed by the 4G-Cephs in the 1990-ies. These new formulations were to become indispensable for the clinicians, and were accordingly over-used. Consequently, bacteria became exposed to heavy selection pressure and reacted by optimising their b-lactamase structures, which leaded to extend the substrate spectra to also include 2G-, 3G- and 4G-Cephs and monobactams. Resistance determinants inactivating also 3G- and 4G-Cephs are called extended-spectrum b-lactamases (ESBL) and they belong to three main groups (TEM, SHV and CTX-M) with different variants. Jacoby and Bush set up an internet platform for all authors reporting new b-lactamases (*http://www.lahey.org/Studies/*). This platform - when accessed in August 2014 – had 219 TEM-, 188 SHV-, and 159 CTX-M b-lactamases on display: truly a formidable evolutionary record within just three decades. Because of the diversity of ESBLs, their detection and confirmation became difficult so that special selective media and confirmations tests needed to be developed and commercialized (Figure 1).

The occurrence of bacterial isolates producing ESBLs also underwent a remarkable development, and, with time, became an issue of much concern. Although ESBL producers were at first sporadic opportunistic pathogens, mainly E. coli, isolated from long-term hospitalized patients, they were soon found responsible for nosocomial (within hospitals) outbreaks. Moreover, ESBL-encoding plasmids were soon transferred into many other species such as *Salmonella sp.* or *Pseudomonas aeruginosa*. By the end of the century, ESBL producers had disseminated around the world, and, interestingly, CTX-M resistance determinants had replaced TEM- and SHV types as the dominating ESBL family for as yet unknown reasons. By around 2005, ESBL producers made up an ever increasing proportion among isolates from patients of private practitioners, heralding a shift from the hospital to the general public.

Switzerland is a country with highly developed livestock and food technological standards as well as a sophisticated medical system. By installing nationwide infectious disease experts and hospital hygienists etc., it imposes strict prescription guidelines for the prudent use of antibiotics in human and veterinary clinical practice as well as in agriculture.

Consequently, based on the One Health perspective, it is of interest, to search for producers of ESBLs along the food chain, in patients from primary care, in healthy humans, in wild animals, and in the environment. The aim is to (i) collect sets of strains from the mentioned origins, (ii) characterize all strains in much detail using molecular methods, and (iii) compare the sets in order to gain insight into possible routes of dissemination.

Knowing about the shift of prevalence of such organisms from hospitals to the general public from foreign studies, food was primarily suspected as a vehicle, and in particular meat and animal products, because of the well-known therapeutical application of antimicrobials in animal husbandry. Consequently, fecal carriage of ESBL producers in various farm animals and corresponding food products such as meat and milk were assayed in Switzerland. Fecal swabing from cattle, pigs, sheep, and chickens at slaughter yielded ESBL-positive isolates in 13.7%, 15.3%, 8.6%, and 63.4% of samples, respectively. In contrast, no ESBL producers were found in minced beef or pork from retailers, and neither in bulk raw milk samples. However, 78% of poultry samples from retailers yielded E. coli positive for CTX-M-1, and 15% of cutting boards from a hospital kitchen grew ESBL producers after processing of poultry meat and, again, CTX-M-1 was predominant. Concurrent studies on humans in Switzerland revealed that 5.8% of healthy

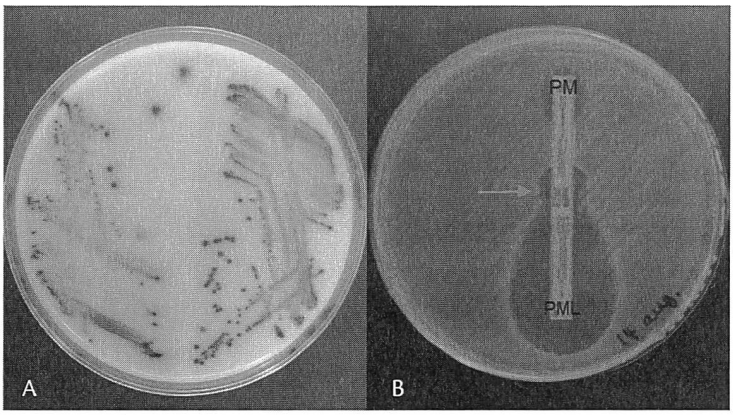

Figure 1 *(coulours see web version). Selective Medium for ESBL producers with suspected ESBL-producing colonies (A), and confirmation test for ESBL-producers (B).*

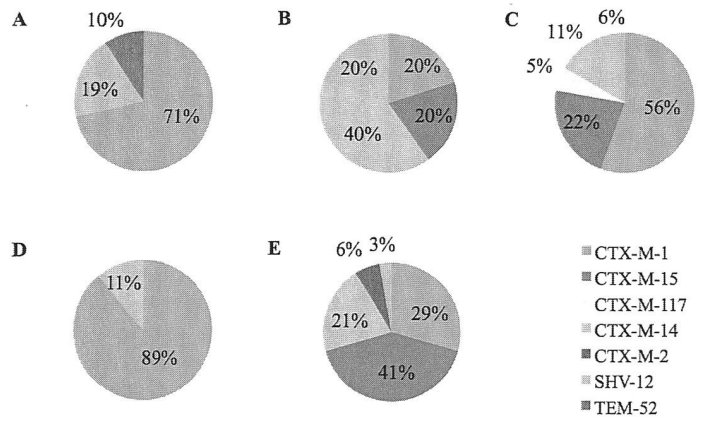

***Figure 2** (coulours see web version). Prevalence in Switzerland of blaESBL genes in Enterobacteriaceae of farm-animal or healthy-human origin. A, chickens; B, sheep, C, cattle; D, pigs; E, healthy humans. (Graphics taken from Ref. 7 with written permission from the original publisher)*

subjects and 5.2% of primary care patients carried ESBL producers in their stool. Further characterizing the bacteria collections of these studies provided an astonishing multiplicity of ESBL variants (Figure 2). However, it became obvious that CTX-M-1 was predominant in food animals and poultry meat, while CTX-M-15 (42%) was most frequent in humans (Figure 2). Interestingly, 8/107 (7.5%) isolates from cats and dogs with urinary tract infections turned out to also express CTX-M-15. Considering these percentages and the Swiss consumer habits, animal food products – and particularly poultry - offer a plausible explanation for the 29% of CTX-M-1 producers found among the isolates from human ESBL carriers. However, the main proportion – the 42% of human carriers of CTX-M-15 producers – could not be explained by these studies.

Prompted by the relatively high ESBL prevalences encountered within the realm of humans and farm animals, the scope of the investigation was extended to cover wild animals and the environment. Among hunted ibex, chamois, red deer, and roe deer, a single roe deer was identified as a carrier of E. coli expressing CTX-M-1. Among 298 street pigeons from the City of Zürich one carried a producer of CTX-M-15, and of 30 great cormorants one each was a carrier of E. coli positive for CTX-M-15 or CTX-M-27, rsepectively. Sampling 139 fish caught in two Swiss lakes (Lake Zürich and Lake Thun), and belonging to eight species, identified 26 (18.7%) as ESBL carriers (most frequent ESBL type was CTX-M-15).

Eventually, an investigation into surface waters covering the German-speaking part of Switzerland was performed, whereby 40 rivers and 18 lakes from urban and rural areas as well as low and high altitudes were surveyed. Alarmingly, 21 of the 58 samples from the water bodies (36.2%) yielded a total of 74 Enterobacteriaceae producing ESBLs. A variety of ESBL types were found. However, as in healthy humans, CTX-M-15 was the dominating type (62%). Moreover, ESBL producers were clearly confined to the urban areas, while samples from altitudes above 1000m remained negative even though sampling had been executed during the alpine summer farming season.

In conclusion, ESBL producers are extremely widely disseminated in humans, in food animals and pets, in various wild animals, and even in the urban low altitude surface waters in Switzerland. Careful determination of ESBL types has yielded convincing evidence to allow listing four major findings, (i) food animals, particularly poultry, are an important reservoir of E. coli producing CTX-M-1 ESBL and may be responsible for a part of ESBL producing *E. coli* colonizing humans, (ii) although the reservoir of CTX-M-15 producers has not so far been discovered, CTX-M-15 is with 41% the most frequently found ESBL among healthy humans excreting ESBL producers, (iii) humans and pets largely share the same ESBL type, CTX-M-15, and (iv) surface waters and humans share the most frequent ESBL type, again CTX-M-15. The latter finding strongly suggests that CTX-M-15 producers may be disseminated by human sewage via waste water treatment plants into the environment.[1] ■

[1] For further reading: Institute for food safety and hygiene, Vetsuisse-Faculty, University of Zurich, *www.ils.uzh.ch*; Institute for Veterinary Bacteriology, Vetsuisse-Faculty University of Berne, *http://www.vbi.unibe.ch/content/index_ger.html.*