Mini-review: Epidemiology and zoonotic potential of multiresistant bacteria and Clostridium difficile in livestock and food

Mini-Review: Epidemiologie und zoonotisches Potential von multiresistenten Bakterien und von Clostridium difficile bei Nutztieren und in Lebensmitteln

Abstract

Aim: Information on the epidemiology of multiresistant bacteria (MRB) with zoonotic potential is growing but still remains quite incomplete. This narrative mini-review provides a general overview of the epidemiology of the most important zoonotic MRB in cattle, swine and poultry in Europe.

Methods: A literature search was conducted mainly on the PubMed website including articles published until April 2012.

Results: Livestock-associated methicillin-resistant Staphylococcus aureus (LA-MRSA) especially poses a zoonotic risk to people working in close contact with livestock. These people may become carriers themselves and the hazard of transmission into health-care facilities needs surveillance. Extended-spectrum beta-lactamases (ESBL) producing bacteria are widely spread in both humans and livestock, sharing similar genotypes, especially of the CTX-M-group, which makes a zoonotic transfer very likely. Identical strains of vancomycin-resistant enterococci (VRE) were found both in humans and animals, after ingestion of animal strains transient colonization of the human gut may be possible. Only a few data are available on the transmission of methicillin-resistant coagulase-negative staphylococci (MR-CoNS) between humans and animals. Direct contact to colonized animals may be a risk factor as well as the exchange of resistance genes between human and animal staphylococci. Clostridium difficile (C. difficile) ribotype 078 emerges in livestock and humans and a zoonotic transmission seems probable as genotypes and diseases resemble each other.

Conclusion: All discussed MRB and C. difficile are important nosocomial agents which also occur in livestock and were found in foods of animal origin. Further analysis is needed to reveal the exact transmission routes and to perform a reliable risk assessment.

Keywords: livestock, zoonoses, MRSA, Clostridium difficile, E. coli, ESBL, vancomycin, VRE, multiresistant

Zusammenfassung

Zielsetzung: Die Intention des vorliegenden narrativen Mini-Reviews ist es, dem Leser einen Überblick über die Prävalenz und Epidemiologie multiresistenter Bakterien in Europa bei Rindern, Schweinen und Geflügel zu geben und deren zoonotisches Potential zu beleuchten.

Methode: Es wurde eine PubMed-Literaturrecherche unter Einschluss bis April 2012 publizierter Artikel durchgeführt.

Ergebnisse: Der livestock-associated Methicillin-resistente Staphylococcus aureus (LA-MRSA) ist nicht nur bei Nutztieren, sondern auch häufig bei engen Kontaktpersonen nachweisbar. Dem Eintrag durch kolonisierte und infizierte Personen ins Gesundheitswesen muss deshalb Beachtung

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geschenkt werden. Bakterien, die die Fähigkeit besitzen, β-Laktamasen mit einem erweiterten Wirkspektrum (ESBL) zu bilden, sind ebenfalls bei Mensch und Nutztier zu finden. Insbesondere die ESBL vom Typ CTX-M stehen im Verdacht, zwischen Mensch und Tier übertragen zu werden. Einige Studien legen nahe, dass eine Transmission von Vancomycin-resistenten Enterokokken (VRE), z.B. nach oraler Aufnahme kontaminiertier tierischen Lebensmitteln, auf den Menschen möglich ist. Bezüglich des zoonotischen Potentials von multiresistenten Koagulase-negativen Staphylokokken (MR-CoNS) existieren hingegen nur wenige Publikationen. Es gibt jedoch erste Hinweise, dass eine zoonotische Übertragung möglich sein könnte und auch der Austausch von Resistenzgenen zwischen humanen und tierischen Bakterien scheint prinzipiell möglich. Die Nachweisrate von Clostridium difficile (C. difficile), v.a. des Ribotyps 078, hat bei Mensch und Tier gleichermaßen zugenommen. Nicht nur die Genotypen, auch die verursachten Infektionen weisen unabhängig von der betroffenen Spezies Gemeinsamkeiten auf.

Schlussfolgerung: Alle betrachteten multiresistenten Erreger sowie C. difficile spielen eine erhebliche Rolle bei nosokomialen Infektionen in der Humanmedizin und sind ebenfalls bei Nutztieren und Lebensmitteln tierischen Ursprungs zu finden. Weitere Studien sind nötig, um die exakten Transmissionsrouten zu identifizieren und eine valide Risikobeurteilung durchzuführen.

Schlüsselwörter: Nutztiere, Zoonosen, MRSA, Clostridium difficile, E. coli, ESBL, Vancomycin, VRE, multiresistent

Introduction

Increasing resistance against antimicrobial substances in bacteria is a major problem in human as well as veterinary medicine [1], [2]. Multiresistant bacteria (MRB) with reduced susceptibility against different antibiotic classes are of exceptional clinical importance, as therapeutic options are very limited or no longer exist. While the role of MRB in human medicine is well acknowledged, the veterinary aspects of this problem have been largely neglected for a long time. The pathogenic potential of MRB, their zoonotic potential, i.e., the multiple ways of transmission to humans by direct and indirect contact and vice versa, as well as the economic implications altogether account for the huge public health impact of MRB in livestock.

There are several possible transmission pathways. First, there are agents with a wide host range, which can be directly transmitted from animal to human. Second, the antibiotic resistance genes can be transmitted from animal bacteria to commensals or infectious agents of humans through the food chain or direct contact. The third pathway is the direct transfer of obligate pathogen bacteria through food; to some extent also by contact to animals which mainly induces gastrointestinal infections (e.g., serotypes of the genus Salmonella) [3], [4]. Indirect transmission through vectors like the air, vermin, manure, contaminated water, etc. is also probable [5], [6], [7], [8]. A transmission from human to animal seems possible as well [9]. Transmission may lead to asymptomatic colonization as well as infection. In contrast to other publications that focus on one specific MRB, this mini-review is meant to give an overview on the most important MRB and their role in livestock in Europe.

The most common MRB in human and veterinary medicine is the methicillin-resistant Staphylococcus aureus (MRSA) which first gained public attention for causing severe nosocomial human infections. Some years ago, animal strains like ST398 were detected in livestock, posing a new risk to human health [10]. Besides MRSA, other MRB colonizing the human digestive tract as well as the intestine of livestock have come into focus. Extended spectrum beta-lactamas (ESBL)-producing bacteria induce nosocomial infections in humans, with a rising incidence [11], [12]. Livestock has frequently been found to carry ESBL-producing bacteria of the blaCTX-M gene family, these genes are occasionally similar to the ones in human specimens [13], [14], [15]. Other potential pathogens in the animalistic digestive tract are vancomycin-resistant enterococci strains (VRE). This pathogen caused uproar in the 90s, when the glycopeptide antibiotic and growth promoter avoparcin was suspected to cause cross-resistance with antibiotics prescribed in human medicine [2], [16], [17]. Methicillin-resistant coagulase-negative staphylococci (MR-CoNS) are only gaining delayed public attention. CoNS are a heterogeneous group: in human medicine they are the most common cause of central line-associated bloodstream infections (CLABSI) [18], in contrast, in veterinary medicine some species of CoNS are known as a cause for mastitis in dairy cattle [19]. The zoonotic potential of these organisms is largely unknown, only few are regularly found in humans and in animals. The Gram-positive anaerobic Clostridium difficile is not a MRB by definition, it is included in this review because of rare therapeutic options
due to intrinsic resistances. It is able to cause severe nosocomial diarrhea in human medicine [20], [21] and it has recently been recognized as a potential pathogen for young animals and as a zoonotic agent in veterinary medicine [22].

**Methods**

**Search strategy**

The literature was reviewed in MEDLINE on the internet homepage of the National Library of Medicine and by Google scholar. The search was done from June 1, 2011 to April 1, 2012. The following search terms were applied: “MRSA; multiresistant; *Staphylococcus aureus*; ESBL; extended spectrum beta lactamases; *Clostridium difficile*; VRE; vancomycin-resistant enterococci; MR-CoNS; multiresistant coagulase-negative staphylococci; resistance” linked with “and” to “animal; poultry; swine; pig or cattle”. In addition, the citations in each study found during the main search were reviewed for potential relevance. Finally, standard textbooks on infection control, bacteriology and microbiology were examined for information.

**Selecting studies**

All publications found with the mentioned keywords were checked for relevance. Publications about wildlife, pets and laboratory animals were excluded. The selection was limited to publications written in English and German. Mainly, publications describing the situation in Europe were used as well as a few relevant publications from America and Asia. At least one of the investigators decided on the relevance of each report. Reports were not blinded to the investigators so that they knew the names of the authors of all studies.

**Results**

**Methicillin-resistant Staphylococcus aureus (MRSA)**

*Staphylococcus aureus* (SA) is an important facultative pathogen and nosocomial agent in human medicine. The methicillin- or multiresistant *Staphylococcus aureus* (MRSA) is resistant to all β-lactam antibiotics. Resistance to other antibiotics like e.g., quinolones or macrolides is very common [23]. Due to several resistances, therapeutic options are very limited. MRSA can cause inter alia, skin and soft tissue infections, pneumonia or sepsis [24]. Besides hospital-acquired MRSA (HA-MRSA), community-associated MRSA (CA-MRSA) exists in non-hospitalized people. The third group is the livestock-associated MRSA (LA-MRSA), frequently belonging to the multi-locus sequence type ST398. Apart from the prominent ST398, many other sequence types of MRSA strains have been described in livestock. Some strains are exclusive to animals (e.g., ST151, ST771, ST130, ST837), others were detected in various hosts (e.g., ST22, ST254) [25], [26], [27], [28].

The methicillin resistance of MRSA is provoked by the mecA gene which is one common mobile genetic element located on the staphylococcal cassette chromosome mec (SCCmec). MecA encodes the penicillin-binding protein 2a (PBP2a), which has a low affinity to β-lactam antibiotics [1]. In 2011, a new variant emerged, that was not detectable by conventional MRSA tests. It was named mecA_{mecC} or mecC, belonging to different MRSA-types like CC130, CC705 or ST425. MecC-positive MRSA may cause bovine mastitis as well as wound infection in humans [29], [30]. It is a new diagnostic and therapeutic challenge to veterinary and human medicine and the global spread needs further investigation.

The Dutch were the first who found the connection between livestock and human reservoirs of MRSA. Voss et al. detected MRSA in a child of a pig farmer; despite several attempts of decolonization, the child and its family remained MRSA-positive. Constant re-colonization from a non-human reservoir was suspected and the farmer’s pigs were tested and found MRSA-positive [10]. This case triggered extensive research on the epidemiology of MRSA in pigs. Finally, the strain was identified as multilocus sequence type (MLST) 398 or frankly MRSA ST398. This strain was thereafter repeatedly found in pigs, farmers and contacts. Pigs show a particular high colonization with MRSA ST398. Accordingly, swine form an important reservoir for the transmission to humans [10] (Table 1). In the Netherlands, 39% of tested pigs and 81% of pig herds were found to be MRSA-positive at the slaughterhouse [31]. One group found pig holdings with a prevalence of 13% concerning the individual animal and 18% with regard to the positive herds in the German Federal States of North Rhine-Westphalia and Lower Saxony. 23% of the persons with close animal contact were colonized with ST398 [32]. While these results may seem quite low in comparison to the study of the Netherlands, another study at the Dutch-German border showed 70% of colonized herds with ST398 [33]. Cuny et al. screened pig farms in different German regions and found an even higher prevalence in pig herds of 82.5%. Furthermore, 86% of the pig farmers working with MRSA-positive pigs were also MRSA-positive, as well as 4.3% of the family members and 45% of the tested veterinarians. Humans without close contact to pigs did not show an increased colonization [34]. Interestingly, pigs raised in an alternative system were not found to be MRSA-positive [35].

In 2008, the European Food Safety Authority (EFSA) determined the prevalence of MRSA in holdings with breeding pigs in Europe. While in some countries MRSA was not detectable (e.g., Finland, Denmark), others showed a relatively high prevalence. Spain reached the highest level with 46%, followed by Germany (43.5%) and Belgium (40%). The average among the European Union revealed a prevalence of 14% in stocks with breeding pigs and of 26.9% in production holdings [36].
SA and MRSA are also important facultative pathogens for ruminants, where they appear either as a pathogen provoking clinical mastitis of the dairy cow or as opportunistic colonizer of veal calves [37]. For decades, SA has been known to cause mastitis and huge economic damage in dairy cattle [38], [39], [40]. The prevalence of clinical infections of the bovine udder with MRSA seems to be rather low at the moment [41], [42]; the colonization of veal calves might be more frequent. In the Netherlands, Graveland et al. detected a prevalence of 28% in the individual calf and a herd prevalence of 88% in 2010. Veal calf farmers were colonized at 33% and their family members at 8%; in comparison less than 0.1% of the Dutch general public without animal contact was identified as MRSA carrier. Furthermore, this study showed that the intensity of the animal contact and number of positive animals in the herd have a huge influence on the likelihood of human colonization [43].

As in pigs and ruminants, livestock-associated MRSA has been found in poultry. A comparison of Belgian SA-isolates from poultry from the 1970s and isolates from 2006 showed a significantly higher occurrence of antimicrobial resistance in the younger samples and all MRSA isolates were associated with ST398 [44]. Inter alia, the increase of resistance rates may be due to the use of antimicrobials. In another Belgian study, MRSA was found in broilers but not in laying hens which is presumably a result of the different antibiotic use [45]. Dullweber investigated the prevalence of MRSA in dust samples and tracheal swabs taken from broilers in northwest Germany and found 31.8% and 62.5% of swaps MRSA-positive, respectively [46].

The detection of MRSA in poultry meat is possible, as well [47], [48]. MRSA is also found in meat of other animal species like pig or cattle. At the slaughterhouse cross-contamination between the carcasses of MRSA-positive and -negative animals may be possible and retail meat can show a high prevalence of MRSA: In the Netherlands, 10.6% of beef, 15.2% of veal and 10.7% of pork from retail trade were MRSA-positive, but it was also found in lamb, mutton, game and poultry products [49]. Another Dutch study found only 2.5% of pork samples MRSA-positive [50] and in Spain the prevalence in foods totals 1.6% [51]. The varying prevalence may be explained by different sampling strategies and methods. MRSA can also occur in cheese and raw milk [52]. Therefore, the question arises whether MRSA is transmittable to humans through foods of animal origin if specific hygiene rules

Table 1: Prevalence of MRSA in different livestock species and in people with close animal contact (incomplete list)

| Year | Author          | Country | Prevalence per animal | Prevalence per herd | Prevalence in mankind |
|------|-----------------|---------|-----------------------|---------------------|-----------------------|
| 2005 | Voss et al. [10]| NL      |                       |                     | 23% of the pig farmers |
| 2009 | EFSA [36]       | D       | 43.5 % pig            |                     |                       |
| 2007 | De Neeling et al. [31] | NL   | 39% pigs              | 81% pig             |                       |
| 2008 | Meemken et al. [32] | D    | 13% pigs              | 18% pig             | 23% of the persons with close animal contact |
| 2008 | Van Duijkeren et al. [185] | NL | 11% pigs              | 23% pig             |                       |
| 2010 | Battisti et al. [186] | I     | 38% pig               |                     |                       |
| 2009 | Cuny et al. [34] | D       | 82.4 % pig            | 86% pig farmers     | 45% veterinarians     |
| 2009 | Köck et al. [33] | D       | 70% pig               |                     |                       |
| 2010 | Frick [187]     | D       | 33.3% pigs            | 45% pig             | 29.3% pig farmers     |
| 2011 | Broens et al. [188] | NL | 67–71% pig            |                     |                       |
| 2008 | Van Rijen et al. [189] | NL   |                       | 32% of the persons with close contact to veal calves and pigs |
| 2010 | Graveland et al. [37] | NL  | 28% veal calves       | 88% veal calf       | 33% of the farmers    |
| 2009 | Persoons et al. [45] | B     | 10.7% broiler         | 14.3% broiler       |                       |
| 2010 | Dullweber [46]   | D       | 62.5 % broiler        |                     |                       |
are neglected. In 2009, the EFSA assessed the risk to human health posed by MRSA through food. At that time no evidence for an increased risk of human colonization or infection through contaminated foods was found [53]. In general ST398 harbors less virulence factors than most HA-MRSA, nevertheless it may induce severe infections in humans [54], [55], [56], [57]. The number of infections due to ST398 is still low, in German hospitals infections with MRSA related to CC5, CC22 or CC45 are dominating [23]. The lineages differ significantly by geographical region, country or continent.

In Germany and other countries, pig farmers are defined as risk patients for MRSA and admission screening is recommended [58], [59]. Livestock veterinarians are at risk as well, especially those who work at pig farms [60]. Livestock itself usually is an asymptomatic carrier of LA-MRSA, but exudative epidermitis in pigs, mastitis in cow and several infections in other animal species and pets are described [61], [62], [63], [64].

**Extended spectrum beta-lactamases (ESBL)**

Extended spectrum beta-lactamases (ESBL)-producing bacteria occur commonly in Enterobacteriaceae and non-fermenting bacteria. These plasmid-encoded enzymes provide a wide resistance against most β-lactam antibiotics. ESBL-producing bacteria mainly cause lower urinary tract infections (UTI) in humans; wound infections or bloodstream infections are also possible [65], [66]. Primary a nosocomial pathogen, it is nowadays also found in the community causing UTIs [12]. The treatment of severe infections is complicated by co-resistance to other antibiotic classes (e.g., quinolones, aminoglycosides) [67].

Besides humans, ESBL-producing organisms are found in pets, wild animals, zoo animals and livestock [68], [69], [70], [71], [72]. *E. coli*, *Salmonella* spp. and *Klebsiella* spp. are the most important ESBL producers in animals. *E. coli* and *Klebsiella pneumonia* also are the most frequent human ESBL isolates [73].

The TEM-52, SHV-12, CTX-M-1, CTX-M-14 and CTX-M-15 enzymes are ESBL enzymes frequently found in food producing animals and foods [74], [75]. Recently, the CTX-M group became the prevalent group in human medicine as well [76], especially in *E. coli* and *Klebsiella* spp. In humans, SHV-12, CTX-M-1, CTX-M-9, CTX-M-14 and CTX-M-15 are predominant enzymes in the European Union, while CTX-M-15 can be found worldwide [73], [76], [77].

In Denmark, a research group found a CTX-M-1 producing *E. coli* in pigs, pig farmers, manure and the air, which all shared the same IncN-plasmid *bla*_{CTX-M} [14], i.e. the environment also could play a role as an accessory risk factor [78], [79].

*E. coli* and *Klebsiella* spp. are important causes of mastitis in dairy cattle, but normally livestock only is an asymptomatic carrier of ESBL producers [80]. Madec et al. analyzed fecal samples of diseased (6.2% ESBL) and healthy (5.8% ESBL) cattle and isolated especially ESBL-producing *E. coli*. The majority of these contained genes of the CTX-M-1 group [81] which is in general a commonly found ESBL in livestock [74]. Comparing a conventional dairy cattle farm to an organic dairy farm in the Czech Republic, much more ESBL-producing bacteria (39% against <1%) were found in the conventional farm, which may demonstrate the effect of a much greater usage of cephalosporins [82].

Besides wild birds – which are not under the selective pressure of antibiotics – chicken and turkeys are frequent ESBL carriers [83], [84]. First, during the Spanish antimicrobial resistance surveillance program between 2000 and 2001, ESBL-producing bacteria were found in healthy chicken [85]. Since then, a lot of studies have been able to demonstrate the existence of ESBL-producing bacteria in poultry [86], [87], [88], [89], [90]. A study compared ESBL-producing *E. coli* of animal and human sources, the most isolates clearly differ from each other. Otherwise, the clonal lineage B2-*E. coli* O25:H4-ST131 producing CTX-M-9 and the D-E. coli O25a-ST648 group producing CTX-M-32 was found in poultry, which were very similar to those found in humans [91].

Recently, a Swiss study group found a very high prevalence of 63.4% ESBL-producing bacteria in healthy chicken fecal samples at the abattoir, the prevalence in pig, cattle and sheep samples varied between 8.6–15.3% [75]. A Dutch research group analogously found about 80% of poultry meat positive for ESBL-producers, those are highly similar to human rectal swabs obtained from hospitalized patients [15]. Several reports provide evidence of food-borne clinical outbreaks caused by multidrug-resistant *Salmonella* spp. [3], [4], [92]. However, there are also indications of transmission of ESBL-producing *E. coli* from foods of animal origin to humans or vice versa [15], [93]; a Dutch report showed that 19% of tested patients harbored ESBL genes which were indistinguishable from those in poultry isolates [13]. The comparison of pulsed-field gel electrophoresis (PFGE) patterns between poultry, poultry farmers and slaughterers demonstrates that direct animal contact may also be an important route for transmission [94]. An exchange of resistance genes between animal and human bacterial strains even seems possible [14].

**Vancomycin-resistant enterococci (VRE)**

Enterococci are commensals of the human and animal intestinal microflora. Besides their intrinsic resistance to cephalosporins, enterococci can acquire resistance e.g. to glycopeptides such as vancomycin through transmissible genetic elements. *Enterococcus faecalis* is the most frequent isolated strain in human patients, followed by *Enterococcus faecium*. These enterococci also occur in animals. Several different genotypes have been detected until now, vanA and vanB play an important role in human medicine. Even livestock is a frequent vanA carrier [17], [95], [96], [97]. The vanA gene is usually located in the transposon Tn1546 [98]. While animals are mainly asymptomatic carriers, VRE may lead to severe nosoco-
mial infections in humans, such as UTIs or wound infections [99], [100], [101]. Reports about increasing detection of VRE in livestock caused serious concern in Europe in the 1990s [102], [103], [104]. The application of the glycopeptide-antibiotic avoparcin, used for growth promotion in livestock fattening, was controversially discussed. There was strong suspicion of causing cross-resistance with vancomycin/teicoplanine; therefore a severe risk for human medicine was supposed. This has led to a ban of avoparcin in 1986 in Sweden, followed by Denmark and Germany and finally the entire EU since 1997 (Commission Directive 97/6 EC). However, some critics also doubted a correlation between avoparcin and increasing antibiotic resistance [103], [105], [106].

In 1995, VRE vanA-type was isolated from thawing liquids of frozen poultry and from raw minced meat of pigs in Germany [107]. In 1997, up to 15% and 16%, respectively, of samples from pork and broilers were found VRE positive in Denmark [108]. With the ban of avoparcin the occurrence of VRE in the intestine of healthy communities decreased from 12% (1994) to 3% (1997) [2] and also the prevalence occasionally decreased in meat [2], [103], [109].

Otherwise, in 2002, Heuer et al. tested the occurrence of VRE in Danish broiler farms, still finding a high prevalence of positive broiler flocks. VRE has even been detected in the environmental samples after cleaning and disinfection due to known persistence [110]. A transmission to following broiler herds seems probable. The co-selection by macrolides is presumed to be another cause of the persistence of VRE in the absence of avoparcin. The gene for macrolide resistance is located on the same plasmid as the vanA gene [111].

A high prevalence (77.1%) in poultry fecal samples was found in Austria in 2005, while the prevalence in samples from cattle and swine was much lower (21.6–23.3%) [112]. Recently, Ramos et al. still found 25.3% VRE-positive fecal samples in pigs in Portugal, but in contrast none were detected in bovine samples [113]. Even if the prevalence of VRE seems to decrease in several animals, VRE may persist in some areas and species. Processed food may likewise act as vector of VRE besides living animal. Determining the zoonotic potential, van den Boogard et al. found 50% of the sampled turkeys and 39% of the farmers VRE-positive as well as at least 20% of the turkey slaughterers and 14% of samples of area residents without direct contact to those animals [102]. This demonstrates that close contact may be a risk factor for transmission between animals and humans.

Human VRE isolates can harbor the same Tn1546 variant found in livestock and foods, indicating a horizontal gene transfer in the intestine [114], [115]. However, transient colonization of the human intestine was demonstrated after ingestion of VRE of animal origin [116], [117]. Furthermore, the in vivo transfer of an avian vanA gene from E. faecium to a human vancomycin-susceptible E. faecium strain in volunteers was shown in 2006 [118]. This indicates that foods of animal origin may be a vector of resistance genes. VRE, isolated from pigs and humans of several European countries and the United States, were compared by PFGE in a study from Freitas et al. E. faecium clonal complex 5 (CC5) and CC17 were found in both animals and humans, showing similar or even identical PFGE patterns. CC5 E. faecium can also be detected in patients with UTIs [5]. Several different sequence types can be found both in hospitalized patients and livestock (e.g. ST16) [119], [120].

**Methicillin-resistant coagulase-negative staphylococci (MR-CoNS)**

Methicillin-resistant coagulase-negative staphylococci (MR-CoNS) represent a heterogeneous group with huge species diversity. The methicillin resistance is mediated through the SCCmeC, similar to the resistance mechanism in MRSA. Inter alia, CoNS are commensal organisms of human and animal skin and mucous membranes. *S. epidermidis, S. haemolyticus* and *S. hominis* are the most important species in human samples [121], [122]. CoNS and especially MR-CoNS are known as relevant nosocomial pathogen in humans. The impact of MR-CoNS has been increasing for a period of 20 years; nowadays approximately one third of central line-associated bloodstream infections are caused by CoNS in Germany and almost two third of these samples are methicillin-resistant [18].

MR-CoNS have also been classified as emerging animal pathogens [123] as they are an important causative agent of mastitis in dairy cows and small ruminants. Different species of staphylococci are detectable, depending on the location; the skin colonization may be different than the colonization of the udder. The CoNS causing subclinical, or less often, clinical mastitis are i.a., *S. xylosus*, *S. simulans*, *S. warneri* or *S. chromogenes* but may also be *S. epidermidis, S. haemolyticus* and *S. hominis* [19], [124], [125] (Table 2).

Subclinical mastitis due to MR-CoNS in cattle results in high economic losses caused by a decreased milk yield and an increased milk cell count. In this case, cows frequently get a dry cow therapy at the end of lactation, i.e., an antibiotic is directly injected into every udder quarter. This may lead to increasing resistance with penicillin-resistant CoNS being found in approximately 30% of the treated dairy cows [126], [127], [128]. Resistance in CoNS have also been found in pig [129], poultry, small ruminants [130], [131], [132] and veal calves [133]. Besides mastitis in dairy cattle (including small ruminants), livestock are typically asymptomatic carriers.

MR-CoNS are divided into a lot of species and subspecies, some of them only occur in certain animals or humans. But a lot of species have a broad host range. A direct transfer from animal to humans with close contact seems to be possible [131], this could be a threat especially to immunocompromised people. Another hazard is the horizontal transfer from resistance genes. Livestock are a huge reservoir for MR-CoNS and a transfer from resist-
ance genes to other CoNS species or S. aureus is very likely [134], [135], [136], [137]. The same SCCmec types were already found in CoNS and S. aureus [138]. The relevance of a transfer to humans via foods is still little-known, but it is found in meat and bulk tank milk [131]. Whether foods of animal origin are dangerous to human health has to be verified in future investigations.

Table 2: Coagulase-negative Staphylococci in animals and their occurrence in humans [121], [122], [132], [190]

| Staphylococci species in animals | Occurrence in humans |
|---------------------------------|----------------------|
| S. cohnii                       | XX                   |
| S. chromogenes                  | XX                   |
| S. epidemidis                   | XXX                  |
| S. fleuretii                    | X                    |
| S. haemolyticus                 | XXX                  |
| S. hominis                      | XXX                  |
| S. hyicus                       | X                    |
| S. lentus                       | X                    |
| S. saprophyticus                | XX                   |
| S. sciuri                       | X                    |
| S. simulans                     | XX                   |
| S. warneri                      | XX                   |
| S. xylosus                      | XX                   |

XXX very frequently; XX moderate; X infrequent

Clostridium difficile (C. difficile)

C. difficile is a spore forming and toxin producing anaerobic Gram-positive bacterium; frequently found in humans, animals and foods [139], [140], [141], [142], [143], [144]. It is a common cause of healthcare-associated diarrhea; a direct connection between the use of antibiotics and pseudomembranous diarrhea due to C. difficile is well acknowledged in human medicine [145]. The capability of forming spores makes Clostridia very resistant to environmental influences. C. difficile can produce different toxins: the two major toxins are toxin A and toxin B; some strains can produce a binary toxin. Toxin A is an enterotoxin and toxin B provides cytotoxic effects, whereas the effects of the binary toxin have not yet been completely clarified [146], [147]. Some strains, such as ribotype 027 can produce all three kind of toxins and harbor a mutation in the tcdC gene, a toxin regulatory gene. In human medicine, the hypervirulent ribotype 027 is presumably related to increased mortality and is of worldwide concern [148], [149]; the occurrence of this strain is also described in domestic animals and foods [150]. Besides this ribotype, other strains like 001, 014/020, 053, 017 or 078 are described in human isolates in Europe, with huge geographical differences [151], [152], [153], [154].

In livestock, ribotype 078 is commonly found [155], [156], [157], [158], but, e.g., ribotype 017 has also been described in farm animals [144]. Both ribotypes can cause severe intestinal human diseases [149], [159]. The pathogenic potential of C. difficile for pigs is currently not completely clarified, but it seems to play an important role in neonatal diarrhea. Alvarez-Perez isolated C. difficile in 25.9% of the Spanish newborn piglets; more than 94% carried genes to produce toxin A and B. C. difficile was detectable in diarrheic but also in clinically completely inconspicuous animals [22]. Using an enrichment technique, Hopman et al. were able to detect 100% of the tested piglets positive on C. difficile. Sows, the environment and the air were also tested positive and the possibility of an airborne transmission was discussed [157]. There seems to be an association between maturing of swine and other animal species and the decrease of C. difficile prevalence [141], [160], [161]. The pathogenicity of C. difficile for cattle, especially for calves, is still controversial. Occasionally, a higher prevalence in healthy calves than in diarrheic ones has been described, but the Clostridia in diseased calves were more often toxin producers [144]. Costa et al. found a prevalence of 61% in veal calves and they detected a tetracycline resistance in 76–93% of the C. difficile isolates [162].

To our knowledge only few data exist on C. difficile in poultry and there is no explicit evidence for an animal pathogenic potential in chicken or turkey. A study in Slovenian chicks found a prevalence of 100% in two week old animals and 40.9% in 18 week old ones. Furthermore, a lot of different ribotypes were detectable [141]. The zoonotic aspect of C. difficile is not completely clarified. As mentioned above, the same ribotypes may occur both in humans and animals, with ribotype 078 having emerged at the same time in humans and livestock. Furthermore, the identical C. difficile strains were already found in diseased pigs and humans [163].

In North America, C. difficile can be often isolated from meat [142], [164], [165]. For example in Canada, 20% of retail minced meat samples harbored C. difficile, including the human pathogenic ribotypes 077 and 014, one variant was highly similar to the ribotype 027 [143]. C. difficile contamination has also been confirmed in processed poultry meat in several countries all over the world [142], [164], [166]. The prevalence is low in meat in Europe. In Sweden, 2.4% of the meat samples were positive for C. difficile, all occurring in minced beef [167]. De Boer et al. found also a low prevalence in the Netherlands, 1.6% of the meat was sampled positive [166]. In Austria, 3% of meat samples harbored C. difficile [168]. Mortification of C. difficile through the preparation process is not reliable due to its capacity of spore forming [169]. Nevertheless, cases of transmission via foods have not been proven yet, therefore its role as a probable food-borne pathogen remains unclear.
Discussion

Bacterial multiresistance to antibiotics in livestock causes increasing concern in veterinary as well as human medicine. Still, the prevalence, transmission and zoonotic potential of multiresistant bacterial pathogens in livestock are largely unknown. While the livestock-associated MRSA has become somewhat prominent, the role of other pathogens, especially Gram-negative organisms, has not been widely acknowledged yet. With this mini-review, which is not considered exhaustive, we therefore tried to give an overview on the existing evidence and epidemiology of MRB in animals in Europe.

Healthcare and veterinary professionals should be aware of the increasing occurrence of ST398 in livestock; the same applies to the occurrence of new variants. Direct contact to animals has repeatedly been found to be associated with MRSA-colonization and infection in humans [34], [170]. Airborne transmission to other animal species and to insects, which can in turn become vectors, seems possible, too [8], [171], [172]. According to the Federal Institute for Risk Assessment (BfR) in Germany and the scientific opinion published by the EFSA, the risk of MRSA-transmission associated with foods or food handling is very low, but strict adherence to general hygiene guidelines in households is recommended to minimize the residual risk [53], [173]. It seems advisable that not only pig farm workers, but all subjects professionally exposed to close animal contact are classified as risk patients before admission to hospital. The EFSA confirmed that not only pigs, but also veal calves and broilers represent primary reservoirs for ST398 [53].

ESBL-producing Gram-negative rods may become an increasing problem in veterinary medicine in the next years. β-lactam antibiotics are the most applied group of antibiotics in veterinary medicine and a large therapy failure would lead to enormous economic and animal welfare problems [174]. Moreover, β-lactam antibiotics are also of utmost importance in human medicine. For Germany, only very limited data exist on the epidemiology of ESBL-producers in livestock, but the available data indicate a relevant ESBL prevalence in animals [175]. Meat has also been found to be frequently contaminated with ESBL [13], [176], even if it is of organic origin [177]. Reasons for the high prevalence in organic chicken meat could be multifarious, e.g., cross-contamination at the abattoir [178] or colonization of the parent animals. The high prevalence, especially found in poultry and poultry meat, the probable transmission to farmers [14] and the similar ESBL genes found in hospitalized patients [13], [15] show the importance of livestock as reservoir. Nonetheless, it is difficult to prove a direct transfer from non-pathogenic ESBL-producers via food or animal contact. Most reports compare gene patterns, but the origin of the resistance genes remains unclear.

The history of vancomycin resistance shows, that a restrictive policy can help to control antimicrobial resistance on a national and European scale. Seventeen years after the ban of the growth promoter avoparcin in the European Community, resistance rates in enterococci have at least not increased in livestock. Unfortunately, as a result the interest of veterinary medicine in VRE has noticeably decreased, even though studies show that VRE persists in livestock and the environment and is still a serious threat. The prevalence of VRE in human medicine is very heterogeneous in Europe. The predominant amount of European countries has shown an increase of VRE since 2000 (e.g., Germany, Czech Republic, France, Hungary, Norway, Spain, Ireland) [179]. Presumably, the increased prescription of vancomycin in human medicine for treatment of MRSA and severe C. difficile infections plays a major role in the spread of VRE [180]. The potential transmission of the vancomycin resistance to S. aureus is likewise a serious concern, additionally reducing the treatment options [181]. A transient colonization of the human gut with enterococci from animal sources is possible, and even the transfer of resistance genes has already been shown [117], [118]. Therefore, there is reasonable concern on the zoonotic hazards posed by VRE of livestock and foods of animal origin, but the precise extent of the hazard remains unclear.

The impact of animal MR-CoNS on human medicine is currently unclear. Livestock and companion animals are often carriers of MR-CoNS and therefore form an important reservoir. A transmission of resistance genes to staphylococci with pathogenic potential to humans, as well as the transmission through direct contact and foods of animal origin (e.g., raw milk) is conceivable [131], [134].

C. difficile infection (CDI) has primarily been a nosocomial problem. Recently, CDI has occurred increasingly in the community [182], [183]. Livestock and foods of animal origin are discussed to be the main reservoir, but direct evidence is sparse. Another reason or at least a cofactor for the increase of C. difficile in the community may be the selective pressure induced by antibiotic use in hospitals and outpatient treatment. The prevalence of toxin-producing C. difficile in newborn humans is at a high level, i.e., up to 70%. Furthermore, almost all newborn piglets are colonized, but usually, animal and human newborns are not affected by colonization. During the maturation, the recovery rate decreases in livestock as well as in humans. The maturation of the immune system is presumed to be a factor for the development of clinical symptoms in older age groups [141], [184].

Conclusion

MRB are emerging pathogens with increasing importance for veterinary as well as human medicine. The underlying promoters for the spread of resistance, selection- and colonization-pressure caused by extensive use of antimicrobial chemotherapy, are basically similar for all MRB mentioned. While concerns with antimicrobial resistance and antibiotic use are currently rising in medicine as well as in the public, further studies are needed to analyze the epidemiology in and transmission chains to animals.
and humans. To implement evidence-based intervention measures, the risk associated with livestock husbandry, food chain work and companion animals has to be quantified. Interdisciplinary research between human and veterinary medicine is therefore highly desirable.

Notes

Competing interests

The authors declare that no competing interests exist.

Author’s contributions

CD did the research and drafted the manuscript. NOH, FW and AK contributed by advising, revising, reading and approving the final script.

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