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# Antimicrobial resistance in zoonotic bacteria: lessons learned from host-specific pathogens

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## Abstract

The relative contribution of veterinary and human clinical treatments to the selection of antimicrobial resistance in zoonotic pathogens remains controversial. In this review, we consider bacterial pathogens that differ in host specificity and address their resistance profiles: pathogens that only occur in the human host, pathogens that are specific to particular food-producing animals and pathogens that occur in both host types. Compared with those pathogens restricted to a single animal host, pathogens found in both human and animal hosts appear to have higher incidences of resistance. However, the most urgent and severe resistance problems occur with pathogens exclusively infecting humans. Differences exist in the available genetic repertoire of a bacterial species and these are reflected in the observed resistance patterns; it is important to note that different bacterial species do not automatically result in similarly resistant populations when they undergo comparable selection in different host species. Thus, within a bacterial species, prevalence of resistance can differ between populations isolated from different hosts. For some species, fluctuations in dominant subpopulations, for instance particular serotypes, can be the most important factor determining resistance. The frequently expressed opinion that veterinary use of antimicrobials is at the heart of many resistance problems may be an oversimplification of the complex forces at play.

**Keywords:** antibiotic resistance, zoonosis, food-borne pathogen, veterinary medicine, human health

## Introduction

Antimicrobials provide a tremendous selective pressure on any susceptible bacterial population, whereby cells that are less susceptible are at a great advantage to survive and multiply. Depending on the mechanism of action of the antimicrobial, the severity of selective pressure and the possible genetic strategies that render bacteria either less susceptible or cause partial or full resistance, a population can shift sooner or later from 'completely susceptible' via intermediate stages to one that in the laboratory is determined to be 'resistant'. This can happen in any environment, including the living host, be it human or animal.

The term 'resistance' can mean different things and even when the minimum inhibitory concentration (MIC) of an antimicrobial is given, this can vary according to the testing methodology. The breakpoint MIC for an antimicrobial agent can be either the threshold above which a given bacterial pathogen no longer survives or multiplies *in vitro*, the MIC value above which it is unlikely to respond to treatment, or a description of the wild-type population (Simjee *et al.*, 2008). These *in vitro* and clinical breakpoints may not be identical, due to the pharmacokinetic parameters resulting from different drug dosing regimens. An epidemiologist interested in resistance development within bacterial populations more likely uses a biological MIC or epidemiological cut-off value to separate a susceptible (wild-type) population from a less

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**Table 1.** Summary of resistance patterns in various human pathogens

| Species | Colonization site; disease | High prevalence of resistance | Threatening an increase of resistance | Comments |
|---|---|---|---|---|
| *Some human-specific pathogens and their most common resistances* | | | | |
| *Helicobacter pylori* | Stomach; peptic ulcer | Clarithromycin, metronidazole, amoxicillin | Fluoroquinolones? | Second-line treatment options still available |
| *Mycobacterium tuberculosis* | Lung, other organs; tuberculosis | Isoniazid, rifamycin, streptomycin | Fluoroquinolones, kanamycin | XDR-TB[1] hard to treat |
| *Neisseria gonorrhoeae* | Reproductive organs, urinary tract; gonorrhea | Penicillins, tetracyclins, quinolones | Azithromycin on the rise | Single-drug treatment still considered |

[1]XDR-TB = extensively drug-resistant tuberculosis.

susceptible population. The latter may have obtained resistance determinants, or alternatively reduced susceptibility results from changes in expression levels of, for instance, porins or efflux pumps. This epidemiological cut-off value is often lower than the clinical breakpoint (Bywater *et al.*, 2006); it conceptually differs from a clinical breakpoint as it does not necessarily predict likelihood of treatment success or indeed clinical failure.

In this article, we do not deal with the mechanisms by which bacteria become resistant against particular antimicrobials, nor how such resistances can spread. We ignore which selection pressure is needed and is effective for a bacterial population to shift from 'susceptible' to 'resistant' and by which cut-off parameters such a shift is measured and defined. Instead, we compare three types of bacterial pathogens that differ in host specificity and zoom in at their resistances: pathogens that only occur in the human host, pathogens that are specific to particular food-producing animals and pathogens that occur in both host-types.

## Resistances in pathogens specific to humans

Some pathogens can only multiply in the human host, in which case any resistance observed must be the direct or indirect result of human intake of antimicrobials. We will present three such examples, each with a different route of infection. *Helicobacter pylori* is a colonizer of the stomach causing peptic ulcer in a minority of carriers, and related to the onset of gastric cancer. It is mainly transmitted orally from mother to child; family members usually have similar genotypes. *Mycobacterium tuberculosis* spreads via airborne droplets, and although infection is also asymptomatic in the majority of cases, it is so widespread that mortality rates are extremely high. Tuberculosis is treated with antimicrobials upon detection regardless of symptoms, at least in developed countries. Although *M. tuberculosis* is generally considered a human pathogen, transmission to animals has been described following close and prolonged contact; outbreaks in wildlife have also been described (Alexander *et al.*, 2002). Our third example, *Neisseria gonorrhoeae*, is a sexually transmitted pathogen that is treated whenever detected. The results are summarized in Table 1.

### *Resistance patterns in* H. pylori

Discovery of this organism in 1984 came as a big surprise since the stomach epithelium was considered a sterile environment. Maybe because of this mindset, as soon as the spiral bacteria were detected, eradication was propagated. The discussion on whether and when *H. pylori* eradication is desired is still ongoing, but in the meantime a large number of individuals have been treated with single or multiple therapy strategies, and this has left its mark on the bacterial population. The abstract of a recent publication begins 'The prevalence of antimicrobial drug resistance is now so high that all patients infected with *H. pylori* should be considered as having resistant infections' (Graham and Shiotani, 2008). As triple therapy of clarithromycin/metronidazole, amoxicillin and a proton-pump inhibitor is now ineffective in 80% of cases, quadruple therapy is considered a suitable option and quinolones are suggested as a second-line approach.

With the experience we have with *Campylobacter jejuni* (a gastrointestinal pathogen that colonizes both humans and animals, and which is taxonomically closely related to *H. pylori*), quinolones may only provide a short-term solution, as reduced susceptibility to fluoroquinolones in *C. jejuni* can occur with a single mutation, and *H. pylori* may soon learn that trick. Resistance is not restricted to developed countries, as an interesting overview presented recently illustrates (Vakil and Megraud, 2007). Efforts to eradicate *H. pylori* by means of antimicrobials have, in approximately 25 years, clearly demonstrated that bacteria mutate and selection results in a life-saving solution, for the bacteria, that is.

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### *Resistance patterns in* M. tuberculosis

Present estimates suggest that one-third of the global population is infected with *M. tuberculosis*, causing approximately 3 million deaths yearly (Ducati *et al.*, 2006). The combat of this pathogen is as old as the discovery of antibiotics, though a majority of infected people live in developing countries, where treatment is often unavailable. Compared with the short-term courses usually needed to treat *H. pylori* (7–10 days therapy), slow-growing *M. tuberculosis* can only be eradicated with months-long medication, making patient compliance a serious issue. The first-line treatment remains a quadruple therapy with isoniazid, a rifamycin, pyrazinamide and ethambutol/streptomycin (Shi *et al.*, 2007). Not surprisingly, resistance to each of these antimicrobials is on the rise. Second-line treatment relies on fluoroquinolones, clarithromycin and/or azithromycin. The abbreviation XDR-TB (for extensively drug-resistant tuberculosis) has been specifically coined for bacteria simultaneously resistant to at least rifampicin and isoniazid (both part of the first-line cocktail), to fluoroquinolones and to at least one of three injectable second-line drugs: amikacin, kanamycin and/or capreomycin (Jain and Mondal, 2008). This leaves very little treatment alternatives. XDR-TB has been found on every continent and is estimated to constitute 6% of multidrug-resistant tuberculosis cases (Jain and Mondal, 2008). This scary example illustrates where the story of resistance can lead to.

### *Resistance patterns in* N. gonorrhoeae

Resistance patterns in this Gram-negative organism, the most common cause of sexually transmitted disease (STD) in a number of countries including the UK, reflect the history of antimicrobial discoveries. First, resistance to penicillins was recorded, followed by resistance to tetracyclines and now quinolones. Azithromycin resistance has also been documented to be above 5% in a European sentinel surveillance study (Martin *et al.*, 2006). Current guidelines for first-line treatment include a third-generation cephalosporin such as cefixime or ceftriaxone (Roy *et al.*, 2005; Tyson, 2005). With experience from other pathogens, it may be prudent to consider multidrug medication rather than rely on single treatment regiments.

## Resistances in pathogens specific to food animals

Compared with human-specific pathogens, far fewer data are available on resistance patterns in pathogens exclusively found in food animals. Some infectious diseases are controlled by culling rather than by antimicrobial treatment, with the result that there are few publications on resistance. A few examples are given for pathogens that specifically infect food-producing animals, notably cattle, pigs and poultry. Organisms were selected for the commonness of their disease, economic importance, comparable sites of infection, and possibly for taxonomic relatedness between them. The results are summarized in Table 2.

### *Pathogens specific to cattle*

The first example of a cattle-specific disease is Johne's disease, caused by another species of the *Mycobacterium* genus: *Mycobacterium avium* subsp. *paratuberculosis* (MAP). (*Mycobacterium bovis*, perhaps a more familiar member of this genus, is not exclusively found in cattle.) Whether or not MAP is a zoonotic pathogen depends on the reader's willingness to accept the possible link to Crohn's disease. Owing to lack of data on resistance patterns, a comparison between human-specific *M. tuberculosis* and bovine MAP cannot be made.

For *Mycoplasma bovis*, a common intracellular pathogen in cattle identified in up to one-third of all pneumonia cases in calves, resistance was frequently found to tylosin, spectinomycin, lincomycin, tetracycline and oxytetracycline in a Belgian study (Thomas *et al.*, 2003). It should be noted that there is no standardized procedure for determining *in vitro* susceptibility of *Mycoplasma* spp., so that various definitions of '*in vitro* resistance' are in use. These reported resistances do not necessarily result in treatment failure and thus *Mycoplasma* spp. exemplify a possible conflict between *in vitro* MICs and clinical breakpoints. Based on the fact that *Mycoplasma bovis* is not replicating outside cattle, we can conclude that the observed *in vitro* reduced susceptibilities must result (directly or indirectly) from agricultural use of antimicrobials. Such a conclusion would be less sound for pathogens able to colonize multiple hosts.

Two major bacterial causes for bovine respiratory disease (BRD) are *Pasteurella multocida* and *Mannheimia haemolytica*. Both organisms can also infect other animals and humans so they are not strictly cattle-specific. Animal bites frequently result in *P. multocida* soft-tissue infections in humans; respiratory tract infections are mostly observed in elderly patients with underlying lung disease, where penicillin or doxycycline is a recommended treatment (Klein and Cunha, 1997). Nevertheless, *P. multocida* infections are far more common in cattle than in humans. German data suggest that in BRD isolates resistance to streptomycin is most common (30% in 2002/2003) followed by trimethoprim (12%), tetracycline (11%), chloramphenicol (10%) and nalidixic acid (10%) (Kaspar, 2006). A comparison between six European countries showed low prevalence (<10%) to most tested antimicrobials in most countries, with the exception of 24% tetracycline resistance in Italy and 20% in The Netherlands; streptomycin was not tested (Hendriksen *et al.*, 2008b). Japanese data identified 16% of BRD isolates exhibiting intermediate or resistant MIC values for

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**Table 2.** Summary of resistance patterns in various pathogens specific to food-producing animals

| Species | Disease | High prevalence of resistance or threatening an increase of resistance |
|---|---|---|
| *Some cattle-specific pathogens and their most common resistances* | | |
| *Mycobacterium avium* subsp. *paratuberculosis* | Johne's disease | No data available |
| *Mycoplasma bovis* | Pneumonia | Tylosin, spectinomycin, lincomycin, tetracycline, oxytetracyline[1] |
| *Pasteurella multocida*[2] | Respiratory disease | Streptomycin, tetracycline in some countries |
| *Mannheimia haemolytica*[2] | Respiratory disease | Streptomycin is rising, tetracycline |
| *Some pig-specific pathogens and their most common resistances* | | |
| *Streptococcus suis* | Pneumonia, meningitis, arthritis | Tetracycline, gentamicin and penicillin (some countries) |
| *Actinobacillus pleuropneumoniae* | Severe pleuropneumonia | Tetracyclin, gentamicin is rising |
| *Mycoplasma hyopneumoniae* | Chronic pneumonia | Macrolides, lincosamides, fluoroquinolones[1] |
| *P. multocida*[2] | Respiratory disease | Oxacillin, streptomycin, trimethoprim |
| *M. haemolytica*[2] | Respiratory disease | Oxacillin, streptomycin |
| *Some poultry-specific pathogens and their most common resistances* | | |
| *Ornithobacterium rhinotracheale* | Respiratory disease | Insufficient data but resistances to gentamicin, ampicillin and tetracycline are rising |
| *Mycoplasma gallisepticum* | Chronic respiratory disease | Insufficient data but resistances to fluoroquinolones are rising |
| *P. multocida*[2] | Fowl cholera | None reported |

[1] *In vitro* resistance to macrolides for *Mycoplasma* spp. does not necessarily indicate likelihood of clinical failure.
[2] *P. multocida* and *M. haemolytica* are not species-specific but human infections are uncommon.

benzylpenicillin (Yoshimura *et al.*, 2001). For these isolates, aminoglycosides were less active (19% resistant to dihydrostreptomycin), whereas ceftiofur and fluoroquinolones were highly active.

*M. haemolytica*, uncommonly found in human, is the most frequently isolated cause of BRD. In Germany, resistance is frequently found against tetracycline (14%) and streptomycin (44%) (Kaspar, 2006), and these data from 2002/2003 show a sharp increase, especially for streptomycin, compared with data from 2001 (Wallmann *et al.*, 2003). Tetracycline resistance was also common in some European countries, such as France (33–40%), Portugal (38%) or The Netherlands (31–51%) (Hendriksen *et al.*, 2008b). However, reported prevalences varied considerably from year to year in this study, possibly due to relatively low numbers of analysed isolates.

## *Pathogens specific to pigs*

Resistance to tetracycline is extremely common for porcine pathogens. For *Streptococcus suis*, a frequent cause of pneumonia, meningitis and septicemia in pigs, a European study comprising isolates from seven countries found low persistence of resistance to gentamicin, spectinomycin and trimethoprim/sulfametoxazole but 75% resistance to tetracycline and 55% to tilmicosin. The pathogen was near to completely susceptible to fluoroquinolone, penicillin and ceftiofur (Wisselink *et al.*, 2006). A follow-up study with more recent isolates showed that this was changing in some countries, such as Poland (8% resistance to penicillin and 53% to gentamicin, samples from 2004), or Portugal (13 and 100% to penicillin and gentamicin, respectively) (Hendriksen *et al.*, 2008a). German data from 2004–2006 confirm high prevalence of tetracycline resistance (70%), in addition to 17% gentamicin and 28% erythromycin resistance; penicillin-resistant *S. suis* was not detected, however (Schwarz *et al.*, 2007).

High prevalence of tetracycline resistance was also observed in *Actinobacillus pleuropneumoniae*, causing severe porcine pleuropneumonia with frequent mortality, for data from Spain (Gutiérrez-Martin *et al.*, 2006). This prevalence had increased in the last decade, as had, to a lesser extent, resistance to gentamicin. Low prevalence of resistance was identified for penicillins, trimethoprim, sulfisoxazole and nalidixic acid.

For *Mycoplasma hyopneumoniae*, as a third example of a porcine pathogen causing pneumonia, resistance to macrolides/lincosamides and fluoroquinolones combined with susceptibility to oxytetracycline and doxycycline have been described (Vicca *et al.*, 2004). These three porcine examples show that observed resistances are organism-dependent, even if they cause similar disease in the same host. Such differences are more likely a reflection of the genetic repertoire of the bacteria than exposure due to clinical treatment. This also illustrates that not every exposure results in resistance at the same rate for every bacterial species.

Both *P. multocida* and *M. haemolytica* can cause porcine as well as BRD, and it is interesting to compare reported resistances in these different hosts. Both organisms isolated from swine respiratory disease

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(SRD) in Germany were most commonly found resistant to oxacillin (32% for *P. multocida* and 38% for *M. haemolytica*) and the latter was resistant to streptomycin in 19%; low prevalences were reported for all other compounds (Wallmannn *et al.*, 2003). More recent data suggest that 28% of *P. multocida* are resistant to trimethoprim (Kaspar, 2006). Nevertheless, porcine *P. multocida* isolates are generally less frequently resistant to antimicrobials than bovine isolates (Kaspar, 2006). A clinical breakpoint for amoxicillin was recently proposed for porcine respiratory tract pathogens (Schwarz *et al.*, 2008); however, resistance to amoxicillin is not reported as common in porcine *P. multocida* or *M. haemolytica*.

### *Pathogens specific to poultry*

For *Ornithobacterium rhinotrachialae*, a poultry respiratory pathogen with important economic consequences, recent data on antimicrobial resistance are limited. One study from the US reported annual increases of prevalence between 2 and 7% for a number of antibiotics, including gentamicin, ampicillin and tetracycline (Malik *et al.*, 2003). As an example of avian *Mycoplasma* infection, fluoroquinolone-resistant *Mycoplasma gallisepticum* and *Mycoplasma synoviae* have been reported from Israel (Gerchman *et al.*, 2008). Similar results were obtained from The Netherlands for *M. synoviae*, which was found susceptible to doxycycline, tylosin and tilmicosin (Landman *et al.*, 2008). Reported tylosin resistance in this organism suffers from lack of agreement on a breakpoint and lack of standardized methods for testing. Despite such uncertainties, unpublished data suggest that macrolides can still be clinically effective against *Mycoplasma* in poultry even though *in vitro* MICs suggest otherwise, illustrating again that laboratory testing may not always give clinically relevant data (P. Silley, unpublished observations). It is interesting to compare these findings with the cattle-specific *M. bovis* (where resistance to tylosin was frequent but fluoroquinolones remain effective) and porcine *M. hyopneumoniae* (notably resistant to macrolides and fluoroquinolones) (Table 1). The observed resistance patterns of these related species are possibly reflecting the selective pressures they encounter, as a result of different medication of the host animal.

Finally, *P. multocida* can again be included here, as it is the cause of fowl cholera. German data suggest low prevalence of resistance in poultry isolates to all tested compounds including tetracycline (Wallmann *et al.*, 2007). This is surprising, as bovine isolates have shown that the organism is quite capable of developing tetracycline resistance, and tetracycline resistance in poultry isolates of *Campylobacter* is common in Germany (Luber *et al.*, 2003). Such examples show that it is not so simple to attribute particular resistance patterns to presumable selective pressures as a consequence of usage of that antimicrobial in food animals.

## Resistances in zoonotic pathogens

Since humans share a number of pathogens with food-producing animals (where they can be pathogenic or benign), it is frequently expressed that particular resistance patterns detected in human pathogens result from veterinary antibiotic use. The frequent use of antibiotics as growth promoters in agriculture was challenged and subsequently banned in Europe (Phillips, 2007). Even though some links between observed resistance in particular bacterial species and the use of those compounds in agriculture seemed extremely obvious, close examination of the details revealed a number of complications (Wassenaar, 2005). A detailed analysis of the apparent link between fluoroquinolone resistance in *C. jejuni* and its presumed increased virulence was recently published (Wassenaar *et al.*, 2007), illustrating that even this case may not be as clear-cut as it appeared.

We cannot easily compare antibiograms of veterinary and human isolates of the same pathogen, to assess the contribution of selection in both hosts. The literature on resistances in pathogens that can colonize multiple hosts is a plethora of publications using various MIC definitions, describing bacterial subpopulations selected for a particular disease, or host, or even for a pre-selected resistance, such as publications describing resistance patterns of methicillin-resistant *Staphylococcus aureus*. The variables tested are frequently different in papers written from a veterinary or a public health perspective. Even when considering one invariant organism and agent combination, there remain multiple variables that influence the outcome of monitoring studies.

Ignoring differences in methodology to determine MIC values, definitions of the term 'resistance' and bias in sampling data (all of which substantially influence the outcome), the most important parameters that introduce variation are country, host and year of isolation. It is oftentimes impossible to find comparable data for which only one of these parameters differs. A European initiative attempted to make comparisons within one microorganism, tested under standardized conditions, from various countries for the years 2002, 2003 and 2004 (Hendriksen *et al.*, 2008b). These results can be combined with those from Italy (Moroni *et al.*, 2006) and Germany (Kaspar, 2006). The latter is a publication of the German GERM-Vet monitoring program, initiated to determine the current status of antimicrobial susceptibility of bacterial pathogens from animals in Germany. This initiative has introduced a scientific rigour to surveillance in that it has addressed many of the variables that can otherwise confound interpretation of data (Wallmann *et al.*, 2003). It is hoped that these standards will be adopted in other countries. Recent publications of Hendriksen *et al.*

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(2008a, b) surveying resistance across Europe among bacterial pathogens and indicator bacteria for pigs and cattle, although not using a harmonized methodology, are a step in the right direction, as indeed are the increasing numbers of national surveillance schemes.

## S. aureus*: bovine mastitis and human opportunistic infections*

The problem that a subpopulation from one host species cannot be directly compared with those of other host species is most clearly illustrated by *S. aureus*. Mastitis in dairy cows is a frequently occurring problem that usually requires antimicrobial treatment. The bacterial causes are diverse, but *S. aureus* is one of the major culprits. Regional differences in reported resistances in mastitis-causing *S. aureus* populations can be dramatic, such as 59% prevalence of sulfonamide resistance in France but only 4% in Denmark and 0% in Spain (Hendriksen *et al.*, 2008b). In that comparative study, low levels of resistance were reported for most of the compounds tested except for 10–49% for penicillin, with Italy (43%), Latvia (49%), England (38–46% depending on the year), Denmark (23–40%) and Spain (33–44%) among the regions reporting higher prevalence, compared with only 4% in France. However, ampicillin, amoxicillin and doxycycline had not been tested, for all of which high prevalence of resistance was reported (99, 100 and 47%, respectively) in *S. aureus* from bovine mastitis in Italy in 2004 (Moroni *et al.*, 2006). Thus, the selection of tested compounds can give different impressions of severity of the resistance problem. Moreover, with such dramatic regional or national differences, comparisons of human and animal isolates should ideally only take place within one region.

How should we compare veterinary findings with *S. aureus* infections in humans? In human medicine, resistance to one compound raises red flags: methicillin, a beta-lactam whose resistance in *S. aureus* is usually accompanied by resistance to macrolides, aminoglycosides, clindamycin and sometimes quinolones or rifampin. Nosocomial infections of methicillin-resistant *S. aureus* (MRSA) are a well-known threat. The incidence of MRSA in blood cultures in various European countries differs, with highest reported incidences in the South and East. The UK is an exception, recording 44% MRSA in blood cultures, as high as Greece, Portugal or Rumania, compared with 0.6% in Denmark or 0.9% in The Netherlands (Beovic, 2006). In addition, community-acquired MRSA is on the rise in many countries.

*S. aureus* is also a common benign colonizer of the nasopharynx and skin. Surveillance programs have been targeted at MRSA, but by zooming in on this resistant subpopulation, the true variation in the overall *S. aureus* population is clearly not assessed. An appropriate question is to ask which of two investigated bacterial populations, nosocomial or community-acquired MRSA, would be more adequate to compare with the animal isolates causing bovine mastitis. A mastitis case in a herd of cattle may be somewhat comparable with a nosocomial human infection in a hospital, as in both settings individuals are in close contact. However, animals clearly undergo extreme environmental exposure compared with the confounded human patients, and they may be less vulnerable to opportunistic infections. Comparing *S. aureus* isolates from healthy human individuals (community carriers of MRSA), to use the alternative approach, would not resemble the medication pressure posed on the bacterial population that both nosocomial infective agents and veterinary pathogens may have undergone. The dilemma is solved because the bacterial populations of benign colonizers of humans are different from those causing either nosocomial infections or bovine mastitis, as established by genotyping data such as MLST (Deurenberg *et al.*, 2007).

A case where both populations may overlap was identified for pig farmers in The Netherlands, who are more likely to be MRSA carriers with genotypes identical to those colonizing pigs (Khanna *et al.*, 2008). These observations have been confirmed in other countries, and a possible epidemic has been forecasted (Wulf and Voss, 2008). For human medicine, treatment options are all that matter. The discovery of vancomycin-resistant *S. aureus* (methicillin-resistant or not) is of extreme concern. In the case of MRSA patients, treatment is often restricted to trimethoprim/sulfamethoxazole, doxycycline or linezolid (Powell and Wenzel, 2008). This makes the findings of Moroni and coworkers even more disturbing (Moroni *et al.*, 2006). There is an immediate need for standardized and extended antibiogram testing of *S. aureus* in food animals (cattle as well as pigs) for both methicillin-susceptible and -resistant populations, in order to anticipate future treatment possibilities.

## C. jejuni/coli

A lot has been said about fluoroquinolone resistance in *C. jejuni/coli* and the possible link to use of fluoroquinolones in poultry, and these arguments will not be repeated here. As a result of such discussions, fluoroquinolones use in poultry was banned in the US in 2005. Whether this decision was justified remains disputable. It is, however, interesting to see that this ban does not appear to have resulted in a reduction of fluoroquinolone resistance in *Campylobacter* isolated from poultry in the US, as deduced from data made available online by the USDA (http://www.ars.usda.gov/sp2UserFiles/Place/66120508/CampyMICAll.swf).

## Escherichia coli*, a complex species*

*E. coli*, the guinea pig of microbiology, is a species with a complex epidemiology. Some strains of the species are

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benign to both human and animal, others are pathogenic to particular hosts, and benign strains can become opportunistic pathogens, for instance causing urinary tract infections (UTIs). Particular strains may be related to particular sites of infection, whereas other strains are more versatile. Antimicrobial resistance surveillance has mostly concentrated on particular isolation sites (mostly for one host only), frequently related to particular disease manifestations. A systematic literature review was performed by Erb and coworkers on antimicrobial resistance reported for *E. coli* isolated from humans (Erb *et al.*, 2007). In absolute numbers, most antibiotic-resistant organisms are acquired in the community, not in hospitals, so that this represents the biggest reservoir of resistance. In asymptomatic populations, ampicillin resistance varied between 13% (in The Netherlands, 1994) and 100% (in Mexico, 1996). The same wide variation was seen for trimethoprim (same extremes, same countries), and ciprofloxacin resistance was already about 25% in Spain in 1999 (Erb *et al.*, 2007). There was no difference in resistance prevalence between stool isolates from healthy individuals and blood or urine isolates from patients. This is in accordance with the view that *E. coli* infections are mostly caused by ascending infections by normal bowel flora.

An interesting observation is that *E. coli* isolated from wild animals living in the Antarctic or Gabon, believed to be unexposed to people, were completely susceptible to all antibiotics tested (Skurnik *et al.*, 2006). This raises the question of what biological purpose resistance genes had and have in the absence of antimicrobial pressure. After all, resistance genes have evolved long before humans started to apply antimicrobials, and must have a role in the natural ecology of bacteria.

Antimicrobial resistance in *E. coli* causing UTIs in humans is of major concern, especially the increase in incidence of expanded-spectrum beta-lactamases (ESBLs) (Pitout and Laupland, 2008). These pose a threat to the 'last option' antibiotics ceftazidime, cefepime and azteonam (Beovic, 2006). In that review, concern about the increase in co-trimoxazole resistance with community-acquired UTIs is also expressed. As the author states, the candidate future treatment of this common infectious disease with fluoroquinolones or beta-lactams is likely to set another vicious circle of resistance in motion. Hospital-acquired UTIs are probably even more frequently treated with antimicrobials than community acquired UTIs. A survey was conducted to investigate resistance and treatment of UTIs caused by *E. coli* and other organisms on one particular day in November 2003 (Europe) and November 2004 (Europe plus Asia). A total of 56% of the hospitalized urological patients were receiving antimicrobial therapy on the studied day, of which 46% were for prophylaxis, 26% for microbiologically proven UTI, 21% for clinically suspected UTI and 7% for other infections. The most commonly used antibiotics were fluoroquinolones (35%), cephalosporins (27%), penicillins (16%), aminoglycosides (15%) and co-trimoxazole (9%) (Johansen *et al.*, 2006). Such treatment practices put the criticism of prophylactic treatment practiced in veterinary medicine into perspective.

*E. coli* can also cause mastitis in cattle, so that we can compare the resistance patterns observed in such a population with that of *S. aureus* isolated from the same niche. Amoxicillin, tetracycline and streptomycin resistances have the highest prevalence in The Netherlands reaching out to 20% in *E. coli* from bovine mastitis (MARAN, 2005), followed by trimethoprim/sulfamethoxazole (about 10%) and kanamycin and neomycin (below 10%). Coagulase-negative *S. aureus* isolated from bovine mastitis in the same country, same year, are frequently (40%) resistant to penicillin and sometimes (6%) to oxacillin. Again, the different genetic repertoire of these organisms is most likely responsible for these differences. Similar to the Dutch data, *E. coli* and *S. aureus* from bovine mastitis cases in Germany were never amoxicillin/clavulanic acid-resistant but the German isolates report lower incidences for tetracycline and streptomycin resistance in mastitis *E. coli* (Kaspar, 2006).

*E. coli* isolated from cattle suffering from either mastitis or diarrhea was compared in ten European countries (Hendriksen *et al.*, 2008b). However, from the way the data are presented, it seems that in some countries mastitis isolates and in other countries diarrhea isolates were analysed. This makes comparisons somewhat difficult.

*E. coli* isolated in Germany from various animal sources (urinary/genital, respiratory and gastrointestinal tract infections in cats, dogs, horses or swine) were all compared under standardized conditions (Grobbel *et al.*, 2007). The highest incidences of resistance were reported for sulfamethoxazole (18–59%), tetracycline (14–54%) and ampicillin (14–39%), whereby isolates from cats, dogs and horses were generally more frequently susceptible.

One subpopulation of *E. coli* that cannot be left out here is Shiga-toxin-producing *E. coli* (STEC, also called VTEC for verotoxigenic *E. coli*), which is associated with contaminated beef and vegetables. A recent study from Ireland showed that multidrug resistance in VTEC (mainly O157 and some O111 and O26 isolates from cattle carcasses, beef and humans) is uncommon (1.4%) (Walsh *et al.*, 2006). Nevertheless, one isolate from ground beef was resistant to ten antimicrobials belonging to seven different antimicrobial classes. One would think that such observations are of concern, and ask for careful surveillance. However, in comparison with other well-covered food-related zoonotic organisms, hardly any international comparison study is available for this important pathogen. Publications describing national data are mostly based on pre-2002 isolates, describe one isolation source only, frequently live cattle or beef at retail, or concentrate on particular resistances (ESBL-producing *E. coli*) without considering the pathotype. Thus, despite a vast interest in this 'hamburger bug', a comparison as presented for other

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zoonotic pathogens cannot be made due to lack of published data. In addition to this lack of data, it should be mentioned that antimicrobial treatment of human STEC infections is controversial as their usage may exacerbate symptoms, particularly the hemolytic uremic syndrome.

## Salmonella enterica*: serovars come and go*

Important insights can be gained from an understanding of resistance in *Salmonella*. *Salmonella* resistance profiles strongly correlate to specific serovars. Fluctuations in dominant serotypes will be the most important factor determining the observed resistance levels for *Salmonella*. Threlfall *et al.* (2006) made this point very forcibly as they investigated the changes in the occurrence of antimicrobial resistance in *S. enterica* serotypes Enteritidis and Typhimurium from human infection in England and Wales in 2000, 2002 and 2004. They showed that the incidence of strains of *Salmonella* Enteritidis with resistance to nalidixic acid coupled with decreased susceptibility to ciprofloxacin had more than doubled between 2000 and 2004, whereas the overall levels of resistance in *Salmonella* Typhimurium had fallen by approximately 25%. In relation to published data on veterinary sales of antimicrobials in the UK, the findings demonstrated that changes in the incidence of resistance did not correlate with changes in veterinary usage (Threlfall *et al.*, 2006). For *Salmonella* Enteritidis, important factors in the increased incidence of resistance were foreign travel and the consumption of imported foods contaminated with drug-resistant strains. For *Salmonella* Typhimurium, the most important factor has been an overall decline in the occurrence of multiple drug-resistant *Salmonella* Typhimurium definitive phage type 104, a change in serotype prevalence. These studies have demonstrated that changes in the incidence of resistance in predominant *Salmonella* spp. in humans in England and Wales from 2000 to 2004 are multifactorial. The important point made here is that resistance rates were shown to be a function of serotype prevalence rather than antibiotic usage.

## Concluding remarks

Resistances in a selection of pathogens specific to humans or food animals have been presented here. Clearly, multidrug resistance impairing medication is a more severe problem in those human pathogens presented. This may partly be a reflection of the selected examples; however, all presented animal pathogens are common causes of disease in farming practice, requiring antibiotic treatment.

Compared with those pathogens restricted to a single animal host, pathogens found in both human and animal hosts appear to have higher incidences of resistance. Such comparisons become difficult to properly evaluate, as the organisms vary in their available genetic repertoire of resistance. Examples have been given to illustrate that not every exposure results in resistance at the same rate for every bacterial species (e.g. different resistance patterns in pathogens causing porcine pneumonia). Differences in the available genetic repertoire are one explanation for this, but the story is more complex. Some organisms develop resistance to a particular compound in one animal host but not in another (e.g. *P. multocida* tetracycline resistance), although that compound is licensed for use in either host. For other pathogens, such as *Salmonella*, the rise and fall of particular subtypes may coincide with particular resistance patterns, so that these patterns are not necessarily a reflection of antimicrobial use.

It was not our intention to 'name, shame and blame' as that is not going to help solve the resistance challenge. We accept that antimicrobial use, in whatever host, provides a selective pressure that can result in less susceptible bacterial populations. Nevertheless, by looking at different pathogens with different host distributions, the frequently expressed opinion that veterinary use of antimicrobials is at the heart of many problems seems to miss the point. It is clear that the most serious and acute problems of multidrug resistance are in human medicine and it is here where solution and prevention are mostly needed. We need active research to come up with novel strategies in our fight against infectious diseases.

Some directions have already been mentioned where more data are needed. The scientific field is very active in developing new strategies beyond the next-generation compound that can give temporarily (but potentially life-saving) relief at best. Novel approaches to combat bacterial infections and their resistances include the development of inhibitors of resistance genes, a concept with proven functionality for beta-lactamases. Inhibitors of antibiotic efflux, where maybe plants can teach us a few useful lessons, and novel antibiotic strategies, such as compounds upsetting the intercellular communication on which many bacterial pathogens rely, are also possibilities worth exploring (Wright and Sutherland, 2007). Finally, the exponentially increasing number of complete bacterial genomes currently being sequenced can be mined to identify novel gene candidates as antibacterial targets (Mills, 2006).

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