Veterinary Use of Antimicrobials and Emergence of Resistance in Zoonotic and Sentinel Bacteria in the EU

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With 1 figure

Summary

Antimicrobials are essential for treatment of sick animals, but even if used correctly, may eventually lead to antimicrobial resistance. While this represents a potential hazard to humans, the great majority of resistant human pathogens, especially the more important ones, are unrelated to animal sources. A survey of informed medical opinion suggested that of the human antimicrobial resistance problem, <4% was seen as potentially linked to animal sources. This proportion related largely to zoonotic bacteria which by definition have the capacity to carry resistance between species, although the evidence for resulting harm remains limited. A recent study compared resistance among chicken, pig and cattle isolates of Salmonella spp., Campylobacter spp. and Escherichia coli from a series of EU countries. When tested against antimicrobial agents, this survey showed variation of resistance between countries, between hosts and between organisms. Such variation may give insight into preferred methods of antimicrobial administration or disease control, but it is clear that the epidemiology of antimicrobial resistance induction and dissemination in animals remains complex and is yet to be fully understood.

Introduction

Antimicrobial agents are used therapeutically in individual animals to treat diseases such as pneumonia or enteritis but are also used to treat outbreaks of disease in a group of animals. Antimicrobial treatment is needed for reasons of animal welfare and for control of infectious diseases including zoonotic conditions. In addition, economic considerations are also relevant – implying on one hand a further incentive to treat disease, but on the other a preference to use an older, inexpensive treatment rather than a newer more expensive one.

Animal Sources of Human Antimicrobial Resistance

Any use of an antimicrobial agent, even when rational and careful, may lead eventually to antimicrobial resistance, albeit at a rate difficult to predict. When such resistance arises in animals, it can constitute a ‘hazard’ in that the organism may be zoonotic, or may transfer genetic material to a human pathogen. The crucial question is the degree of risk posed by the hazard. This has been the subject of debate, with a division between those who are very concerned about the risk (Witte, 1998) and those who believe that the evidence for a substantial risk remains sparse (Phillips et al., 2004). Various risk assessments have been conducted in attempts to quantify the degree of risk, and the methodology has recently been reviewed (Snary et al., 2004). The authors concluded that in many cases, risk assessments were impeded by shortage of suitable data sets.

With the exception of the zoonotic infections such as non-typhoid salmonellosis, the great majority of infectious diseases in humans are separate from animal infections in both causal pathogen and in epidemiology. Consequently the great majority of resistance in man is generated through the human use of antimicrobial agents. For instance, methicillin-resistant Staphylococcus aureus is one of the most troublesome forms of resistant infection encountered in human medicine yet has no known causal connection with animals, where it is rarely encountered.

In an attempt to quantify the contribution of animal sources and of individual bacterial species to the sum of resistance in human pathogens, a sample of expert medical opinion was surveyed (Bywater and Casewell, 2000) using a questionnaire which listed 20 bacterial pathogens which had been identified as presenting problems to human health. The bacteria listed for assessment were in an authoritative report from the Scientific Steering Committee of the European Union Directorate General XXIV (Report, 1999). The respondents were senior microbiologists from both the EU and the US, mostly holders of chairs of medical or clinical microbiology, who assigned scores for three criteria to each bacterial species or subgroup.

The criteria assessed were:

1. The burden of ill-health, assessed according to the prevalence and severity of infection (mortality, post-infection sequels, treatment cost, etc.) resulting from infection with that species.
2. The restriction of treatment choice expected for each bacterial species in the presence of resistance.
3. The likelihood of an animal source for resistance in the particular bacterial species.

The results from the questionnaires were integrated to allow pathogens to be ranked in order of perceived importance with respect to resistance, and to identify the perceived contribution of animal sources in each case (Fig. 1). This indicated that the most important pathogens in human health were those where animal sources were absent or trivial. In fact the sum total contribution of animals to human resistance was assessed as <4%. These were, as expected, linked mostly with the zoonotic enteric infections.
Zoonotic infections such as salmonellosis can by definition originate in animals, and if antibiotic resistance has been acquired in the animal source, it may be passed to the human recipient. However, antibiotic treatment is only rarely indicated for non-typhoid *Salmonella* infections, and there are rather few documented cases where treatment has clearly been compromised by resistance originating from an animal source (Piddock, 2002). Similarly infections caused by *Campylobacter* spp. may theoretically fail to respond to antibiotic in the presence of resistance from an animal source, but again documentation of treatment failures linked to animal sources of resistance is hard to find. Nevertheless, as resistance will sometimes be passed from animals to humans and vice versa in zoonotic infections, the information on the incidence of resistance among animal isolates is clearly relevant.

**Prevalence of Antimicrobial Resistance in Zoonotic and Sentinel Bacteria**

Surveys of resistance have been carried out in several EU countries such as Denmark (DANMAP, 2003), Sweden (SVARM, 2003), UK (Veterinary Laboratories Agency, 2001) and the Netherlands (MARAN, 2002). While on a national basis these have yielded interesting results, variation between methods of sampling and resistance determination makes comparison difficult. What is required for international comparison to be meaningful is a study using a standard methodology in different countries. Such a study has been carried out by CEESA (the European Animal Health Study Centre, Brussels, Belgium). This European Antimicrobial Susceptibility Surveillance in Animals (EASSA) investigated the resistance of isolates of commensal *Escherichia coli* (included as an indicator or sentinel species), *Campylobacter* spp. and *Salmonella* spp. from food animals in eight European countries, four per host and per bacterial species. Faecal samples were taken at slaughter from broiler chickens, slaughter pigs and beef cattle between 1999 and 2001. A total of 2118 *E. coli*, 271 *Salmonella* spp. and 1325 *Campylobacter* spp. were isolated in national laboratories and sent to a central laboratory for standardized maximum inhibitory concentration (MIC) testing. MICs were determined against a range of antimicrobials selected for their importance in human medicine. The results (Bywater et al., 2004) showed considerable variation between countries in the resistance seen, particularly for the older compounds tested. However, for newer compounds (fluoroquinolones and third generation cephalosporins) resistance was usually absent or low. The northern countries (particularly Sweden), tended to show a lower incidence of resistance than did the southern countries such as Spain. Isolates from cattle showed a lower incidence of resistance than did isolates from the other two species.

**Why Should Resistance Vary Between Countries?**

The reasons for the variation seen between isolates from different countries, which could clearly not be accounted for by methodology variation, may be linked with the quantity of the antimicrobial used, the time over which it had been available, the route or dosage by which it was administered, or with some other epidemiological factor.

Of the above options, it is tempting to ascribe the variation in the resistance seen to variation in the amounts of antimicrobial used in different countries. Consumption data have been difficult to obtain, although the animal health industry organizations have provided information on sales of their members’ products in both the EU (FEDESA figures published by the EMEA, 1999). The ability of the animal health pharmaceutical industry organizations to identify usage is often frustrated by the presence of ill-defined generic supplies flowing across borders and the fact that not all companies are members of industry bodies. The most effective approach is for the figures to be obtained by governments, either through voluntary information yielded through direct contact with companies (e.g. as is carried out in the UK), or by statutory obligation to report all sales, as is the case in Denmark. However, any comparison of gross overall sales figures is confounded by the differences in the numbers of animals between countries, and the frequent inability to identify the proportion of different species receiving a particular formulation.
Moreover, variation in consumption of antimicrobials may be insufficient to explain the differences in resistance seen. This was illustrated by the recent report of an isolated South American community with virtually no antimicrobial exposure, yet substantial antimicrobial resistance among intestinal flora of humans (Bartelloni et al., 2004). Resistant isolates have also been found in small wild rodents living in woodland a distance removed from human or animal contact (Gilliver et al., 1999) and in free-living rodents and insectivores (Hauschild et al., 2003). Furthermore, resistance may be strongly influenced by the dissemination of particular strains, and so be largely independent of antimicrobial exposure (Hancock et al., 2000). For example, enrofloxacin resistance in Salmonella typhimurium isolated from Belgian cattle decreased between 1991 and 1998 (Imberechts et al., 2000). This decrease did not appear linked to a reduction in fluoroquinolone consumption, and was best accounted for by the clonal spread of strain DT104, which was largely sensitive to fluoroquinolones. Thus possession of detailed information on antimicrobial usage in animals, while interesting and informative, may fail to yield definitive answers.

**Why Should Resistance Vary Between Host Species?**

The most striking host species difference seen in the EASSA study was between isolates from cattle on one hand and pigs and poultry on the other, where resistance was generally lower in cattle isolates. While this may be a reflection of lower antimicrobial usage in cattle than in the other species, it may also have reflected the age at slaughter, which also influences the resistance patterns observed. Calves typically show a higher incidence of resistance among enteric bacteria than do adult cattle regardless of antimicrobial exposure (Khachatryan et al., 2004). The incidence of resistance to an antimicrobial agent in a particular population is therefore the result of a number of interacting factors, with antimicrobial consumption merely one, albeit important factor.

**Conclusions**

The veterinary use of antimicrobials clearly contribute to resistance among zoonotic organisms in animals, which could be a source for resistance in humans. While the contribution of animals to the overall problem of human resistance is likely to be very small, there is a clear obligation to use antimicrobials in animals in a manner least likely to promote resistance. The variation seen in resistance among zoonotic and indicator organisms in different countries may give an indication of the preferred veterinary practices in antimicrobial usage, but the epidemiology of resistance is complex and may not allow for simple explanations.

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