Withdrawal of growth-promoting antibiotics in Europe and its effects in relation to human health

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Abstract

The glycopeptide avoparcin, bacitracin, the macrolides spiramycin and tylosin, and the streptogramin virginiamycin were withdrawn as growth promoters in the European Union between 1995 and 1999 on the basis of the Precautionary Principle. Relevant resistance thereupon diminished among enterococci (the indicator organisms) isolated from animal and human faeces. However, animal enterococci were shown to differ from those that caused human infections, although their resistance genes were sometimes indistinguishable and thus probably have a common origin. Before the ban, human clinical isolates of enterococci resistant to vancomycin or teicoplanin were uncommon in many, but not all, parts of Europe and resistance to quinupristin/dalfopristin in the case of Enterococcus faecium was very rare. After the ban, these resistances increased in prevalence almost universally, to the detriment of human health. Campylobacters, normally susceptible to macrolides, increased in prevalence before and after the ban. Analyses suggest that the added risk to human health from resistance among enterococci and campylobacters selected by growth promoter use is small, whilst the benefit to human health from their use, hitherto largely ignored, might more than counterbalance this.

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1. Introduction

‘Whenever the evidence in a dispute is inconclusive the scientific vacuum is filled by the assertion of contradictory certitudes’, John Adams [1].

It is now more than a decade since the Union-wide withdrawal of selected growth-promoting antibiotics started in Europe. Sweden had discontinued their use in 1986, and the Danes withdrew the glycopeptide avoparcin, rapidly followed by the rest of the European Union (EU), in 1995. By the middle of 1999, the growth-promoting use of bacitracin, spiramycin, tylosin and virginiamycin had ceased in the whole EU on the basis of the Precautionary Principle, since it was agreed by those who had the task of managing the perceived hazard that evidence of actual risk to human health was not forthcoming [2]. This puts the question of harm to human health in the field of virtual risk, with all that goes with that categorisation [1]. The application of the Principle, which discounts the contradictory interpretations of scientific findings, still carried with it an obligation that further evidence be obtained [3]. It seems reasonable now to assess both whether such evidence has indeed been sought and what has been the effect of the withdrawal of these antibiotics in relation to human health.

There are those who believe that the case against antibiotic growth promoters is settled. For example, Collignon, commenting on a review of which I was a co-author [4], expressed dismay that we ‘were defending what nearly all microbiologists know are grave abuses of antibiotics’ [5]. Mølbak [6] and Angulo et al. [7] have expressed a similar opinion. However, others are not so sure. Those of us who wrote a review of the evidence in 2004 and the reply to criticisms [4,8] clearly do not agree. Going beyond our statements, Wassenaar has it that ‘veterinary usage of antimicrobial agents does not cause ‘a major health risk’ [9]. Accepting that there are still two points of view, Lord Soulsby, the chairman of
the House of Lords committee that strongly supported their discontinuation, has recently admitted that controversy continues and that expectations of limitation of antibiotic use may be naïve [10]. Turnidge, also commenting on our review, recognised the continued controversy [11]. Conflicting views continue to be held, probably because attempts to produce further evidence for or against discontinuation in the context of antibiotic growth promoter use have been few. It seems that many of those in a position to obtain the evidence have not been persuaded of the need for it, presumably feeling that the regulatory battle has been won without such scientific efforts. Indeed, the Court of First Instance of the European Communities in Luxembourg concluded in 2002 that there was still disagreement among scientific experts and ruled that the ban should stand, still on the basis of the Precautionary Principle [12]. Forrester and Hanekamp have recently discussed legal implications of the judgment [13]. One has to have some sympathy for the lawyers called upon to make such decisions, although one might have hoped that they would understand that natural scientists are not able to offer proof, but merely hypotheses that might be more or less persuasive. When asked for guarantees of future events—for good or ill—the scientist should make it clear that the question is not one that should be asked, if the court will permit him to do so!

It is unfortunate that there has been no opportunity for disinterested discussion of the discontinuation of antibiotic growth promoters in a purely scientific forum, whose objective might have been to produce a balanced view on what is agreed and what is disputed in relation to science, and more importantly, how the lack of evidence might be tackled. Furthermore, the true breadth of the conflict of interest, apparent to some of us in meetings that have taken place, for example that held in Copenhagen [14], is not apparently widely recognised. The editors of the Journal of Antimicrobial Chemotherapy have recently drawn attention to religious, personal, political, academic or financial conflicts of interest, and while insisting on transparency in relation to the last of these, have invited investigators to give guarantees of future events—for good or ill—the scientist should make it clear that the question is not one that should be asked, if the court will permit him to do so!

Leaving virtual risks to human health aside, there have been a number of attempts to assess other outcomes of the European antibiotic withdrawals, which, it should be remembered, was based on a totally uncontrolled experiment. I have several times suggested that if their laboratory microbiological experiments were conducted to similar standards, the investigators would be rightly castigated, and I continue to see no reason why lower standards should be acceptable in field experiments. Nonetheless, a World Health Organization (WHO)-sponsored group concluded that the Danish experiment had been a success, but it is notable that they did not assess its cost, including the provision of alternative measures, and they did not assess its effect on human health [16].

2. Effects of the ban

2.1. Observance of the ban

It seems clear that the ban was obeyed, with objective evidence in those countries that collect statistics on the details of antibiotic use. For example, in Denmark, the growth-promoting use of the banned antibiotics declined from ca. 100 tonnes in 1997 to nil by the end of 1999, and remained so [17]. The Norwegians [18] followed a similar path. However, macrolides, previously used both for growth promotion and for the prevention and treatment of infection, continued to be used legitimately for disease control, and their use for therapy increased markedly after the ban [17].

2.2. Advances in scientific methodology

Improvement in the techniques relevant to the surveillance of the microbiological effects of growth-promoting antibiotics is worthy of comment. Methods for speciation of relevant bacteria have improved and have been more widely used, especially in the distinction between Enterococcus faecalis and Enterococcus faecium, in which context streptogramin resistance was important [4]. There has also been progress on the standardisation of antibiotic resistance breakpoints [19], important for valid comparison of resistance rates from time to time and from place to place. A clearer general appreciation of the difference between microbiological (or epidemiological) and clinical breakpoints is still needed. Genetic methods are now well developed for the detection of resistance genes. One has only to look back at the original methods of typing enterococci, introduced largely with the aid of the work that has been done to improve our knowledge of staphylococcal relationships and evolution, particularly fruitful for methicillin-resistant strains [20]. According to the multilocus sequence typing website (http://www.mlst.net), systems now exist for typing both E. faecalis and E. faecium, in which context streptogramin resistance was important [4]. There have also been advances in genetic profiling, for example among enterococci from infected humans [21]. Campylobacters from animal and human isolates are also a good target for such studies. Methods of surveillance have also improved and been more widely applied [22]. Finally, one might note an increased interest in analysis of risk and benefit, exemplified in the debates on oily fish and micronutrients [23,24].

2.3. Food–animal faecal flora

The ban was followed by, and very probably resulted in, a reduction in the prevalence of resistance among so-called indicator bacteria in the faecal contents of food animals, of which enterococci are important in relation to the anti-Gram-positive growth-promoting antibiotics. In a multinational
studying involving six European countries, which by chance was conducted in two periods immediately before and after the ban came into effect [25], there was a statistically significant decrease in prevalence of *E. faecium* strains resistant to spiramycin and tylosin or to virginiamycin. There was no change in the already low prevalence of glycopeptide resistance (not surprising since avoparcin use had been discontinued earlier) or in susceptibility to bacitracin (to which the enterococci are usually resistant regardless of the use of the antibiotic, as shown by results from Sweden where it had not been used for many years). These findings corroborate and extend those from Denmark, Sweden and The Netherlands [4]. In 2005, streptogramin resistance rates had fallen from 40–60% in the late 1990s to 16% in pigs and 13% in chickens in Denmark [17]. It has been concluded that the resistance gene pool has been reduced, and this view was supported by the WHO review panel [16]. A more conservative view would be that one of the streams had been cleared whilst other sources of pollution may have been created. The size of the pool cannot even be guessed at. However, even this conclusion requires caution, since more sensitive methods of detection of resistant enterococci reveal that the resistant organisms may lurk in smaller numbers. A recent study in Portugal illustrates this point. In chicken collected in retail outlets, no vancomycin resistance was detected in 19 isolates of *E. faecalis* and in only 2 of 14 *E. faecium* isolates in non-selective cultures, but was detected in 8/8 and 61/61 isolates, respectively, in cultures on plates containing 6 mg/L vancomycin. A similar result was obtained for high-level gentamicin resistance with plates containing no antibiotic or 125 mg/L gentamicin. On the other hand, resistance to tetracycline, ciprofloxacin and quinupristin/dalfopristin was commonly detected on non-selective plates [26]. Such results might be expected if samples contained few enterococci resistant to vancomycin or gentamicin but larger numbers resistant to the other antibiotics. The significance of reduced numbers of resistant enterococci rather than total absence remains to be studied.

Other organisms that might be expected to have become more susceptible as a consequence of the ban are campylobacters in relation to macrolides, although the increased use of therapeutic macrolides in food animals [17] may have mitigated the effect. It is a problem that *Campylobacter jejuni* and *Campylobacter coli* are intrinsically of only modest susceptibility to macrolides, with erythromycin minimum inhibitory concentrations (MICs) typically ranging from 0.5 mg/L to 4 mg/L for strains without acquired resistance [17,27]. The Danes consider this to indicate susceptibility, whilst their neighbours, the Norwegians, have considered them susceptible for animal isolates but of intermediate susceptibility for isolates from humans [18]: the latter conclusion is in keeping with the pharmacology of erythromycin in humans whilst the former is a purely microbiological (or epidemiological) breakpoint [19]. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) clearly has more work to do! Considering only the microbiological (MIC > 16 mg/L) resistance of *C. jejuni*, the prevalence has always been low in the faecal flora of food animals in Denmark between 1996 and 2004 — usually 0–1% in broilers (with the exception of a 5% result in 2000) and 0–4% in cattle (with the exception of 8% in 2001) [17]. A European study showed a similar low prevalence of macrolide resistance in isolates of *C. jejuni* from chickens and cattle [27]. The case of fluoroquinolones is not directly relevant here since they were not used as growth promoters. However, it may be noted that resistance levels in isolates from broilers never exceeded 8% and levels from cattle were always below 10% except in 2000 and 2002 (15% and 11%, respectively) until it shot up to almost 30% in 2005 [17]. In other parts of Europe, the prevalence of fluoroquinolone resistance in animal isolates varies widely [22,27].

### 2.4. Carcass and animal-derived food contamination

One might expect that the prevalence of resistant enterococci from food animals at slaughter might be similar to the prevalence in organisms contaminating animal-derived food. The evidence is confusing. For example, in 2005, whilst the prevalence of macrolide resistance in *E. faecium* was 50% in the faecal content of pigs, it was only 13% in Danish pork, whilst 59% of isolates from pigs were resistant to tetracycline but only 21% of isolates from pork [17]. On the other hand, in 2004, the last year for which results are currently available, resistance rates for streptogramins were very similar for *E. faecium* from domestic broilers and broiler meat (24% and 17%) and from domestic pigs and pork (13% and 13%) [28]. It may be that enterococcal contamination often arises from other sources (such as food handlers or by cross-contamination) or that some antibiotic-resistant strains survive better on meat, but virtually nothing is known of the dynamics within the normal enterococcal pool.

For campylobacters, macrolide resistance had a compatible prevalence of 0–3% in *C. jejuni* from Danish chickens and broiler meat in 2004 and 2005 [17,28].

### 2.5. Human faecal flora

It was established before the withdrawal of avoparcin that vancomycin-resistant enterococci (VRE) could be found in the faeces of healthy humans, with a prevalence varying depending on the methodology used. A decline in prevalence was noted after the ban. Likewise, streptogramin-resistant *E. faecium* was found in human faeces [4]. In the UK in 2001, only four streptogramin-resistant *E. faecium* strains, inhibited by 8–32 mg/L virginiamycin, were isolated from 2000 human faecal samples collected in a rural community [29]. However, in Denmark, resistance to streptogramins of human faecal isolates of *E. faecium* had reached 54% in 2005, although MICs were only marginally elevated [17], in some contrast to the rates of resistance for either domestic or imported chicken or pigs (see Sections 2.3 and 2.4). On the other hand, the prevalence of macrolide resistance also increased in 2004 and 2005, having previously fallen in parallel with results for

pigs and pork [17]. Both of these changes occurred 5 years after the ban of streptogramins and macrolides as growth promoters.

2.6. Human clinical isolates

The prevalence of vancomycin resistance among clinical enterococcal isolates varied widely in Europe before the growth promoter ban [4] and has continued to do so [30]. It remains possible that the increases in prevalence of glycopeptide-resistant enterococcal infection seen in some countries during the period when avoparcin was being used in animals (before 1995 in the EU) might have been related to the high prevalence of similar resistance in food–animal strains—but events in the USA clearly showed that such a source was not necessary. We have rehearsed our own reservations at some length [4]. Appropriate molecular methods have recently been applied to human outbreaks of infection. It seems possible now to conclude that the animal bacteria themselves are not an important cause of serious infection in humans [21] but that resistance genes in animals and humans are on occasion the same [31]. Transferred genes may thus have had a role, but if so it required the extra factor of human antibiotic use to bring about increases in the frequency of clinical isolates. The increasing use of vancomycin for treatment of necrotising enterocolitis or methicillin-resistant *Staphylococcus aureus* (MRSA) infection may have been a factor—as was probably the case in the USA [4]. Since the ban, many parts of Europe are increasingly experiencing epidemics of virulent resistant enterococci, clearly well adapted to humans, whatever the source of their resistance genes [21]. According to the European Antimicrobial Resistance Surveillance System (EARSS) 2004 annual report [30], the incidence of VRE among invasive isolates of *E. faecium* reached more than 25% in Greece, Ireland, Israel, Portugal and the UK in 2005. Overall, 9% of the *E. faecium* isolates submitted to EARSS were vancomycin resistant in 2004, rising to 14% in 2005 [30], a phenomenon that the ban was surely expected by some to prevent. However, Scandinavia and much of Eastern Europe reported very few or no isolates of VRE. It is also clear that streptogramin resistance in *E. faecium* was rare among human clinical isolates during the period of extensive virginiamycin use in animals but increased rapidly when quinupristin/dalfopristin started to be used [4]. Ironically, in view of their concern, Denmark is among the few countries not reporting on enterococci to EARSS.

As a contribution to the discussion of potential sources of campylobacter, it is interesting to study reports of quinolone and tetracycline resistance in chicken and human isolates of *C. jejuni* in Denmark. The discrepancies have been a stimulus for endless apologetics. Considering only quinolone resistance, over the past few years resistance rates have not been above 8% for broilers or broiler meat but reached 29% for domestically acquired human campylobacter infection in 2004. This has been attributed to the ingestion of imported chicken, isolates from 49% of which were fluoroquinolone resistant in 2004 [28]. It is not clear that the 30% importation rate quoted for chicken meat is capable of explaining the discrepancy between food and human isolates in any simple way. This discussion is relevant to growth promoters only in the case of macrolides, since erythromycin resistance rates are similar in chicken and human *C. jejuni*, a finding that is compatible with the hypothesis that chickens are a major source of human campylobacteriosis, at least in Denmark, and that macrolide use in chickens might be the driver of macrolide resistance in humans. However, since there are sources of campylobacter other than food animals, efforts spent in controlling antibiotic use—or even campylobacters—in animals are likely to have a limited effect on humans. Perhaps a thorough investigation of the types involved would contribute and a start has been made. In a recent study in Austria, in which modern molecular typing methods were used, differences between animal and human strains were striking; of 102 types, only three (in ten isolates) were found both in animals and humans [32]. The castigation meted out in response to our suggestion that chickens may not be the most important source of campylobacter infection [4,8,33–36] may yet prove not totally deserved.

2.7. Human health

The crucial question is what effect the growth promoter ban has had on human enterococcal and campylobacter infection. The question should nowadays be separated into the questions of benefit and harm.

2.7.1. Benefit

In Denmark, the ban could have had little benefit in relation to enterococci since human infection caused by organisms with relevant resistance, such as VRE or streptogramin-resistant *E. faecium*, was always vanishingly rare there [4]. In the rest of Europe, increases in the prevalence of infections with such organisms has already been noted [30]. The clinical impact of VRE in immunocompromised patients is not questioned, and efforts to reverse trends are clearly desirable, but no benefit from the ban is apparent, unless it is argued that the increases in incidence, escalating almost 10 years after the ban, might have been still greater.

For *C. jejuni*, the Danes have found no obvious benefit from the ban of macrolides as growth promoters since human isolates in Denmark are consistently, albeit marginally, more often macrolide resistant than are isolates from chickens, whether home-produced or imported, and the increased therapeutic use of macrolides in food animals appears not to have selected resistant campylobacters [17].

2.7.2. Harm to human health arising from the ban

The use of growth-promoting antibiotics in food animals might benefit human health, a possibility apparently not considered important by enthusiasts for a ban. A potential mechanism is the deterioration in animal health observed after the ban and arguably the result of the ban—
argument not universally accepted. Whatever the reason for the undoubted deterioration of animal health, there was a sustained increase in the use of therapeutic antibiotics in food animals in the years after the ban, introducing new pressures on antibiotics of direct relevance to human disease (unlike most of the growth promoters). The effects of this have been varied, with resistance to some of them increasing and some not affected. Thus, pig enterococcal isolates have become more often resistant to tetracyclines but not to erythromycin despite increased therapeutic use of both [17].

But another problem of potentially greater importance arises. Unhealthy animals, including those that are subclinically infected and would not be rejected as food for human consumption, are more likely to produce faecally contaminated carcasses than are healthy animals, probably because they are less standardised in size. This results from damage to the intestines during mechanical evisceration. The visible faecal contamination is accompanied by increased bacterial contamination [37] and it has been shown in one investigation that campylobacter contamination levels may increase by ten-fold [38]. Such contamination might have an effect throughout the food chain up to ingestion by humans—and although adequate hygiene and thorough cooking would be expected to counter this, it is well recognised that deficiencies in both are not uncommon. There is an urgent need for this possibility to be investigated further—and the experiments are not difficult to devise or perform! The relentless increase in the prevalence of human campylobacteriosis in the EU [22] is so far unexplained, but we are not aware of any effort to investigate its potential relationship to the cessation of use of growth-promoting antibiotics.

The authoritarian denial of such harm potentially arising from growth promoter withdrawal [34] is not a sufficient response, especially from those who have seen significance in equally unproven relationships between growth promoter use and harm.

2.8. Risk and risk–benefit assessment

In the absence of direct evidence of harm to human health, it has been suggested that risk analysis and mathematical modelling might usefully inform the debate. The methodology of risk analysis has significantly improved, especially with the emphasis on quantitation. Several purely risk analyses, both qualitative and quantitative, have now been published, as discussed by Snary et al. [39]. All of them suggest a small additional risk either of death or prolongation of illness arising from growth-promoter use. The importance of this extra morbidity and mortality is not doubted. However, as Lothario said to Anselmo, who invited him to test his wife’s fidelity on his behalf, ‘for men to execute designs which are clearly of more hurt than benefit, is the province of madness and temerity’ [40]. When we made the suggestion that harm to human health might arise from the ban (and we admitted to having no direct evidence) we too were accused of ‘madness and temerity’ [33–36], although more for disagreeing with interpretations and the views of ‘experts’ rather than with the basic science [8]. The methodology of cost–benefit analysis is just evolving, and I am aware of only two published cost–benefit studies, relating to the use of virginiamycin [41] or macrolides [42], which conclude that the benefit to human health arising from the use of growth-promoting antibiotics outweighs the risk. More such analyses are called for.

3. Conclusions

In the face of continuing enthusiasm for the growth promoter ban in Europe several years after its introduction, we attempted to assess the evidence, emphasising the evidence against it since others had often failed to admit dissent. Overall, little seems to have changed.

It is agreed that the ban on growth-promoting antibiotics has resulted in their actual withdrawal in those countries that have relevant surveillance. It is also agreed among scientists that the human pathogens likely to be affected by the ban on antibiotic growth promoters in the EU are enterococci and campylobacters (since other common zoonotic pathogens are not susceptible to them) and these have been the target of surveillance. It is further agreed that the ban resulted in an immediate diminution in the number of animals and humans carrying resistant faecal enterococci, at least in easily detectable numbers. The story is rather different when more sensitive methods of detection are used. This may have resulted in a diminution of the resistance gene pool, a reasonable hypothesis but not a validated scientific conclusion since the pool has never been measured. However, the prevalence of some resistance among animal faecal isolates has subsequently decreased only partially or has even increased, probably as a result of the increased use of therapeutic antibiotics in animals in response to an increase in the prevalence of certain infections. Not all are agreed as to whether these infections in food animals have resulted from the ban or have had an independent origin. Whatever the explanation, the increased use of therapeutic antibiotics has persisted. Whilst resistant faecal bacteria from animals may contaminate animal-derived food, this is not the only source of the relevant species. Food contaminants may reach humans via the imperfectly protected food chain. In the case of enterococci, this might result in transient human faecal carriage of strains of animal origin, and this might in turn provide an opportunity for resistance gene transfer to resident human enterococci, although controversy continues as to whether this specific genetic transfer occurs in real life. But this has not been shown to occur naturally in man [43]. Controversy regarding the effect on human health continues, complicated by the confounding effect of recognised as well as potential virulence mechanisms. Meanwhile, analyses suggest that a small risk to human health arises from the use of a variety of growth-promoting antibiotics, whilst the first risk–benefit analyses suggest that this risk might be more
than compensated by benefits to human health arising from their use.

We are thus little further advanced in the scientific debate than we were 10 years ago when the Scientific Committee for Animal Nutrition (SCAN) advised that evidence of harm to human health from growth-promoting antibiotics was lacking. It has been suggested that since the ban on antibiotic growth promoters in Europe is a fait accompli, it is time to move on. If this means that novel scientific effort, as opposed to more of the same, will be devoted to the major problem of antibiotic resistance in human pathogens, I applaud it. However, if it is shown that there is harm as well as good arising from the EU ban, I would hope that disinterested scientists will rediscover an interest in antibiotic growth promoters.

References


