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The VRE Story - Overview

John Turnidge

Women's and Children's Hospital
North Adelaide, South Australia

Enterococci with acquired resistance to vancomycin and other glycopeptides (VRE) were first found as a cause of human infections in the Europe in 1986, and very soon afterwards in the United States. A possible link between the use of antimicrobials in food animal husbandry and vancomycin-resistant enterococci (VRE) subsequently arose in 1994 in Europe. A number of European investigators detected vancomycin-resistant *Enterococcus faecium* (VREF) in the normal flora a certain food animals, in raw meats from those animals and in sewage in Germany, Denmark and the UK. Later studies in Europe suggested that VRE were common in intensively raised food animals, especially poultry and pigs, their waste and their meats, and that carriage of VRE in some segments of the population common.

The prevalence in European food animals of VRE was attributed to the use of a glycopeptide, avoparcin, which was both related to and caused cross-resistance to vancomycin. Controlled studies in Denmark on pig and poultry farms supported this contention. Avoparcin had been introduced into food animal production primarily as a growth promoter, but had found a number of secondary roles such as in broiler chicken production for the prevention of necrotic enteritis, a condition associated with *Clostridium perfringens* and high grain diets. Use of growth promoters such as avoparcin led to healthier and larger animals, and animals that reached their slaughter weight more quickly, and hence their use was widespread in animal husbandry.

Considerable debate ensued in Europe about the relevance of those findings to human health, as relatively few clinical cases of VRE infection were being seen compared to their commonness in food animals and the environment. The WHO became involved in an effort to establish some international principles about the use of antimicrobials in food producing animals. One intriguing study from Belgium showed that the oral administration of vancomycin or teicoplanin to human volunteers resulted in an increase in VRE carriage from 28 to 64 %. This phenomenon was explained as the presence of VRE carriage acquired in the community and amplification of low numbers of VRE from below detectable levels to detectable levels in many VRE carriers. A further important piece of the puzzle was the demonstration of two major gene clusters encoding glycopeptide resistance, *vanA* and *vanB*, and that all the animal isolates were of the *vanA* genotype, and overwhelmingly *E. faecium*.

The story of animals are a source became less clear as VRE evolved in the United States. VRE were first seen in the North East of continental US and spread rapidly south-west such that it was detected in southern California within a few years. The predominant species was *vanA E. faecium* although *vanB E. faecium* were seen with some frequency, and the infections seen were nosocomial and predominated in intensive care settings. Studies on animals and the environment failed to find any VRE. It was noted that avoparcin had never be licensed for use in the US, and although there may have been a small black market for it, the lack of use in animals resulted in essentially no animal reservoir. Hence the epidemiological picture that emerged was quite different from Europe.

Factor	European VRE	US VRE
Avoparcin in food animals	Yes	No
Predominant type colonising humans	<i>vanA E. faecium</i>	<i>vanA E. faecium</i> but <i>vanB E. faecium</i> common
Frequency of documented human infections	Uncommon to rare	Common
Reports of outbreaks	Uncommon to rare	Common
Hospital antibiotic use	Comparatively low	High

Other confounding evidence included notable differences between human and animal strains of *vanA E. faecium* when subjected to a range of molecular typing techniques. The hypothesis emerged that animal strains were being ingested by humans and the gene cluster, being located on a transposon, was being transferred in the

human gut to human strains. Attempts to prove this by ingesting animal strains were unsuccessful, but the phenomenon was proven in the gnotobiotic mouse.

The Europeans placed a temporary and then a final ban on avoparcin and four other agents (thought to be associated with VRE selection) for use in animals as growth promoters in food animals in 1996. This followed significant pressure from some member countries that had eliminated (Sweden) or were eliminating (Denmark) growth promoters. With mounting disquiet over the role of avoparcin in particular, the producer eventually withdrew the antibiotic from the world market in 2000.

Meanwhile, the focus has shifted to another last-line human antibiotic, quinupristin-dalfopristin (QD), and the analogue virginiamycin which is used in food animals for a range of prophylactic and therapeutic purposes. QD is used in humans as one of the few available treatment options for serious infections caused by vancomycin-resistant *E. faecium*. If animal VRE were making their way into humans, and were also resistant to QD, then one of the critical last-line agents would be lost. Virginiamycin-resistant enterococci, including strains of VRE, have certainly been found in food-producing animals wherever virginiamycin has been used. At present, no country outside Europe has elected to ban virginiamycin, although regulators in the US and Australia are both scrutinizing its continued use.