Animal growth promoters: to ban or not to ban?
A risk assessment approach

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Abstract
The use of antibiotics for animal growth promotion has been controversial because of the potential transfer of antibiotic resistance from animals to humans. Such transfer could have severe public health implications in that treatment failures could result. We have followed a risk assessment approach to evaluate policy options for the streptogramin-class of antibiotics: virginiamycin, an animal growth promoter, and quinupristin/dalfopristin, a antibiotic used in humans. Under the assumption that resistance transfer is possible, models project a wide range of outcomes depending mainly on the basic reproductive number ($R_0$) that determines the potential for person-to-person transmission. Counter-intuitively, the benefits of a ban on virginiamycin were highest for intermediate values of $R_0$, and lower for extremely high or low values of $R_0$.

Keywords: Animal growth promoters; Streptogramin resistance; Policy alternatives; Risk assessment; Uncertainty

1. Introduction
Controversy continues to surround the issue of the potential transfer of antibiotic resistance from animals to humans. One group of antibiotics which have received particular attention in recent years are the streptogramins, to which the products virginiamycin and quinupristin/dalfopristin (Synercid) belong. Virginiamycin has been used world-wide for more than 25 years as an animal growth promoter (AGP) in poultry, cattle and swine. In the United States (US), quinupristin/dalfopristin was approved for use in humans in 1999 for the treatment of infection with Enterococcus faecium and other Gram positive organisms. Its primary medical use is for the treatment of vancomycin resistant E. faecium (VRE) which is now endemic in US hospitals [1].

There is clear evidence that the use of antibiotics in animals and humans leads to the selection of resistant organisms. From the public health perspective, the possibility of an additional source of resistant organisms and genes, namely those present on animal food products, presents a cause for concern because of the potential for treatment failure and the human costs, including death and prolonged illness, associated with such failures. This concern has lead to the banning of certain AGPs, including virginiamycin, in Europe and consideration of similar bans within the US and Australia. The banning of AGPs can of course also have negative effects, for example, increases in production costs and thus end-product prices, and therefore the policy decision must involve a trade-off between the public health and economic benefits. Since the European ban, additional scientific evidence has been accumulated suggesting a link between antibiotic use in animals and antibiotic resistant bacteria in humans, but uncertainty about the transfer of streptogramin resistance remains.

Given the current evidence relating to the transfer of enterococcal resistance from animals to humans, it is impossible to reliably quantify the probability of transfer or the magnitude of the associated adverse human health effects.
What can, however, be investigated is the conditional contribution that the use of antibiotics in animals makes to the problem of resistance in humans. In other words, under the hypothesis that transfer is possible, the human health risks associated with antibiotic use in animals can be assessed.

In this paper, we adopt a conditional risk assessment approach. In particular, we consider, for the US, the use of virginiamycin in broiler chickens and the subsequent exposure of humans to streptogramin resistant *E. faecium* (SREF). We also incorporate the human contribution to the problem, primarily person-to-person transmission affected by the use of the antibiotics in the hospital environment. By considering these two components, we have described the likely public health effects of banning virginiamycin as a growth promoter.

The findings presented here are derived from the integration of two models describing (i) human exposure to SREF from consumption of chicken and (ii) the transmission of SREF in community and hospital populations. Their integration results in a novel model that provides a comprehensive microbiological risk assessment (MRA). From this MRA we gain insight into the potential effect of a ban as well as an understanding of future research requirements.

2. Microbiological risk assessment

The hazard of interest in this risk assessment is increased resistance to streptogramins in clinical strains of *E. faecium* (SREF). Included are both chicken and human strains, which have evolved as a result of either virginiamycin or quinupristin/dalfopristin use. Colonization of hospital individuals with SREF is treated as the adverse outcome. The assumption is that colonization and infection with SREF are related. Consequently, by describing the relationship between virginiamycin use and increased prevalence of SREF in humans, the impact of a ban can be investigated. The alternative approach would be to add a module for infection and treatment failure based on this underlying model, compounding the complexity and adding uncertainties, without providing further useful insights.

Evidence for the presence of SREF in chickens in countries where virginiamycin has been, or is used is extensive. In Europe, resistant isolates have been reported in Denmark [3] and Germany [4]. In the US, SREF has been isolated from commercial poultry houses and litter samples [5], chicken farms [6] and chicken purchased in grocery stores [7]. In addition, a large study by the European Federation of Feed Additive and Nutritional Companies (FEFANA) has stratified a difference in the proportion of resistant isolates between countries where the AGP has been used and those where the AGP has never been used [8].

The possibility that SREF strains of chicken origin, or genetic material from such strains, can be transferred to, and established within human populations is much less certain. Testing of chicken and human faecal samples has demonstrated different patterns of resistance; SREF from humans showed borderline levels of resistance, rather than the high-level resistance found in chickens [9]. Based on genetic similarity, *E. faecium* appear to be host and habitat specific; strains of animal origin rarely establish in humans [10,11], and clinically important enterococci are a distinct subset of *E. faecium* [12]. Enterococci are considered to be promiscuous [13], so the most likely method of resistance transfer appears to be that genetic elements conferring resistance are transferred from animals to SREF in humans. Based on this evidence, it appears that the transfer of SREF from animals to humans may occur at low, but unknown rates.

3. The risk assessment model

The risk assessment model used is an integration of some of the features of the exposure assessment (EA) model and the household-to-hospital (HH) model of Smith et al. (2003) [2]. It is used to provide insight into the effect of a ban in the use of virginiamycin, by determining the prevalence of hospital SREF after long-term quinupristin/dalfopristin use.

The model is conditional on the assumption that clinically significant strains of SREF will evolve as a consequence of virginiamycin use, either through human colonization or the transfer of resistance genes. It does not attempt to estimate the probability of such an event and thus assumes, for example, that all clinically significant strains of SREF are equivalent. Similar approaches have been taken for other pathogens, where the current data is not sufficient to estimate the proportion of animal strains that could potentially cause human problems [13].

3.1. The EA model

The EA model estimates the rate of exposure to chicken strains of SREF, per person per day. This estimate is then used to calculate the community prevalence of SREF, assuming that chickens are the only source of the organism. The rate of exposure is assumed to be proportional to the prevalence of SREF in broilers at the time of slaughter. The constant of proportionality represents the combined effects of processing, storage and cooking on the prevalence of SREF contaminated curcas and the rate of consumption of broilers. Observational studies in Denmark [3] and other European countries [8] have shown that the prevalence of resistance in broiler flocks declines following a ban in the use of growth promoters. From this empirical evidence, the decline is observed to occur exponentially and after around 5 years, a constant prevalence that is approximately 25% of the pre-ban level is reached. This constant level is subsequently maintained and can be described as the equilibrium prevalence. Once the equilibrium prevalence is reached, it can be assumed that the rate of exposure to SREF via broilers will also be constant or in equilibrium.
Based on the empirical evidence, the rate of exposure at any time following a ban \( F(t) \) was estimated from the pre-ban rate of exposure \( F(0) \), the rate at which exposure due to contaminated broilers declines following a ban \( \lambda \) and the equilibrium rate of exposure \( \mu \). Details of the calculation of \( F(t) \) are provided in the Appendix A.

### 3.2 Community prevalence

Exposure in the community and prevalence in the hospital are linked through the admission of colonized individuals from the community into the hospital population. In order to link the EA and HH models, we need to describe the changes in community prevalence following declines in exposure. It is assumed that community prevalence at some time following a ban \( C(t) \) can be calculated as the product of the rate of exposure to SREF from broilers, the probability of colonization following exposure \( P_{\text{ex}} \) and the duration of colonization \( D_C \). It is acknowledged that community prevalence will also be influenced by person-to-person transmission [2] and the model could be extended to include this, however, we consider such transmission to be more relevant within the hospital where the antibiotic is used and therefore have simplified the community model to give initial insights.

### 3.3 The HH model

Many MRA models integrate results from exposure assessment with dose–response models to give estimates of risk such as the probability of infection per serving or annual incidence [15]. This approach assumes direct exposure and does not account for person-to-person transmission. Such an assumption is useful for zoonotic pathogens such as camplyobacter where person-to-person transmission is rare (see, for example, [14,16]); in contrast commensal bacteria such as \( E. \ faecium \) are frequently transmitted from person-to-person without infection (17). Understanding person-to-person transmission requires population dynamics models [17–19].

The HH model considers two distinct, but related, populations, the community and hospital. Each of these populations is divided into a number of groups and the transmission dynamics are described by a set of differential equations.

### 3.4 The integrated model

Since quinupristin/dalfopristin is only used in hospitals, hospital prevalence is key to determining the efficacy of the antibiotic. For this reason, the HH model was simplified for integration with the EA model. In particular, transmission within the community is not considered.

The model considers four groups or ‘compartments’ of individuals (Fig. 1): unexposed and not on antibiotics (U), unexposed and on antibiotics (V), colonized at a low-level and not on antibiotics (Y) and colonized at a high-level and on antibiotics (Z). In each compartment, all individuals have the same characteristics with respect to antibiotic treatment and colonization status. Following the work of [17,20], two types of colonized individual are included to reflect the difference between low-level (transient, with recovery a week or so after exposure) and high-level (persistent, with recovery for after months or years) colonization. This is important because antibiotic use may have an effect on persistence and shedding and thus transmission. The model does not consider the spread of resistance in terms of the interaction between resistant and susceptible strains due to the limited amount of information available to describe this interaction.

Individuals move from one group to another as follows. Unexposed and low-level colonized individuals are prescribed antibiotics at a rate \( \rho \) per individual per day and the effects of the antibiotic are assumed to last as long as they remain hospitalized; prescription results in low-level colonized individuals becoming colonized at a high-level. Following contact with either low-level or high-level colonized individuals, unexposed individuals become colonized; if they are on antibiotics they are colonized at a high-level and if they are not on antibiotics they are colonized at a low-level. The contact parameters combine information about the contact rate with hospital staff and level of hygiene and sanitation within the hospital. Individuals are discharged from all groups at a rate \( \delta \) and new individuals from the community enter at this same rate. Due to the fact that antibiotic use is confined to the hospital, new individuals are either unexposed or colonized at a low-level according to the community prevalence of SREF.

Although recently hospitalised individuals may be readmitted, we have ignored increased community prevalence due to recent hospitalisation. The simplification is valid for two reasons. Firstly, the size of the community is much
larger than the hospital population, and therefore community prevalence increases quite slowly. Secondly, the uncertainties identified by both the EA and HH models were large. These uncertainties would be compounded in a more detailed model and hence the key dynamics and influencing factors may be hidden. Adopting a simpler model increases transparency while focusing on the key parameters.

3.4.1. Parameter values

The parameter values used in the integrated model are outlined in Table 1. The initial prevalence of colonized individuals in the hospital was determined by the fraction of individuals colonized on admission, assuming a ban coincides with the beginning of human prescription [2]. All of these individuals will be colonized at a low-level because antibiotics are not used in the community. The hospital size was assumed to be 700 and the average length of stay in hospital was taken to be 5 days. The rates of transmission from low-level and high-level colonized individuals were assumed to be 0.0001 and 0.01, respectively. These values are discussed in [2].

The rate at which exposure declines following a ban ($\lambda$) and the prescription rate ($\rho$), are varied to investigate the effects of policy options and the potential for nosocomial transmission. In particular, we consider no regulation of virginiamycin use ($\lambda = 0$) and regulation leading to an exponential decline in exposure, as assumed by the EA model ($\lambda = 0.005$). In addition, we investigate the influence of antibiotic use at three assumed levels, $\rho = 0.001, 0.002$ and 0.004. This parameter determines the potential for epidemic spread within the hospital as defined by $R_0$, the number of individuals colonized from a single colonized individual in an otherwise naïve population. For this model, an expression for $R_0$ is

$$R_0 = \frac{\eta H}{\rho + \delta} + \frac{\rho}{\rho + \delta} \frac{\beta H}{\rho + \delta}$$

When $\rho = 0.001$, $R_0 \approx 0.52$ and the potential for epidemic spread is low, when $\rho = 0.002$, the potential for epidemic spread is medium and $R_0 \approx 0.69$ and finally when $\rho = 0.004$, the potential for epidemic spread is high and $R_0 \approx 1.03$. Because $R_0$ is also dependent on $H$, $\delta$, $\eta$ and $\beta$, we could generate similar results by changing any of these parameters to give low, medium and high epidemic spread potential.

The initial equilibrium community prevalence was estimated to be 1%. This was based on testing of 320 human faecal samples as part of US National Antimicrobial Resistance Monitoring (NARMS) programme [8]. This data have several associated caveats. In particular, low-level resistance was recorded and isolated strains may have been transient. Based on empirical evidence, the EA model assumes that the post-ban equilibrium rate of exposure will be 25% of its original value. Following this assumption, the community prevalence a long time after the ban (post-ban the equilibrium prevalence) is set equal to 0.0025.

It is acknowledged that both the pre- and post-ban equilibrium community prevalences are uncertain parameters and thus it could be argued that a sensitivity analysis of these parameters would be valuable. However, because we have summarised transmission in terms of $R_0$, this is unnecessary. Community prevalence will influence hospital prevalence and the greater the potential for transmission within the hospital (i.e. the larger the value of $R_0$) the less influence these ‘community’ parameters will have. Thus, changing their values will lead to noticeable differences at low $R_0$ only; the results for medium and high $R_0$ will remain the same and thus the overall qualitative picture will not change.

4. Results

The prevalence of SREF positive individuals is shown in Fig. 2 for the 3 levels of epidemic potential comparing a ban (regulation) to the decision of no ban (no regulation) on the use of virginiamycin. For low epidemic potential, the rate of person-to-person transmission is extremely small and thus the majority of positive individuals are those who were colonised prior to admission. Colonization of these individuals is as a result of exposure to contaminated food and therefore, community prevalence, $C(t)$, is an important factor in determining hospital prevalence. If a ban is enforced, prevalence rapidly falls to a lower level that is maintained by amplification of resistance when the antibiotic is used.

When the potential for epidemic spread is high, the converse is true. In other words, community prevalence has a
minor effect in determining hospital prevalence. Under this scenario, SREF reaches a relatively high prevalence because of antibiotic use and subsequent person-to-person transmission. New strains of SREF may be introduced into the hospital but these will have a minor effect because most transmission will re-expose individuals who are already colonised. As a result, if a ban is enforced, very little difference is observed.

Fig. 2. Prevalence of SREF positive individuals over time for three potential levels of epidemic spread (low, \( \rho = 0.001 \); medium, \( \rho = 0.002 \); high, \( \rho = 0.004 \)) and two policy options (ban of virginiamycin at \( t = 0 \) and no ban of virginiamycin).

Fig. 3. Excess number of SREF positive individuals over time, for three potential levels of epidemic spread (low, \( \rho = 0.001 \); medium, \( \rho = 0.002 \); high, \( \rho = 0.004 \)).
The situation when there is medium epidemic potential is less straightforward; individual strains of SREF introduced into the hospital may become extinct or they may give rise to sub-epidemics, thus amplifying overall prevalence. If a ban is enforced, there is a notable decrease in the equilibrium prevalence, however, the time taken to reach this value would be slightly longer than in the case of low epidemic potential.

Comparison of the three epidemic scenarios is presented in Fig. 3, where the excess number of positive individuals under the no-ban situation are plotted. From these plots it is evident that a ban would have the largest benefit if there were a medium potential for epidemic spread. This is because the potential for sub-epidemics within the hospital is being reduced.

5. Discussion

The approval of quinupristin/dalfopristin in 1999 introduced a new era for the treatment of VRE and a new era of concern for the emergence of resistance to streptogramins. The justification for banning virginiamycin on the basis of the precautionary principle, as the EU recently did, does not initially require a detailed risk assessment. On the other hand, MRA has some important benefits. Firstly, the identification of key parameters and important sources of uncertainty is possible. Secondly, the process facilitates qualitative understanding of the problem. Finally, the availability of the model can promote future scientific discussion and thus lead to more informed decision-making. In situations such as the potential emergence of SREF where large uncertainties are inevitable, these alternative outputs are key and indeed, the estimate of risk could be considered of secondary importance.

In this conditional risk assessment, we have integrated the features of related models describing different aspects of the emergence of SREF, including the exposure to SREF from broilers, community prevalence, and subsequent person-to-person transmission within hospitals. Even for this relatively simple model, the level of uncertainty made qualitative investigation necessary. Based on discussions with microbiologists, we have reduced the large and complicated parameter space to a small set of plausible scenarios. Our results indicate that the effect of banning virginiamycin is extremely sensitive to the potential for epidemic spread ($R_0$). If $R_0 > 1$, a problem with SREF would be created mainly by medical antibiotic use; consequently, a ban on virginiamycin would have a limited effect. In the case where SREF is similar to campylobacter, $R_0 < 1$, community prevalence is the major determinant of hospital prevalence. The problem is small initially and remains small, but a ban would lead to declines in hospital prevalence because epidemics are very unlikely. The greatest effect occurs when $R_0 \sim 1$. Under this scenario, a ban would reduce community prevalence leading to long and sustained declines in the prevalence of SREF in hospital populations. The impact is sustained because hospital prevalence is an interaction between nearly epidemic spread and the constant introduction of SREF into hospitals [21].

One limitation of these models is that they do not incorporate stochastic effects that could lead to different conclusions; the rapid increase in prevalence within a hospital over a short period of time may, in fact, be substantially slower. More importantly, a substantial delay may occur before an epidemic occurs, increasing the benefits of a ban for the case where $R_0 > 1$. The simple deterministic approach was adopted in order that expected dynamics and relationships between parameters could be observed. Thus, it is the qualitative conclusions that are important rather than absolute estimates of risk such as the equilibrium prevalence or the time taken to reach this equilibrium.

The set of plausible outcomes generated from the integrated model mean that policy making with regard to virginiamycin use is not straightforward. Uncertainty exists about many of the model parameters, including the key parameter $R_0$. Before $R_0$ can be reliably quantified, we require detailed understanding of how SREF will emerge, how such emergence is related to quinupristin/dalfopristin use and the use of other antibiotics. It seems likely that SREF and VRE will be similar; VRE has a potential for rapid epidemic spread and that may be managed with extensive hospital control. A similar scenario may be likely for SREF, but there is probably much variation between hospitals.

6. Conclusion

Despite the large uncertainties surrounding the problem of resistance transfer from animals to humans, the qualitative results derived from this conditional assessment are useful. They demonstrate that there are a number of plausible biological scenarios, each of which would be best followed by different policy options: when the potential for epidemic spread is large, banning virginiamycin would have a limited effect whereas when the potential for epidemic spread is low, a ban would lead to declines in hospital prevalence because epidemics are very unlikely. The greatest effect would occur for medium epidemic potential in which case a ban would reduce community prevalence leading to long and sustained declines in the prevalence of SREF in hospital populations. The question of which scenario is most plausible is debatable. Thus, it seems reasonable to conclude that the weight of evidence does not yet support either policy direction. More importantly, more scientific evidence needs to be collected to reduce the identified uncertainties. In particular, the risk assessment has shown that we need data to understand the potential for nosocomial transmission and thus determine the likely value of $R_0$. Without such data, the policy direction will remain inconclusive.
This results in Eq. (B.1)

\[ F(t) = \mu + [F(0) - \mu]e^{-\lambda t} \]  \quad (A.1)

Here \( F(0) \) is the pre-ban rate of exposure, \( \mu \) is the equilibrium rate of exposure and \( \lambda \) is the rate at which exposure declines following the ban.

Appendix B. Community prevalence

It is assumed that community prevalence, defined as \( C(t) \), is proportional to the rate of exposure to SREF from broilers and that the constant of proportionality represents the likelihood and duration of colonization following exposure. This results in Eq. (B.1)

\[ C(t) = \frac{F(t) \rho \beta P_{\text{ban}} D_C}{\lambda t} + C_0 \]  \quad (B.1)

where \( \rho \beta \) is the rate at which exposure to SREF is proportional to the rate of exposure to SREF from broilers and that the constant of proportionality represents the likelihood and duration of colonization following exposure.

Substituting Eq. (A.1) into Eq. (B.1) gives

\[ C(t) = C_L + C_0 e^{-\lambda t} \]

where \( C_L = \mu P_{\text{ban}} D_C \) is the equilibrium community prevalence a long time after the ban and \( C_0 = (F(0) - \mu)P_{\text{ban}}D_C \) is the difference between the current and post-ban equilibrium community prevalence.

Appendix C. The Integrated model

The model is described by the following set of coupled differential equations

\[ \frac{dU}{dt} = -(qY + \beta Z)U - \rho U - \beta U + \delta H[1 - C] \]

\[ \frac{dV}{dt} = -(qY + \beta Z)V - \rho V - \delta V \]

\[ \frac{dY}{dt} = (qY + \beta Z)U - \rho Y - \delta Y + \delta HC \]

\[ \frac{dZ}{dt} = (qY + \beta Z)V + \rho Y - \delta Z \]

where \( H = U + V + Y + Z \) is the hospital size, \( \delta \) is the discharge rate, \( \rho \) is the rate at which antibiotic use affects nosocomial transmission and \( C \) is the community prevalence estimated from Eq. (B.1), and \( (qY + \beta Z) \) is the per-capita colonization rate. It is assumed that homogenous mixing occurs between individuals and that \( q \) and \( \beta \) are the rates of transmission from low and high-level colonised individuals, respectively. These equations were solved numerically to describe the prevalence over time.

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