Virginiamycin Use and the Emergence of Streptogramin Resistance in *Enterococcus faecium*

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NOTE: The following supplemental material is provided to accompany our paper, "Assessing risks for a pre-emergent pathogen: virginiamycin use and the emergence of streptogramin resistance in *Enterococcus faecium*, THE LANCET, Infectious Diseases (Journal Website), Vol. 3, April 2003, pp 241--249. All questions and correspondence should be directed to the corresponding author, David L. Smith. For more complete bibliographic information, we refer readers to cite our paper.

A Note about Mathematical Models

This work is an extension of our broader goal to understand and the current epidemic of antibiotic resistance in nosocomial pathogens, especially vancomycin resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). The emergence of resistance to antibiotics is a complicated problem involving multiple interacting factors. Despite the complexity, a need exists for simple models. In some ways, the model we describe here is neither as simple as it could be, nor as complex as the real problem. Some very important details have been omitted in order to focus on the way that one factor--virginiamycin use--interacts with all the other factors and contributes to the problem.

The measure of a model is not whether it is true, but whether it is useful. All models are abstractions and simplifications; the issue for scientists is to develop models that find an appropriate balance. Here, we have made simplifying assumptions to emphasize those aspects that are most relevant to policy makers. We have focused on the colonization with SREF rather than infection; because the risk of infection with SREF is related to exposure, and the risk of exposure is related to the prevalence of SREF. Therefore, we are interested in understanding the factors that lead to increases in the prevalence of SREF.

These simple mathematical models should be used to help us reason through a problem. The model provides a transparent formulation of a complicated problem. The model allows us to change one **parameter** and see how changes in that parameter affects a response **variable** that we are interested in. For example, we can ask the question, "If SREF are present on 70% of all chicken products sold in the store, yet less than 1% of people are colonized with SREF, is it reasonable to conclude that there are no risks associated with virginiamycin use?" Of course, this question depends on many other parameters and assumptions in the model. Since the model is already complicated, and there is substantial uncertainty associated with all these parameters, we are left with a complicated answer. Our solution to this problem was to identify six cases that were representative of other cases.

We emphasize that the logic proceeds from **IF ...** to **THEN ...** ; conclusions are tentative, based on the best informal assessment of likely scenarios. We emphasize that the FDA's mandate for their decision is a **"reasonable expectation of no harm."**

The Mathematical Model

In the mathematical models, we have made simplifying assumptions to emphasize those aspects that are most relevant to policy makers. We have focused on the colonization with SREF rather than infection; because the risk of **infection** is affected by the rate of **exposure** to SREF. The risk of exposure depends on many things, including the number of other patients who are **colonized** with SREF. Virginiamycin use, synercid use, and use of other antibiotics are all factors that may lead to increased prevalence of SREF in humans. Our model provides a basis for judging how each of these factors impacts the emergence of SREF.

Animal-to-Human Transmission

To quantify the public health consequences of virginiamycin use, it is necessary to quantify the rate at which new strains of SREF appear in the human population as well as the origins of these strains. New SREF strains may enter humans from exposure to contaminated animal food products, from other environmental sources, or from the evolution of SREF strains already established in humans. To attribute decreased efficacy of synercid to virginiamycin use two questions must be answered 1) How frequent is animal-to-human transmission of SREF? 2) What fraction of new strains of SREF in humans are due to the use of virginiamycin? Answers to both questions are necessary before the impact of virginiamycin use can be evaluated.

To estimate the consequences of virginiamycin use, it is necessary to quantify the rate that these events may occur. We let μ denote the rate (per person, per day) that new strains of SREF are introduced into humans, regardless of how. A fraction of these new strains may occur as a direct consequence of virginiamycin use. We let ξ denote this fraction, the remaining fraction, $1-\xi$, would occur even if antibiotics had never been used. Obtaining estimates of μ and ξ present a conundrum; estimates of these parameters could only be obtained if SREF had already emerged. Because of this, substantial controversy, biological complexity, and uncertainty exists about these parameters, μ and ξ.

Exposure and Colonization

The total density of enterococci in human guts range up to 10^{11} CFU per gram of stool. Natural fluctuations in the population densities and persistence of antibiotic resistant and antibiotic sensitive strains of enterococci in humans are poorly understood from a quantitative perspective. We use the terms ``exposure,'' ``colonization,'' and ``infection'' to refer to different aspects of enterococcal population dynamics in humans. Exposure refers to the introduction of new SREF strains through ingestion of SREF that survives the gastric barrier to reach the large bowel. Exposure includes new strains ingested following contact with animal food products or fecal-to-oral transmission from a colonized human. In the gut, SREF compete with the established flora and may be bombarded by the human immune system. Most SREF populations are transient, pass through the gut with residence times that are similar to food, and may be present at very low densities. Under some conditions, SREF may colonize in the human gut and establish more persistent populations. The difference between exposure and colonization is significant from a quantitative perspective; exposure is common but transient, while colonization is rare but persistent. Infection occurs when enterococci establish populations in the blood-stream, urinary tract, wounds, or other human tissues where they cause disease. Most humans who become infected with VRE are immunocompromised because of chemotherapy, or at increased risk of infection because of intubation, or contamination of open wounds.

Without antibiotic use, antibiotic resistant bacteria would probably remain rare in human populations. Antibiotic use may increase population densities of VRE leading to increased shedding and transmission, and it may perturb the gut leading to increased colonization rates by VRE. Increased transmission and colonization rates may be associated with perturbations to the microbial community that eliminate some species of bacteria, especially sensitive enterococci. Other factors may also be involved, such as changes in the biochemical environment or depression of the host immune system. Enterococci are naturally resistant or have acquired resistance to most antibiotics, so many antibiotics that do not have therapeutic effects on enterococci may influence the population densities and colonization rates of SREF.

We assume that exposure is common and transient, but colonization is rare but persistent. Second, we assume that the density of SREF within a human gut increase following antibiotic use. We assume that the increased population density can be usefully approximated by classifying colonized humans as either colonized by low-density SREF populations or colonized by high-density SREF populations. Under these assumptions, humans are either unexposed, exposed, colonized by low-densities of SREF, or colonized by high-densities of SREF; we let U, X, Y, and Z denote the number of humans in each state, respectively. Our model couples a community population and a hospital population, so we use subscripts to identify the number in each state in each location. For example, Y_c represents the number of humans in the community who are colonized while Y_h is the number of humans in the hospital who are colonized.

Human-to-Human Transmission

Following exposure, we assume that SREF either colonize, or the population passes through the gut and is lost. In hospitals, exposed or colonized humans may take antibiotics that amplify SREF population densities. We let α denote the rate that each exposed human loses SREF populations, θ denote the rate that exposed humans are colonized, and ρ denote the rate that hospital patients are prescribed antibiotics that amplify SREF densities. Since antibiotic use amplifies SREF in humans who were exposed or colonized, and colonization occurs at a higher rate in amplified humans, antibiotic use increases the fraction of humans in the community who are colonized.

The risk of infection or colonization with SREF is related to the colonization pressure, a measure of the total amount shed by other patients, including both the number of patients shedding and the population densities (or loads) of SREF within each patient. We assume that SREF from humans with amplified populations is shed at much higher rates, increasing the probability of transmission. We assume that SREF are shed from colonized humans, but more SREF are shed by humans with high-density populations. Under random mixing, the average rate that humans are exposed from human-to-human transmission is $\eta Y + \beta Z$, where η is the contact for humans with low-density SREF populations, β is the contact parameter for high-density SREF, and $\beta >> \eta$.

The net per-capita rate of exposure including both animal-to-human and human-to-human transmission is called colonization pressure, denoted Λ the average waiting time to exposure under constant colonization pressure is $1/\Lambda$. Colonization pressure in the community includes exposure to new strains and community transmission, $\Lambda_c = \mu + \eta_c Y_c + \beta_c Z_c$. Colonization pressure in hospitals is $\Lambda_h = \mu + \eta_h Y_h + \beta_h Z_h$. Both terms include animal-to-human transmission.

Also, we assume that antibiotic use ends when a person is discharged from the hospital, and SREF densities decline. Some humans revert to being colonized, while others revert to being unexposed. We let γ denote the rate that they recolonize, and φ denote the rate that SREF is lost.

Admission and Discharge

Communities and hospitals are linked by patient admission and discharge. We assume that the size of the two populations is constant over time, and patients are admitted and discharged at random. We let H denote the size of the hospital population, C denote the size of the community population it serves, and g denote the discharge rate from the hospital. Since the hospital population is smaller than the community, the per-capita rate of admission rate from the community is much lower than the per-capita rate of discharge from the hospital. The total rate of discharge is d H, which is exactly balanced by admission from the community, so the per-capita admission rate is denoted $a = g H / C$.

The establishment of SREF in hospitals may be disproportionately affected by the transfer of patients from long-term care facilities, those who visit the hospital frequently, or those who are hospitalized longer than average. Quantitative risk assessments would need to be modified to incorporate these important sources of heterogeneity, but we have ignored these modifications of the model to focus attention on other aspects.

Community Transmission

Equations:

$$d U_c / dt = - \Lambda_c U_c + \alpha X_c + \sigma Y_c + \gamma Z_c - a U_c + g (U_h + V_h)$$
$$d X_c / dt = \Lambda_c U_c - (\alpha + \theta) X_c - a X_c + g X_h$$
$$d Y_c / dt = \theta X_c + \varphi Z_c - \sigma Y_c - a Y_c + g Y_h$$
$$d Z_c / dt = - (\varphi + \gamma) Z_c - a Z_c + g Z_h$$

$$\Lambda_c = \mu + \eta_c Y_c + \beta_c Z_c$$

Hospital Transmission

A diagram of the model is the following, and the equations follow:

Equations:

$$d U_h /dt = - (\Lambda_h + \rho) U_h + \alpha X_h + \sigma Y_h + \gamma Z_h - g U_h + a U_c$$
$$d V_h /dt = \rho U_h - \Lambda_h V_h - g V_h$$
$$d X_h /dt = \Lambda_h U_h - (\alpha + \theta + \rho) X_h - g X_h + a X_c$$
$$d Y_h /dt = (\theta + \rho) X_h + \varphi Z_h - \sigma Y_h - g Y_h + a Y_c$$
$$d Z_h /dt = \rho (X_h + Y_h) + \Lambda_h V_h - (\varphi + \gamma) Z_h - g Z_h + a Z_c$$

$$\Lambda_h = \mu + \eta_h Y_h + \beta_h Z_h$$

Parameters

Parameter	Estimate	Explanation
$1/ \alpha$	5 days	Duration of transient SREF
$\theta /(\alpha + \theta)$	0.001	Probability of colonizing.
$1/ \sigma$	100 days	Duration of colonized SREF.
$1/ (\gamma + \varphi)$	30 days	Duration of amplification effect
$\gamma /(\gamma + \varphi)$	0.30	Probability of re-colonizing.
μ	varied	Animal-to-human exposure rate.
ξ	varied	Fraction of μ due to virginiamycin use
1/g	5 days	Average hospital stay
H	700	Number of Hospital Patients
C	50,000	Community Population
ρ	varied	Antibiotic prescription rate
$\eta_c C / \sigma$	1 person	R_C^Y, # Exposed in Community by each Y
$\beta_c C/ (\gamma + \varphi)$	100 people	R_C^Z, # Exposed in Community by each Z
$\eta_h H/ g$	1/10 person	R_H^Z, # Exposed in Hospital by each Z
$\beta_h H / g$	2 people	R_H^Y, # Exposed in Hospital by each Y