Emergence of antibiotic resistant *Salmonella* Typhimurium: The effect of antibiotic therapy on a single pen of grower-finisher pigs

Kimberley Kavanagh[1], Louise Kelly[1,2], George Gettinby[1], Emma Snary[2]

[1]Department of Statistics and Modelling Science, University of Strathclyde, Livingstone Tower, 26 Richmond Street, Glasgow, G1 1XH, UK.

[2]Centre for Epidemiology and Risk Analysis, Veterinary Laboratories Agency, New Haw, Surrey, UK.

Introduction

The emergence of antibiotic resistant bacteria is a major cause for concern in both human and animal health. In particular there has been concern that the use of antibiotic therapy in agriculture could lead to the emergence of resistant bacteria which would pose a threat to human health via the food chain. *Salmonella* Typhimurium (STM) is the most prevalent serotype of the genus Salmonella isolated from pigs (Defra, 2003) and a major cause of food poisoning in humans following the ingestion of pork products.

In order to analyse the effect which metaphylactic antibiotic treatment can have on the emergence of resistant STM, a compartmental differential equation model has been developed. This approach has been successfully used to explain transmission dynamics of antibiotic resistant bacteria in humans by Austin et al (1997). The conceptual model presented enables the emergence of resistant STM, due to antibiotic treatment, in a single pen of grower finisher pigs to be studied. Analysis of the model aims to indicate the key factors of treatment administration which influence the emergence of resistance.

Schematic Representation

Conceptual Model Assumptions

- At any time a pig can be classified into one of three groups dependent on its STM colonisation status (Figure 1)
- The pigs are treated metaphylactically. Blue and green compartments denote compartments occupied by treated ($\tau = 1$) and untreated ($\tau = 0$) pigs, respectively.
- The pigs remain in their pen for the duration of the grower-finisher stage.
- The number of pigs in the pen, N, is fixed.
- There is no external source of infection with STM
- Resistance develops by selection of pre-existing resistant mutants with probability, σ, by transmission of resistant STM at rate β or by transmission of a resistance plasmid at rate ξ.
- The baseline treatment is assumed to be 100% efficient against sensitive STM (a=1) and 0% efficient against resistant STM (b=0)
- Treatment is assumed to last 7 days unless otherwise stated

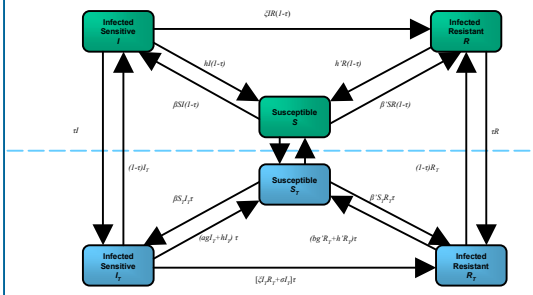

Figure 1: Flow diagram showing spread and treatment of STM infection in a single pen of grower-finisher pigs

Conceptual Model Equations

$$\frac{dS}{dt} = \left[h'R + hI - \frac{\beta SI}{N} - \frac{\beta' SR}{N} + S_T\right](1-\tau) - S\tau$$

$$\frac{dI}{dt} = \left[\frac{\beta SI}{N} - hI - \frac{\xi' IR}{N} + I_T\right](1-\tau) - I\tau$$

$$\frac{dR}{dt} = \left[\frac{\beta' SR}{N} - h'R + \frac{\xi' IR}{N} + R_T\right](1-\tau) - R\tau$$

$$\frac{dS_T}{dt} = \left[(ag+h)I_T + (bg+h')R_T - \frac{\beta S_T I_T}{N} - \frac{\beta' S_T R_T}{N} + S\right]\tau - (1-\tau)S_T$$

$$\frac{dI_T}{dt} = \left[\frac{\beta S_T I_T}{N} - (ag+h)I_T - \frac{\xi' I_T R_T}{N} - \sigma I + I\right]\tau - (1-\tau)I_T$$

$$\frac{dR_T}{dt} = \left[\frac{\beta S_T R_T}{N} - (bg+h')R_T + \frac{\xi' I_T R_T}{N} + \sigma I + R\right]\tau - (1-\tau)R_T$$

Results

Model Dynamics

Long term dynamics: Estimation of R_0

- R_0 is defined as the number of secondary infections from a single primary infection, Anderson and May (1991).
- R_0 is calculated for both sensitive and resistant strains assuming fitness cost to resistant organisms, $\beta < \beta'$
- As seen in Table 1, both values are both less than 1.This indicates that STM only has a trivial endemic equilibrium, i.e. infection will die out in the long term assuming no infection enters the pen from elsewhere.

Sensitive	Resistant
$R_0 = \beta/h$	$R_0 = \beta'/h'$
R_0=0.0014	R_0=0.0013

Table 1: Calculation of R_0

Long run dynamics with 7 day treatment

- 7-day treatment implemented in a fully sensitively infected population
- Treatment selects for a pre-existing mutant in 10% of infected pigs
- Under assumed field conditions, initially a resistant population emerges, however it cannot be sustained and dies out slowly.
- By day 84, the approximate time of slaughter, a resistant population remains with prevalence 16.2%, which could pose a potential public health risk.

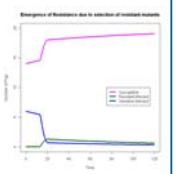

Figure 2: Model dynamics over 120 day time period showing the emergence of resistant infected group due to selection of pre-existing resistant mutants.

Effect of Treatment Efficacy

Effect of increasing the efficacy against resistant strains, b

- Increasing the efficacy of the treatment in tackling resistant STM infection decreases the prevalence of emerging resistance.
- Emergence is minimised when b=1, with prevalence after 84 days of 1.6%, this however may not be attainable in practice.

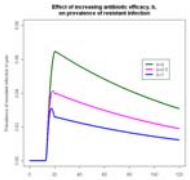

Figure 3: Prevalence of resistant infected pigs in the pen following 7 day antibiotic treatment of efficacy b, against resistant strains, commencing on day 13. a =1.

Effect of Duration of Treatment

Effect of varying the duration of treatment

- Increasing the duration of the treatment period leads to an increase in the prevalence of emerging resistance.
- 14-day treatment will, however, lead to the lowest prevalence of total infection in the pen as more sensitive infected pigs will recover.

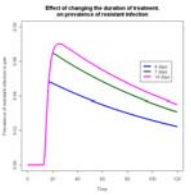

Figure 4: Prevalence of resistant infection present in the pen for differing treatment periods , a=1, b=0.

Combined Effect: Best attainable strategy

Best attainable strategy

- Emergence of resistance is minimised when the treatment efficacy against both sensitive and resistant strains is 100%. It is, however, unlikely that antibiotic treatment will be able to achieve this target and remove all resistant strains. If possible, this scenario would lead to a resistant infected prevalence at slaughter of 0.0047.
- Figure 5 illustrates a potentially more attainable scenario where 50% of resistant STM infection is removed and treatment period is 14 days. This combination removes all sensitive infected organisms and lowers the prevalence of resistant infection. The prevalence of resistant infected pigs at slaughter is now 1.35%, significantly lowered from 16.2% under the treatment scenario illustrated in figure 2.

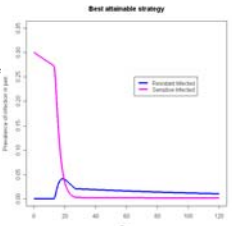

Figure 5: Treatment period is increased to 14 days to eradicate sensitive STM. b=0.5 decreases the maximum prevalence of resistant strains

Conclusions

- Under assumed field conditions, antibiotic therapy will initially result in the emergence of a resistant infected sub-population. Although this population will decay it will still remain at time of slaughter when 16.2% of pigs are infected with resistant STM. This could present a potential health risk to humans.
- This resistant infection may also pose a risk to subsequent batches of pigs entering the pen and also to pigs in surrounding pens if proper cleaning and disinfection is not undertaken.
- The various interventions investigated succeed in lowering the prevalence of resistant infection present at slaughter. However, even with the potentially attainable strategy, 1.35% of pigs would be infected with resistant STM following initial colonisation with sensitive STM and subsequent treatment
- Under the model assumptions the sustainability of resistance seems inevitable due to the relatively fast turn-over in the pig production cycle.

References

Anderson R M, May R M (1991) *Infectious Diseases of Humans: Dynamics and Control.* Oxford University Press.

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