PHARMACOKINETICS OF ANTIMICROBIALS AT DIFFERENT LEVELS OF THE INTESTINAL TRACT AND THEIR RELATIONSHIP TO *ESCHERICHIA COLI* RESISTANCE PATTERNS IN THE PIG

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Summary

The first part of the paper looked at the pharmacokinetics of a liquid non-absorbable compound as it passed along the small intestines of adult pigs. Only 38.8% of the dose was recovered in the upper small intestine, 71.5% in the middle third, but 100% in the lower third or ileum over a 12 hour period. The first time point was at two hours after dosing, when the stomach had passed 51% of the dose and 71.5% by 4 hours. It was thought that inadequate sampling points prior to two hours meant that a substantial portion of the dose had been missed in the upper small intestine and had already passed down to the lower small intestine. A calculation was made, based on the area under the curve (AUC) from the stomach and added to the upper small intestine and this increased the recovered dose to 81.6%. Using the routine in-feed usage pharmacokinetic data of AUC projected over 24 hours and available gut or faecal concentration data or estimations, the mid-small intestine concentrations were compared with the epidemiological cut-off values (ECOV) for various antimicrobials against porcine E. coli from Danish slaughterhouse monitoring and diagnostic isolates. Similarly, the clinical breakpoints (CBP) (one dilution lower than the NCCLS resistance breakpoints) were also examined in this AUC/MIC analysis. Most of the bacteriostatic antimicrobials were around or exceeded the AUC/MIC ECOV ratio of 24, which denotes inhibition, and all the bactericidal compounds exceeded 100. When the AUC/MIC CBP ratios were examined, the majority of bactericidal antimicrobials exceeded 100, except enrofloxacin, and for the bacteriostatic compounds, spectinomycin was well below. Trimethoprim and sulphonamides alone were also consistently low, but when used in a combination, their synergistic bactericidal activity exceeded the 100 threshold. Fundamental pharmacokinetic/pharmacodynamic analysis of antimicrobials in gut contents appears to be applicable to E. coli infections in the small intestine.

Introduction

The pharmacokinetic (PK) parameters, especially of antimicrobials used for the treatment of intestinal infections of the pig, and their relationship with the pharmacodynamics (PD) of enteric bacteria are increasingly being

described (Burch, 2005a; Burch, 2005b; Burch, 2006). There are three major regions of significance; the upper and mid small intestine (duodenum and jejunum) for *Escherichia coli* infections, the lower small intestine (ileum) for *Lawsonia intracellularis* infections and the large intestine (colon) for *Brachyspira hyodysenteriae* and *B. pilosicoli* infections. It is the purpose of this paper to firstly look at the maximum concentration (Cmax) area under the curve (AUC) and rolling mean (RM) relationships based on a non-absorbed product and compare them with different sections of the pig gut. Secondly, to look at PK concentrations found in the small intestine and relate them to the antimicrobial resistance patterns displayed by *E. coli* from slaughterhouse pigs and diagnostic cases, which may well have received antimicrobials prior to submission.

Part 1 - Materials and Methods

Clemens *et al* (1975) looked at the passage of food along the intestinal tract of adult pigs, using liquid markers (polyethylene glycol and chromium-labelled ethylenediaminetetraacetic acid (Cr-EDTA), which was singly dosed by stomach tube mid-meal to pigs fed every 12 hours. The flow and percentage of dose in various sections of the gut (stomach, upper small intestine, mid small intestine, lower small intestine, were determined, following sequential slaughter of the pigs at 0, 2, 4, 8, 12, 16, 20, 24, 38, 50 and 60 hours post-feeding.

Using these basic figures, the pharmacokinetic parameters, Cmax, AUC and RM could be calculated for each stage of the pig's small intestine over a 12 hour (0-12 hours) time period. As the product did not enter the mid colon for two hours, a 2-14 hour time period was used in the calculations. To determine the AUC 24 hours, the RM over 12 hours could be multiplied by 24 or the AUC 12 hours doubled, which reflects a pig's normal feeding of at least twice a day.

Results

The intestinal flow results based on Cr-EDTA measurement and PK results are shown in Table 1 and Fig.1.

Table 1 - Cmax, AUC 12 hours and Rolling Mean (RM) and concentration ratio for Cr-EDTA in gut contents of the pig

	Cmax (%)	AUC 12 h (% h)	Rolling Mean (%)	Ratio (%)
Upper small intestine (duodenum)	7.5	38.8	3.2	10.7
Mid small intestine (jejunum)	37	71.5	6.0	20.1
Lower small intestine (ileum)	16	100	8.3	27.7
Large intestine 2-14 hours (mid-colon)	44	359	29.9	100

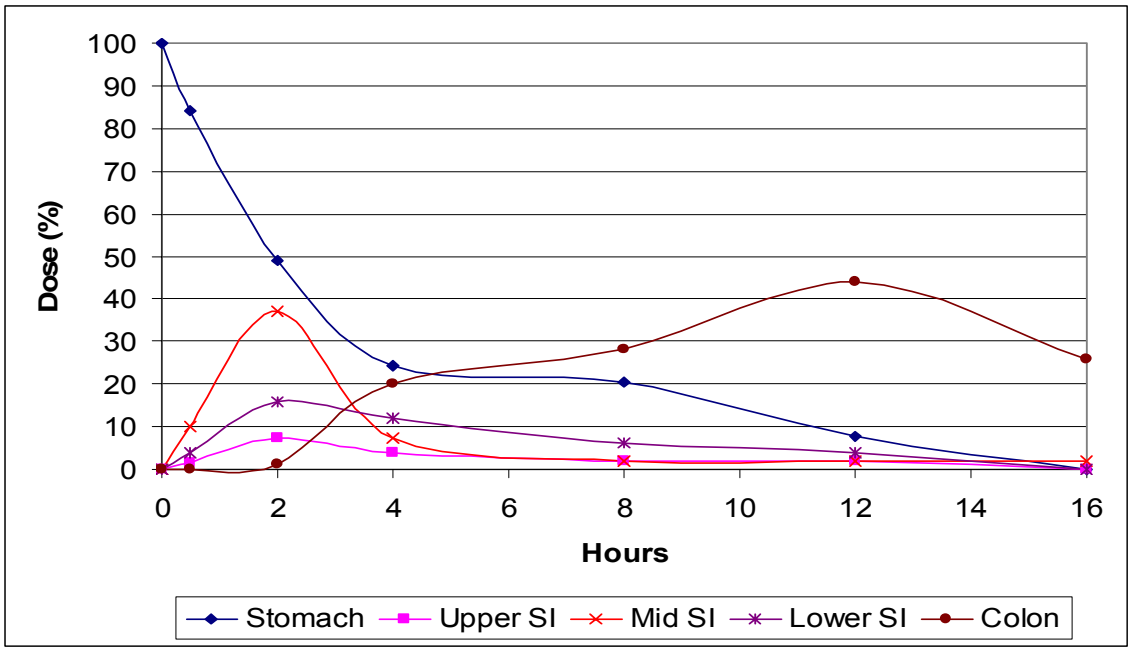

Fig. 1 - Dose (%) found in the stomach, upper, mid and lower small intestine and colon contents against time

The first samples were taken at 2 hours and only relatively low levels were found in the upper small intestine, with a Cmax of 7.5µg/ml being determined, although 51% of the dose had passed out of the stomach by then and 76% by 4 hours. The dose recovery from the upper small intestine, in the 12 hour period, was only 38.8%, showing that a substantial amount of the dose had been missed. The jejunum's Cmax was much higher, at 37µg/ml, and 71.5% of the dose was recovered. The ileum had a Cmax of 16µg/ml and 100% of the dose was identified.

By measuring the content of the intestines at 2 hours after dosing, it was thought that a substantial amount of the dose had already passed the duodenum and jejunum and was already reaching the ileum. An estimate was made, using

the same AUC in the duodenum that was lost from the stomach in that 2 hour period and a Cmax of 37µg/ml was estimated at a time (Tmax) of about 20minutes and then 81.6% of the dose would have been recovered. This suggests that the time interval for making these gut calculations should be reduced below 2 hours to give more accurate assessments higher up the gut (see Table 2 and Figs. 2 and 3) and possibly at more frequent intervals to increase the recovery percentage to 100%.

Table 2 - Revised Cmax, AUC 12 hours and Rolling Mean (RM) and concentration ratio for Cr-EDTA in gut contents of the pig

	Cmax (%)	**AUC 12 h (% h)**	**Rolling Mean (%)**	**Ratio (%)**
Upper small intestine (duodenum)	7.5	38.8	3.2	10.7
Upper small intestine (estimate)	**45**	**81.6**	**6.8**	**22.7**
Mid small intestine (jejunum)	37	71.5	6.0	20.1
Lower small intestine (ileum)	16	100	8.3	27.7
Large intestine 2-14 hours (mid-colon)	44	359	29.9	100

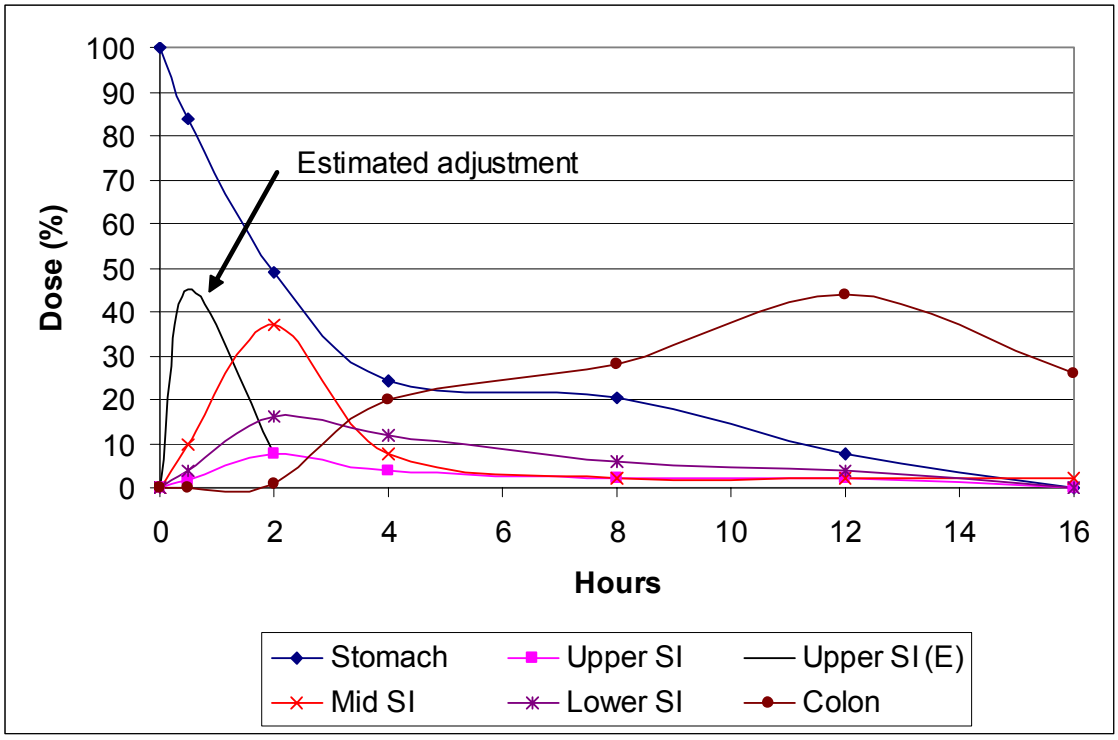

Fig. 2 - Dose (%) found in the stomach, upper (plus estimated adjustment), mid and lower small intestine and colon contents against time

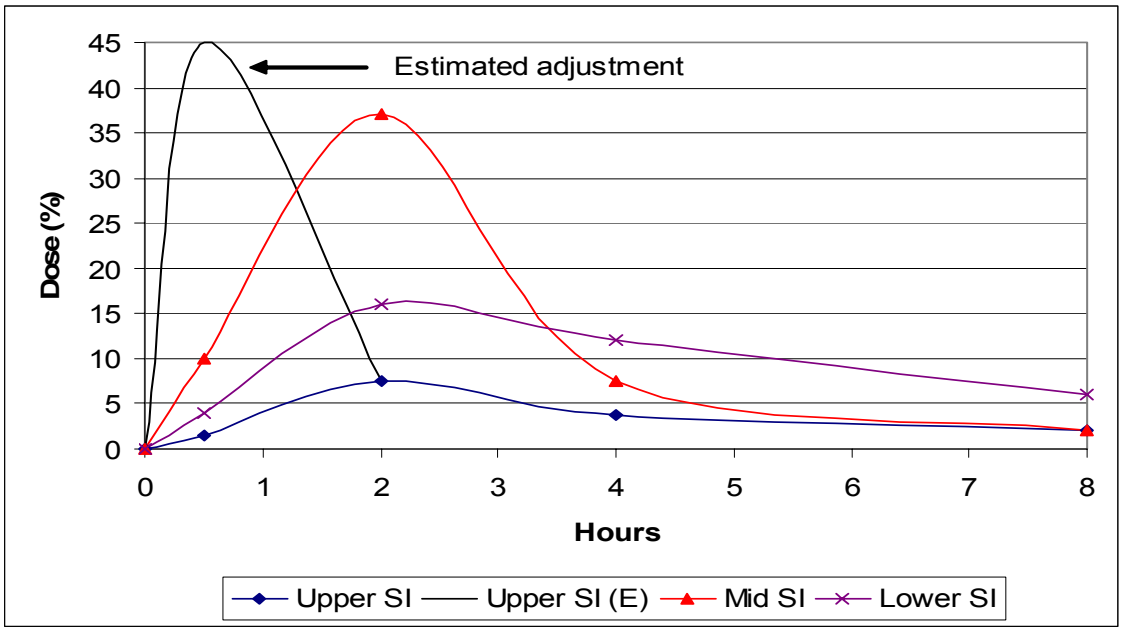

Fig. 3 - Dose (%) found in the upper (plus estimated adjustment), mid and lower small intestine contents against time

From Fig.3, a wave effect along the small intestine can be observed, of decreasing peaks but higher baseline levels as the Cr-EDTA passes down the small intestine, before concentrating in the colon.

Discussion

The rolling mean and AUC figures for the duodenum, jejunum and ileum are about a quarter of the colon figures over a 12 hour period. This was demonstrated by DeGeeter *et al* (1980) when lincomycin was fed at 220ppm in the feed to 30kg pigs for 23 days (see Fig. 4). The concentration in the stomach was small, suggesting much of the lincomycin had already left the stomach, possibly four hours or more after feeding, and levels in the duodenum and jejunum were also low, but increasing in the ileum. The ileum/colon concentration ratio was 24%.

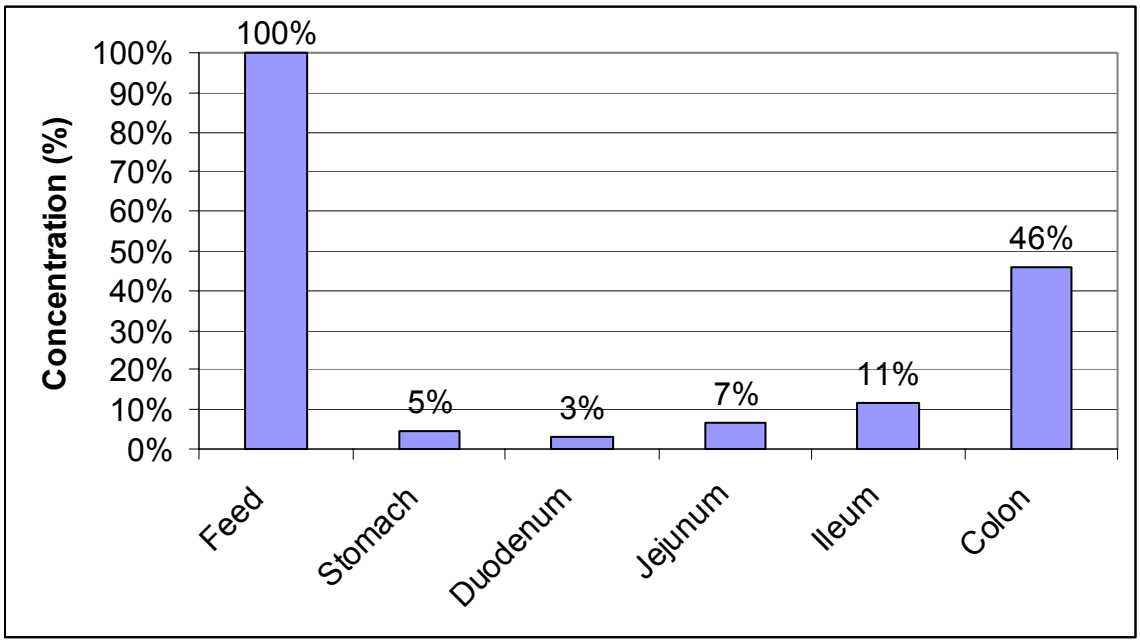

Fig. 4 - Lincomycin concentrations (% feed concentration) in various parts of the pig's gut following feeding at 220ppm for 23 days

Gastric emptying time in the pig has been reported by a number of authors and can be slowed by feeding (Casteel *et al*, 1998), by formulation (Davis *et al,* 2001) liquids which pass through quicker than micro-pellets and by age (Snoeck *et al*, 2004). They showed that suckling pigs had a faster gastric emptying time than weaned pigs, two days and two weeks after weaning, but pigs three weeks after weaning had a similar gastric emptying time to adults, as in the Clemens *et al* (1975) work. Transit-time data through the small intestine was limited, usually by the complexity of the pig's intestines on radiography and also by inadequate and prolonged interval measurement. Davis *et al* (2001) reported it as 3-4 hours for liquids and Snoeck *et al* (2004) >7 hours (90% clearance) for micro-pellets in meal.

Wiuff *et al* (2002) studied the pharmacokinetics of enrofloxacin in unfasted grower pigs, 8-10 weeks of age, following administration by injection and orally by intubation at 2.5mg/kg bodyweight, and treated each day for 5 consecutive days. Plasma, gut and gut content samples were taken at 2, 3, and 6 hours after the final treatment (see Table 3 and Fig. 5).

Table 3 - Enrofloxacin concentrations (µg/ml or g) in plasma and gut contents after oral administration at 2.5mg/kg bodyweight (Cmax figures in bold)

	2 hours	**3 hours**	**6 hours**
Plasma	0.31	**0.40**	0.30
Jejunum 1	**5.4**	4.9	2.2
Jejunum 2	8.6	**11.3**	3.5
Ileum	4.9	**6.8**	4.6
Caecum	1.0	4.2	**4.8**
Colon	0.8	1.8	**5.8**
Rectum/faeces	0.6	0.3	**2.3**

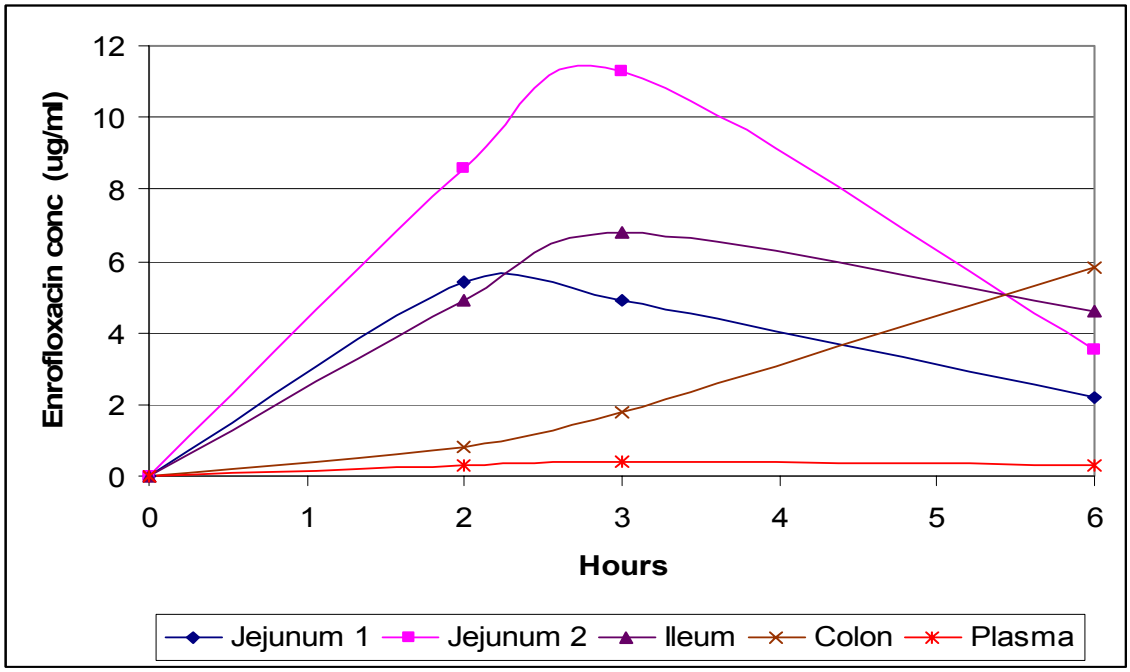

Fig. 5 - Enrofloxacin concentrations (µg/ml or g) in plasma and gut contents after oral administration at 2.5mg/kg bodyweight

Concentrations of enrofloxacin in plasma and intestinal contents were similar between intra-muscular and oral administration, suggesting that after intra-muscular administration, enrofloxacin is excreted via the bile relatively unchanged. The metabolite ciprofloxacin was only recorded at low levels. With the extra time interval at 3 hours, the upper small intestine (jejunum 1) had peaked at 2 hours, but jejunum 2 (mid small intestine) kept on increasing to 3 hours, reaching a much higher level. The ileum concentration peak also occurred at three hours and remained higher at 6 hours and the colon levels were starting to accumulate, which mirrored the findings of Clemens *et al* (1975), except the mid-jejunal peaks may be later at three hours and account for the shortfall in dose recovery of only 71.5%.

Concentrations in the small intestine depend on a number of factors such as gastric emptying, the presence of liquids or food and particle size, the absorption from the gut, the excretion of active substance or active/inactive metabolites back into the intestine via the bile. Breakdown of the product by acids (penicillin G), enzymes, bacteria and binding also have an effect. As food and fluids are absorbed, there is a concentration effect as the product goes down to the ileum and finally into the colon. The environment in the colon would also have an effect. It is primarily an anaerobic environment, which limits the activity of some antibiotics like the aminoglycosides and some fluoroquinolones. Faecal binding can also have a major impact and enrofloxacin's bioactivity was reduced by 42% according to the Wiuff *et al* (2002) study, using a microbiological and high pressure liquid chromatography (HPLC) assay. Bacterial breakdown of a compound is also considered a likely problem.

Information on antimicrobial concentrations in the faeces or colon contents are more readily available and are sometimes reported in maximum residue limit (MRL) data for products or in the pharmacological section of assessments for products. These concentrations are relatively stable and less volatile than those in the small intestine; hence, they are useful for trying to determine effective concentrations and the application of PK/PD principles in the small intestine, particularly against infections such as *E. coli*.

Part 2 - Application of pharmacokinetics in relation to *E. coli* resistance patterns in pigs

Kahlmeter *et al* (2003) discussed the harmonisation of MIC breakpoints for antimicrobial susceptibility testing in Europe. Currently, there are two approaches, the microbiological approach and the clinical approach. The former looks primarily for wild type patterns of MIC determination and then increases in MICs demonstrate the possible development of resistant mutants. Clinically, we would expect an antimicrobial to work against the wild type isolates, i.e. basic susceptibility. However, depending on the level of the antimicrobial in the blood or tissue, intermediately susceptible mutants might be still susceptible. These intermediate mutants might be the first step for some antimicrobials, e.g. the fluoroquinolones, before complete resistance development. The setting of these breakpoints is sometimes difficult and depends on the type of bacteria and the type of antimicrobial and varies between authorities, hence the need for harmonisation. Terminologically, there are some difficulties, but they are trying to introduce 'epidemiological cut-off value' for the wild type bacterial susceptibility point and 'clinical breakpoint,' which may have a substantially higher MIC, up to the point where clinically successful treatment is still likely to occur and where resistance begins. This was graphically demonstrated by Bywater *et al*, 2006 (see Fig. 6).

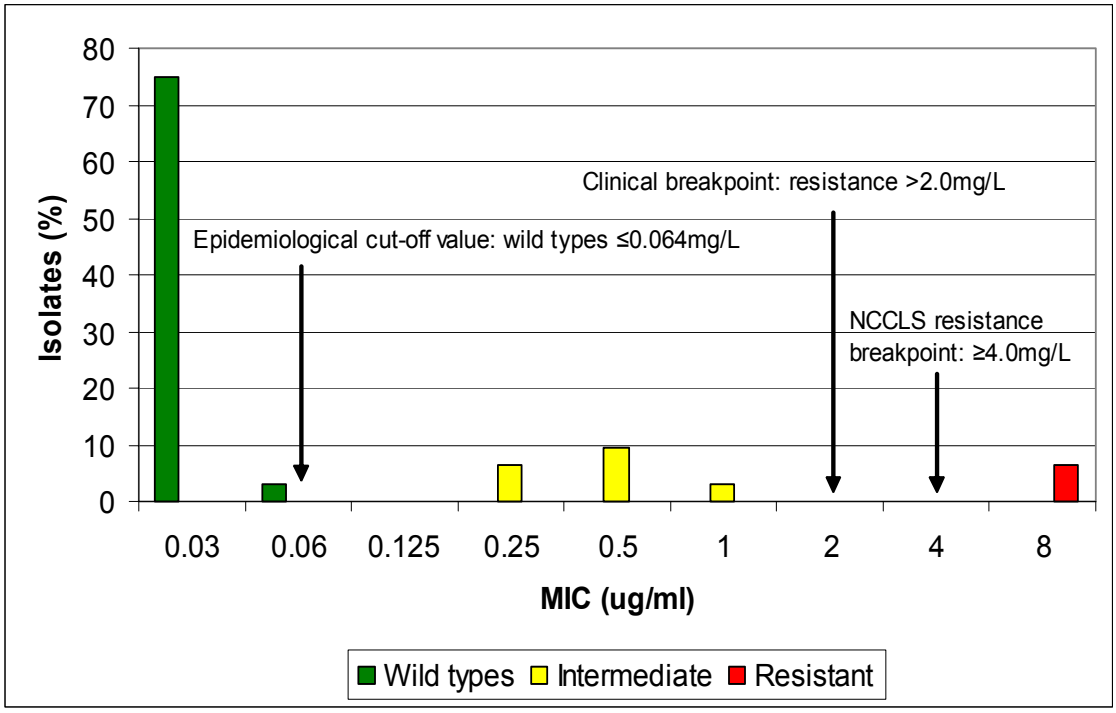

Fig. 6 - MIC patterns for susceptible wild types (epidemiological cut-off value) intermediate susceptible (clinical breakpoint) and resistant isolates

The purpose of this section is to look at some of the MIC patterns of epidemiological slaughterhouse samples and compare them with clinical isolates submitted for diagnostic purposes and which may have been exposed to antimicrobial therapy in the pig prior to submission (Danmap 2004, 2005). Danmap used the NCCLS (now the Clinical and Laboratory Standards Institute – CSLI) antimicrobial resistance breakpoints and these can be considered one dilution higher than the clinical breakpoint. Examples of antimicrobial gut concentrations, where available, will be compared with the MIC patterns.

Enrofloxacin (ciprofloxacin):

From the Wiuff *et al* (2002) data, the Cmax for plasma was 0.40µg/ml and 11.3µg/ml in the mid small intestine after oral administration at 2.5mg/kg bodyweight. Normally for fluoroquinolones, to obtain the optimum bactericidal effect, one looks for a Cmax, 10 times the MIC i.e. 0.04 and 1.13µg/ml respectively, or 100-120 times the AUC 24 hours (Toutain, 2003). This data was not available in the Wiuff *et al* (2002) study as they only looked at a 6 hour time period. However, the rolling mean figure over 12 hours can be used, assuming the pig is dosed twice a day, and multiplied by 24 to give the AUC 24 hours.

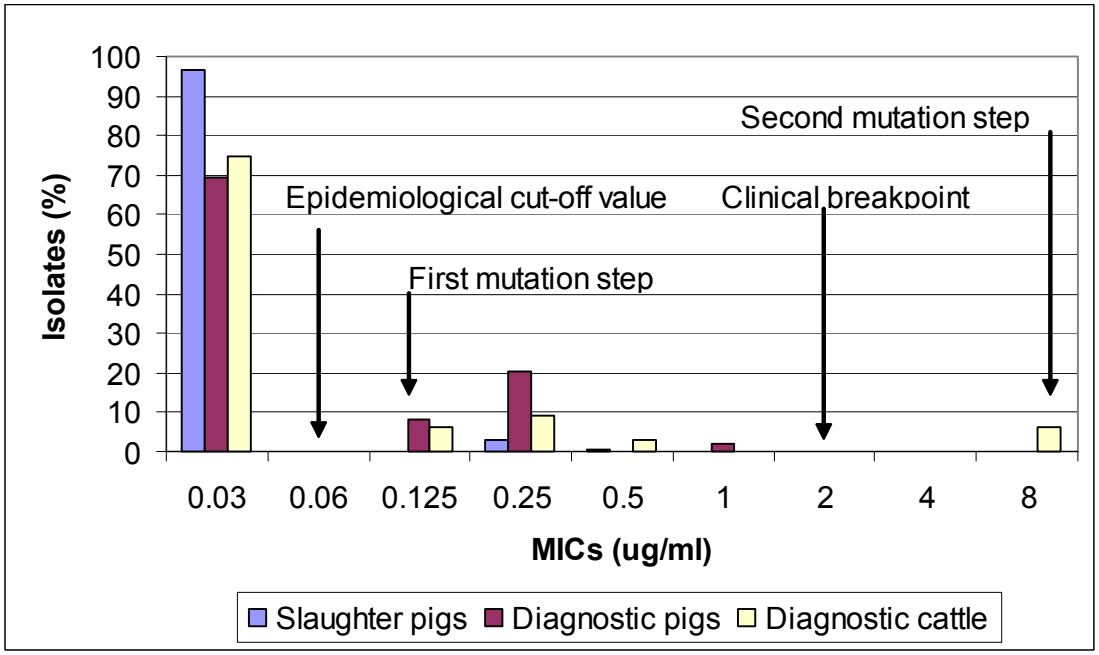

Fig. 7 - Ciprofloxacin MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49) and cattle (32)

These data demonstrate the classic fluoroquinolone resistance pattern. The epidemiological cut-off value is ≥0.06µg/ml, which is nearly reached by the $1/10^{th}$ of the plasma Cmax and is reached following injection, demonstrating that a good bactericidal effect can be expected even in a systemic infection. The next group have had a first step mutation and are nalidixic acid resistant. An almost identical pattern is shown by the porcine strains for nalidixic acid and ciprofloxacin except for the value of the MIC (see Fig. 8).

The clinical breakpoint has been set at >2.0µg/ml and this is exceeded by the gut concentrations, but is potentially only 1/3rd of the jejunum 2 Cmax. In this case, the Cmax would be 11 times higher than the last diagnostic mutant, potentially giving highly effective bactericidal treatment of these mutants after oral dosing administration, if they were situated in the gut only, but not systemically. This has clinical significance in neonatal scours in piglets as systemic invasion by *E. coli* can occur. It also highlights the importance of applying the pharmacokinetics to the target tissue, e.g. gut contents, not just plasma. The bovine diagnostic data was included to demonstrate the next mutation, which has led to full resistance, most likely in calves. However, by using fluoroquinolone levels, which kill not only the wild types, but also the fist step (nalidixic acid) resistant mutants, the chances of full resistance development is much reduced (Drlica, 2003), as demonstrated here in pigs.

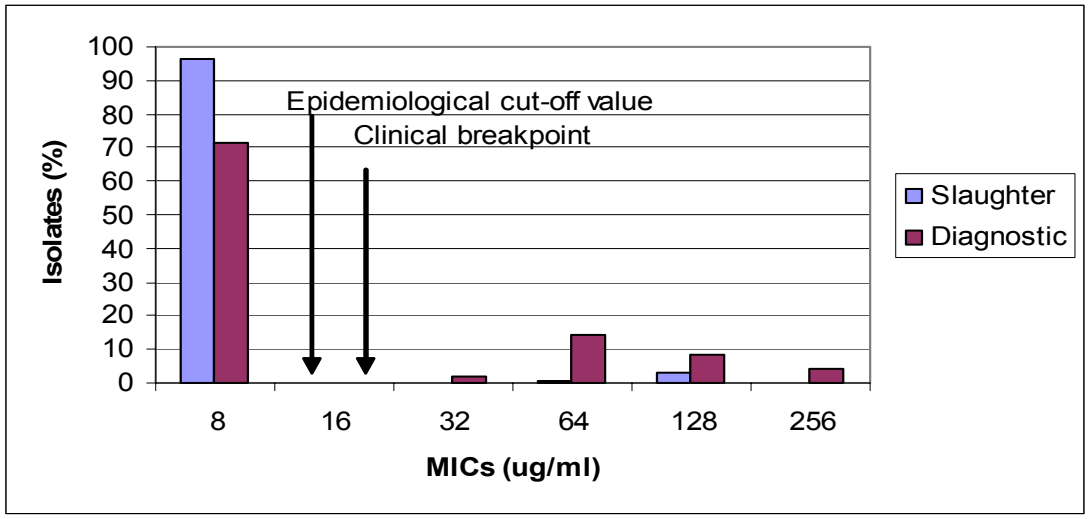

Fig. 8 - Nalidixic acid MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

Other absorbable antimicrobial MIC patterns:

Tetracycline:

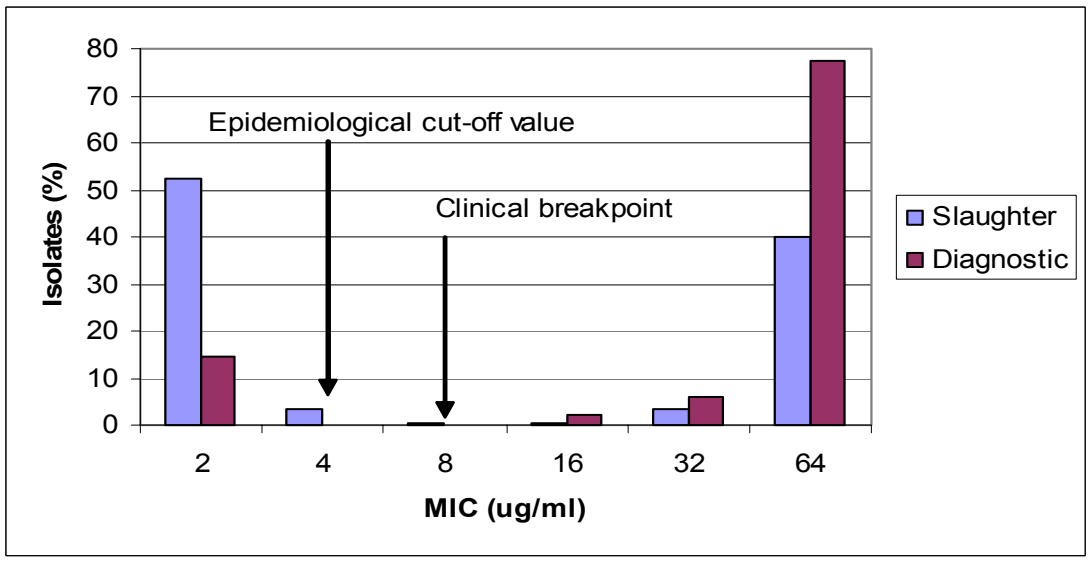

Fig. 9 - Tetracycline MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

Work by Hansen *et al* (2002) recorded the bioactive concentration of chlortetracycline, a primarily bacteriostatic antibiotic, in pig faeces after oral administration in the feed at 800ppm. This gave a bioactive residue of 112µg/g chlortetracycline in the faeces. The usual incorporation rate of chlortetracycline is normally 300-400ppm, which would give 42-56µg/g in the faeces and approximately 11-14µg/g in the small intestinal contents (faecal conc. x 25%, based on Clemens *et al*, 1975). These figures support the overall susceptibility

pattern and also the shift, which can be expected after treatment to the right and an increase in resistance.

Ampicillin and amoxycillin + clavulanic acid:

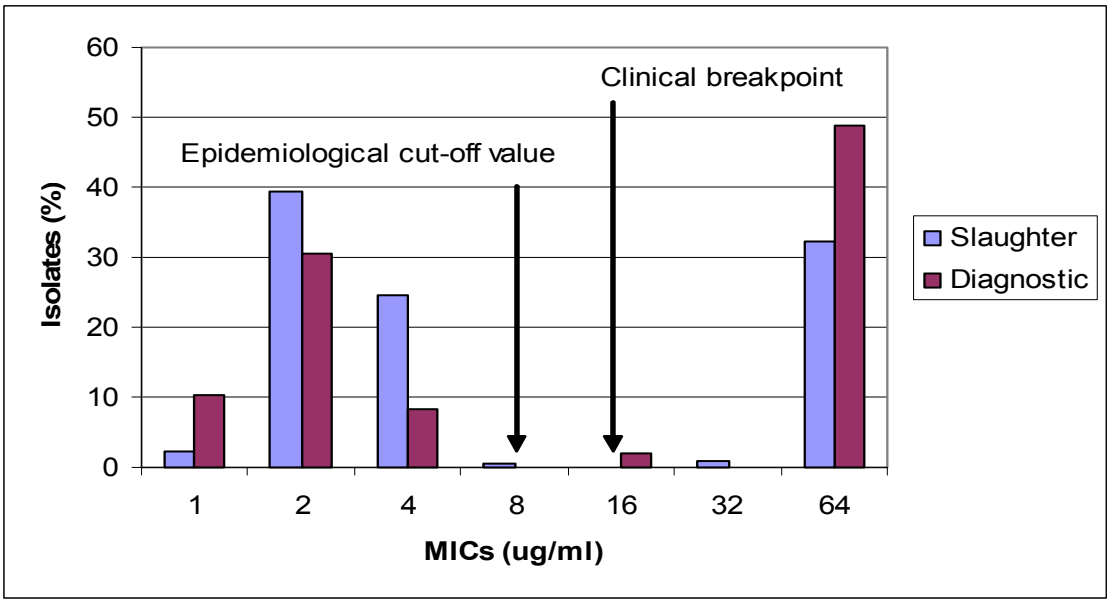

Fig. 10 - Ampicillin MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

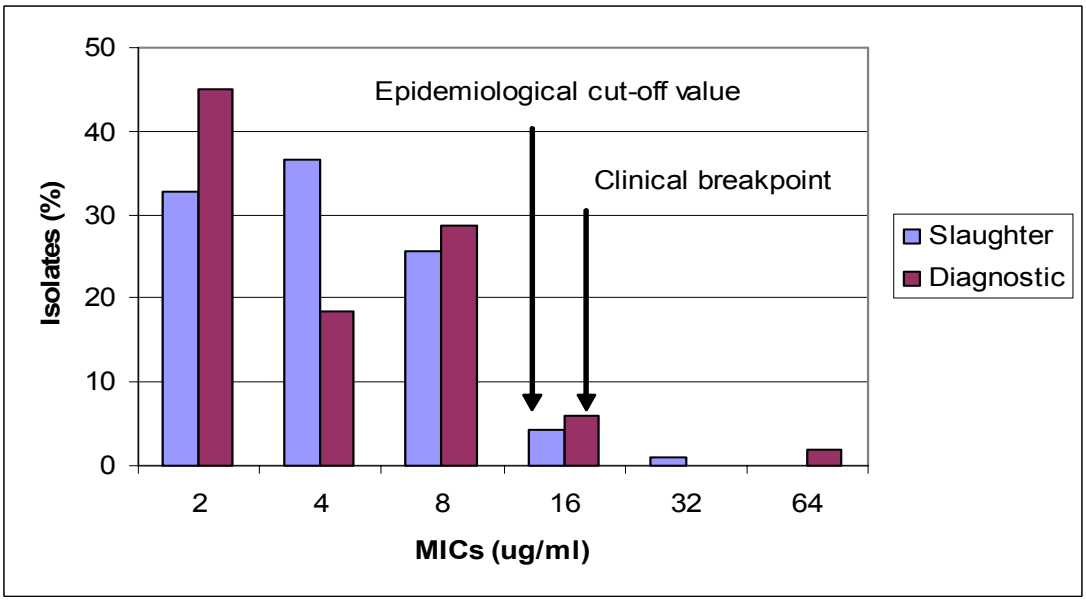

Fig. 11 - Amoxycillin + clavulanic acid (2+1 ratio) MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

The susceptibility profile of ampicillin, a time-dependent bactericidal antibiotic, is quite distinctive with regard to cut-off value and clinical breakpoint. Amoxycillin, which has a similar activity to ampicillin, with the addition of clavulanic acid, makes a marked difference in susceptibility profile and resistance reduction. Clavulanic acid is a beta-lactamase enzyme inhibitor, thereby demonstrating the importance of beta-lactamase production by *E. coli* as a resistance mechanism to protect them against beta-lactam antibiotics.

Trimethoprim and the sulphonamides:

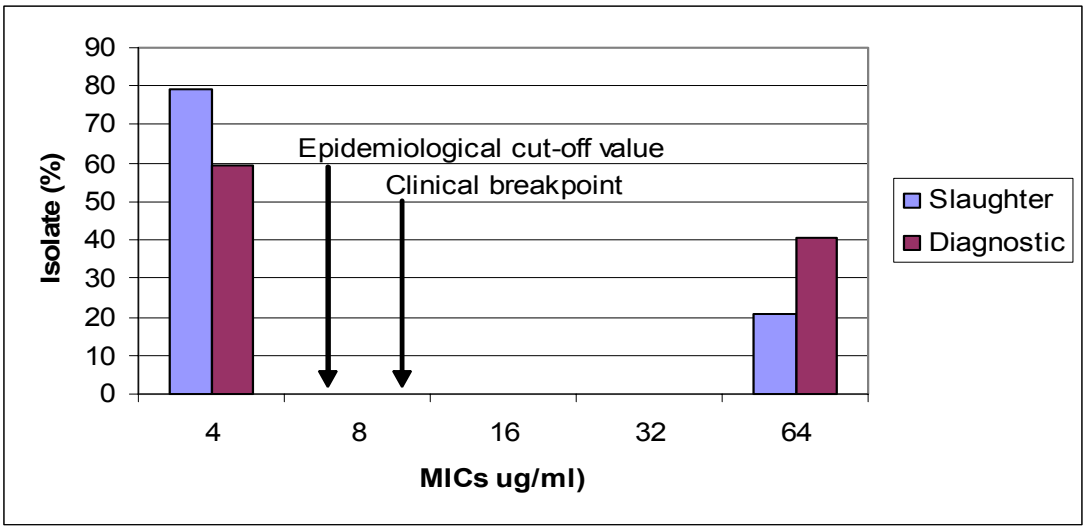

Fig. 12 - Trimethoprim MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

Resistance to trimethoprim is usually due to a plasmid or chromosomal production of a binding resistant dihydrofolate reductase enzyme, so that trimethoprim cannot bind to it and interfere with folic acid synthesis by inhibiting a precursor tetrahydrofolic acid (Prescott, 2000). The resistance, once induced, appears complete. On its own, trimethoprim is bacteriostatic and it is only in combination with sulphonamides that it becomes bactericidal.

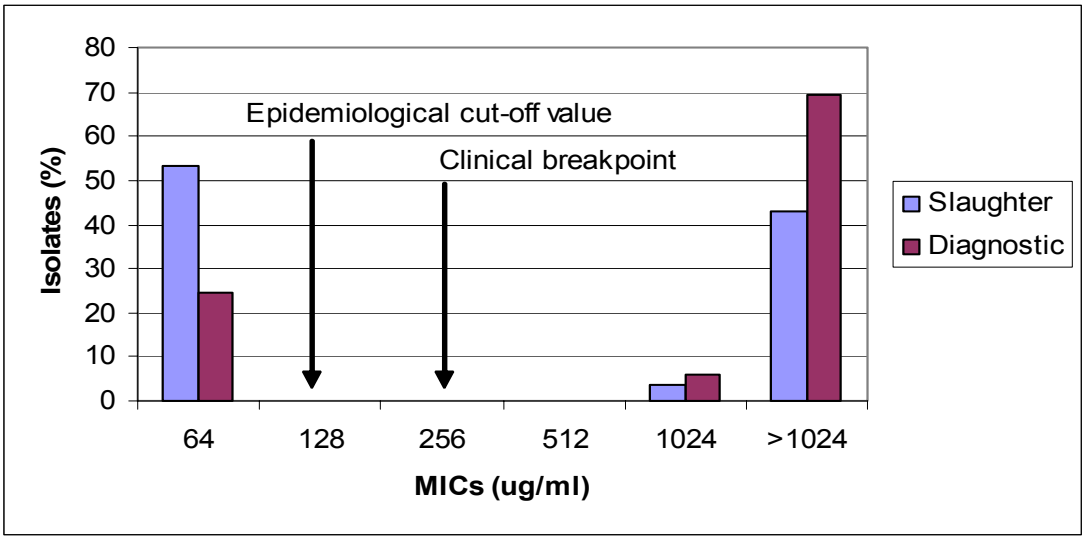

Fig. 13 - Sulphonamide MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

Sulphonamides also interfere with folic acid production by competitively blocking para-aminobenzoic acid to the enzyme dihydropterate synthetase and resistance is commonly plasmid mediated and either blocks penetration of the bacterial cell or produces sulphonamide-resistant enzymes.

The two compounds are more commonly used together in pig medicine and a MIC pattern is described in SVARM 2005 (2006) in porcine diagnostic submissions (see Fig. 14).

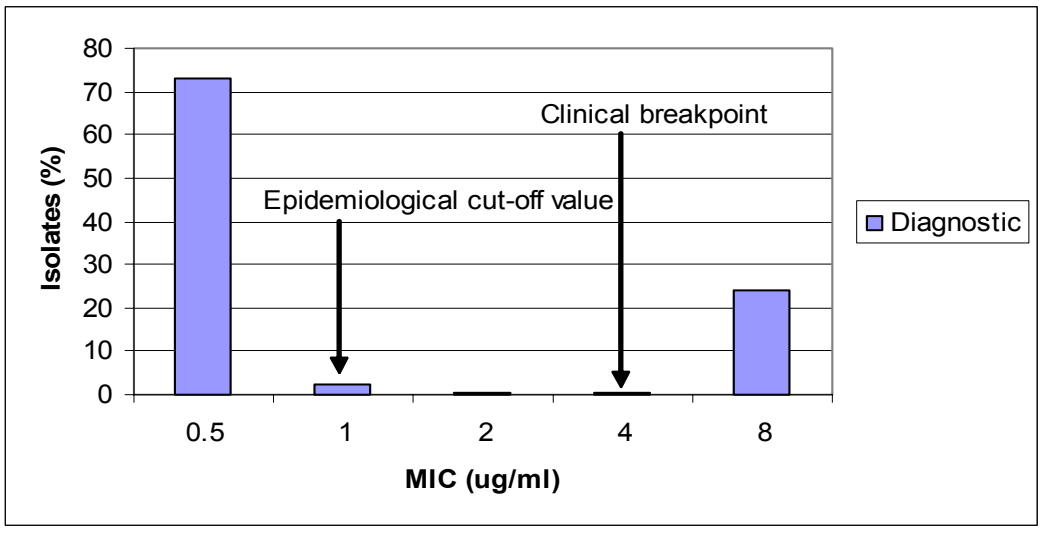

Fig. 14 -Trimethoprim/Sulphamethoxazole (1/20 ratio) MIC patterns against *E. coli* from porcine diagnostic submissions (325)

Due to the synergistic activity between the two compounds, there is a shift to the left in antimicrobial activity, but there is still a relatively clear-cut pattern of susceptibility and resistance.

Pharmacokinetic relationship analysis:

Unfortunately, there is little data to include in the analysis, except for enrofloxacin and chlortetracycline, so a variety of assumptions have been made so that a comparative analysis of the absorbable products can be achieved. The common level of the antimicrobial in feed is used. The bioavailability of the product (amount absorbed) is subtracted, the concentration in the faeces is 2.5 times the amount of compound after the bioavailability factor has been calculated. The jejunal concentration is 25% of the faecal concentration, to give the rolling mean, which is then multiplied by 24 hours to give the AUC 24 hours. This figure is divided by the epidemiological cut-off value (ECOV) or the clinical breakpoint (CBP) to give a figure, to assess the effect of the antimicrobial.

Table 4 - Estimated antimicrobial pharmacokinetic relationship analysis for absorbed/partially absorbed products against their epidemiological cut-off values (ECOV) and clinical breakpoints (CBP)

Antimicrobial	Feed level* (ppm)	Bioavail (%)	Faeces conc (µg/g)	Jejunal conc (µg/ml)	AUC 24 hours	Epidem COV (µg/ml)	AUC/ECOV	Clin BP (µg/ml)	AUC/CBP
Enrofloxacin	100	90	-	3.8	92**	0.06	1533	2	46
Chlortetracycline	400	20	56***	14	336	4	84	8	42
Ampicillin	300	30	525	131	3150	8	394	16	197
Amoxicillin/ Clavulanic acid (2/1)	300/ 150	30	525	131	3150	16	197	16	197
Trimethoprim	50	90	12.5	3	75	8	9	8	9
Sulphonamide	250	90	63	6	375	64	6	256	1
Trimethoprim/ Sulphonamide (1/20)	300	90	75	19	450	1	450	4	113

*Based on 20ppm = dose of 1mg/kg liveweight per day
** Wiuff *et al*, 2002, estimated data
*** Hansen *et al,* 2002, data

The jejunal AUC 24hours can be estimated from the Wiuff *et al* (2002) data and the analysis shows that the AUC/ECOV is hugely exceeding the 100-120 ratio for bactericidal antimicrobials, but the AUC/CBP falls below to 46, which demonstrates that it is below the optimal cidal effect for fluoroquinolones against *E. coli* in the small intestine.

For bacteriostatic products, like chlortetracycline, an AUC/MIC figure should be at least 24 to show that the drug concentration exceeds the MIC for most of the 24 hour period. This is approximately correct for the AUC/CBP figure and the AUC/ECOV figure, suggesting a good inhibitory effect. Ampicillin is bactericidal and the estimated gut concentrations would be sufficient to kill *E. coli* at the nominated CBC. This would be similar for amoxycillin and clavulanic acid. Trimethoprim is bacteriostatic on its own and does not reach the inhibitory AUC/ECOV figure of 24, nor at the clinical breakpoint. It is even worse for sulphonamides on their own, but it falls into place when the two products are combined together and their synergistic effect comes into action. There is a very high AUC/ECOV figure of 450, which would be bactericidal, and also at the clinical breakpoint.

Comparison of non-absorbed compounds:

Antimicrobials, which are not absorbed from the gut, should follow a similar pattern and concentration relationship to Cr-EDTA in the Clemens *et al* (1975) data.

Spectinomycin:

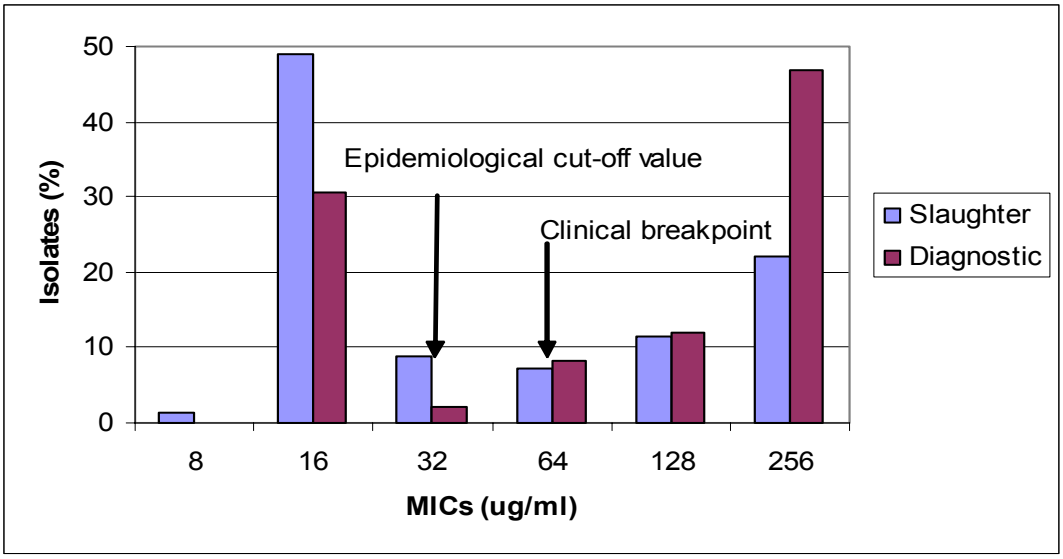

Fig. 15 - Spectinomycin MIC patterns against *E. coli* from porcine slaughter data (n=208) and porcine diagnostic submissions (49)

Spectinomycin, an aminocyclitol antibiotic, is commonly used in pigs in combination with lincomycin at 44ppm, respectively. It is primarily

bacteriostatic, but, at four times MIC, may become bactericidal (Prescott *et al*, 2000). Using the earlier calculations, the concentration in faeces would go up to 110ppm and the rolling mean concentration in the small intestine would be about 27.5ppm or µg/g. This is a very similar level to the depression in diagnostic MIC of 32µg/ml. The clinical breakpoint of 64µg/ml looks quite high by comparison. However, the spectinomycin content in the soluble formulation is higher and could reach closer to 80µg/ml. Resistance is usually chromosomal, but does not show cross-resistance to the aminoglycosides. It is mainly gut active, but some product is absorbed.

Neomycin:

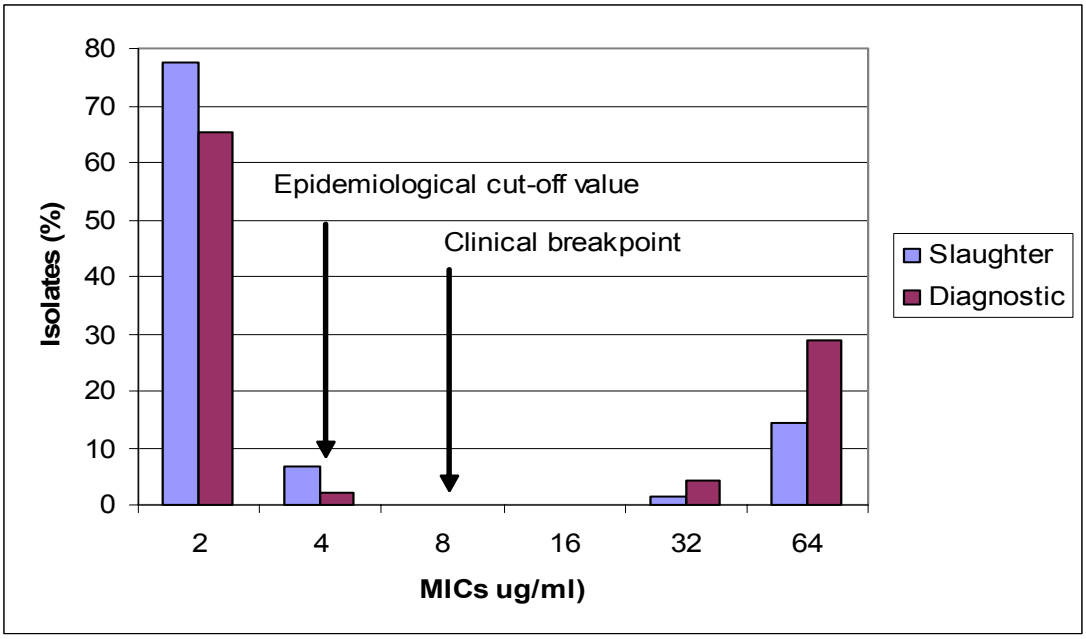

Fig. 16 - Neomycin MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

Neomycin is an aminoglycoside and is bactericidal in a concentration-dependent way. It is mainly gut active, but some material is absorbed. Resistance is primarily plasmid induced and enzymes are produced which alter the drug and interfere with its binding to the ribosome. Reducing its permeability into the bacterial cell is a less common means of inducing resistance. Transport across the cell membrane is an oxidative process and therefore aminoglycosides are not active in anaerobic conditions, such as the large intestine.

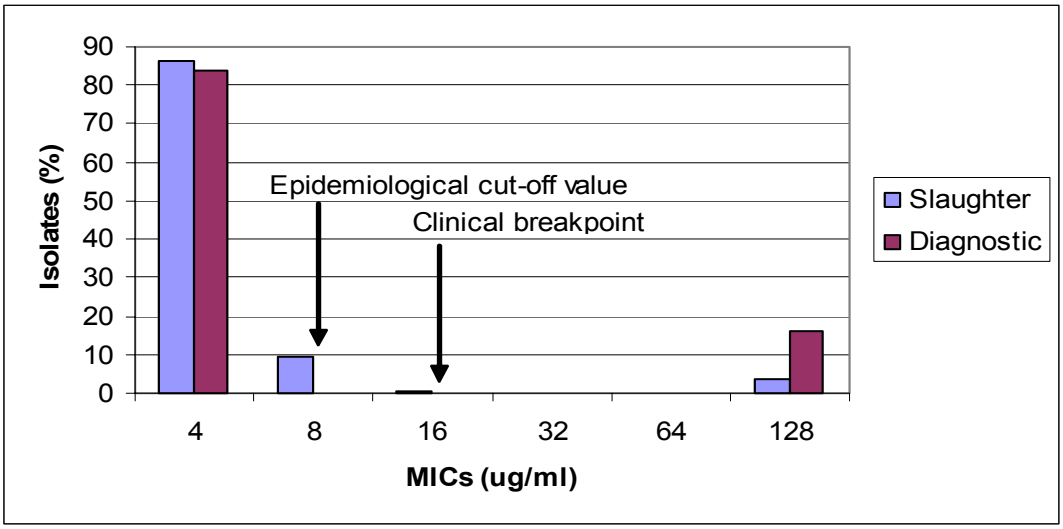

Fig. 17 - Apramycin MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

Apramycin is another aminoglycoside, which is more enzyme resistant than neomycin. The same methods of resistance do apply. Small quantities of the product are absorbed, but most pass through the intestines unchanged.

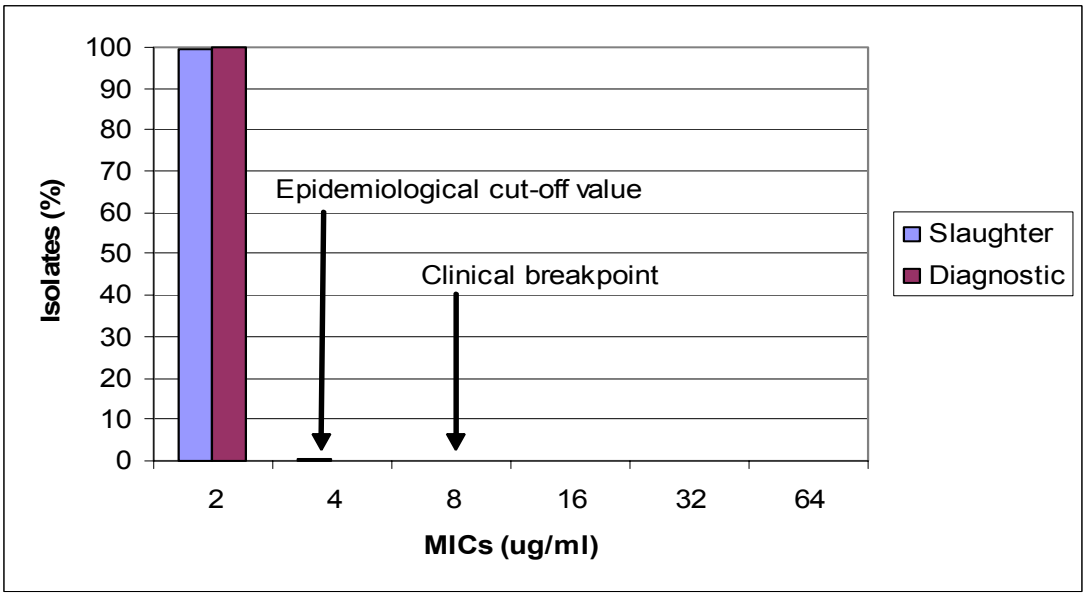

Fig. 18 - Colistin MIC patterns against *E. coli* from porcine slaughter data (n = 208) and porcine diagnostic submissions (49)

Colistin is polymixin E, which acts on the surface of bacteria and disrupts the structure of the cell membrane and increases cell permeability. It is primarily active against aerobic gram negative bacteria such as *E. coli*. Colistin is hardly absorbed from the intestine. Resistance is rarely acquired, although some *Pseudomonas aeruginosa* have done so as a result of decreased bacterial permeability.

Table 5 - Estimated antimicrobial pharmacokinetic relationship analysis for poorly absorbed products against their epidemiological cut-off values and clinical breakpoints

Antimicrobial	Feed level* (ppm)	Bioavail (%)	Faeces conc (µg/g)	Jejunal conc (µg/ml)	AUC 24 hours	Epidem COV (µg/ml)	AUC/ECOV	Clin BP (µg/ml)	AUC/CBP
Spectinomycin	44	10	99	25	594	32	19	64	9
Neomycin	220	10	49	124	2970	4	743	8	371
Apramycin	100	10	225	56	1350	8	169	16	84
Colistin	66	10	149	37	891	4	223	8	113

*Based on 20ppm = dose of 1mg/kg liveweight per day

Spectinomycin is approaching an inhibitory effect at the AUC/ECOV level, but would be considered too low for the clinical breakpoint. All the other three antibiotics reach bactericidal concentrations (AUC/ECOV = >100). Neomycin and colistin also appear to be bactericidal at the clinical breakpoint, whereas apramycin is just a little short.

Conclusions

Clemens *et al* (1975) and several other authors would produce more accurate pharmacokinetic data in the small intestine if they had increased the number of samples and looked earlier than two hours after administration. However, compensatory calculations can be made to overcome this.

Although there is limited published data on gut pharmacokinetics of antimicrobials in the pig, it generally conforms to PK/PD relationship values for bactericidal compounds. These values also conform well to antimicrobial resistance patterns, especially with the epidemiological cut-off value and mostly with the clinical breakpoints, except for spectinomycin and enrofloxacin.

Although PK/PD relationships cannot be completely precise, by the nature of the double-dilution method of MICs and inter-laboratory differences, standardization is increasing the chances of harmonisation and the data developed confirms what a powerful tool PK/PD analysis can be.

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