

Edited by:
**Dennis Scott BVSc
MACVSc**

Ethical Agents Ltd
54 Hobill Ave Wiri
PO Box 97-110 Manukau City
Manukau 2241

Ph 09-262-1388 Fax 09-262-1411
Freephone 0800 800-624
email eage@xtra.co.nz
website www.ethicalagents.co.nz

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Aspirational Goals

Following the Paris talk-fest New Zealand proclaimed a target to reduce greenhouse gas emissions to 30 per cent below our 2005 levels by 2030. A noble aspiration but is it achievable?

The New Zealand Government in 2011 decided to have New Zealand smoke free by 2025. Sound familiar? This is another noble goal, driven by political expediency. Full credit must go to the Maori party and its political offshoot, the much maligned Mana Movement, for instigating the move.

They were motivated by the fact that smoking is rife among Maori youth, in effect killing young Maori.

The baton was picked up by the coalition government thanks to the pressures of MMP and is being pushed by Smokefree NZ.

Currently 85% of Kiwis are non-smokers and the aim of the aspirational goal, despite being called smoke free by 2025, is to have number of smokers down to 5%.

In July 2015 NZVA stated

that the profession would not need antibiotics for the maintenance of animal health by 2030.

"Full credit must go to the Maori party and its political offshoot, the much maligned Mana Movement"

Again it is an aspiration and, like the smoke free goal, is about changing attitudes and habits rather than being a blanket statement.

2025 is only nine years away, which is not a long time to achieve the smoke free goal but an extraordinarily long time in politics. Will the political will still be there?

The motivating factor is the health of young Maori, and others.

Therefore a cynic could be forgiven for thinking that this is the least likely of the targets to be achieved.

Apart from the noble sentiments the greenhouse gas emissions are also connected with trade. In the long run the target may be met, not because of the honourable intentions but compliance may be forced upon us by overseas markets.

Veterinarians are professional, educated people and the smart money would be on their mission being a whole lot more successful than the politicians.

Like smoke free the goal is aspirational and not literally achievable but it is about mind set changing. Like the greenhouse emissions outside forces have the potential to play a part, so it is all about keeping the veterinary profession as the stewards of antibiotic use in animals.

This is the real goal for 2030 and it would be awesome if the other goals were also achieved.



AM Resistance and Economic Theory

A recent presentation by Mark Bryan, NZVA Board member, contained an interesting analogy between antimicrobial resistance (AMR) and economic collapse brought about by collateralized debt obligation (CDO).

A CDO is a complicated debt sharing arrangement dreamt up by the financial industry whereby loans are divided into tranches with varied returns according to risk, the higher the risk the greater the return. A CDO can be thought of as a promise to pay investors in a prescribed sequence, based on the cash flow the CDO collects from the pool of bonds or other assets it owns. If some loans default and the cash collected by the CDO is insufficient to pay all of its investors, those in the lowest, most "junior" tranches suffer losses first. The last to lose payment from default are the safest, most senior tranches; consequently the junior tranches receive a higher interest rate.

These were not a big issue until 2000 when they became more popular, and so this is taken as the discovery date. Around 2005, as the CDO market continued to grow, subprime mortgages began to replace the diversified consumer loans as collateral leading to the whole subprime mortgage market that drove the worldwide economic collapse of 2008.

The analogy showed that CDOs went from discovery to disaster in only 9 years, and anti microbial resistance (AMR) is looking like progressing the same way but in a 100 year time period.

It is an interesting and powerful analogy but it is not the only one linking AMR to economics.

At the time of the Great Depression of the 1930s. John Maynard Keynes brought crucial insights

into how an economy functioned in its entirety. He believed a free market economy did not automatically tend to full employment. An economy could get stuck in a situation where substantial unemployment could be a permanent reality. Keynes also pointed out that during a severe recession if all households decide to cut their spending and save or repay debt then this is likely to make the recession even worse. His recommendation for ending the Great Depression was for governments to pump up demand in their economies by borrowing and spending.

"Stringent measures in New Zealand will not fix the problems overseas where AM usage is rampant."

The Keynesian model however began to break down in the 1970s as government borrow and spend policies had led to massive public sector debts and rampant inflation.

Monetarism, whereby a central bank should cut interest rates to encourage the private sector to borrow and spend during an economic downturn became the go to policy in the 1980s (think Rogernomics coming to the fore in our own country at this time).

Like Keynesian economics monetarism also has a dark downside; the private sector in many Western economies is now saddled with huge debts and the lower interest rates seen during downturns have also led to numerous asset bubbles in property and shares over the past 30 years. They have also led to a significant growth in wealth inequality in many countries.

The famous trickle-down effect, espoused in the 1990s has also

proven to be mythical. Money does not trickle down; the rich do not become more fabulously rich by creating jobs or opportunities for others but rather by using excess funds to bid up the prices of existing assets such as property, shares and art works.

"What has all this got to do with AMR?" you may well ask. What is quite clear is that the financial industry has not solved their problems with a one size fits all approach. Like bans panaceas do not work. The response should be tailored to the situation.

The populist panacea for AMR ills in the medical world is to ban or restrict veterinary use, but this is an over-reaction based on the problems in individual countries being extrapolated over the entire world.

New Zealand, with its extensive farming systems, does have low usage levels compared to most other countries. The New Zealand veterinary profession has also shown admirable foresight in having a plan to go forward and proven to be responsible stewards of antimicrobial therapies.

Other countries have been far more profligate in antimicrobial use ranging from prophylactic and metaphylactic use in the Americas, through to outright abuse of antimicrobials important to human medicine as seen in southern Europe and Africa, and to the environmental pollution from manufacturing plants in Asia.

Measures desperately need to be taken in these areas but draconian measures would be counterproductive in the NZ situation. The financial world has been prone to taking stringent measures quite suddenly in response to various crises, often taking a populist approach with

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AM Resistance and Economic Theory

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messianic zeal, and encompassing virtually all in the system, much to the detriment of world economies as a whole.

The all-embracing populist moves have always proven to be self-destructive in the long run and, just as differing political systems suit different populations of the globe, different economic answers are required for different economic systems; there is no overarching panacea that can simply fix all ills.

It is the same with AMR. Stringent measures in New Zealand will not fix the problems overseas where AM usage is rampant.

Nowhere is this better exemplified than with fluoroquinolone usage. The Iberian Peninsula absolutely abuse fluoroquinolones with 78.2% of use being group therapy, in drinking water.

The Australian authorities are rather smug with their policy of not allowing any fluoroquinolone use in food producing animals.

They justify this approach by pointing out that fluoroquinolone

resistance in humans is much lower in Australia than in Spain.

New Zealand allows individual therapy of food producing animals, albeit with strict conditions. Yet the level of fluoroquinolone resistance in humans in New Zealand is even lower than that in Australia.

Quite clearly the misuse of these drugs in some areas of the world needs to be reigned in, but applying the blanket Australian ban to a conforming country like New Zealand would serve no useful purpose whatsoever and, in fact, would be counterproductive in terms of animal welfare.

Just as in the financial world, there is no magic, 'cure all' fix in nature.

The New Zealand veterinary profession has picked up the baton, shown leadership and proven to have responsible AM stewardship.

As long as we are keeping our house in order then the major focus on AMR should be on where the issues are, Asia, Southern Europe and the Americas.

The capitalist countries gleefully looked on at the fall of communism without taking cognisance of the failings in their own systems.

As far as AMR is concerned the New Zealand approach should be looked upon as a model of what might be achieved but the approaches for other countries may need to be vastly different if they are going to achieve the crucial aim of control over AMR.

Clearly, as in economics, there is no 'one size fits all' solution. We still have time to remedy the situation as CDOs developed over ten times faster than AMR and after all, as Mark Bryan stated, "we are not bankers."

Acknowledgements:

Mark Bryan: presentation to Symposium on Infectious Diseases, March 22-23, 2016, Wellington

Wikipedia data on CPOs

Peter Lyons: Free market doctrine's bubble about to burst. NZ Herald March 2016

Toronto Surgeons

Three Toronto surgeons were playing golf together and discussing surgeries they had performed.

One of them said, "I'm the best surgeon in Ontario. In my favorite case, a concert pianist lost seven fingers in an accident; I reattached them, and 8 months later he performed a private concert for the Queen of England.

The second surgeon said. "That's nothing. A young man lost an arm and both legs in an accident; I reattached them, and 2 years later he

won a gold medal in track and field events in the Olympics."

The third surgeon said, "You guys are amateurs? Several years ago a man was high on cocaine and marijuana and he rode a horse head-on into a train traveling 80 miles an hour.

All I had left to work with was the man's blonde hair and the horse's ass.

I was able to put them together and now he's running for President of the U.S.A!"



To Treat or Not To Treat - That is the Question!



For a large part of the 20th century academics felt treating gram negative mastitis with antibiotics was not justified. The prevailing feeling was that it was more beneficial to continually strip the udder and treat the animal symptomatically. (Robertson *et al*) The question was not “which antibiotics to use but whether antibiotics were indicated at all.” The use of antibiotics was considered virtually useless because of the short duration of infection and the high spontaneous cure rate (Hogan and Smith).

Even now antibiotic use in gram negative mastitis is controversial, although technology has advanced a long way over the last few decades. Much early work was devoted to the effects of TMPS or amoxicillin and, in the latter part of the century, to enrofloxacin.

Suojala *et al*, found no benefit in treating with enrofloxacin plus supportive treatment over supportive treatment only. Guterbock *et al* found no improvement in cure rates with either amoxicillin or cepharin over oxytocin alone.

“In all cases, adjunctive therapy with NSAIDs such as Tolfedine and also oxytocin is recommended.”

However the arrival of newer drugs such as cefquinome and marbofloxacin have altered the playing field. Solid arguments can be made for their use on therapeutic grounds, especially considering animal welfare, but resistance development must always be kept at the forefront.

The RUMA (responsible use of medicines in agriculture guidelines have this to say about critically important antibiotics, “Fluoroquinolones, 3rd and 4th

generation cephalosporins and long acting macrolides have an important place in the therapeutic armoury for serious diseases of both animals and humans. The use of these classes in both human and veterinary medicine has produced particular debate and the following guidelines for use should be followed.

Fluoroquinolones, 3rd and 4th generation cephalosporins and long acting macrolides should only be used therapeutically not for prophylaxis.

Products should be chosen on therapeutic efficacy and while withdrawal periods for meat and milk are a consideration, any choice should be primarily based on likely efficacy and bacterial sensitivity. Ideally, sensitivity testing should take place prior to or in parallel with use.”

Whilst both cefquinome and marbofloxacin are on the WHO list of antibiotics deemed critically important for human use (cefquinome is a 4th generation cephalosporin and marbofloxacin a fluoroquinolone) they both have relatively low MICs for E coli strains encountered in bovine mastitis cefquinome having an MIC₉₀ of 0.13 µg/ml (Shippel *et al*) and the MIC₉₀ for marbofloxacin being at an exceedingly low 0.016µg/ml (Schneider *et al*). These levels indicate a high efficacy against the target organism.

However, although MIC is an important consideration, pharmacokinetic values are also vital in determining efficacy, and the nature of the disease itself must be taken into account when deciding whether or not to treat.

The pharmacokinetics of drugs, when married to the peak concentration (C_{max}) or the area under the

curve (AUC) can give a reliable estimation of efficacy.

“a responsible way to use antibiotics with respect to minimising resistance development.”

This is emphasised by the work done with ceftiofur, which has an MIC for E coli of 0.25µg/ml but experimentally E coli challenged cows, dosed intravenously with 3 mg of ceftiofur/kg every 12 hours (higher than label dosing), have concentrations less than 0.2µg/ml of milk throughout the trial meaning that ceftiofur is not likely to attain concentrations in milk that are effective in reducing bacterial numbers (Erskine). Wenz *et al* (2005) could also find no benefit for the use of ceftiofur for mild cases of mastitis.

C_{max}/MIC as an efficacy indicator is used mainly for concentration dependent drugs such as marbofloxacin and the AUC/MIC more for time dependent drugs such as ceftiofur and cefquinome.

With marbofloxacin dosed at 2mg/kg the maximal concentration (C_{max}) observed in milk after the first administration was 1.024 µg/ml meaning a C_{max}/MIC ratio of 67 and an AUC/MIC ratio of 407h, indicating expected high efficacy in treating coliform mastitis as the endpoints of 10 and 250h respectively are reached (Schneider *et al*).

E coli mastitis (as with other types of gram negative mastitis) is generally an acute, often a per-acute syndrome with one piece of research claiming that 72.6% of E coli mastitis is acute. (Deutz *et al*. Der prakt. Tierarzt, 1999, 80:614).

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48% of cows with acute coliform mastitis have a bacteraemia (Wenz *et al*, 2001) and this is often life threatening.

The acute nature of the disease would suggest:

- 1) That it can be life threatening.
- 2) Any decision on antibiotic therapy must be made empirically.
- 3) Prolonged antibiotic therapy may not be necessary.

Therefore, while antimicrobial use may not be necessary in mild or subacute E coli infections, it seems good veterinary practice to consider antimicrobials for acute or per-acute coliform mastitis.

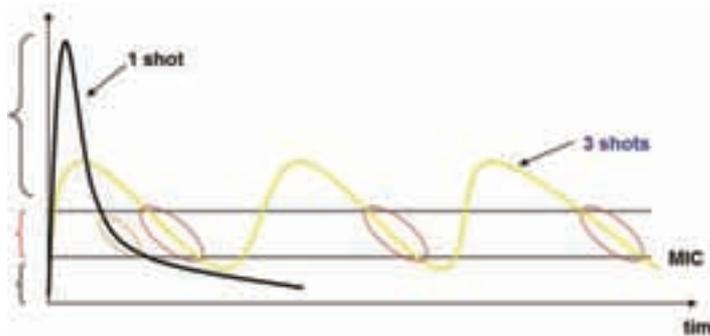
The decision, in this case, would not be whether to use antibiotics or not but which antibiotic to use.

There would be no time for culture and sensitivity so an empirical decision would have to be made, based on case history, clinical signs, pharmacological knowledge and clinical experience.

The PK/PD ratio of marbofloxacin at the 2 mg/kg dose rate make it a very effective antibiotic for such use (Schneider *et al*). Since then however Vétoquinol have devel-

oped a new regime of treatment with the same molecule in order to minimise resistance development.

This is the single injection short acting antibiotic (SISAAB) concept whereby a concentration dependent antibiotic such as marbofloxacin is given at a much increased dosage, above not only the MIC but also the mutant protection concentration (MPC) of the target organism so that resistance development is minimised.



As well as reduced selection for resistance, with the single injection regime there is only one decay curve so there is much less time spent in the danger area of resistance selection, at or just above MIC. Longer acting drugs with long tails also spend much more time in this area.

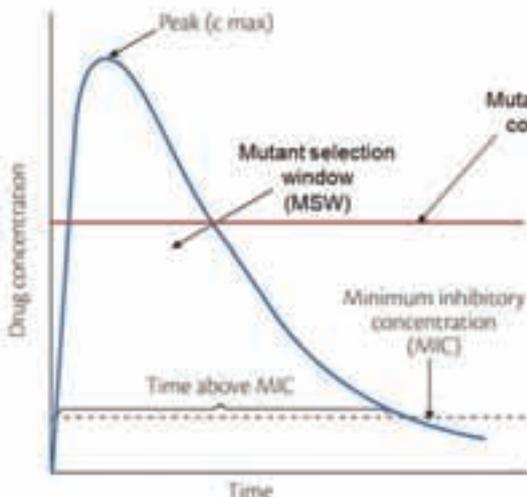
Forcyl is the new patented formulation of marbofloxacin dosed in the SISAAB manner at 10 mg/kg, five times the previous rate of 2 mg/kg. Theory would suggest that if the 2 mg/kg dose is effective, as shown by Schneider *et al*, then the 10 mg/kg dose must surely be so and this has been shown in the work by Pillet *et al* and also by

Grandemange and Woehrle. This work attests not only to the efficacy but also the safety at the much higher dose rate.

In summary, the literature appears to show little benefit for using antibiotics for mild or chronic cases of coliform mastitis but for acute cases, particularly with systemic involvement, then marbofloxacin at a 10 mg/kg dose rate is not only extremely effective but, with the SISAAB concept, is a responsible way to use antibiotics with respect to minimising resistance development.

In all cases, adjunctive therapy with NSAIDs such as Tolfedine (Grandemange *et al*) and also oxytocin is recommended.

A full reference list for this article is on the following page.



CPD Vouchers

The dairy downturn has had many ramifications and the lack of confidence has many practices ordering hand to mouth. This is a natural response but makes the task of planning the season, for suppliers with overseas supply lines, much more difficult.

Forward ordering, especially with perishable items, can be difficult for clinics but is a nightmare for companies. Out of stocks at peak times are a real possibility and that situation does not help anybody.

To counter this, Ethical Agents has come up with a promotional plan to encourage forward ordering. This was born from the realisation that many rural clinics are cutting back on CPD spend this year.

So the deal is, for any \$5000 forward order a voucher of \$500 for NZVA based CPD programmes will be issued.

"A forward order is any order received before July 11; this is the cut-off date!"

A forward order is any order received before July 11; this is the cut-off date! Naturally a \$10,000 order will receive two vouchers and so on.

The vouchers have been designed in conjunction with NZVA and will be honoured by them. For participants the voucher will go to the clinic and EA will then send the



\$500 on to NZVA head office. A win/win for all concerned!

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Serafit Protect

Another new offering is from the worlds oldest suture manufacturer Serag Weissner. This is a suture designed to minimise post operative infections.

The actual idea is not novel as triclosan impregnated sutures have been available in the past. However triclosan has many problems and lower efficacy is just one of them. The chemical itself has been incriminated as a carcinogen and triclosan resistance is rife around the world.

What the team at Serag have come up with is a braided suture impregnated with chlorhexidine, which has a more efficient kill rate, no known resistance and very low toxicity, including no suspicion of carcinogenicity.

The new product will be in sachets and is suited for specialist surgery such as dentistry, gynecology, urol-

ogy, ligatures, dermatology and gastroenterology.

Every size is available in HR or DS needle, all sachets are 70cm and the good news is that there is no price increase, it is priced exactly the same as standard Serafit.

It has the normal Serafit attributes, minimal memory, good knot stability, pliable, and easy slide.

They are the standard purple colour of Serag sutures; darker shapes against lighter ones are easier to see, that's why they choose purple, a much easier colour to see for internal sutures than common pink.



Legal and Logical

A young Law student, having failed his Law exam, goes up to his crusty old professor, who is renowned for his razor-sharp legal mind.

Student: "Sir, do you really understand everything about this subject?"

Professor: "Actually, I probably do. Otherwise I wouldn't be a professor, would I?"

Student: "OK. So I'd like to ask you a question. If you can give me the correct answer, I will accept my mark as it is. If you can't give me the correct answer, however, you'll have to give me an "A".

Professor: "Hmmm, alright. So what's the question?"

Student: "What is legal but not logical, logical but not legal, and neither logical nor legal?"

The professor wracks his famous brain, but just can't crack the answer.

Finally he gives up and changes the student's failing mark into an "A" as agreed, and the student goes away, very pleased with his little riddle.

The professor continues to wrack his brain over the question all afternoon, but still can't get the answer.

So finally he calls in a group of his brightest students and tells them he has a really, really tough question to answer: "What is legal but

not logical, logical but not legal, and neither logical nor legal?"

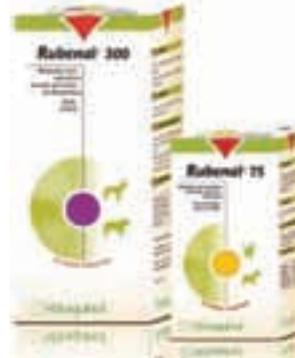
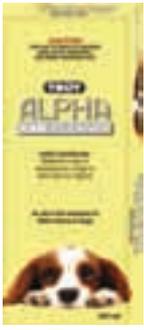
To the professor's surprise (and embarrassment), all the students immediately raise their hands.

"All right" says the professor and asks his favorite student to answer.

"It's quite easy, sir" says the student "You see, you are 75 years old and married to a 30 year old woman, which is legal, but not logical.

Your wife has a 22 year old lover, which is logical, but not legal.

And your wife's lover failed his exam but you've just given him an "A", which is neither legal, nor logical."



Mahatma Gandhi

When Gandhi was studying law at the University College of London, a professor, whose last name was Peters, disliked him intensely and always displayed prejudice and animosity towards him.

Also, because Gandhi never lowered his head when addressing him, as he expected... there were always "arguments" and confrontations.

One day, Mr. Peters was having lunch at the dining room of the university, and Gandhi came along with his tray and sat next to the professor. The professor said, "Mr Gandhi, you do not understand. A pig and a bird do not sit together to eat."

Gandhi looked at him as a parent would a rude child and calmly replied, "You do not worry professor.

I'll fly away," and he went and sat at another table.

Mr. Peters, reddened with rage, decided to take revenge on the next test paper, but Gandhi responded brilliantly to all questions. Mr. Peters, unhappy and frustrated, asked him the following question. "Mr. Gandhi, if you were walking down the street and found a package, and within was a bag of wisdom and another bag with a lot of money, which one would you take?"

Without hesitating, Gandhi responded, "The one with the money, of course."

Mr. Peters, smiling sarcastically said, "I, in your place, would have taken the wisdom."

Gandhi shrugged indifferently and responded, "Each one takes what he doesn't have."

Mr. Peters, by this time was fit to be tied. So great was his anger that he wrote on Gandhi's exam sheet the word "idiot" and gave it to Gandhi. Gandhi took the exam sheet and sat down at his desk trying very hard to remain calm while he contemplated his next move.

A few minutes later, Gandhi got up, went to the professor and said to him in a dignified polite tone, "Mr. Peters, you signed the sheet, but you did not give me the grade."

