The role of control of avian mycoplasmas in antimicrobial stewardship

There is considerable pressure worldwide to decrease antibiotic use in poultry meat and egg production. In Western countries poultry industries have had to consider removing antimicrobials at growth promoter levels (including anticoccidial ionophores in some cases) from production systems.

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In Asia it is still common to administer prophylactic antibiotics at therapeutic levels in feed during lay for one week every 4-8 weeks.

Although the targets of this treatment are mycoplasma infections the impact is very likely to be considerably greater selection for resistance than the abuse of antimicrobials for growth promotion.

This dependence on antibiotics in Asia and some other parts of the world results from the impact of this therapy on mycoplasma infections.

We now have mycoplasma vaccination regimens that can control mycoplasma problems more effectively than antimicrobial therapy and mycoplasma negative replacement stock are becoming more readily available, enabling this high-frequency-high-dose use of anti-microbials to be discontinued, considerably improving our stewardship of antimicrobials in poultry.

Antimicrobial stewardship

Antimicrobial stewardship is the application of strategies to optimise use of antimicrobials, with the aim of maintaining their effectiveness for the longest time possible.

Maintaining an antimicrobial drug's effectiveness for both animal and human treatment is the ultimate aim, but if the risk to effectiveness for human treatment is considered too high, animals might not be able to be treated with effective antimicrobials at all.

Because of their importance in human medicine, some antimicrobials or classes of antimicrobials should not be used in animals at all, and especially not in food producing animals, because of the potential for these animals to transmit multi-resistant bacteria via food to a large number of humans.

Genetic resistance to antimicrobial drugs is considered to be ubiquitous, albeit at low levels in the absence of selective pressure.

Multiple resistance is probably less likely to occur in unexposed populations (as different antimicrobials and corresponding antibiotic resistance genes have evolved in different niches) and is likely to evolve under the pressure of therapy, and particularly in situations where populations of bacteria are exposed to multiple drugs in close succession.

In some organisms antimicrobial resistance and resistance to other factors (including heavy metals and disinfectants) are encoded on a single plasmid and are presumably co-selected.

As a result, just ceasing use of one antimicrobial drug will not necessarily decrease the selection pressure for organisms with resistance to it if the organism is still being exposed to other selectors. This is a major challenge for poultry production, as we rely on disinfection to decrease bacterial challenge, especially in hatcheries. Heavy metals ions are sometimes included in animal feed (copper and zinc in pig diets).

The selectivity of antimicrobial therapy is limited, and any one antimicrobial will affect both target and non-target organisms. The use of antimicrobials can have effects on a wide range of organisms, especially if they have a broad spectrum of activity. The emergence of resistance in even a non-pathogenic organism is significant, as it may be genetically transferred to other (usually closely related) organisms.

Optimum use

Optimising the use of antimicrobials is the main strategy underlying antimicrobial stewardship. A key component of this is ensuring that they are used only when they are required and only when other methods for controlling and preventing bacterial disease are not available. The development of solutions for problems that are currently being managed using antimicrobial therapy is central to setting up a sustainable production system.

Minimisation of antimicrobial use should be viewed in terms of reducing both the duration and the frequency of exposure. In addition, only one effective antibiotic should be used at a time. It is time to review use of products that include a combination of antimicrobials such as Lincospectin, which includes lincomycin and spectinomycin.

Although it is an efficacious combination, it has the disadvantage of ensuring there is routine and simultaneous selection for resistance to two classes of antimicrobials. Use of antimicrobial combinations that are synergistic are justified (for example, the amoxycillin/clavulanate and sulphonamide/trimethoprim combinations).

While we have often used rotation to prolong the efficacy of antiparasitic drugs in agricultural production systems, the carriage of many antimicrobial resistance genes does not generally impose a significant fitness cost on bacteria, and the haploid genome of bacteria reduces the speed of replacement of resistance genes from a population.

The use of different antimicrobials in the same class is usually considered to be an ineffective approach because in most classes the spectrum of resistance extends across all antimicrobials in the same class. The optimal time to switch from one class to another has not been investigated, although generally it is preferable to focus on use of the drug that is most closely targeted to the pathogen (that is, the drug with the narrowest spectrum of activity).

While some resistance might develop gradually, in most cases only one or two genetic events results in high level resistance. MIC testing can offer greater insight, but bacteria must be isolated before this can be performed. For some bacteria, and particularly the mycoplasmas, this requires considerable expertise. Therapeutic failures need to be investigated

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Table 1. WHO rating of antibiotic importance - 2016.

Drug catagorised by importance rating
HIGH *(Even in humans it is recommended that these drugs should not be used without culture and sensitivity results)* Amikacin, Ciprofloxacin, Piperacillin/Tazobactam, Vancomycin, Cefovecin, Ceftiofur, Imipenem, Enrofloxacin, Moxifloxacin, Ticarcillin/Clavulanate, Ceftriaxone, Rifampicin, Polymyxin B (Colistin)
MEDIUM Cloxacillin, Cephazolin, Clindamycin, Amoxycillin/Clavulanate, Gentamicin, Metronidazole, Cephalexin, Apramycin
LOW Oxytetracycline, Erythromycin, Chloramphenicol, Azithromycin, Florfenicol, Amoxycillin, Neomycin, Penicillin G, Doxycycline, Trimethoprim/Sulphonamide, Clarithromycin

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thoroughly. Such investigations may show that the quality of the antimicrobial drug is substandard (or that the drug is not present in the product in use), that the method of administration is not efficacious, that the action of the antibiotic is being inhibited (for example high calcium levels in layer feed can interfere with tetracyclines), or that resistance is the problem.

The rate of development of resistance is affected by many factors, including the ease of acquisition of mutations conferring resistance and the amount of genetic transfer between different organisms.

It varies greatly between antimicrobial drugs and between different bacterial species. For example fluoroquinolone resistance can develop very rapidly, in part because it requires only two single base mutations, and as a result enrofloxacin is not considered to be an anti-mycoplasmal drug in Thailand, India or China.

The use of antibiotics to control infections may not be appropriate in some cases. For example, salmonella infections (without clinical disease) may be prolonged or augmented by administration of some antibiotics. This may result from destabilisation of the intestinal microflora. Adult birds are naturally very resistant to salmonella colonisation and this protection is conferred by a stable intestinal microflora.

In Salmonella pullorum control programmes in the USA in the 1950s birds were testing negative even though they were still infected because of ongoing use of furazolidone. Similarly, antimicrobial drugs can interfere with serological surveillance of mycoplasma infections.

The benefit from prophylactic administration of antibiotics every 4-8 weeks to chickens in lay is derived from its effect on mycoplasma populations, not a non-specific growth promotion effect. Indeed, the growth promoting effect of tylosin may derive from the exquisite sensitivity of Mycoplasma gallisepticum to tylosin. The availability of mycoplasma-free replacement stock and improved biosecurity (particularly the phasing out of multi-age farms) are assisting in the implementation of improved mycoplasma control without relying on antimicrobial therapy, even when mycoplasma freedom may still be difficult to maintain because of frequent airborne challenge from nearby flocks.

Live vaccination against mycoplasmas offers an effective way to increase the resistance of flocks to airborne challenge, by reducing the risk of infection and ameliorating its effects when it does occur. This is not seen with killed mycoplasma vaccines.

It should be noted that all live mycoplasma vaccines are sensitive to all anti-mycoplasmal antimicrobial drugs (with the exception of Mycoplasma synoviae vaccines, because all strains of M. synoviae are innately resistant to erythromycin).

Surveys of antimicrobial resistance in pathogens and/or commensals and the identification of trends in resistance over time are also used in antimicrobial stewardship programmes. However, the information this surveillance offers is retrospective and can only inform us of the adverse effects of our use of antimicrobial drugs after they have developed. Retention of the efficacy of antimicrobials depends on prospective action and is best monitored by examining antimicrobial use rather than antimicrobial resistance.

In Table 2 we show a proposed medication programme from China which violates nearly every principle of antimicrobial stewardship:

- Use of antimicrobials that should not be used in food production animals or, some would argue, any domestic animals at all.
- Using multiple antibiotics concurrently without any evidence that this is likely to be beneficial.
- Use of multiple classes of antimicrobials in the same animals over a short time frame.
- Use of antimicrobials on a recurrent basis (every six weeks) without fully defining and characterising the target for the therapy.

The benefit of this regimen is most likely to be derived from control of mycoplasma infections. The text in red highlights antimicrobials with anti-mycoplasmal activity – neomycin and spectinomycin are not in red as they are not absorbed from the gut, even though they have anti-mycoplasmal activity in vitro. Resistance to enrofloxacin is very common in the field in Asian countries, but live vaccines are still sensitive. It is also probable that this regimen:

- Would not effectively control salmonellae and may even exacerbate salmonella infections by destabilising the intestinal microflora every six weeks.
- Would interfere with vaccination against mycoplasmas with live vaccines, because it will affect the colonisation and persistence of the vaccine. Mucosal immunity is short-lived and often weakens without continuous antigenic stimulation.

Although antibiotics can affect a wide variety of bacterial infections like Avibacteria, Pasteurella, Brachyspira, Campylobacter spp. and coliforms, the antibiotics can only have effects on bacteria in the bird at the time of treatment.

Uniquely, mycoplasmas chronically infect chickens and have an ongoing potential to cause disease and production effects, rather than these infected birds just being a potential reservoir to infect other flocks. If antibiotics were the best solution to them then we would have solved these problems in the 1950s when antibiotics were first used in food production animals.

The use of antibiotics to 'nurse the birds through stress' may also have a basis in suppression of mycoplasma populations and may not be necessary if mycoplasmas are controlled (freedom or live vaccination). Certainly, clinicians report that many other bacterial and viral infections are simpler diseases in flocks without concurrent mycoplasma field strain infections.

Recently mycoplasma-free replacement stock have become more readily available in China and India, and biosecurity may have been increased by depopulation to control avian influenza and the shift to single age breeder farms. Control of mycoplasmas in breeders makes control in broilers without antimicrobial drugs much easier. Finally, the cost of treating breeder and layer flocks every six weeks is substantial and vaccination is cheaper.

Table 2. Proposed medication programme from China which violates the principles of antimicrobial stewardship.

Age (weeks)	Method	Active(s)	Duration (days)	Supposed reason for usage
1-4	Drinking	Lincomycin & Spectinomycin	4	Mycoplasma and salmonella prevention
7	Injection together with killed vaccine	Enrofloxacin	Primary injection	Mycoplasma and salmonella prevention
11-17	Drinking	Tylosin & Doxycycline	7	Mycoplasma prevention
During transfer	Drinking	Tylosin & Doxycycline	5	Transfer stress prevention
At 5% egg production	In feed	Tiamulin & Doxycycline	5	First laying stress prevention
166-170 days	Drinking	Florfenicol & Amikacin	5	Salmonella prevention
Every 6 weeks after 350 days (alternatives)	Drinking	Gentamicin	5	Salmonella prevention
	Drinking	Amoxicillin & Clavulanate	5	Salmonella prevention
	Drinking	Florfenicol	5	Salmonella prevention
	Drinking	Neomycin sulphate	5	Salmonella prevention
	Drinking	Amikacin	5	Salmonella prevention
	Drinking	Florfenicol & Amikacin	5	Salmonella prevention

Conclusion

Antibiotic stewardship is a long-term strategy to maintain the effectiveness of antibiotics for the benefit of humans. Participation is the responsibility of veterinarians and anyone else making decisions about animal treatments.

The greatest effects are going to come from big reductions in antibiotic use resulting from understanding why antibiotics are being used and improving control of infections that currently make poultry production dependant on antibiotics.

It is argued that the effects of routine antibiotic administration on mycoplasma infections are why benefits are seen from prophylactic treatments in laying flocks. It is also suggested that if you can not run flocks free of MG and MS infections then you should use live mycoplasma vaccination. ■

References are available from the author on request