# HOW AND WHY RESISTANCE TO WORM REMEDIES DEVELOPS

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## Introduction

The age of modern chemistry and pharmaceutical solutions to infectious disease ushered in a renaissance of improved health and productivity of livestock. Starting in the 1960's, the availability of highly effective, safe and broad-spectrum worm remedies (anthelmintics) made parasite control simple and effective. Frequent regularly scheduled treatments with worm remedies kept animals healthy and productive, and had a great cost-benefit return. However, this strategy has turned out to be shortsighted and unsustainable. This is because gastrointestinal nematodes (GIN; commonly referred to as roundworms) of sheep and goats have become resistant to multiple drugs.This problem is extremely common and widespread around the world, and is particularly serious in *Haemonchus contortus* (barberpoleworm or wireworm), but also in other species of GIN (Kaplan and Vidyashankar, 2012). In fact, in many areas of the world, including South Africa, there is a great risk of having no effective worm remedies to use in the near future. Some farms are already in such a predicament. This leads to several important questions. First, why does drug resistance in worms seem to happen so readily and how does this happen? And second, what can be done to slow down the development of drug resistance?

## What is drug resistance and how does it start?

First we should define resistance to worm remedies. Resistance is defined as a heritable genetic change (meaning it is passed genetically directly from a worm to its offspring) in a population of worms that enables some individual worms to survive drug treatments that are generally effective against the same species or worm and stage of infection at the same drug dose rate. In practical terms resistance to worm remediesis present in a population of worms when the effectiveness of the drug falls below that which is historically expected, when other causes of reduced efficacy have been ruled out.

Really, we should not be surprised that worms have become resistant to worm remedies. Everyone is aware that that bacterial resistance to antibiotic drugs is becoming a major problem worldwide. Very similar evolutionary processes also occur with worms. In fact, we now understand quite well that drug resistance is an inevitable consequence of using drugs to kill bacteria, viruses and parasites. With regard to parasitic worms, these organismshave many biologic and genetic features that favor the development of drug resistance, such as short life cycles, high reproductive rates, high genetic mutation rates, and extremely large population sizes. These biologic characteristics lead to rapid rates of evolution and exceptionally high levels of genetic diversity. Therefore, even though mutations that cause a worm to become resistant are very rare, they are constantly occurring due to the enormous sizes of worm populations. For instance, each female *H. contortus* worm produces approximately 5,000 eggs per day. If a flock of sheep averages 1,000 worms per animal (a very modest level of infection), then there are 500 females so that a single sheep will pass 2.5 million eggs per day. In other words, a flock of 100 sheep will shed almost 2 billion eggs per week. These huge numbers provide the opportunities for rare mutations that lead to drug resistance to occur. So – what happens to make these very rare mutations increase in numbers to such a great extent that many or even most worms on a farm have the resistance trait?

As discussed above, initially worms bearing mutations that make them resistant to the drug are very rare within the midst of a very large genetically diverse population, which may number in the hundreds of millions or billions. These resistant individuals and their offspring will remain rare within a worm population, and may even disappear from the population unless they gain a survival advantage over their parasitic competitors. The way they gain such a competitive advantage is by treating animals with worm remedies. Treatment per se does nothing positive for resistant worms, but by killing the drug-sensitive worms, which comprise the vast majority of a parasite population, resistant individuals are able to reproduce for a given interval in the relative absence of competition. As a result, following each and every treatment with a worm remedy, the numbers of resistant worms increase incrementally. The development of drug resistance to levels that are clinically important is usually a slow and gradual process, requiring numerous generations under drug selection (usually taking many

years). This can be best understood with a simple illustration. If say one in one million worms in the population are resistant, and then numbers of resistant worms double with each treatment we will see the following change in frequency of resistant worms over 13 treatments: 1/1,000,000; 1/500,000; 1/250,000; 1/125,000; 1/62,500; 1/31,250; 1/16,000; 1/8,000; 1/4,000; 1/2,000; 1/1,000; 1/500; 1/250; 1/125. So – with just 13 treatments we went from 1 in 1,000,000 to 1 in 125. However, even though this signifies an almost 10,000-fold increase, the drugs are still 99% effective and the resistant worms are not noticed. But then it takes just 6 more treatments to reach complete treatment failure (1/125; 1/62; 1/31, 1/15; 1/8; 1/4, 1/2). In this illustration it took just 19 treatments to change the frequency of resistant worms from one in one million (0.000001%) one in two (50%). But only in the last 3 treatments would there be enough resistant worms present to cause a problem. Of course this is just an illustration, and this process can occur faster or slower depending on numerous factors.

Thus from a practical perspective, drug resistance develops slowly over time, during which time it is impossible to detect. But then levels of resistance increase very rapidly in the last phase, where it is then perceived as a clinical event (treatment failure). Alternatively, resistant worms can be purchased, thus bypassing the many years of worm evolution and drug selection necessary to reach high levels. Depending upon how many animals are purchased harboring resistant worms, treatment failures can occur practically instantly or over a relatively short period. This has great clinical relevance because in either case, resistance can transition from undetectable, to clinically important levels over a very short period of time. Consequently, unless a surveillance program is in place that closely monitors the effectiveness of drug treatments over time (see paper on diagnosis of drug resistance), resistance will not be noticed clinically until levels of resistance are extremely high. This is a major problem because once resistance reaches detectable levels, irreversible changes in the genetic structure of the worm population have occurred, ensuring that "resistance" is fixed in that population forever(Roos et al., 1995). Thus, once resistance is diagnosed as a clinical problem "reversion" to susceptibility likely will never occur.

**Factors that affect the development of drug resistance**

It is easy to understand how resistance may evolve when worm remedies are administered frequently. But what other factors regulate the rate with which resistance develops? Why does resistance develop so much quicker in some parasites and in some hosts than in others? We don't fully know all the answers to these questions but there is much we do know. Firstly, it is important to administer quality drugs at the proper dose level, and to deliver the dose using optimal drenching technique. Under dosing either because of underestimating the animal's weight or sub-optimal delivery of the dose can greatly accelerate the rate with which resistance develops. Similarly, the use of poor quality or degraded drugs (old or stored poorly) can also accelerate resistance because all of these practices allow partially resistant worms to survive that would otherwise be killed by the full dose. However, the most important factor affecting the rate of development of resistance to worm remedies is the proportion of the worm population under drug selection. In other words, of all the worms on the farm, both in the animals and on the pasture, what percent of these worms is experiencing the effect of the worm remedy treatment? The more worms that "experience" or "see" the drug, the more opportunity there is for the resistant worms to gain an advantage. The fewer the number of worms that "see" the drug, the less advantage the resistant worms gain because many of the drug-susceptible worms are still around to dilute the resistant ones. We use the term "***Refugia***" to describe the portion of a parasite population that is not exposed to a worm remedy during a treatment event(Van Wyk, 2001). Parasites in refugiaescape selection pressure from the drug, thus parasites in refugia constitute a reservoir of drug-susceptible parasites that keep the resistant worms diluted to low levels. Examples of refugia include eggs, infective third-stage larvae ($L_3$) and pre-infective larvae ($L_1$, $L_2$) in the environment (on the pasture) and parasitic stages in those individual animals that are not dewormed whenever other herd members are treated. It is noteworthy that at times of the year when worm transmission is high (rainy season) thenumbers of parasites on pasture often comprise >99% of the total parasite population on a farm. In contrast, during hot and dry times of the year few parasitic stages can survive on the pasture, and therefore most of the worms are inside the animals.

To summarize, if we are using worm remedies to treat and control worm infections in our livestock, we cannot stop drug resistance from developing. However, there are things we can do to greatly slow down the rate of development of resistance. Managing refugia is the most important and direct way that we can achieve this. The more parasites that are in refugia, the slower the development of resistance will be to worm remedies. This is because the resistant worms that gain advantage every time an animal is treated are greatly diluted by the untreated refugia. Though managing refugia cannot prevent resistance from eventually occurring, managing refugia on a farm is critical to delaying the inevitable development of resistance and improving the sustainability of worm control programs.

## Conclusion

Despite the occasional development of new types of worm remedies (anthelmintic classes), history clearly demonstrates that the development of resistance consistently outpaces the introduction of new drugs. Clearly then, major changes need to be made in the way that worm control is practiced. It is no longer acceptable for veterinarians or farmers to view GIN parasite control in terms of a “deworming program”. Over the past decade a paradigm shift has occurred in how GIN parasite control must be viewed and practiced. Worm remedies can no longer be viewed as a relatively inexpensive management tool to be used with little thought to maximize animal productivity. Rather, they must be viewed as extremely valuable and limited resources. We must balance our desire for simplicity and ease with the reality that effective long-term control of parasitic worms will only be possible if worm remedies are used intelligently with prevention of resistance as a goal, and as part of a sustainable integrated parasite management (sIPM) system.

## References

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