



## Timely Topics

# Combination dewormers: The Time is Now

AMERICAN CONSORTIUM FOR SMALL RUMINANT PARASITE CONTROL

Resistance to dewormers is a fact of life, and the situation has worsened greatly in recent years. Surveys indicate that most farms have worms resistant to at least two of the three major groups of dewormers. Many have resistance to all three groups, and some farms now have resistance to all available dewormers. But, having worms in your animals that are resistant to dewormers does not mean that all the worms are resistant. For instance, when all the commonly used dewormers were first introduced, their efficacy was greater than 99 percent. Once efficacy falls below 95 percent it indicates that drug resistance is present. At 95 percent, the drug is still very useful, but once drug resistance is present, it usually worsens over time as more and more doses of that drug are given.

As the effectiveness of the dewormer decreases, it provides less and less benefit, and once it falls to less

than 50 percent, it is no longer useful as a sole treatment. Given this situation, what is the best approach for using dewormers? Contrary to popular belief, rotating between dewormers will not prevent resistance from worsening, and is no longer recommended. Rather, dewormers should be used together at the same time in combination.

### How and why do combination treatments work?

Research done in New Zealand has convincingly shown that the best approach is to use several different dewormers all at one time as a combination treatment. In fact, in Australia and New Zealand, there currently are few dewormer products sold as single drugs; most products contain 3, 4, or 5 different groups of dewormers (note: other countries have some dewormers that are not available in the US).

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There are two major benefits to using drugs in combination:

- 1) You get an additive effect with each drug used, thus the efficacy of the treatment increases with each additional drug given (see Table 1 below); and
- 2) By achieving a higher efficacy, there are fewer resistant worms that survive the treatment, thus there is a greater dilution of resistant worms by the susceptible portion of the population (see Table 2).

Furthermore, as seen in Table 2, the sooner you start using a combination, the better off you will be, since you see the greatest difference in the percent of resistant survivors when efficacy of dewormers is high. The more dewormers that are used in combination, the greater the efficacy of treatment will be. However, if all the dewormers individually have poor efficacy, the combination will not reach high efficacy. As seen in Table 1, once efficacy falls to 50 percent, even a combination of three dewormers will still fail to reach a 90 percent efficacy.

As an illustration of why combinations help reduce the development of resistance, but rotation of dewormers does not, let us look at some numbers. If two drugs each with 90 percent efficacy are used in rotation, then each time animals are

**Table 1: Impact of using dewormers in combination on the efficacy of treatments.** The increases in efficacy are due to a simple additive effect as per the equation below: Where D1 = efficacy of dewormer 1, D2 = efficacy of dewormer 2, D3 = efficacy of dewormer 3, C2 = efficacy of D1+D2, and C3 = efficacy of D1+D2+D3  $C2\% = D1\% + (100-D1\%)*D2\%$   $C3\% = C2\% + (100-C2\%)*D3\%$ .

Drug 1 (%)	Drug 2 (%)	Drug 3 (%)	Combination (%)
80	80		96.0
80	80	80	99.2
90	90		99.0
90	90	90	99.9
60	95		98.0
60	60	95	99.2
99	99		99.99
60	60	60	93.6
50	50	50	87.5
40	40	40	78.4

**Table 2: Impact of combinations on percent of resistant worms that survive.** Table shows the percent of worms killed by a single dewormer vs a combination treatment with two dewormers both with the same efficacy, ranging from 80 to 99 percent. The last column shows the magnitude of the difference between percent of worms killed and percent surviving when one or two dewormers in combination are used. Note that the higher the efficacy of the drugs, the smaller the difference in efficacy when used in combination, but the greater the difference in the percent of resistant survivors.

Efficacy of dewormer		Single dewormer	Two dewormers in combination	Fold difference
99	% Killed	99	99.99	1.01x
	% Surviving	1	0.01	100x
98	% Killed	98	99.96	1.02x
	% Surviving	2	0.04	50x
95	% Killed	95	99.75	1.05x
	% Surviving	5	0.25	50x
90	% Killed	90	99.01	1.1x
	% Surviving	10	1.0	10x
80	% Killed	80	96.0	1.2x
	% Surviving	20	4.0	5x



treated 10 percent of the worms survive (the resistant ones). In contrast, if these same two drugs are used in combination at the same time, then the efficacy increases to 99 percent. This calculation involves a simple additive function; the first drug kills 90 percent and the second drug kills 90 percent of the remaining 10 percent [ $90\% + (90\% \times 10\%) = 99\%$ ]. Thus the efficacy achieved is now 10X greater and this then yields 10X fewer resistant survivors.

Because fewer resistant worms survive at each treatment, there is a greater dilution of the resistant worms among the majority of worms in refugia that are still susceptible. This then will greatly slow the development of drug resistance in the overall worm population. In contrast, if using a rotation of drugs, you would get 10X as many resistant worms surviving each time you treat. Additionally, given the high rates of drug resistance that are known to exist, it is likely that one or more of the dewormers will have poor efficacy, thus you risk rotating from an effective (or relatively effective) dewormer to an ineffective dewormer. By using dewormers as a combination, you eliminate the risk of rotating to a poorly effective drug, and get an additive benefit that maximizes the effectiveness of each treatment given.

## Research shows that combinations are the best approach.

But – it gets even better. Dr. Dave Leathwick (AgResearch, New Zealand) published a paper in 2015 in the *Journal International Journal for Parasitology: Drugs and Drug Resistance*, where seven farms previously diagnosed with resistance to at least two groups of dewormers were enrolled in a study where each farm implemented a tailored program of "best practice parasite management." The aim was to ascertain whether the programs, which included the almost exclusive use of combination dewormers, were able to prevent resistance from developing further. Strategies implemented on each farm varied, but had consistent underlying principles to avoid over-use of dewormers, manage refugia (and to ensure that only effective anthelmintics were used, by administering them only as a combination).

After five years, they demonstrated an overall improvement in the efficacy of the dewormers (when tested individually), indicating that the use of dewormers in combination, when applied with other best practices designed to reduce use of dewormers and maintain refugia, caused a reversion back to-





ward susceptibility. So, there now is very strong evidence that using combination treatment is the best method for using dewormers and should be instituted on all farms immediately.

## Precautions and issues to consider

Finally, before using this approach there are a few precautions to be aware of.

- 1) In New Zealand and Australia, products are sold that contain a combination of dewormers, so only one product needs to be administered. In contrast, in the US, no dewormers are yet sold in this formulation, so the dewormers need to be bought and administered separately. This increases the cost as compared to the products available in these other countries. Additionally, the different groups of dewormers are not chemically compatible, thus they cannot be mixed together in the same syringe. Rather, they need to be administered separately, but can be given one immediately after the other.
- 2) All dewormers should be administered at the full recommended dose whether administered singly or in combination.
- 3) When using dewormers in combination, meat and milk withdrawal times will be equal to the dewormer used with the longest withdrawal time period.
- 4) If using dewormers in combination, it is critical to maintain refugia; thus, one should be using a selective treatment approach based on FAMACHA© (see FAMACHA© section of the ACSRPC website ([wormx.info](http://wormx.info)) for more information on this method and for further explanations of refugia). The presence of refugia is essential to realize the full benefits from combinations. In fact, if refugia are not maintained then you will not get the necessary dilution of the resistant survivors, and this will then lead to having multiple-resistant worms that can no longer be controlled with the combination treatment.
- 5) If the efficacy of your dewormers are more than 80 percent, it is possible you may not notice any difference in the clinical response of treatments when applied singly vs. in combination. However, the impact on the further development of resistance could be quite large (see Table 2).
- 6) Any safety precautions that exist for a single dewormer will also exist when used in a combination; however, there are no known additional risks with using more than one dewormer at the same time.

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Written and reviewed by Ray Kaplan, DVM, PhD, St. George's University, Grenada, West Indies.

Edited by Susan Schoenian



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