Strategies to minimise the anticoccidial resistance in the commercial chicken farms

Dr. T. Anna , M.V.Sc., Ph.D.,
Professor and Head,
Dept. of Veterinary Parasitology,
Veterinary College and Research Institute,
Tirunelveli – 627 358, Tamil Nadu.

Chemoprophylaxis and Immunoprophylaxis of chicken coccidiosis

Curative and prophylactic drugs

Anticoccidial drugs – Classification & Mode of action

Common anticoccidials :
Chemicals Vs Ionophorous Antibiotics

Immunoprophylaxis : Need for Anticoccidial vaccine

Live, Attenuated , Precocious line vaccines

Recombinant / Sub unit vaccine

Strategies to minimise the anticoccidial resistance in the commercial chicken farms

Why Chicken coccidia are very prone to resistance?

Anticoccidial resistance (ACR) – Types and Factors

Methods for detection of Anticoccidial Resistance

Anticoccidial programs - Rotation, Shuttle and Immuno shuttle program

Six Golden Rules to minimize the AC resistance

Anticoccidials and Resistance

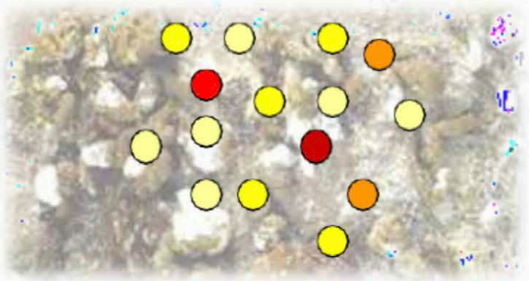
- Continuous use of anticoccidial drugs promotes the emergence of drug-resistant strains of coccidia.
- While there is little cross-resistance to anticoccidials with different modes of action, there is widespread resistance to most drugs.
- Coccidia can be tested in the laboratory to determine which products are most effective.

Why Chicken Coccidia Sp. are more prone to Resistance to Anticoccidials?

- The control of avian coccidiosis has relied almost entirely on chemotherapy, as is evident from the fact that most intensively reared chickens are fed an anticoccidial agent in the diet throughout their period of growth.
- Feed medication is a convenient and cost effective method of enabling large numbers of chickens to be reared under intensive conditions.
- The practice of including drugs in the feed throughout the life of the bird has ensured that few parasites escape the effects of medication.
- In such an environment, parasites are exposed throughout their life cycle to agents designed for their removal and this has inevitably resulted in the development of resistance.

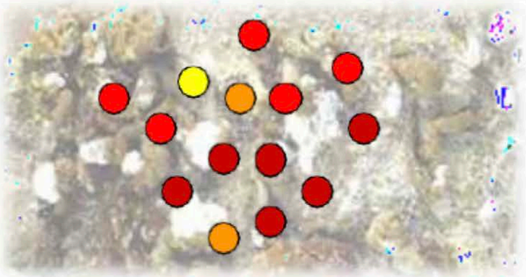
Reduced Sensitivity / Resistance

After some time of use, the efficacy of anticoccidials decreases.

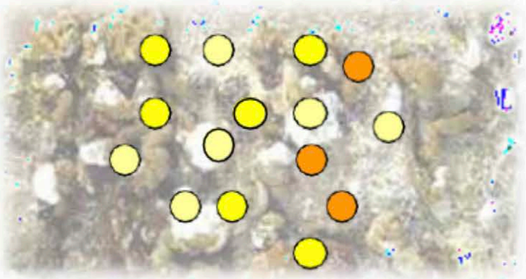


Parasite population

Anticoccidial X



No anticoccidial



High ○ ○ ○ ○ ○ **Low**

Level of sensitivity

(Mathis *et al.*, 1984; Chapman, 2007)

Resistance and Cross Resistance

Reduced sensitivity / resistance

After some time of use

The efficacy of anticoccidials decreases

Cross-resistance

If resistance to one product arises

Other similar products will also work less efficient

Cross Resistance

Chemicals:

- Very different targets to kill *Eimeria* sp
- Occurrence of cross-resistance.
- Repeated usage within 3 years - resistance

Ionophores:

- Have a common mode of action.
- Cross-resistance can be a problem.
- However, big differences between different classes of ionophores

→ implications for cross-resistance
MULTIPLE RESISTANCE

Factors involved in AC resistance development

- Genetic Factors
- Operational Factors
- Biological Factors

Genetic Factors

- Dominance of resistance alleles
- Number of genes involved
- Initial frequency of resistance genes
- Genetic diversity of population
- Relative fitness of resistant organisms
- Chance of linkage disequilibrium
- Opportunity for genetic recombination

(Chapman, 1997)

Common anticoccidial drugs with their mode of action

Anticoccidial Drugs	Mode of action	Affected life cycle stages	Species studied	References
Sulfonamides	Inhibition of folic acid pathway	Second and later schizonts	E. tenella	Wang *et al.*, 1975
Amprolium	Thiamine antagonist	Second generation schizont	E. tenella	James, 1980b
Decoquinate	Inhibit respiration by blocking electron transport in the parasite mitochondrion	Sporozoite	E. tenella	Wang, 1975
Clopidol	Affects electron transport	Sporozoite	E. tenella	Fry and Williams, 1984
Benzeneamines	Uncouple oxidative phosphorylation	Sporozoites	Various species	Bafundo *et al.*, 1989
Monensin	Influx of sodium ions	Sporozoite	E. tenella	Smith and Galloway, 1983
Robenidine	Bind to proteins and cause the uncoupling of the parasite mitochondria	Multiple stages	Various species	Wang, 1982
Halofuginone	Unknown	Asexual stages	Various species	Kitandu and Juranova, 2006
Ionophores	Cation transport across cell membrane	Sporozoites & merozoites	Various species	Smith and Galloway, 1983
Diclazuril	Nucleotide analogue	Both sexual and asexual stages	E. tenella	Maes *et al.*, 1988
Toltrazuril	Act against plastid like genome	Multiple stages	Various species	Hackstein *et al.*, 1995

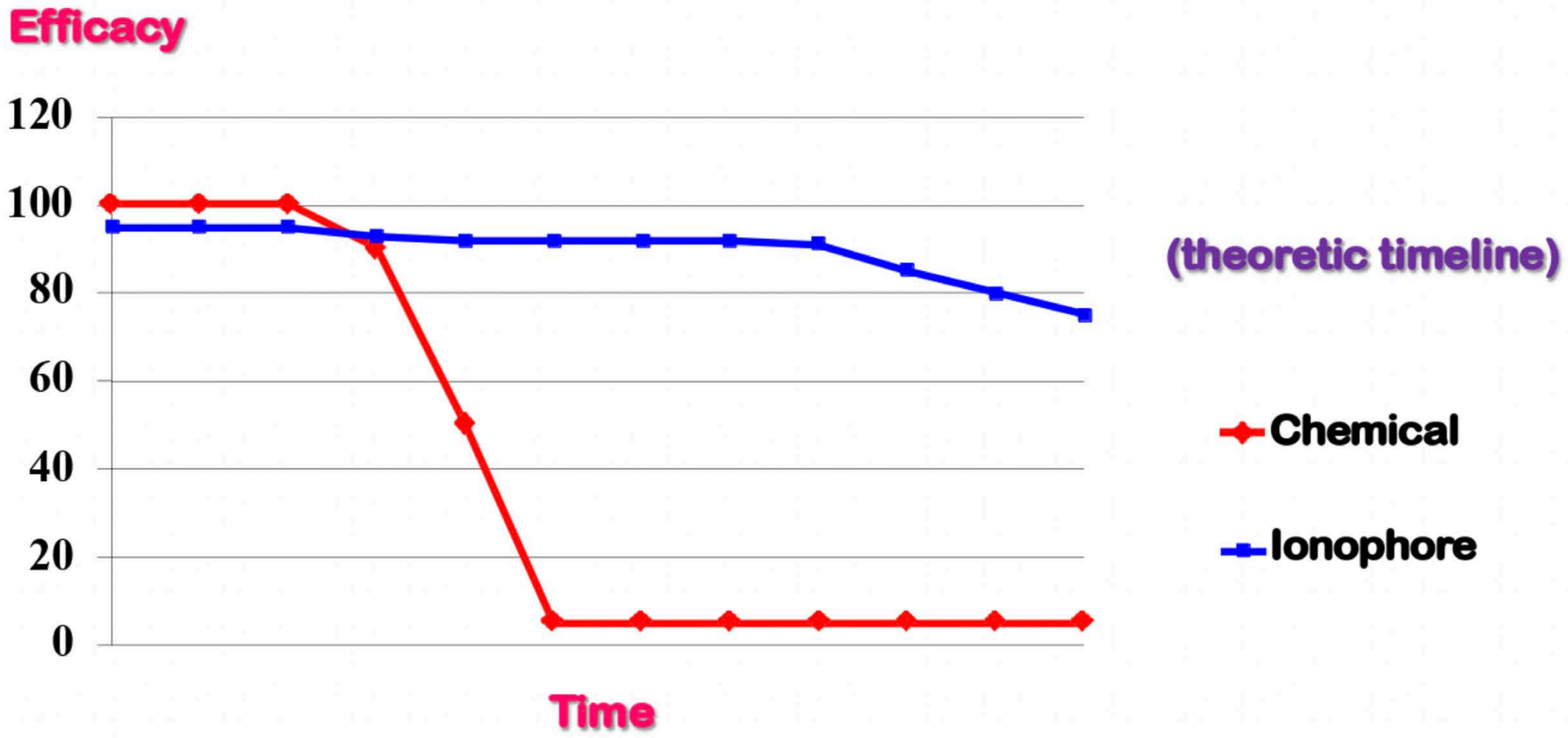
Table Source : Abbas *et al*, 2011

Report on Resistance to Chicken Anticoccidials

Drug	Country	Resistance described	Year
Sulphaquinoxaline	USA	Waletzky *et al.*	1954
	India	Gill and Bajwa	1979
Nitrofurazone	USA	Cuckler and Malanga	1955
	India	Gill and Bajwa	1979
Nicarbazin	Britain	Hemsley	1964
	India	Gill and Bajwa	1979
	Germany	Stephan *et al.*	1997
Dinitolmide	Britain	Hemsley	1964
Amprolium	Britain	Hemsley	1964
	India	Gill and Bajwa	1979
Clopidol	India	Gill and Bajwa	1979
Buquinolate	USA	McManas *et al.*	1968
Monensin	USA	Jeffers	1974
	Gt. Britain	Chapman	1982
	Germany	Stephan *et al.*	1997
Robenidine	USA	Jeffers	1974
	Germany	Stephan *et al.*	1997
Halofuginone	France	Hamet	1986
	Germany	Stephan *et al.*	1997
Lasalocid	USA	Weppelman *et al.*	1977
Arprinocid	Britain	Chapman	1982
Salinomycin	USA	Jeffers	1989
	Germany	Stephan *et al.*	1997
	India	Yadav and Gupta	2001
	Pakistan	Abbas *et al.*	2008a
Narasin	USA	Weppelman *et al.*	1977
Maduramicin	USA	McDougald *et al.*	1987
	Germany	Stephan *et al.*	1997
	Pakistan	Abbas *et al.*	2008a,b
Diclazuril	Brazil	Kawazoe and Fabio	1994
	Germany	Stephan *et al.*	1997
Toltrazuril	Netherlands	Vertommen and Peek	1993
	Germany	Stephan *et al.*	1997

Source : Abbas et al, 2011

Timing of Resistance Development (theoretic timeline)



Evaluation of Anticoccidial Resistance // Methods for detection of ACR

- Four different indices to evaluate the anticoccidial efficacy :

1. Global Index (GI) by Stephan *et al.* (1997)
2. Optimum Anticoccidial Activity (OAA)
3. Anticoccidial Sensitivity Test (AST)
4. Anticoccidial Index (ACI)

- **Holdsworth et *al.*, 2004 *Vet Parasitol.*** 121: (3-4)189-212
  WAAVP Approved Protocol

Global Index – GI by Stephan *et al.* (1997)

- Weight gain
- Feed conversion for the treatment group and the negative control (NNC)
- Lesion score for the treatment group and the infected/non -medicated control (INC).
- Oocyst index
- An oocyst index of 0 to 5 was determined by examination of scrapings from each four segment of intestine for birds sacrificed for lesion score at 7th day post- inoculation.
- The GI for each dietary treatment was calculated as percentage of the GI for the negative control group NNC

$$GI = \%WG_{NNC} - [(FM - F_{NNC}) \times 10] - (OIM - OI_{INC}) - [(LSM - LS_{INC}) \times 2] - (\%mortality/2)$$

Global Index – GI by Stephan *et al.* (1997)

- The GI for each dietary treatment was calculated as percentage of the GI for the negative control group NNC according to the following 5 categories:

- ≥90% GI : Very good efficacy
- 80-89% GI : Good efficacy
- 70-79% GI : Limited efficacy
- 50-69% GI : Partially resistant
- <50% GI : Resistant

Optimum Anticoccidial Activity (OAA)

- In this index, a **GROWTH AND SURVIVAL RATIO (GSR)** is used to calculate the percentage of **OAA** -Optimum Anticoccidial Activity for each treatment as follows:

- Resistant if ≤50%,
- Partially resistant if 51%-74%
- Sensitive if ≥75%

Anticoccidial Sensitivity Test (AST)

- The AST -Anticoccidial Sensitivity Test is calculated based on the reduction of mean lesion score of the treatment group compared with the infected non-medicated group (INC).
- A reduction of
- 0 to 30% - Resistance
- 31- 49% - Reduced sensitivity / Partial resistance
- at least 50% - Full sensitivity

Anticoccidial Index (ACI)

- ACI index = (Relative weight gain rate + survival rate) - (Lesion score x 10 + oocyst value/score).

- Value of 180 or higher indicate that drug is very effective

- value <120 indicate that the drug is not effective.

Solution to ACR : Best use of existing drugs

- The control of coccidiosis is likely to continue to depend on chemotherapy
- Immunoprophylaxis, are now established and offer a practical alternative.
- Until now, as resistance has developed to the older compounds, new ones have been discovered to replace them.
- It is doubtful whether this situation will continue.
- It is important therefore that strategies be devised to obtain the best use of existing drugs.

Effect of higher dose on AC Resistance ?

- It has been shown that parasites resistant to the recommended levels of certain anticoccidial drugs may be suppressed if the concentration of drug is increased.
- Resistance to these higher concentrations, however, is likely to develop rapidly after further selection.
- Increasing the concentration of a drug may therefore only be of use in the short term
- Further more would not be practical because most anticoccidial drugs are used at levels close to those that are toxic to the chicken.

Lower Dose, Frequency and AC Resistance?

- Resistant strains may emerge if anticoccidial drugs have been employed at concentrations lower than those normally recommended for control.
- It would therefore appear to be important to maintain adequate drug levels in the field in order to reduce the possibility of selecting resistant strains.
- A reduction in the use of drugs is desirable since it is generally accepted that the selection of genes for resistance will occur more rapidly as the frequency of treatment is increased.
- Control of coccidiosis may be achieved by giving drugs intermittently, the objective being to prevent the buildup of infection in a poultry house.
- However, such a policy would be unacceptable to the poultry industry because of, for example, the impairment of food conversion that would probably result.

Overcoming Resistance

- Resistance presents a major problem.
- Various programs are used in attempts to slow or stop selection of resistance.
- ROTATION vs SHUTTLE PROGRAMMES

Shuttle Programs

- In which one group of chickens is treated sequentially with different drugs (usually a change between the starter and grower rations), are common practice and offer some benefit in slowing the emergence of resistance.

Step up or Step down Programmes

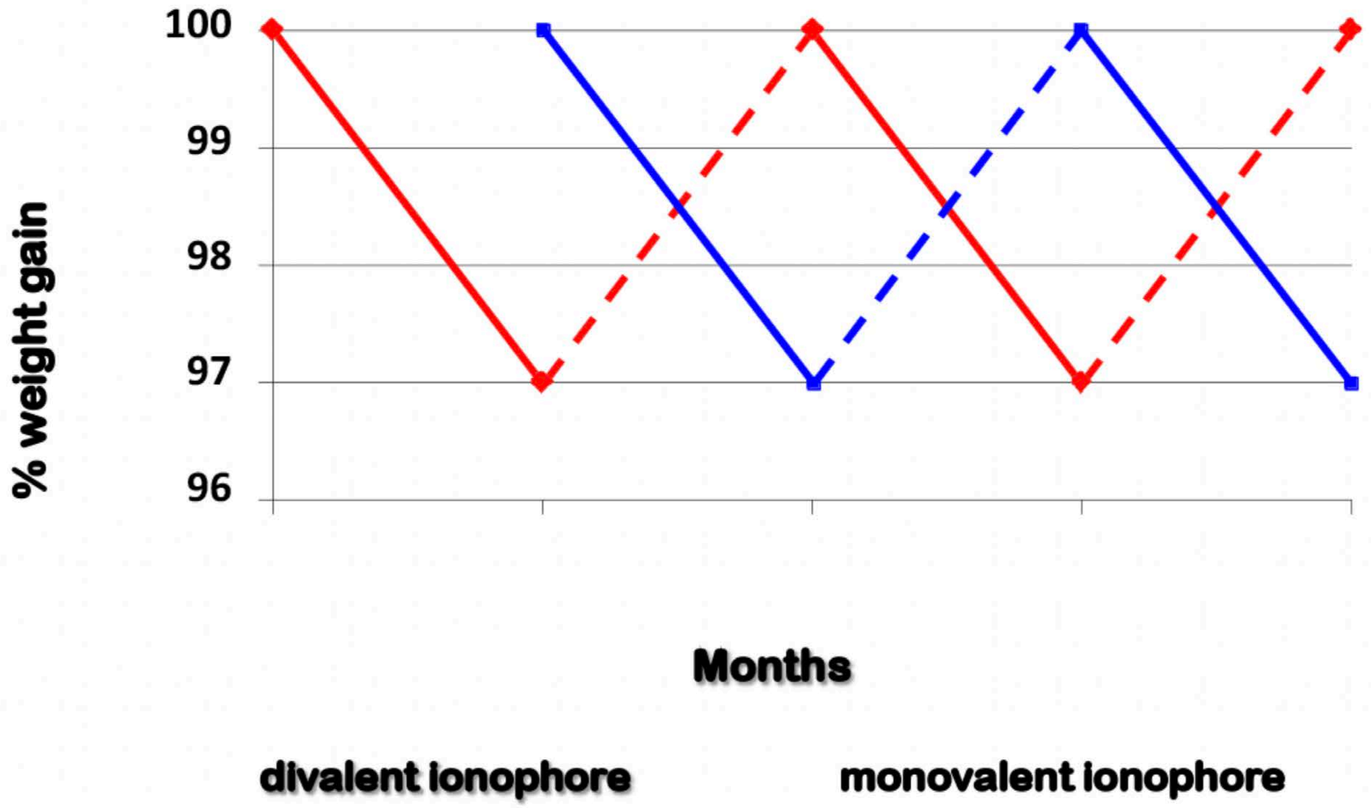
- In a 'step up' programme, ionophores are used at a low concentration in starter feed and used at higher concentration in finisher feed or vice versa in a 'step down' programme.
- Monensin and Salinomycin are used in a step-down fashion to aid in the development of immunity.
- Salinomycin was given to broiler at 60 parts /10^6 from 0 to 4 weeks and at 40 parts/10^6 from 4 to 6 weeks.
- Similarly, we can design it for commercial layers, broiler breeders and layer breeding stock.

Rotation Program

Changing the anticoccidial drug to one of another class after a few cycles

(can be in shuttle or full program)

Rotation = Resting
Helps Anticoccidials To Recover Efficacy



(Chapman and McFarland, 2003)

Rotation Basics

- Ionophore : up to 6 months
- Chemical full : 3 months (1 cycle)
- Chemical in shuttle : 4.5 months (2 cycles)

Caution for using ionophores / Chemicals

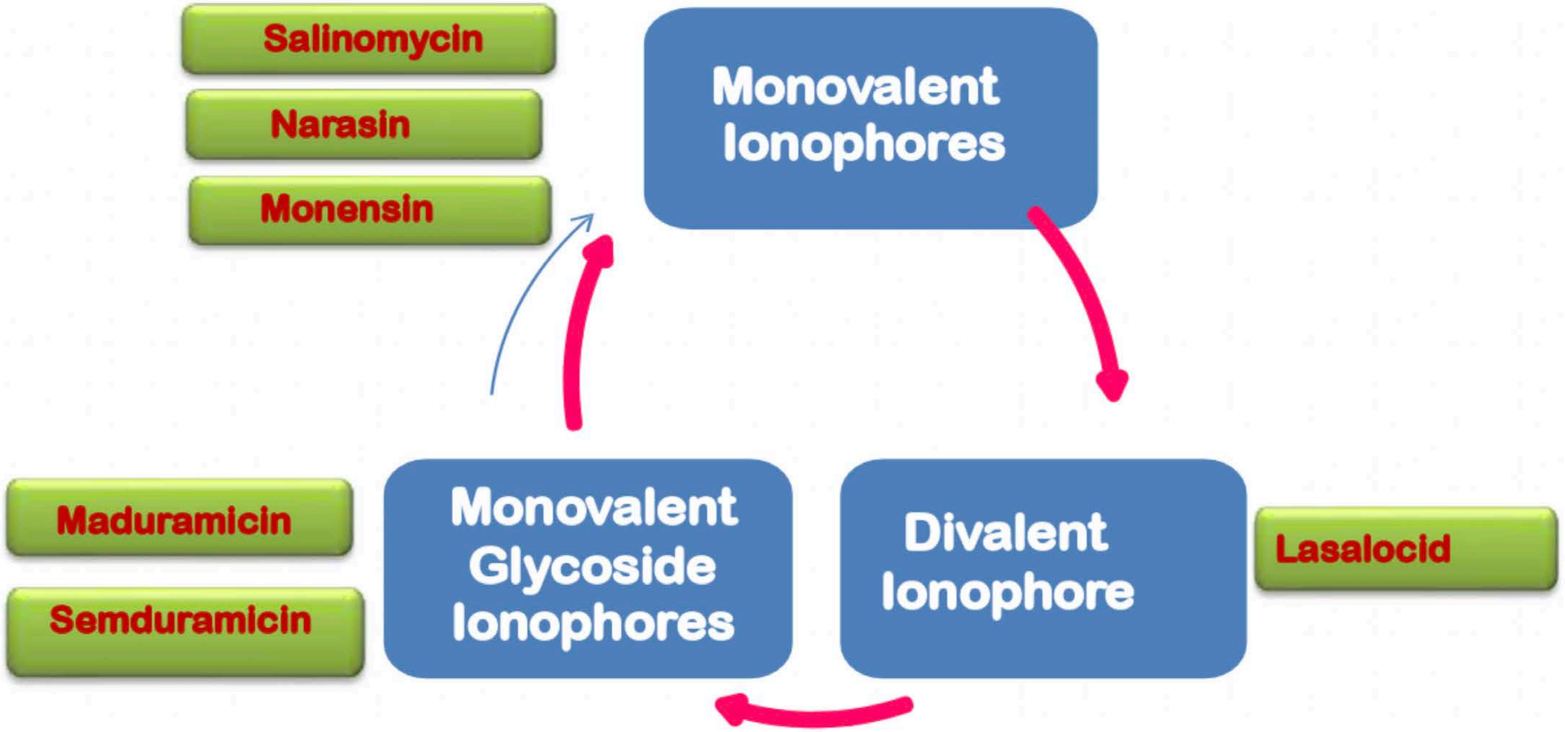
- **After using an ionophore**

  - Do not use it again for at least 6 months
  - (or other ionophore from same class)

- **After using a chemical**

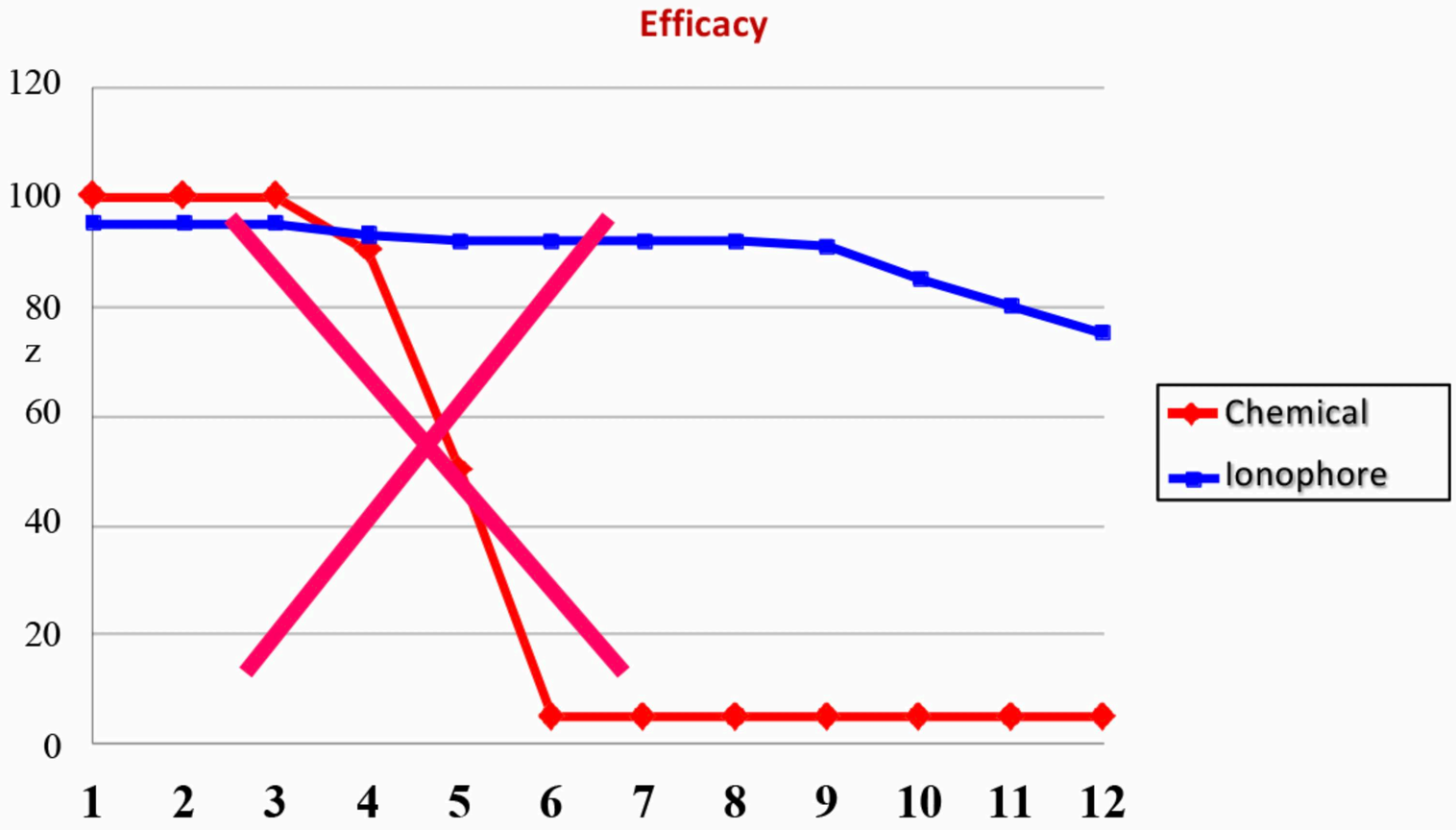
  - Limit use of particular chemical to once a year, if used 3 months in full, give 9 months rest.
  - You can use other chemicals.

Correct Rotation



Don't forget cross-resistance

Rotation Reduces The Risk For Developing Resistance !!!



Alternating cycle of drugs and vaccines

IMMUNO-SHUTTLE

or

BIO-SHUTTLE

IMMUNO-SHUTTLE or BIO-SHUTTLE

- In this approach, anticoccidial vaccines and drugs are administered alternatively during different age groups of birds.
- On Day 1, Anticoccidial vaccine is administered,
- On Day 14-28, Anticoccidial drug is given in grower feed and
- On Day 28-38, the same anticoccidial drug or a different anticoccidial drug in finisher feed at low dose is administered.
- For example Advent® which is a live vaccine containing oocysts of *E. tenella, E. maxima* and *E. acervulina* is administered on day 1
- Followed by Salinomycin (60 g/ton) on day 14-28 and
- Lincomycin (4 g/ton) on day 28-38.
- Results revealed improvement in Feed conversion ratio and an increase in body weight gain

Commercially available anticoccidial vaccines

1. Advent
2. Coccivac-B
3. Coccivac-D
4. Coccivac-T
5. Eimeriavax 4M
6. Inovocox
7. Immucox I, Immucox II, Immucox T
8. Hatchpak Cocci III
9. Paracox 5, Paracox 8
10. Livacox Q, Livacox T
11. Coxabic
12. Hipracox

The Integrated Approach Chapman, 2000

- Anticoccidial drugs
- Shuttle programme / Rotation programme / step up – or down
- Vaccination - Live vaccines Non attenuated or Attenuated /Egg adopted or Precocious line vaccines
- Live vaccines with anticoccidial - Immuno Shuttle
- Botanical anticoccidials
- Non-chemical control may involve the integration of botanical anticoccidials with vaccination for control of coccidiosis. ORGANIC FARMING PRACTICES
- Feeding natural dietary supplements or probiotics to animals to enhance their innate defense mechanisms could effectively reduce or eliminate the need for therapy of these enteric infections
- Ethnoveterinary bioactive products - plant essential oils (EOS)

Conclusions

- Although the appearance of resistance might be delayed Acquisition of multiple resistances in chicken coccidia
- To combat, combine field monitoring and sensitivity testing
- In field monitoring, practical diagnostic techniques can be used such as lesion scoring, faecal oocyst counts and litter oocyst counts.
- Lesions scores are indicative for the severity of the coccidiosis infection and can be made on an average of 5 birds/20,000 on day 21 and 35.
- Periodically faecal oocyst counts OPG on day 14, 21, 28 and 35 in a flock.

Conclusions

- Testing the retention sample (500g) of every feed delivery to check the feed anticoccidial content and Anticoccidials sensitivity test also helps.

- Regular monitoring of *Eimeria* species for development of resistance against different anticoccidial groups has a crucial role in the management of resistance and making a correct choice of an effective drug.

- Use of vaccines, synthetic and botanical anticoccidials in combination and educating the farmers about recommended coccidiosis control practices as strategic and / or tactic measures for the control of coccidiosis would be rewarding.

- Integration of currently available options for the management of drug resistance and control of coccidiosis is suggested.

- It would be worthwhile in future for researchers to focus on evaluation of such integrated programmes.

Anticoccidial Programs: SIX Golden Rules

1. Do not to use same anticoccidial for too long.

2. Give product a sufficiently long rest period after each period of use.

3. Rotate between products of different classes.

4. Use a chemical clean up once a year, it gives a very good reduction infection pressure.

5. Practice Bio / Immuno Shuttle Program

6. Integrated approach with botanicals / Natural products / EO's / Probiotics / Feed additives n-3FA

CONCLUSION

Why Chicken coccidia are very prone to resistance?

Anticoccidial resistance (ACR) – Types and Factors

Methods for detection of Anticoccidial Resistance

Anticoccidial programs - Rotation, Shuttle and Immuno shuttle program

Six Golden Rules to minimize the AC resistance

Trends in the diagnosis and control of chicken coccidiosis

1. Basics in biology of chicken coccidia
2. Post mortem diagnosis of chicken coccidiosis
3. Recent techniques for diagnosis of chicken coccidiosis
4. Chemoprophylaxis and Immunoprophylaxis of chicken coccidiosis
5. Strategies to minimise the anticoccidial resistance in the commercial chicken farms

Thank you