Cyathostomin resistance to moxidectin - Dr Emma Alsop

It is well recognized that small strongyles (cyathostomins) are now the main parasitic pathogen in equines. Due to the use of anthelmintic strategies for the control of large strongyles, which has been extremely successful in reducing morbidity and mortality from this parasitic disease, selection of drug resistant cyathostomes has inadvertently occurred. There is a world wide increase in the reported levels of anthelmintic resistance, and of most concern is the resistance of the cyathostomins to macrocyclic lactones. There is already documented evidence of cyathostomin resistance to the benzimidazoles and pyrantel salts.

There is already reported evidence of reduced efficacy of moxidectin (a potent broad-spectrum endectocide of the macrocyclic lactone (macrolide) antimicrobial class) (Lyons et al 2010; Lyons et al 2011). Moxidectin resistant cyathostomins have also been reported in the UK (Trawford et al 2005). It is the authors own personal experience that there are now cases of moxidectin resistance in the Western Cape. Although this has not been proven on a large scale and is under further investigation, there are cases of a marked reduction in the egg reappearance period and complete failure of moxidectin to reduce fecal egg counts (FEC's). The author is sure that this is not a new thing, and surely not the first recognised incidents of moxidectin resistance in South Africa, but it does now need recognition from the equine veterinary profession. Strategies to slow down the selection for resistance, thereby extending the lifetime of currently effective anthelmintics, must be implemented whenever possible. A proactive approach must be taken involving the input of veterinarians into worming management and client education, if we are to expect chemical control of nematodes to be a viable option for the future. We, as a veterinary profession, must change our approach, take back control over parasite control programs and guide and educate our clients to change their approach, faster than the cyathostomins are changing their genotype.

Here are two tabulated case examples of evidence of cyathostome resistance to moxidectin. Certain assumptions have been made - including that all strongyle eggs seen on McMaster flotation were cyathostomin eggs.

Case one had been previously wormed with fenbendazole and ivermectin, with a failure in reducing the FEC.

All drugs were given at the following recommended doses for the cases below:

Moxidectin 0.4mg/kg per os
Praziquantel 2.5mg/kg per os
Fenbendazole 10mg/kg per os for 5 days

Case	1	2
Date	27 March 2014	
Initial FEC	4100	500
Initial treatment	Moxidectin and praziquantel	
Initial treatment date	10 April 2014	
Follow up FEC	900	1800
Follow up treatment	Moxidectin and praziquantel	
Follow up treatment date	20 April 2014	
Follow up 2 FEC	1000	700
Follow up 2 treatment	Moxidectin, praziquantel, 01.mg/kg dexamethasone iv	5 days fenbendazole 10mg/kg
Follow up 2 treatment date	6 May 2014	
Follow up 3 FEC	2400	0
Follow up 3 Treatment	???	

There are flaws in these case examples such as small case numbers and not differentiating the strongyle eggs seen, but the author feels that they do genuinely represent cyathostome resistance to moxidectin, which requires veterinary thought and attention.

It has been suggested that the criteria used to define anthelmintic resistance are that FEC's should be reduced by 95% after the administration of a macrocyclic lactone or benzimidazole, and 90% after administration of pyrantel, at 10-14 days post treatment (Dargatz et al 2000).

In case 2, moxidectin and praziquantel were repeated even though the FEC had increased in the face of using these drugs. This was in case there had been poor owner

Strongyle eggs: Dr. Dietrich Barth Merck Veterinary Manual

Cyathostomin resistance to moxidectin continued

compliance. The dose administered on 10/04 was done by the author. A FEC reduction of only 39% was achieved. A larvicidal course of fenbendazole resulted in a FEC of zero.

The author also has had many cases of a reduced egg reappearance periods for moxidectin, which has been described at 13 weeks if resistance is not present (Mercier et al 2001).

References

Lyons, E.T., Tolliver, S.C., Collins, S.S., Ionita, M., Kuzmina, T.A. and Rossano, M. (2011) Field tests demonstrating reduced activity of ivermectin and moxidectin against small strongyles in horses on 14 farms in Central Kentucky in 2007-2009. Parasitol Res. 108, 355-60.

Lyons, E.T., Tolliver, S.C. and Collins, S.S. (2010) Reduced activity of moxidectin and ivermectin on small strongyles in young horses on a farm (BC) in Central Kentucky in two field tests with notes on variable counts of eggs per gram of feces (EPGs). Parasitol Res. 107(6):1495-8.

Trawford, A.F., Burden, F.A. and Hodgkinson, J. (2005) Suspected moxidectin resistance in cyathostomes in two donkey herds at The Donkey Sanctuary, UK. Proceedings of the 20th International Conference World Association for Advanced Veterinary Parasitology, New Zealand. P196.

Dargatz, D.A., Traub-Dargatz, J. L. and Sangster, N. C. (2000) Antimicrobic and anthelmintic resistance. Veterinary Clinics of North America: Equine Practice 16, 515-536.

Mercier, P., Chick, B., Alves-Branco, F. and White, C.R (2001) Comparative efficacy, persistent effect and treatment intervals of anthelmintic pastes in naturally infected horses. Vet Parasitol. 99, 29-39.

African horse sickness outbreak resolved

The African horse sickness (AHS) serotype 1 outbreak was resolved on the 17th June 2014 just over 3 months after the initial veterinary control notice was released as a result of positive cases detected in the Porterville region of the Western Cape AHS Protection Zone. The outbreak was initially limited to the AHS protection zone but further cases eventually spread to the AHS surveillance zone. The initial containment zone was amended twice and eventually included the Porterville, Wellington, Piketberg and Tulbagh regions.

AHS cases in Robertson were detected in early April 2014 and during the outbreak this was treated as a separate event given the distance from Porterville and no proof of spread of infection via the movement of infected horses. We later however merged the two areas to include all cases under the same outbreak. Although the movement link between the two main areas of cases could not be made the clinical signs (or lack thereof), low mortality and low morbidity has been similar throughout.

In total there were 36 affected properties. We had 96 confirmed cases. To give an indication of the lack of clinical signs associated with this outbreak: the total number of deaths came to 12 giving a case fatality rate of 12.5%. The total number of sub-clinical cases made up 60 of the 96 cases, showing a sub clinical rate of 62.5%. We are still evaluating our census data but even if we just look at the number of horses on the 36 positive farms (which totalled 866 horses); the morbidity rate was only 11%. In reality this number is going to drop significantly once our full census data is captured for the out-break areas. The above figures are not what we would expect from an AHS outbreak as normally the morbidity, mortality and case fatality rates are significantly higher.

Figure 1: The spatial spread of AHS cases for the serotype one outbreak of 2014 within the Province.

There were four other areas within the Province where AHS cases have also occurred this season: Leeu Gamka, Murraysburg, Beaufort West and Uniondale. These (all non-AHS serotype 1) cases are not linked to the Protection and Surveillance zone cases.
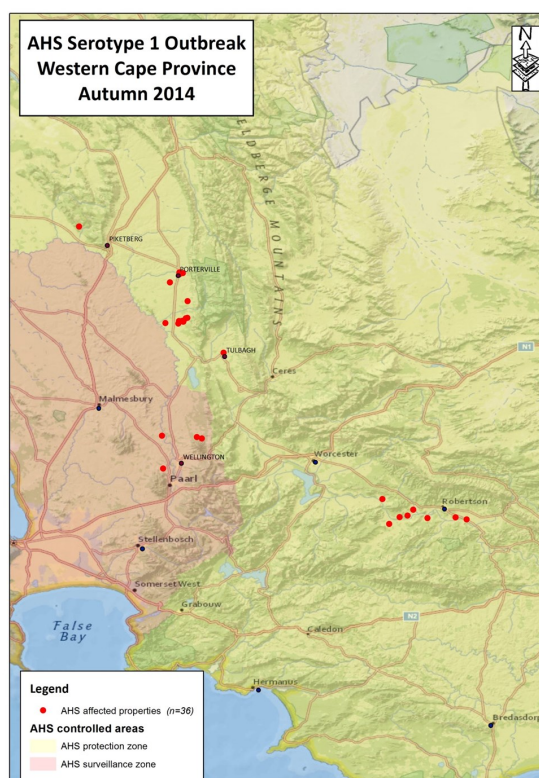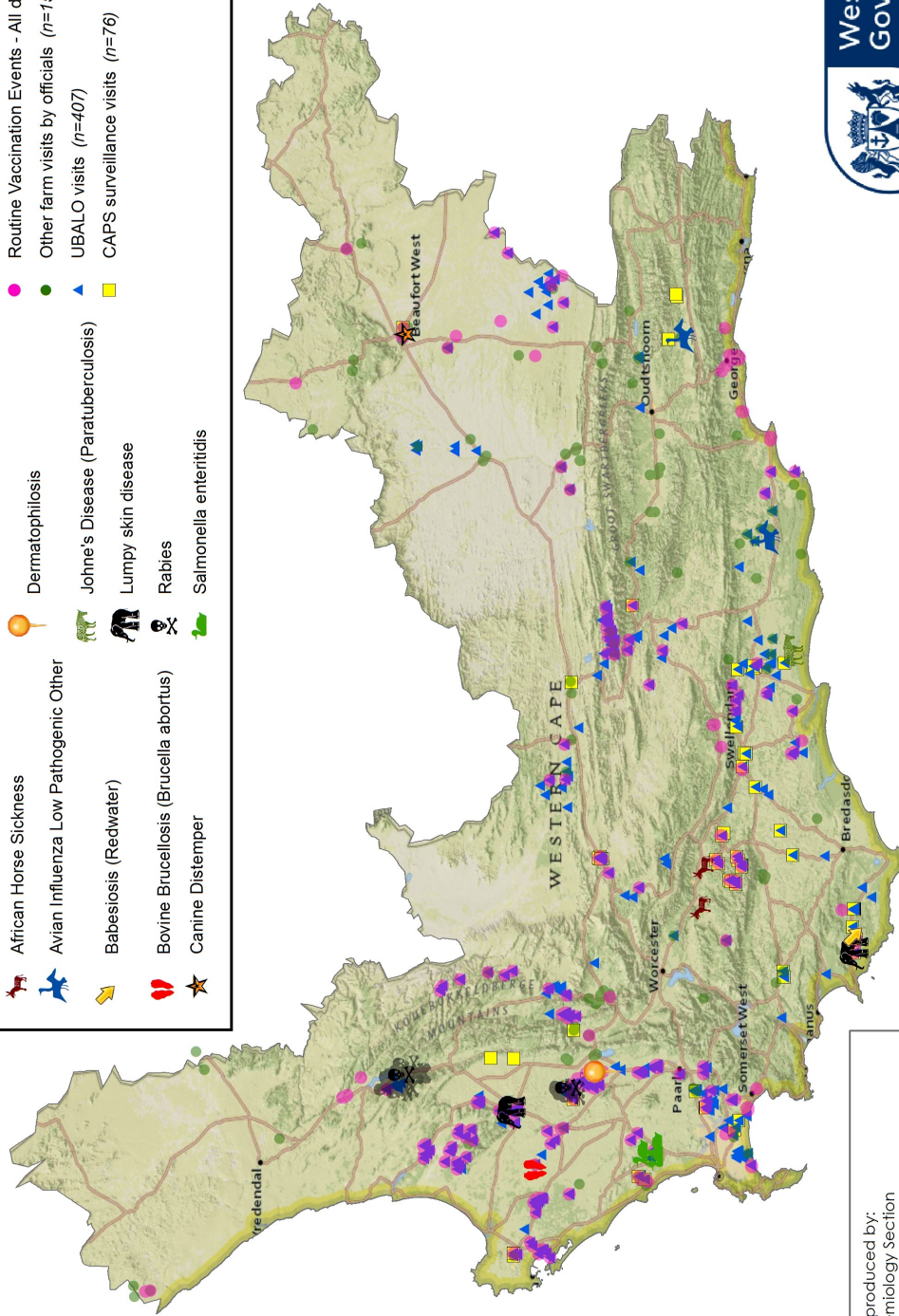
Surveillance & Disease - June 2014

Legend (Outbreaks in bold, follow up transparant)

- African Horse Sickness
- Avian Influenza Low Pathogenic Other
- Babesiosis (Redwater)
- Bovine Brucellosis (Brucella abortus)
- Canine Distemper
- Dermatophilosis
- Johne's Disease (Paratuberculosis)
- Lumpy skin disease
- Rabies
- Salmonella enteritidis

- Routine Vaccination Events - All diseases *(n=515)*
- Other farm visits by officials *(n=156)*
- UBALO visits *(n=407)*
- CAPS surveillance visits *(n=76)*

Beaufort West
Oudtshoorn
George
WESTERN CAPE
Swellendam
Bredasdorp
Worcester
Somerset West
Paarl
Hermanus
Clanwilliam
KOUEBOKKEVELDBERGE MOUNTAINS

0   50   100   200   300
Kilometers

Western Cape Government
Agriculture

Map produced by:
Epidemiology Section
Veterinary Services
Western Cape Department of Agriculture
REPUBLIC OF SOUTH AFRICA

Outbreak events

- Two outbreaks of **lumpy skin disease** were reported: one in **Piketberg**, confirmed by a private veterinarian and the other in **Gansbaai**, where the farmer reported seeing only swelling of the joints without characteristic lumps.

- A serologically positive **H5 avian influenza ostrich** farm was identified in the **Oudtshoorn** area while a confirmed **H7N7 low pathogenic avian influenza** (again in ostriches) was identified in the **Albertinia** region after testing was performed surrounding the H5 case there.

- Two cases of **rabies** occurred in **bat-eared foxes** near **Clanwilliam** and **Piketberg**. Both foxes showed abnormal behaviour: one approaching the farmyard and attacking the farmer's vehicle, and the other appearing tame in a field in the middle of the day. Both foxes were killed on the farms without any human or animal contact.

- A sheep farm in the **Heidelberg** area was confirmed positive for **Johne's disease** after emaciation was seen in the ewes. The farm was placed under quarantine.

- Three broiler farms in the **Malmesbury** area tested positive for *Salmonella enteritidis*

  ⇒ Positive environmental swabs after broilers had already been slaughtered
  ⇒ Positive sampling from carcasses at the abattoir
  ⇒ Positive environmental swabs before slaughter: the infected house was processed last and carcasses sent to the frozen product line.

- A **bovine brucellosis** positive farm near **Moorreesburg** was identified after trace-forward of sales from a positive farm was performed. Another positive farm that had also bought cattle from the original positive farm was completely slaughtered out during June.

- A suspected case of **sheep scab** was investigated by the **Malmesbury** SV office. The case turned out to be one of dermatophilosis.
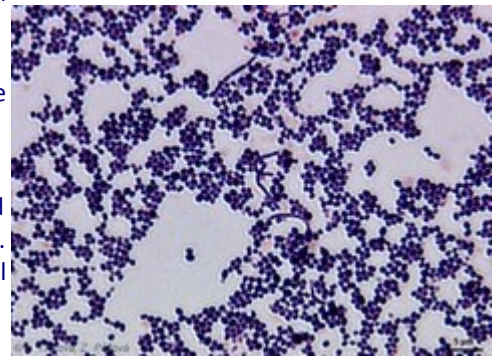
Dermatophilosis congolensis organisms

Total OIE logs

State Vet area	User	Total Logs
SV Malmesbury	michaelc	92
SV Malmesbury	hendrikh	78
SV Vredendal	irmis	51
SV Beaufort Wes	nitav	49
SV Malmesbury	elmienc	46
SV Malmesbury	janicac	43

Total UBALO logs

User	Total events
nitav	44
hendrikh	43
michaelc	42
maresaf	32
wynandf	30
janicac	25

Most rabies vaccinations performed

State Vet area	User	Total
SV George	eddiel	2304
SV George	Flipk	2277
SV George	carell	1681
SV George	ronniek	1539
SV George	Heidia	1444
SV George	johanb	1134

Web based event logging AHT leader boards

Confidence interval - proportion

In this back page lab we are going to establish a confidence interval for a proportion. The background to this is that we are publishing a paper which describes the highly pathogenic avian influenza outbreak which occurred in the Klein Karoo in ostriches during 2011. One of our epidemiologic variables we want to include is a proportion of farms within our control area that ended up being positive. This will hopefully help future epidemiologists as a between farm prevalence is often used in working out a sampling frame for a surveillance strategy. To work out the proportion is very easy (positive farms divided by the population of farms at risk) However, in order to show how confident we are that our between farm prevalence is accurate we wish to add a 95% confidence interval into our proportion because we know that we sampled the majority of farms in the area and we believe our sample strategy was complete enough for an accurate estimate of between farm prevalence. The R code below is what we used to establish our 95% confidence interval of our between farm prevalence for high pathogenic avian influenza in the control zone we established in Oudtshoorn.

Epi Lab color code

Software/Packages/Add-ins required

Software/Packages/Add-ins recommended

Description text

R code to copy/paste into console

R code to copy/paste into console that needs adjustment to your personal workspace

Websites where you can download requirements

Lab #2 requirements

- R - http://cran.r-project.org/bin/windows/base/
- R Studio - www.rstudio.com/ide/download/desktop
- prevalence R package
- Internet connection
- JAGS - http://sourceforge.net/projects/mcmc-jags/

The code

```
#remember that you can just copy and paste the blue lines of data into your R Studio console
#we import the dataset which is a list of farms, their intermediate disease status and their final status based on whether
#they were within the control area we were evaluating. In the dataset I have omitted the column names to illustrate how
#to allocate column names to a dataset. Below we import the dataset and allocate it to a variable called x.
x <- read.csv('http://www.jdata.co.za/backpagelabs/backpagelabs_jdg_ci.txt', header=F)
#set the column names - first column is a reference number per farm, intermediate is the TRUE/FALSE status of disease
#and final status is the disease status of only those farms in our control area
colnames(x)<-c("Ref","Intermediate","FinalStatus")
#now view the top and bottom 6 rows of data in the x variable we have allocated the data to
head(x)
tail(x)
#note that the last two farms, while positive were no in our control area, so now we must exclude them from our analysis
#we use the na.omit function for this purpose and we make a new data set called finalstatuslist
#PLEASE NOTE - the way this seems to work well in R is if the empty data is represented in your source data as NA (not N/A
#or by a blank entry)
finalstatuslist<-na.omit(x$FinalStatus)
#lets see how many rows of data were in our original imported set - should be 248 farms
summary(x)
#now we look at how many rows are in our data where NA has been omitted - should be 246 farms
length(finalstatuslist); summary(finalstatuslist)
#for the denominator for prevalence we need the population at risk (PAR) so lets make this variable
PAR<-length(finalstatuslist)
PAR
```
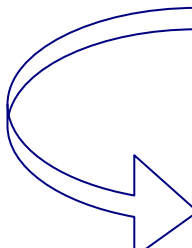
```
#so our total population at risk is 246 farms
#now we need the number of positive farms for our numerator data
POS<-sum(finalstatuslist == "Positive")
#this code essentially sums the events that are Positive (each positive is taken as 1) in our final data set
POS
#so our number of Positive farms totals 40
#a basic prevalence is therefore calculated by:
POS/PAR
# now what this lab is for - the 95% confidence interval. An easy (there are others) way of getting confidence interval
#data for a proportion is by using a function propCI from a package called "prevalence"
#note that this requires the "prevalence" package but also you'll need to install a program called JAGS from the internet
#install it from the website listed under LAB REQUIREMENTS.
#if you haven't installed the prevalence package yet then type this into your R console
install.packages("prevalence")
#now to load the newly installed package
library(prevalence)
#Now for working out the confidence interval - we use the function propCI
propCI(x=POS,n=PAR)
# Here the positive total is the POS data variable we made, the total sampled is the PAR data variable. So you'll see that
#5 different CI's are given. We wont go into it here but they all have differing reasons for being used. Because our
#sample size is relatively big the different CI methods have very similar CI's of between 11.64% and 21.47%.
#for our research we would use the WALD method so I will be using the 4th row of information
#lets try to isolate the row of info we will be using
propCI(x=POS,n=PAR)[4,]
#in summary - x = 40 and is our positive farms, n = 246 and is our population at risk, p = prevalence of 0.1626 (so
16.26%) with a CI of between 0.1164 (so 11.6%) and 20.87%.Our confidence interval confidence level is 95% which is a
standard but it can be changed if you wish
#for our publication we will say that the between farm prevalence of highly pathogenic avian influenza within the
controlled area was 16.26% (95 Conf: 11.6%-20.87%)
```

The output

```
      x   n         p        method level    lower     upper
1 40 246 0.1626016 agresti.coull  0.95 0.1214537 0.2141249
2 40 246 0.1626016         exact  0.95 0.1187775 0.2147668
3 40 246 0.1626016      jeffreys  0.95 0.1205557 0.2125299
4 40 246 0.1626016          wald  0.95 0.1164901 0.2087131
5 40 246 0.1626016        wilson  0.95 0.1217406 0.2138381


      x   n         p method level     lower     upper
4 40 246 0.1626016   wald  0.95 0.1164901 0.2087131
```

Citations

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/

Brecht Devleesschauwer, Paul Torgerson, Johannes Charlier, Bruno Levecke, Nicolas Praet, Pierre Dorny, Dirk Berkvens and Niko Speybroeck (2013). prevalence: Tools for prevalence assessment studies. R package version 0.2.0. http://cran.r-project.org/package=prevalence