Describing differential dairy herd antimicrobial usage patterns in Southwest England using novel means of farm characterisation

Elliot Stanton, Andrew Dowsey, Kristen Reyher

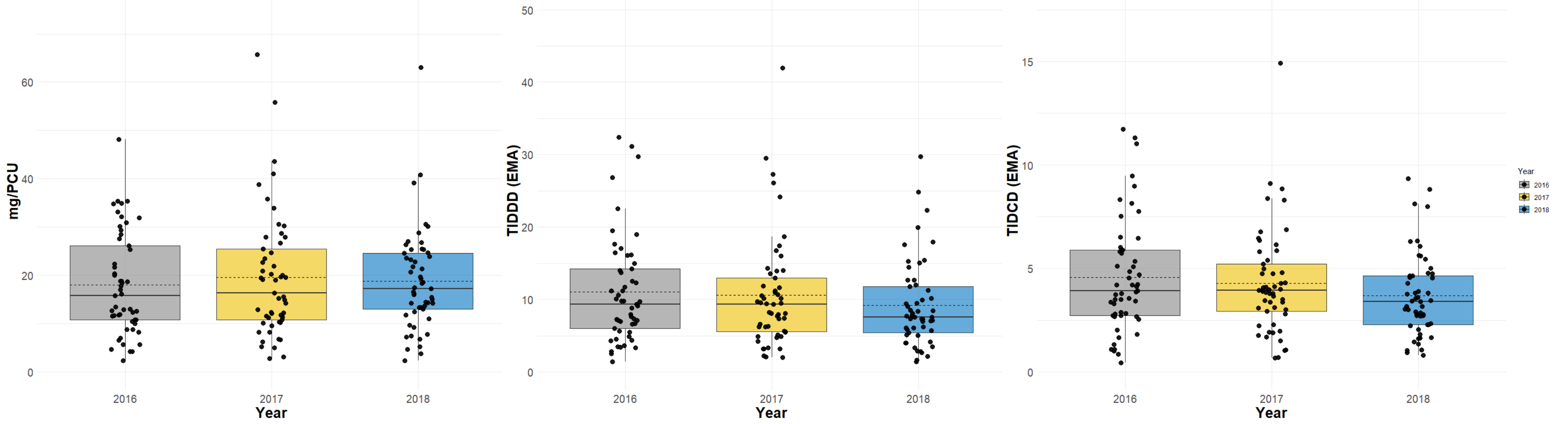
- Understanding how different farm **typologies** use antimicrobials (AMs), provides **intervention targets**.
- Farms can be **grouped** according to combinations of characteristics using **factor analysis of mixed data** and **hierarchical clustering**.
- **Intensive farms** on average use more antimicrobials than **extensive farms**, with different antimicrobial usage (AMU) dynamics dependent on a typology's characteristics.

Introduction: rationale

- There exists a substantial amount of heterogeneity in inter-farm antimicrobial usage (AMU).

Treatment incidence defined daily doses (TIDDD) (EMA): Average number of EMA defined daily doses administered per cow over 1000 days on a given farm.

Treatment incidence defined course doses (TIDCD) (EMA): Average number of EMA defined course doses administered per cow over 1000 days on a given farm.

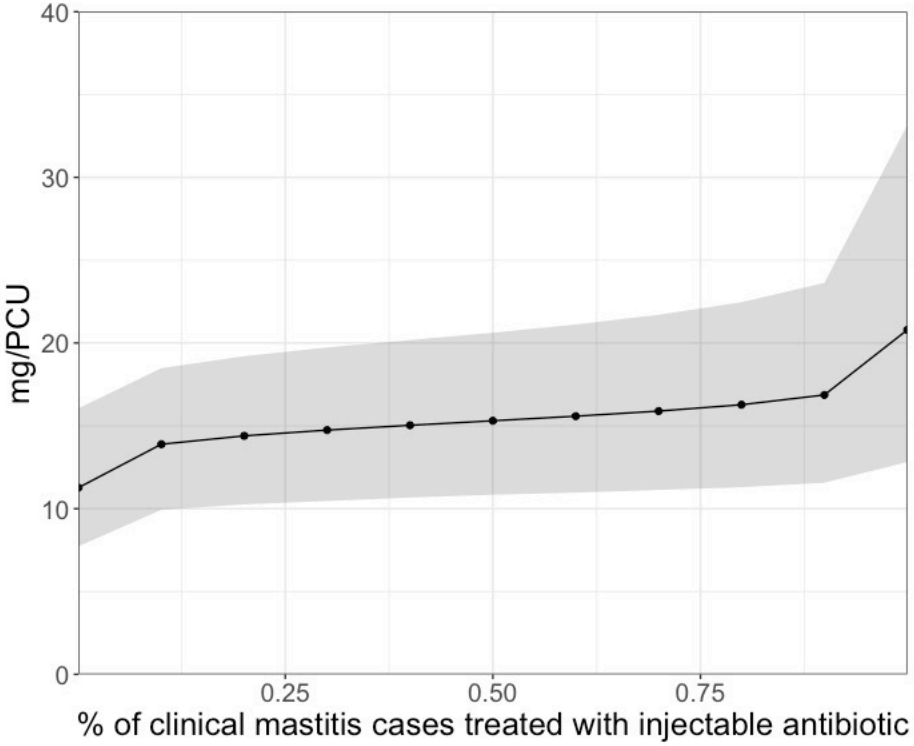


median mean

Introduction: rationale

Predictor		Coefficient Estimate			% Change in mg/PCU AMU		
			95 % CIs			95 % CIs	
	Change	Mean	2.50%	97.50%	Mean	2.50%	97.50%
% Of clinical mastitis cases treated with injectable antibiotic	10-30 %	1.062	1.003	1.119	6.13	0.34	11.89
	30-50 %	1.038	1.002	1.073	3.83	0.21	7.32
	50-70 %	1.038	1.002	1.073	3.83	0.21	7.32
	70-90 %	1.062	1.003	1.119	6.13	0.34	11.89

- By identifying risk factors associated with differential AMU patterns we could develop interventions to achieve AMU reductions.
- Previously we have applied Bayesian regression with a shrinkage prior.

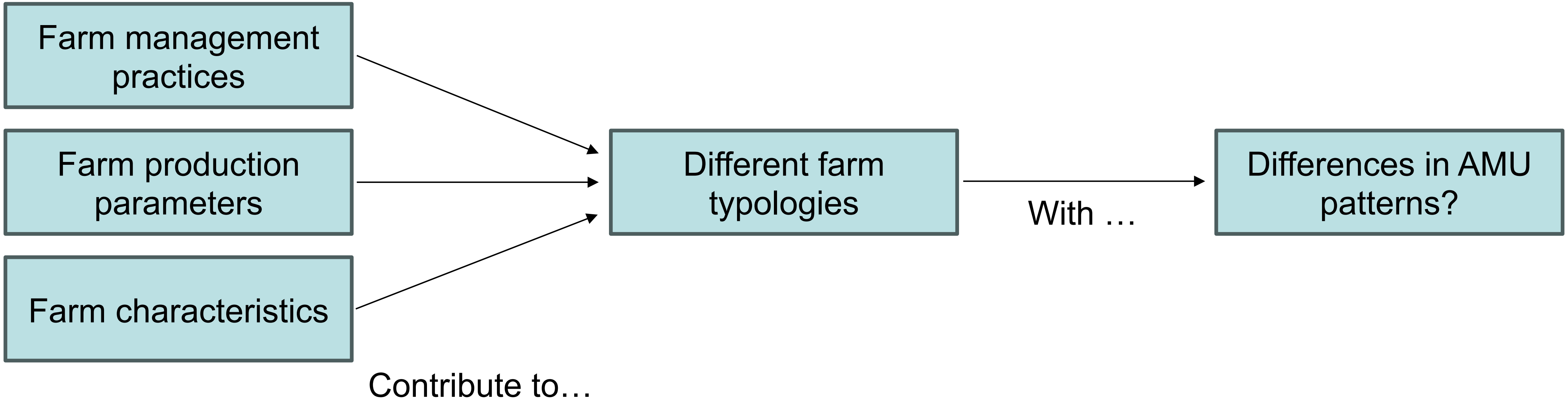


Introduction: rationale

- But farms are complex, and it seems likely that approaches aiming to identify “smoking gun” predictors may not accurately capture this complexity.

Aim: Can we use different dimensionality reducing methods to capture some of this complexity and group farms based on their overall similarity?

Aim: Do these different farm typologies exhibit differential AMU patterns?



Introduction: background

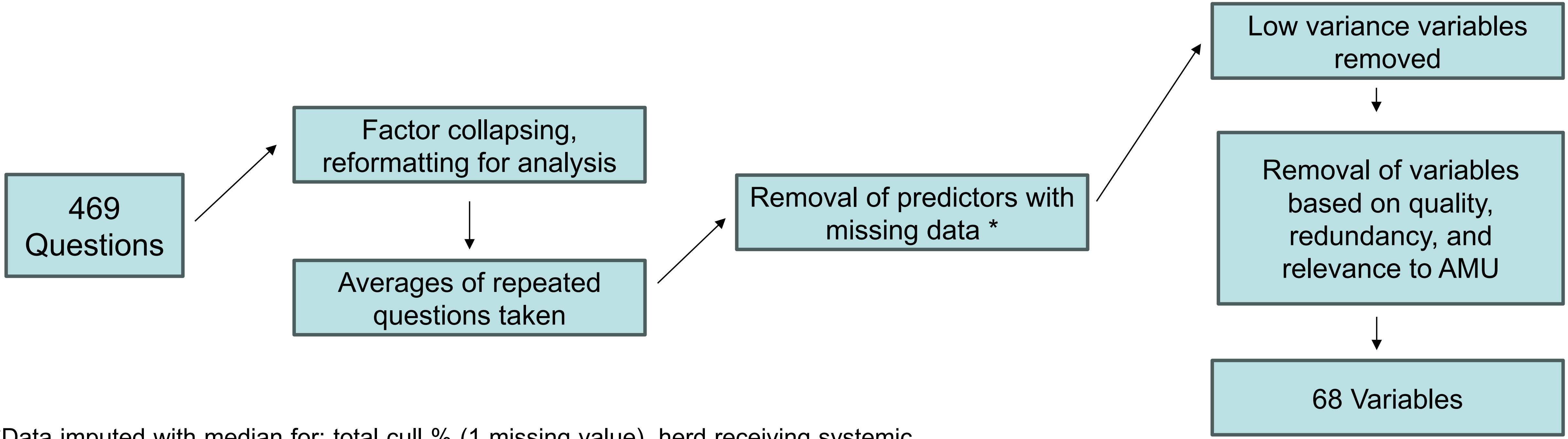
Reduced Antibacterial Drug Resistance and bla_{CTX-M} β-Lactamase Gene Carriage in Cattle-Associated *Escherichia coli* at Low Temperatures, at Sites Dominated by Older Animals, and on Pastureland: Implications for Surveillance

Hannah Schubert,[a] Katy Morley,[a] Emma F. Puddy,[a,b] Robert Arbon,[c] Jacqueline Findlay,[b] Oliver Mounsey,[b] Virginia C. Gould,[a,b] Lucy Vass,[a,d] Madeleine Evans,[a] Gwen M. Rees,[a] David C. Barrett,[a] Katy M. Turner,[a] Tristan A. Cogan,[a] Matthew B. Avison,[b] and Kristen K. Reyher[a]

- Previous studies aimed to identify risk factors associated with the presence of AMR *E. coli* on and around **53 dairy farms** in the Southwest of England in the OH-STAR project.
- This study estimated farm-level AMU using antimicrobial sales records from farm vet practices, each farm has data between 2016 – 2018.
- Outcome here is the mean farm level annual AMU for this period.
- To test for predictors of sample level AMR, four farm management practice questionnaires were completed by farmers in the presence of researchers – 469 questions total, although some of these were duplicated questions.

Methods: questionnaire cleaning

- Questionnaire originally designed with AMR outcome in mind.

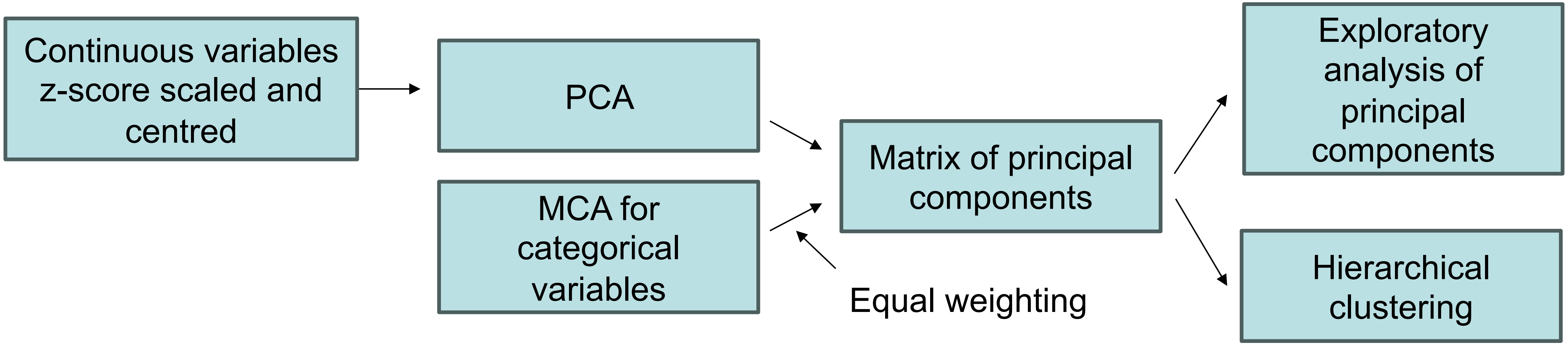


*Data imputed with median for: total cull % (1 missing value), herd receiving systemic AMs at dry off (2 missing values) and mastitis incidence rates (6 missing values).

Methods: Factor analysis of mixed data (FAMD)

- The 68 variables comprised 18 continuous and 50 categorical predictors.
- FAMD[1] was chosen to produce a principal component matrix owing to it retaining the data in their original form.

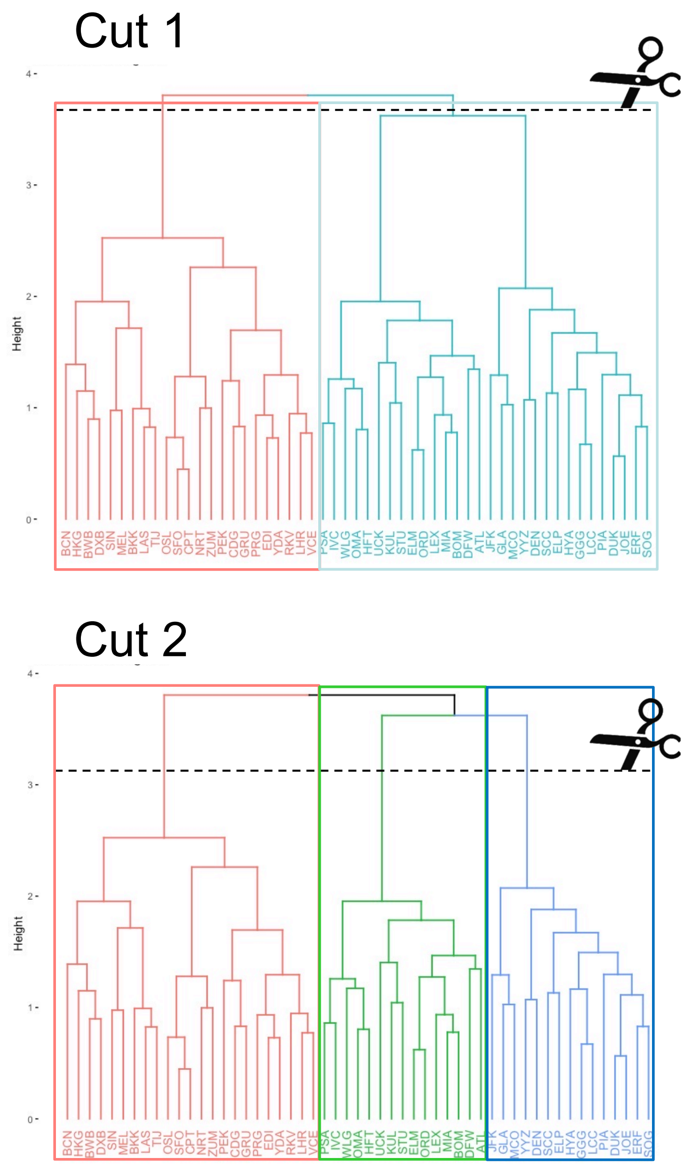
Generation of principal components from questionnaire data – naïve to estimated AMU



[1] Lê, S., Josse, J. & Husson, F. (2008). FactoMineR: An R Package for Multivariate Analysis. Journal of Statistical Software. 25(1). pp. 1-18.

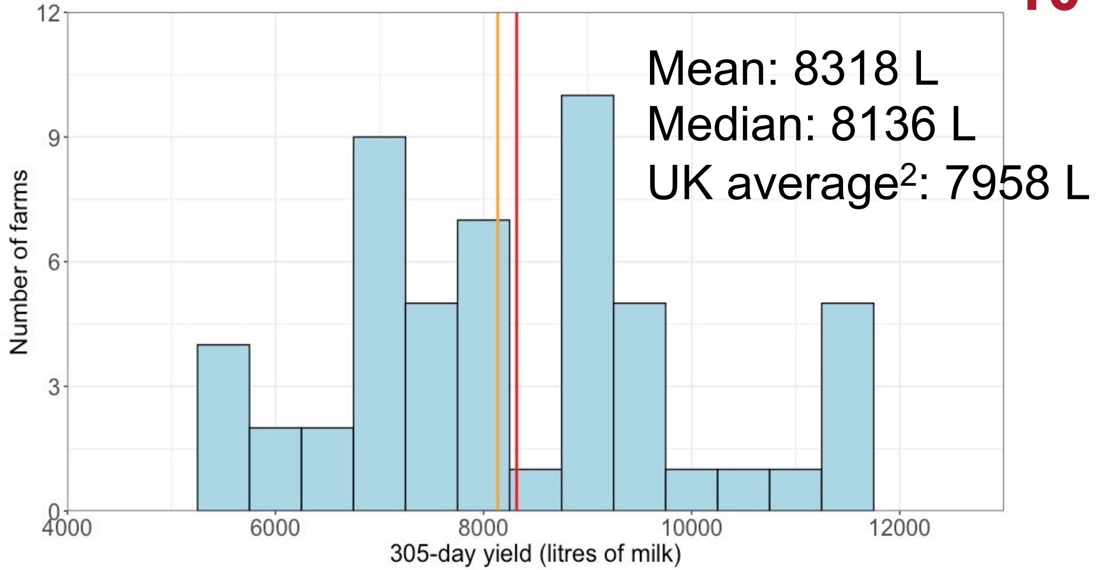
Methods: Hierarchical clustering on principal components (HCPC)

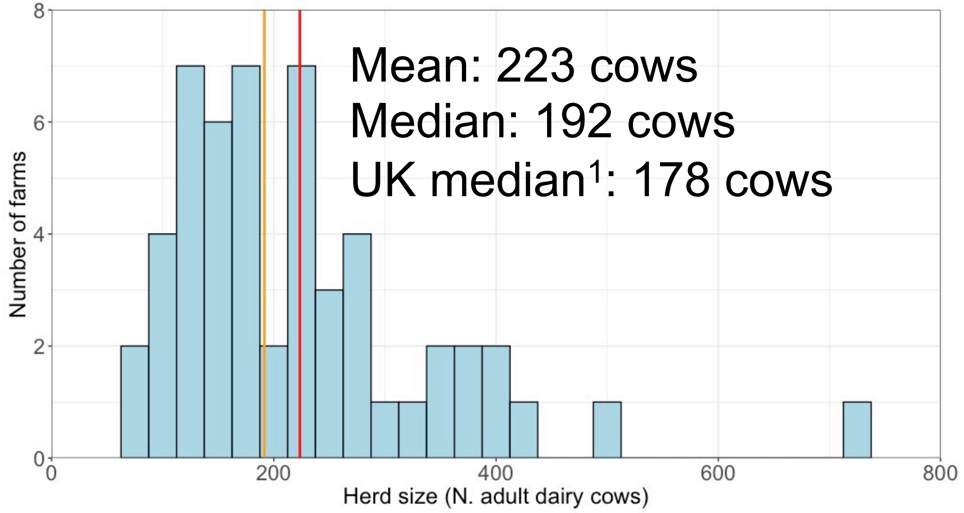
- Agglomerative HCPC (FactoMineR) was used to place farms into discrete partitions.
- Groupings aim to maximise within partition homogeneity and between group heterogeneity.
- Two – five partitions investigated by shifting the cut point towards the tips of the dendrogram to intersect an additional branch at each point, with 3 being suggested as the optimum number based on relative inertia loss.

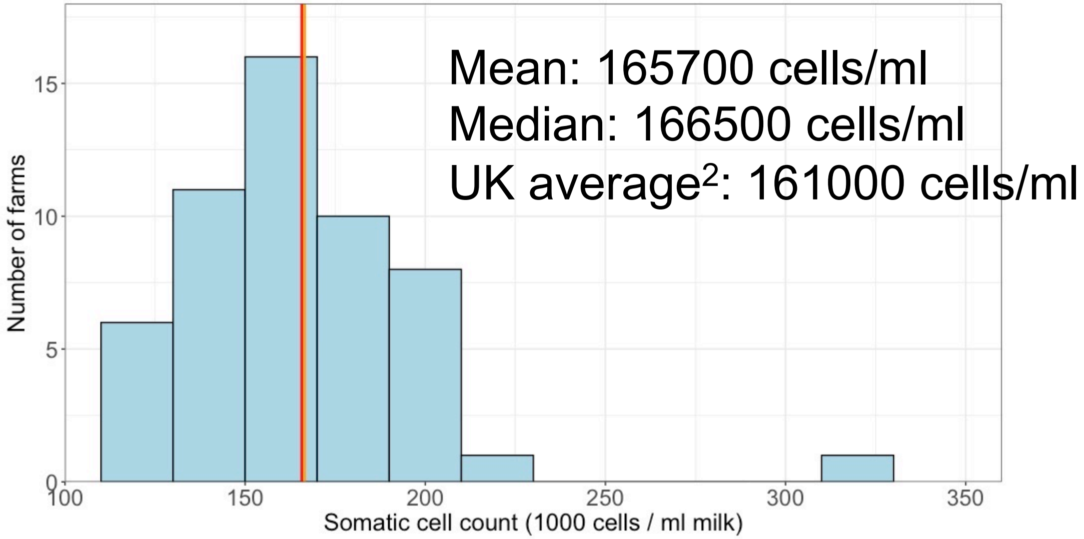


Results: farm characteristics

- Fifty-three farms, broadly similar to UK averages at the time of study.
- Three participating farms reported being organic operations.



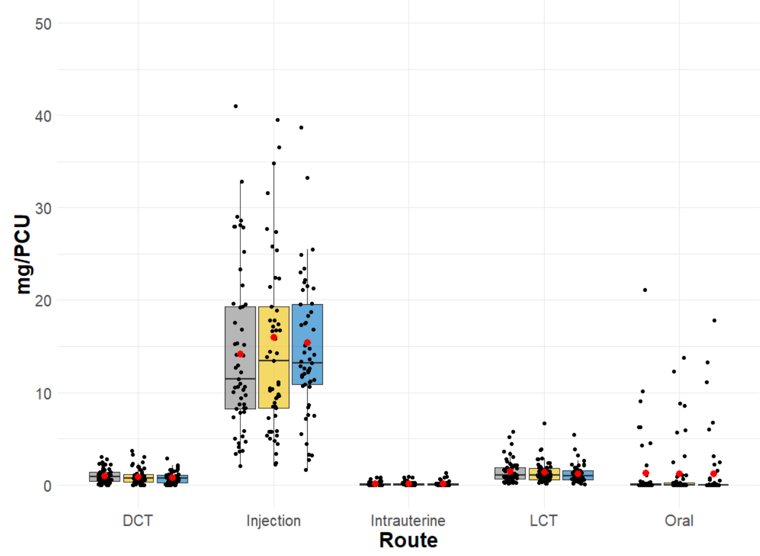


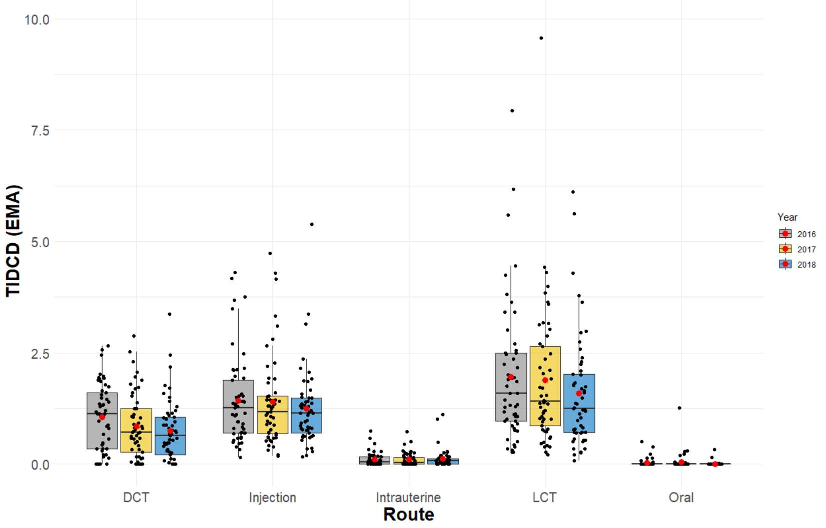


[1] Hanks & Kossaibati annual dairy KPIs 2018
[2] UK Animal Health Database

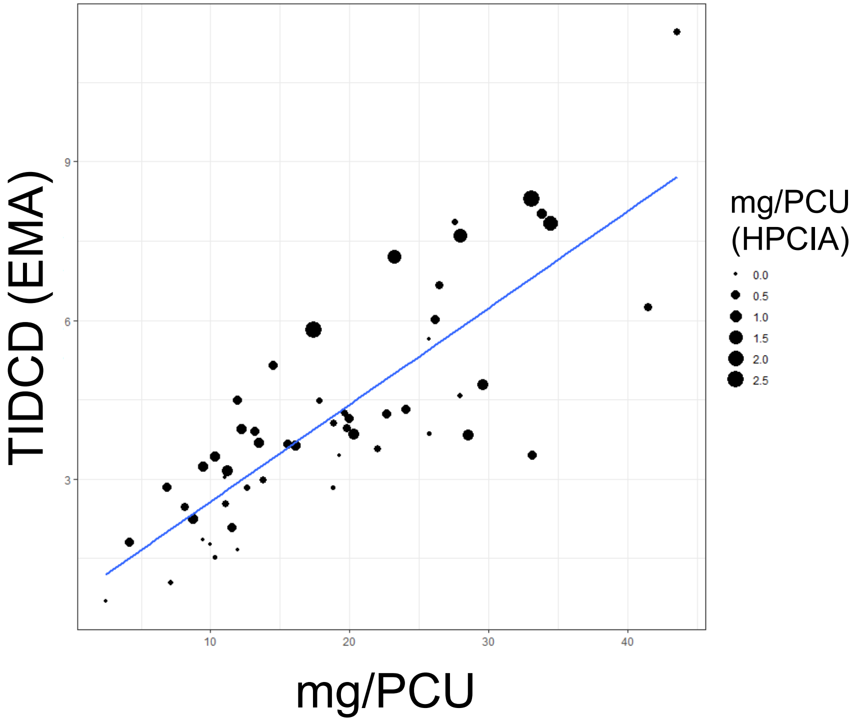
Results: metrics matter

- Reporting in multiple metrics can better highlight the biases of single metric AMU reporting.
- Agreement between metrics is generally good, although can breakdown when higher or lower volumes of higher priority (EMA category B) medicines are used.





● Mean



Spearman's correlation = 0.824, $p < 0.0001$

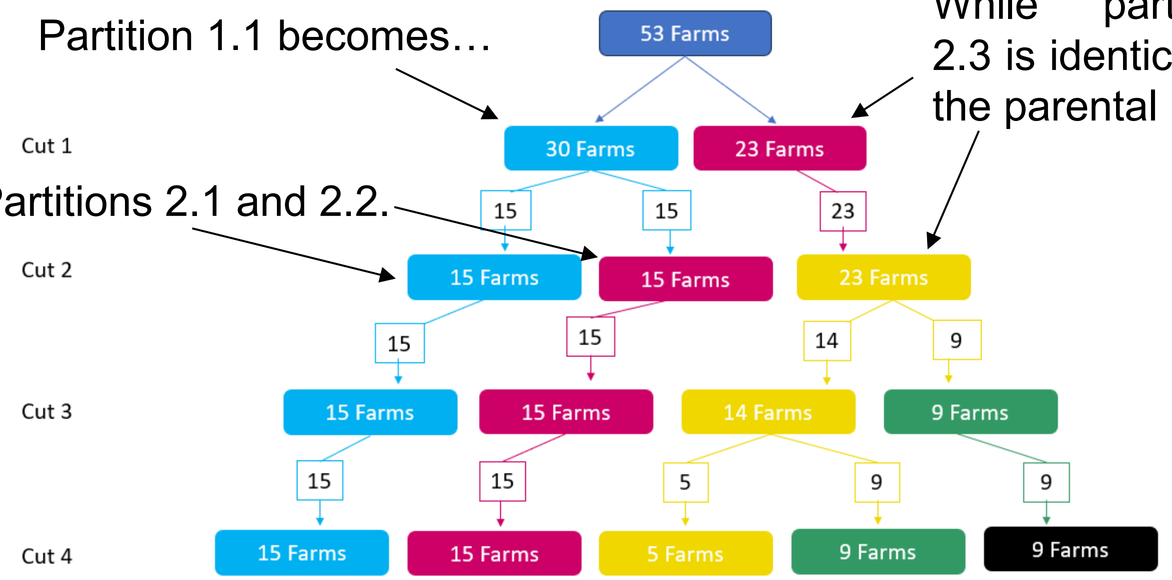
Results: HCPC overview

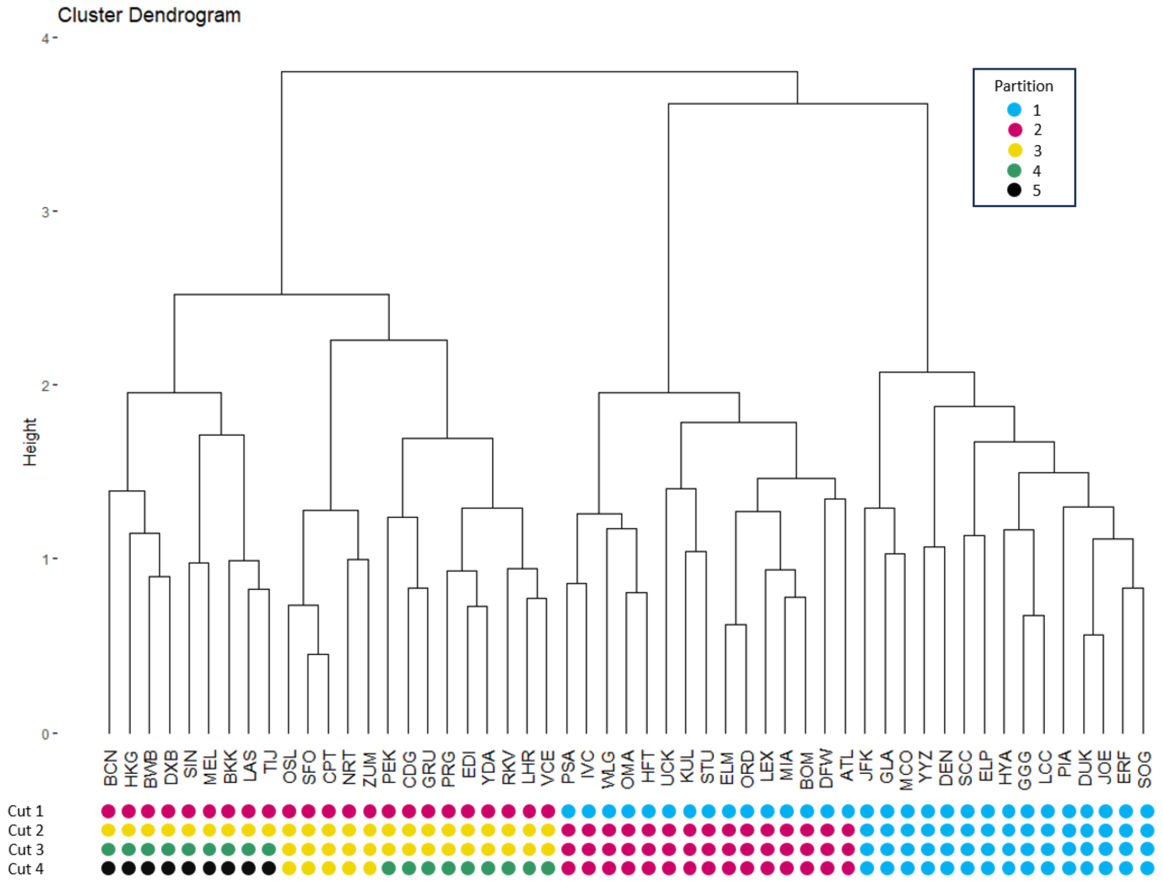
- Hierarchical nature of clustering means that at each cut an additional partition is created through the splitting of a previous partition.
- Cuts 1 and 2 discussed here.

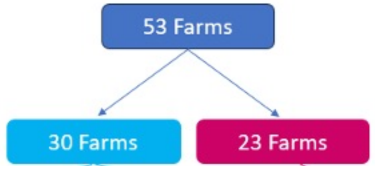
Partition 1.1 becomes…

Partitions 2.1 and 2.2.

While partition 2.3 is identical to the parental 1.2

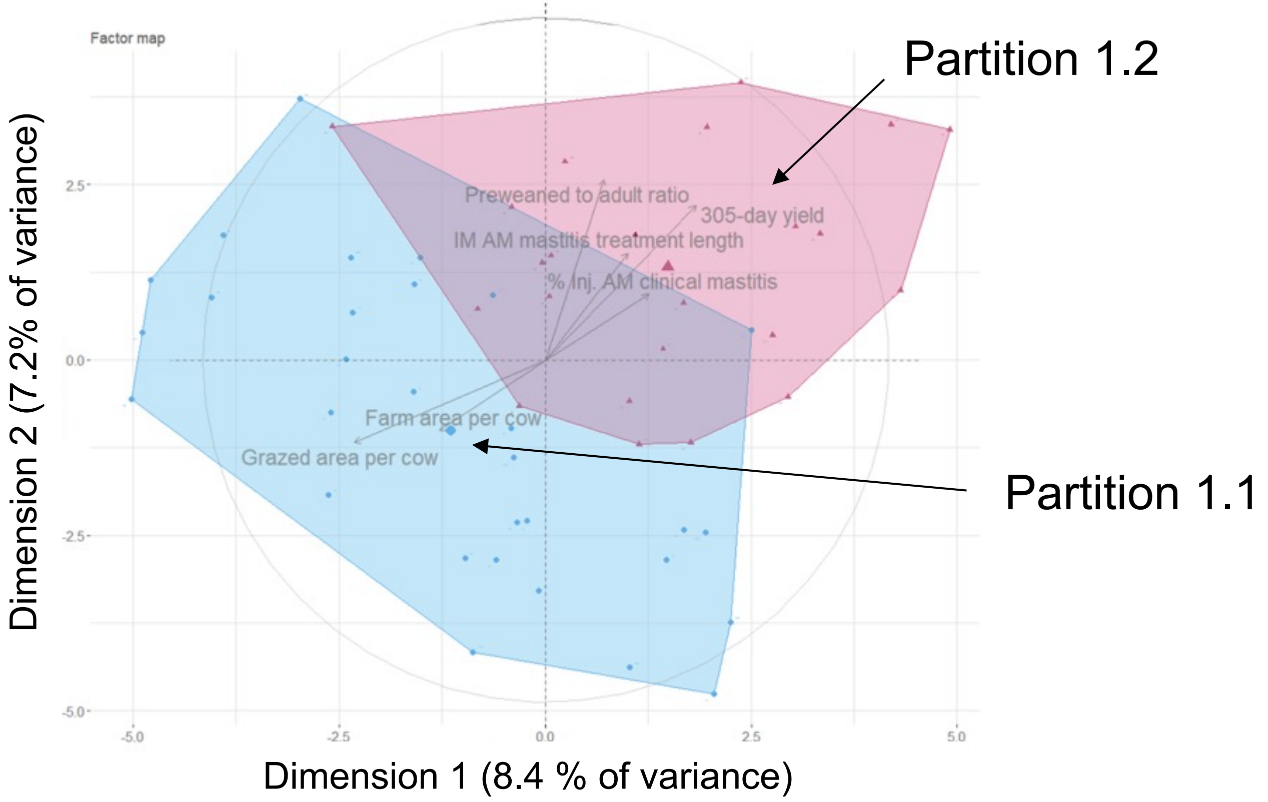






Results: Cut 1

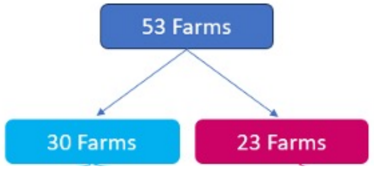
- First cut largely separated based on whether they were lower yielding, more extensive operations (1.1, n = 30, blue) or higher yielding, intensive operations (1.2, n = 23, red).



Variable	Overall Mean	1.1 Mean	1.2 Mean
Total grazed area per adult dairy cow (hectares / adult cow)	0.58	0.69	0.43
Total farm area per adult dairy cow (hectares / adult cow)	0.98	1.13	0.79
Percentage of clinical mastitis cases treated with injectable antibiotic*	23.93	17.76	35.09
Percentage of adult herd culled for reasons other than bovine TB*	22.48	20.80	24.67
Average length of mastitis treatment with 1st line intramammary antibiotics (days)	3.55	3.17	4.04
305-day milk yield (litres)	8318	7807	8984
Ratio of pre-weaned calves to adult dairy cows	0.071	0.056	0.091

*back transformed from logit space

Results: Cut 1



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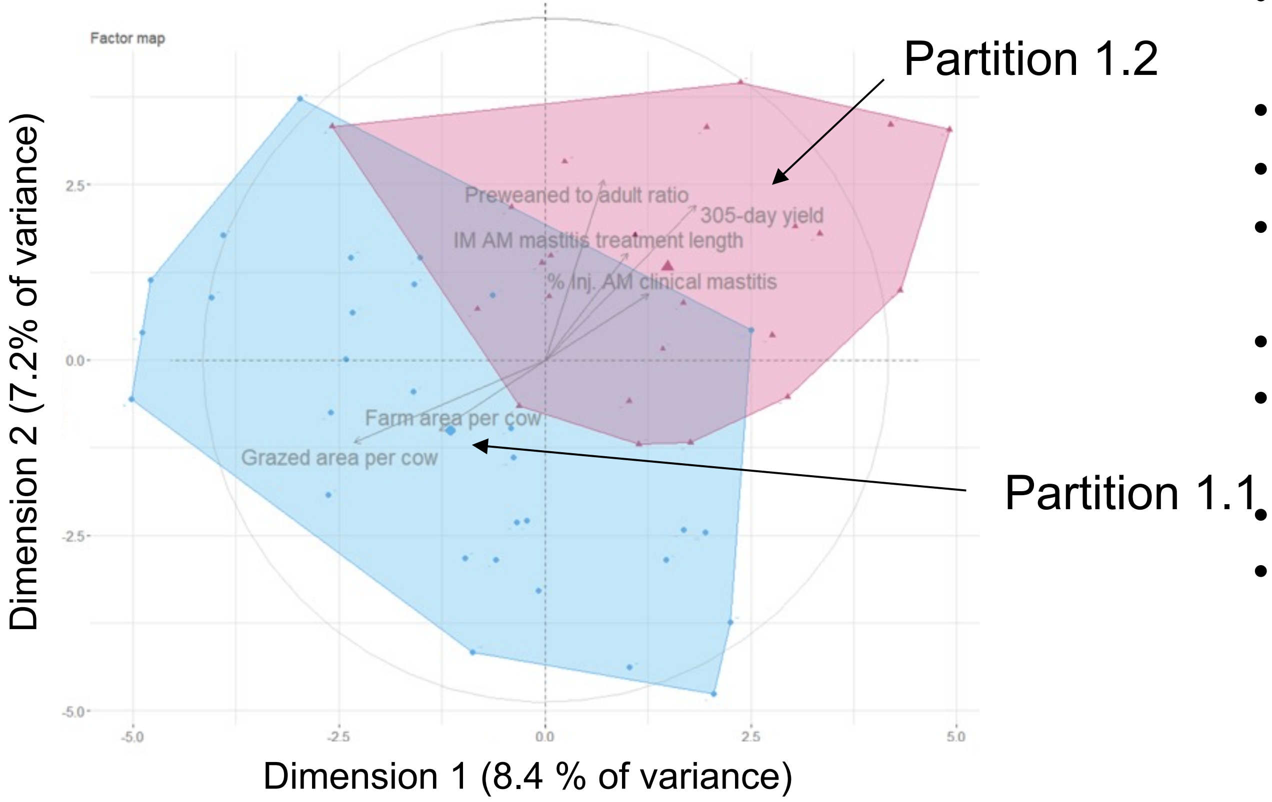
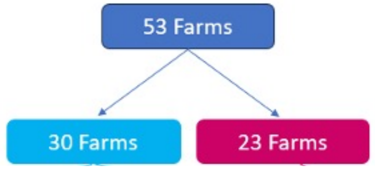


Farms in partition 1.1 More likely to:

- Allow grazing access for lactating animals.
- Use sand bedding for lactating animals.
- Use milk replacers.
- Routinely use footbaths for infectious lameness treatment.
- Fully Isolate incoming stock.
- Feed < 2 Litres of milk per feed for first weeks of a calf's live.
- Use natural service.
- Use injectable antibiotics (rather than topical) in the treatment of infectious lameness.



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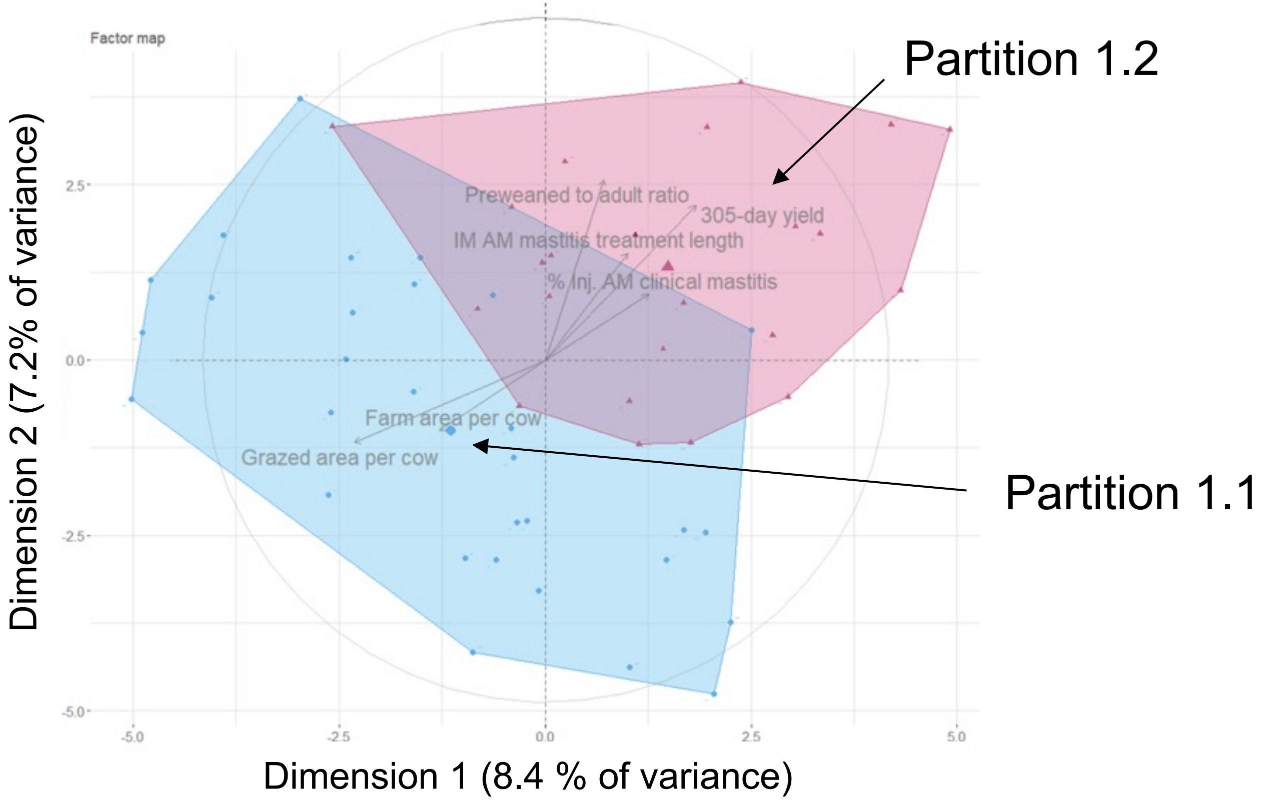
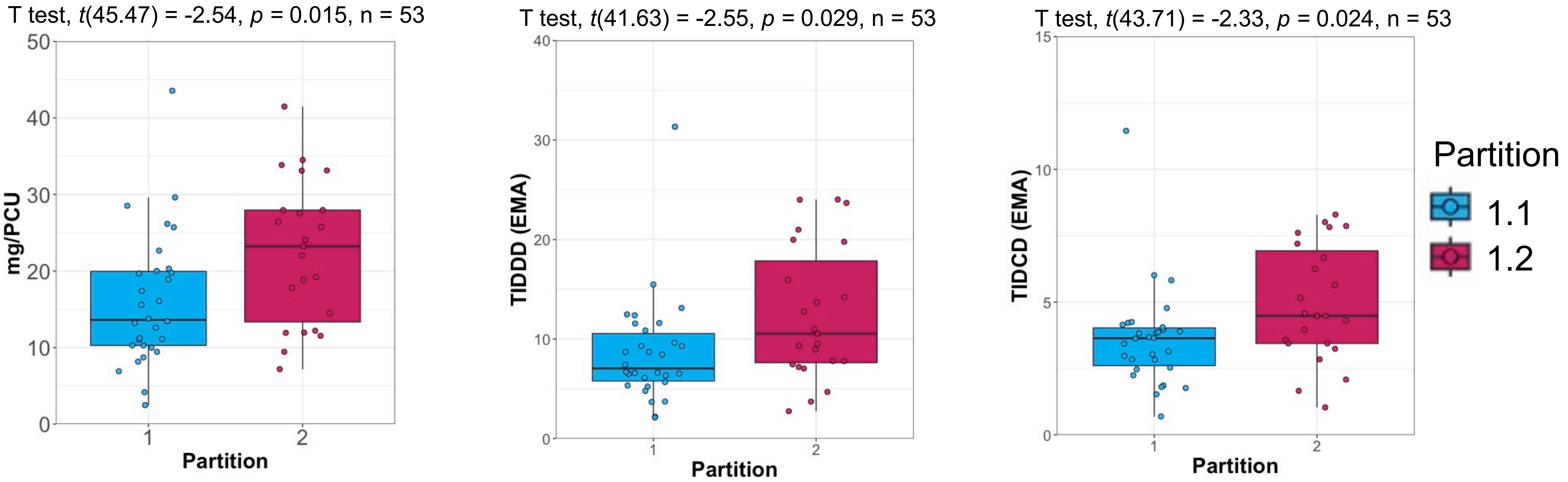


Farms in partition 1.2 More likely to:

- Remove calves from dams within 4 hours of birth.
- Use lime to clean housing areas.
- Use automatic manure scrapers.
- Preventatively administer anticoccidials.
- House calves individually.
- Have dirt flooring in at least some of the main calving area.

Results: Cut 1 AMU

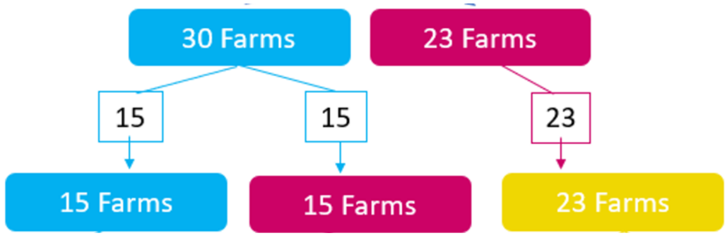


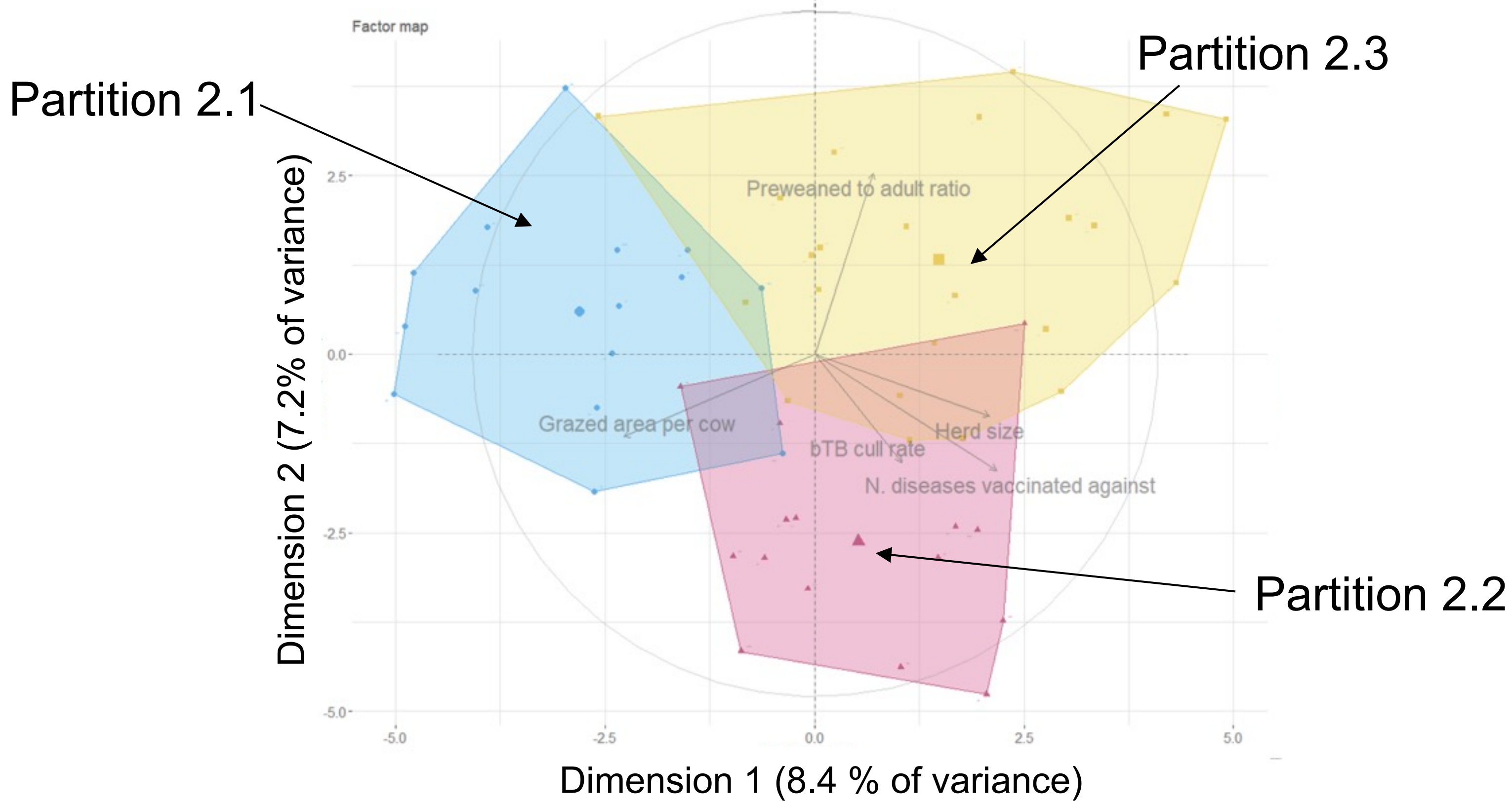
- Difference in AMU between partitions was explained by farms in partition 1.2 using significantly more EMA category D (prudence)* (lowest importance non-HPCIAs).
- While AMU in each route of administration (excluding oral medicines in the mg/PCU metric) was greatest in partition 1.2, the difference in AMU was greatest for injectable medicines.

In EMA categorisation scheme, active ingredient AMs are ranked from A – D based on the importance of resistance to these compounds to human health. Categories A and B can be considered HPCIAs, while C and D are non HPCIAs

Results: Cut 2

- Second cut splits partition 1.1 to form a group of extensive farms with small herds (2.1, n = 15, blue) and a group of farms with few youngstock and higher bTB cull rate (2.2, n = 15, red).





Variable	Overall Mean	2.1 Mean
Total grazed area per adult dairy cow (hectares / adult cow)	0.58	0.80
Percentage of adult herd culled due to bTB in the last year*	3.88	1.35
Average adult herd size	223	155
Number of diseases/pathogens routinely vaccinated against**	3.21	1.73

Variable	Overall Mean	2.2 Mean
Number of diseases/pathogens routinely vaccinated against**	3.21	4.53
Percentage of adult herd culled due to bTB in the last year*	3.88	5.73
Ratio of pre-weaned calves to adult dairy cows	0.071	0.042

*back transformed from logit space

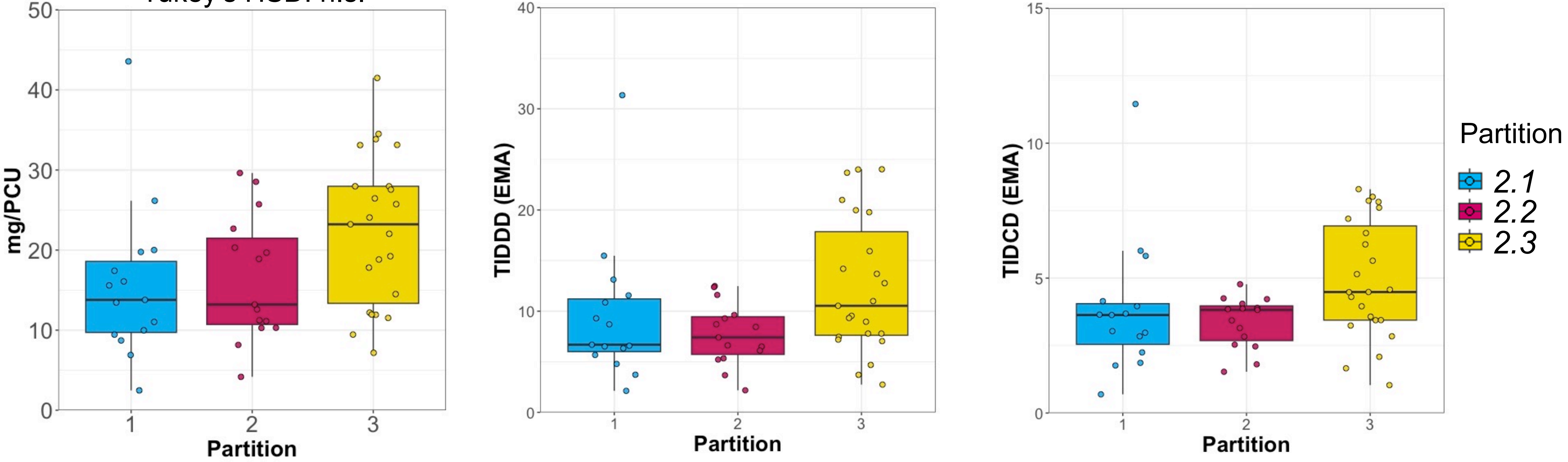
** Diseases/pathogens considered include bovine viral diarrhoea, infectious bovine rhinotracheitis, leptospirosis, Johnes, Salmonella, lungworm, clostridial disease, general diarrhoea, ringworm, and coronavirus

Results: Cut 2 AMU

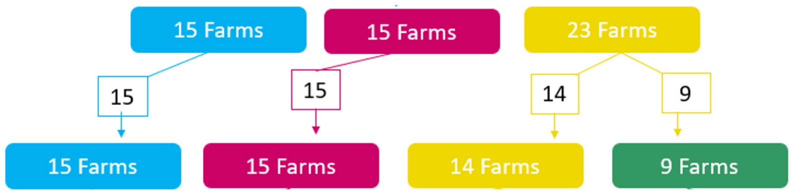
ANOVA $F(2, 50) = [3.26]$, *p 0.047*
Tukey's HSD: n.s.

ANOVA $F(2, 50) = [3.02]$, *p 0.058*

ANOVA $F(2, 50) = [3.00]$, *p 0.059*

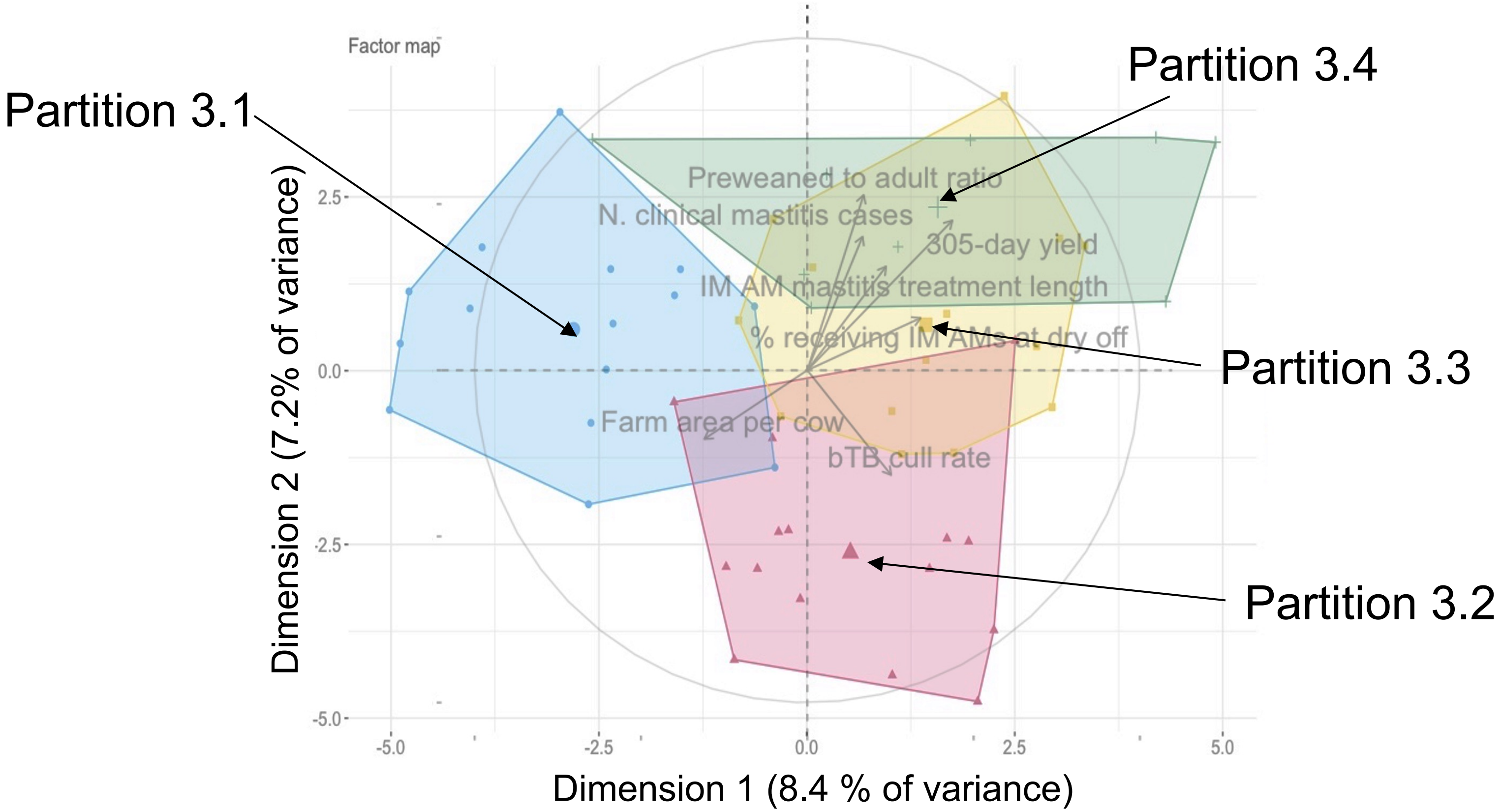


- AMU profiles of partitions 2.1 and 2.2 very similar overall, both remaining lower than partition 2.3.
- Suggests that the variance between farms in these partitions is not associated with different overall AMU profiles as was observed in cut 1.



Results: Cut 3

- Third cut separates the intensive partition 2.3 into farms treating more cows with IM AMs at dry off (3.3, n = 14, yellow) and the highest yielding farms with the highest incidences of mastitis (3.4, n = 9, green) .



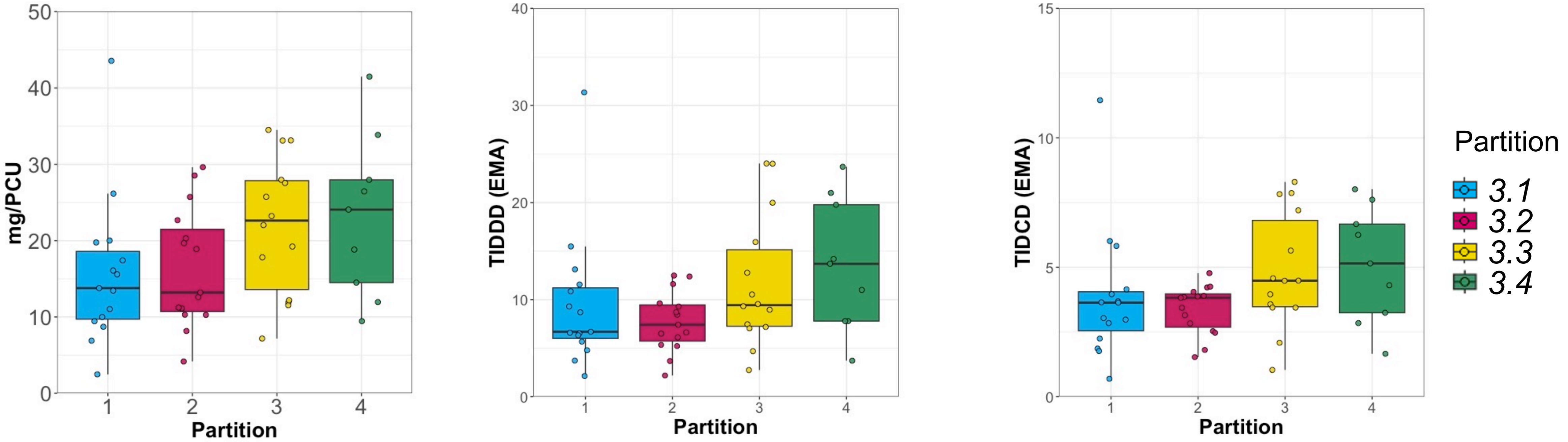
Variable	Overall Mean	3.3 Mean
Percentage of adult herd receiving IM AMs at dry off in the year prior to questionnaire completion.	55.59	71.56
Average length of mastitis treatment with 1st line intramammary antibiotics (days)	3.55	4.14
Total farm area per adult dairy cow (hectares / adult cow)	0.98	0.72

Variable	Overall Mean	3.4 Mean
Annual clinical mastitis cases / 100 cows	33.89	62.33
305-day milk yield	8317	9821
Ratio of pre-weaned calves to adult dairy cows	0.071	0.096
Percentage of adult herd culled due to bTB in the last year*	3.88	0.78

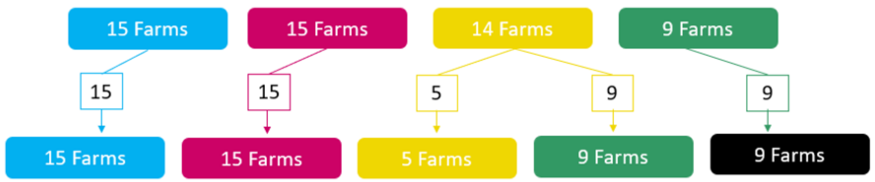
*back transformed from logit space

Results: Cut 3 AMU

ANOVA F (3, 49) = [2.14], *p 0.104* ANOVA F (3, 49) = [2.17], *p 0.103* ANOVA F (2, 49) = [1.99], *p 0.128*

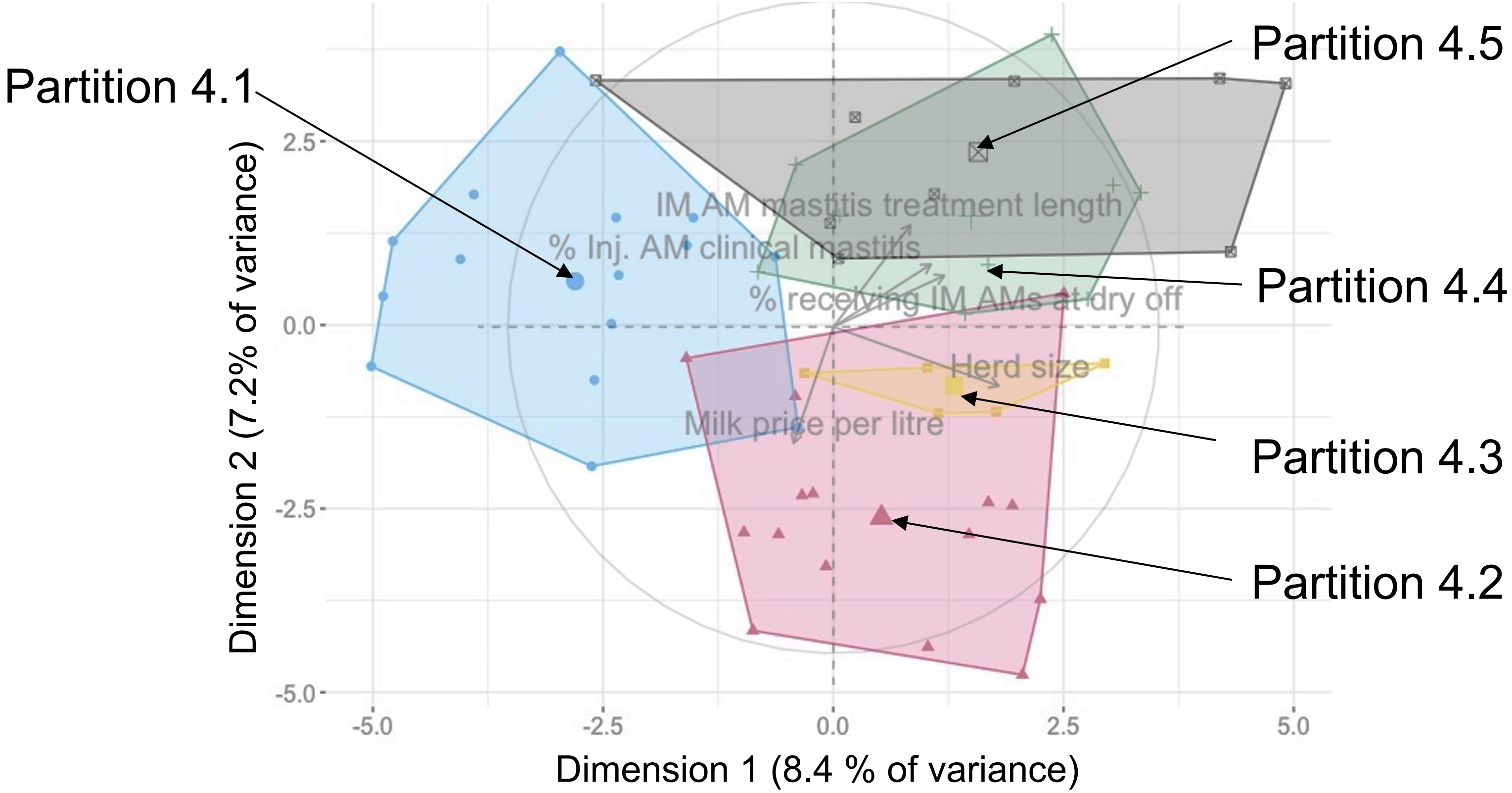


- Note the similarity in usage between partition 3.3 and 3.4 in the mg/PCU and TIDCD metrics, while TIDDD (EMA) usage for partition 3.3. appears lower than partition 3.4 – reflects increased reliance on DCTs for farms in partition 3.3.



Results: Cut 4

- Fourth cut separates the high DCT usage partition 3.3 into a group of large, seemingly commercially successful dairies charging more for their milk (3.3, n = 5, yellow) and a group of farms intensively using antimicrobials to treat mastitis (3.4, n = 9, green).



Variable	Overall Mean	4.3 Mean
Adult dairy herd size	223	388
Milk sale price (pence per litre)	27.79	32.20

Variable	Overall Mean	4.4 Mean
Percentage of adult herd receiving IM AMs at dry off in the year prior to questionnaire completion*	55.59	81.88
Average length of mastitis treatment with 1st line intramammary antibiotics (days)	3.55	4.55
Percentage of clinical mastitis cases treated with injectable antibiotic*	23.93	48.89

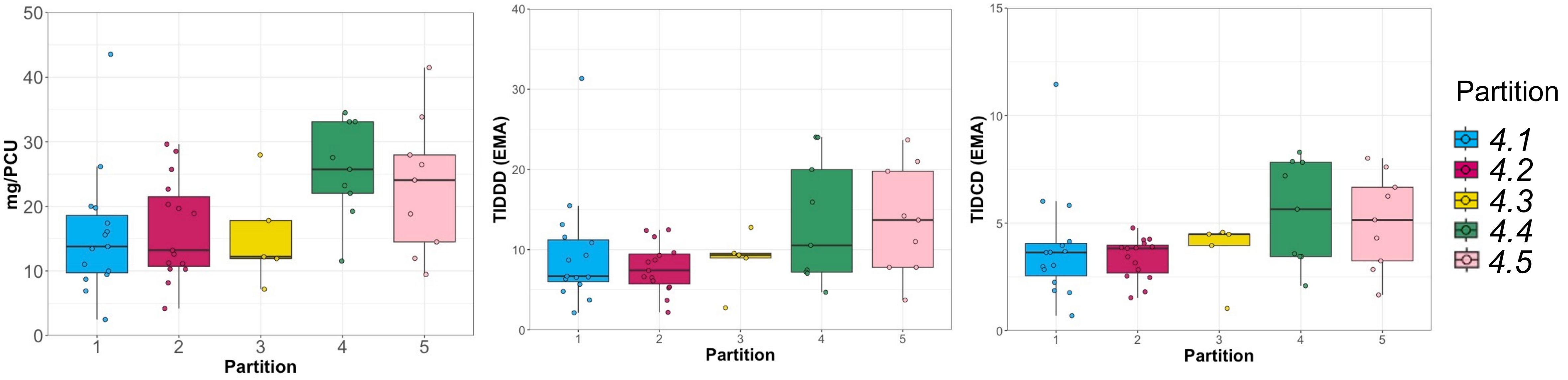
*back transformed from logit space

Results: Cut 3 AMU

ANOVA F (4, 48) = [2.78], *p 0.037*
Tukey's HSD: n.s.

ANOVA F (4, 48) = [2.17], *p 0.086*

ANOVA F (4, 48) = [2.16], *p 0.088*



- The 5 large, commercialised dairies placed in partition 4.3 from the parental 3.3 appear to have low overall AMU across metrics, in line with the smaller, extensive partitions 4.1 and 4.2.
- In contrast the group of farms heavily reliant on AMs to treat mastitis, partition 4.4, have high overall AMU, especially in the mg/PCU metric.

Discussion and conclusions

- Combining a dimensionality reducing technique such as FAMD and hierarchical clustering enables farms to be considered according to their overall typologies based on numerous variables.
- Exploring numerous dendrogram cut points provides a means to sequentially identify the major differences which describe different farm typologies.

- **Farm management characteristics are associated with some of the between farm variability in antimicrobial usage as indicated by significant differences in total AMU being observed between partitions.**

Collaborators and funders:

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Methods: AMU estimation

- Farm records and medicine bin audits unreliable (Rees *et al.*, 2021).
- Observing every usage case unfeasible.
- Accessing sales records relatively easy and shown to be accurate.

Combined sales records → Linked to products → Linked to in house Medicines DB → Calculate mass of active ingredient / doses or courses in sale → Link to farm info

Farm.ref	Date	Description	Quantity
ABC	01/01/2017	BETAMOX 100ML (Sold as Bottle of 100 ml)	1

Medicine
Betamox 150 mg/ml Suspension for Injection

number_am_active_ingredients	concentration	unit_concentration	unit_dose
1	150	mg/ml	mg/kg

$$\frac{mg}{PCU} = \frac{(Concentration \times Volume)}{425\ Kg \times N.adult\ dairy\ cows\ animals}$$

Or…

$$TIDCD_{EMA} = \frac{\text{mass of active ingredient}}{DCD_{EMA} \times 365 \times Animals\ at\ risk} \times 1000$$

$$TIDCD_{EMA} = \frac{\text{units of product used}}{DCD_{EMA} \times 365 \times Animals\ at\ risk} \times 1000$$

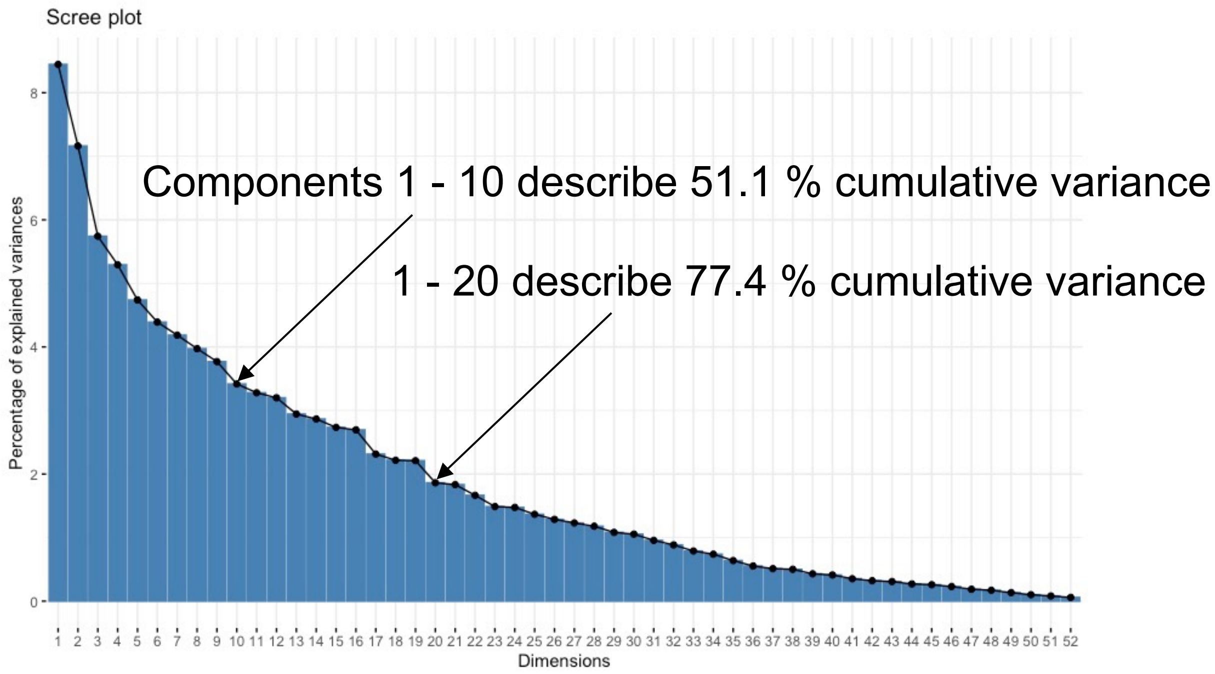
Methods: AMU estimation

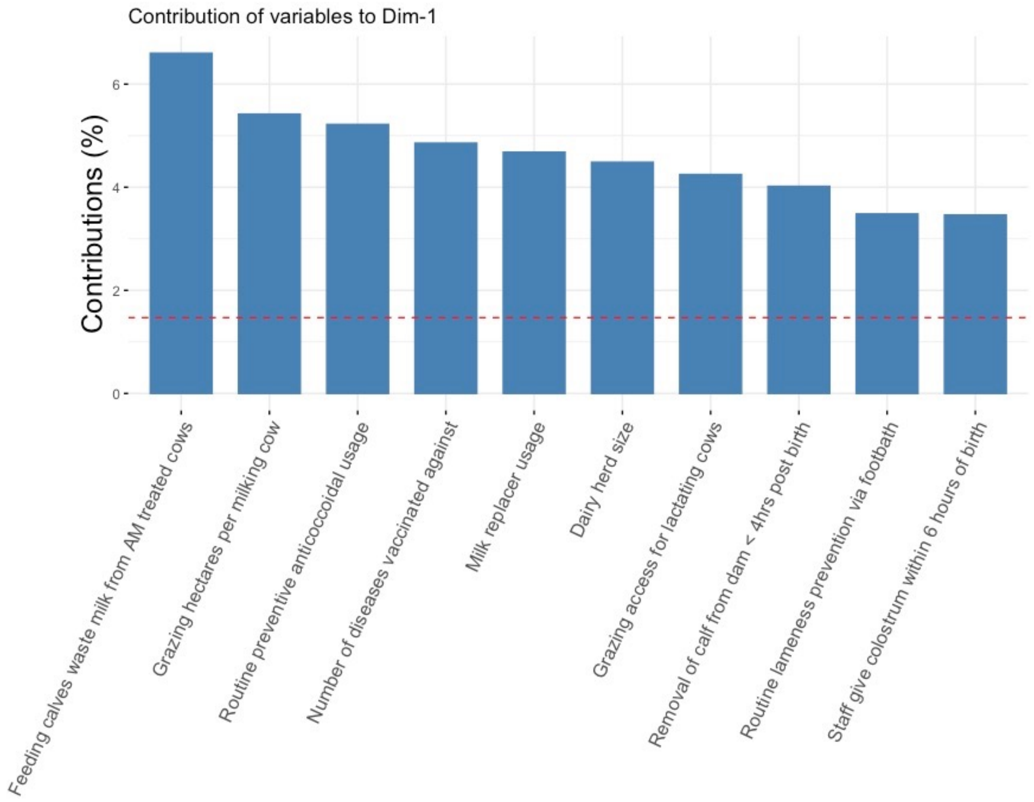
- Some factors to consider in these estimations.

- Complete usage
- Usage at time of sale
- Vet practice the only source of AMs
- Between vet/practice quantity reporting differences
- Topical AMs excluded

Results: FAMD

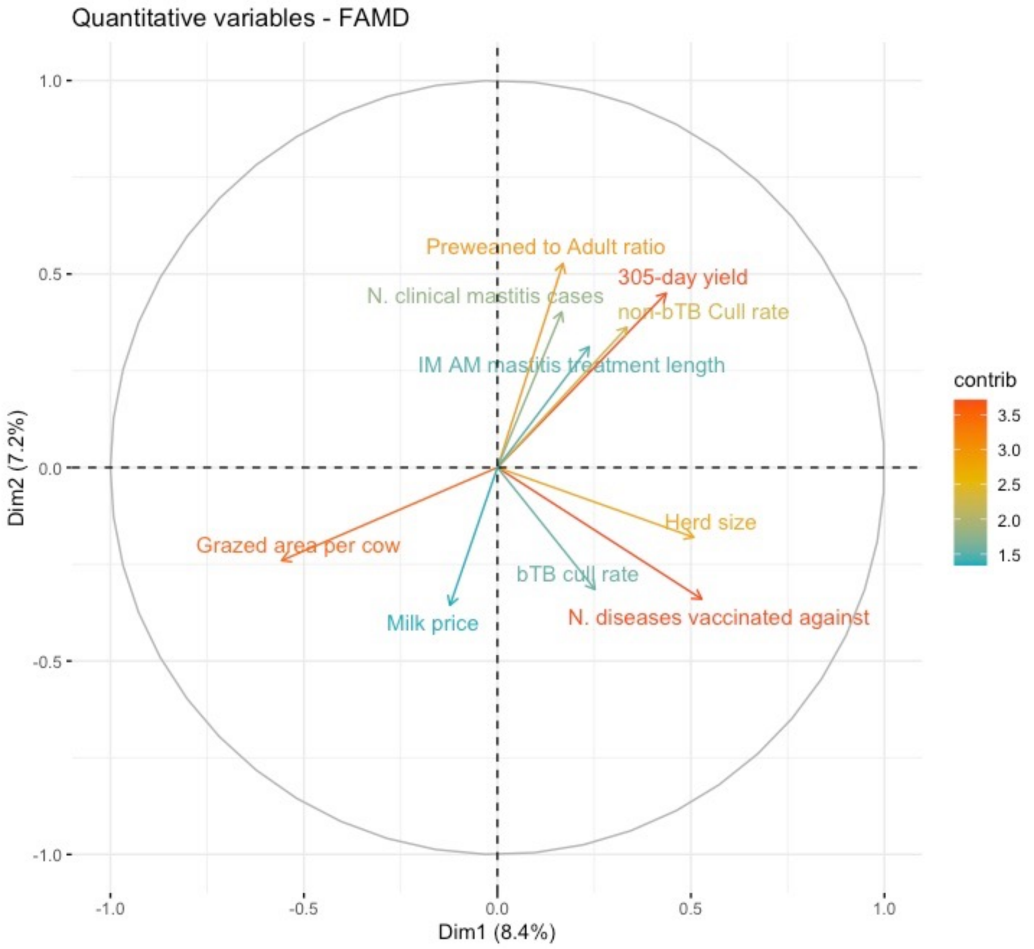
- A direct exploration of the principal components produced from FAMD provides valuable aids to interpretation.





Results: FAMD

- Analysing the contribution of variables towards component scores allows relationships between those variables to be elucidated.
- Variables with a higher contribution in dimensions 1 and 2 are more important in determining an observed farm's score on these dimensions.
- Variables which place close to each other on the plot are correlated with each other, while placement in opposite directions is indicative of negative correlation.



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