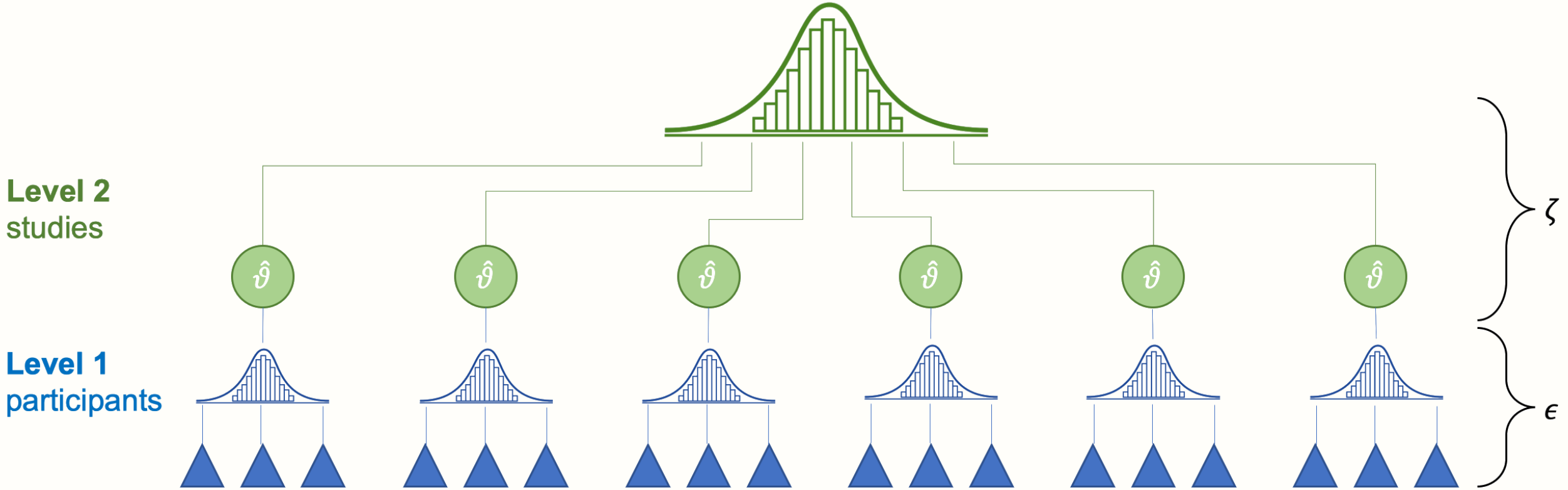

Does antibiotic use in beef cattle production drive antibiotic resistance?

A meta-analysts' perspective

Matt Lloyd Jones
University of Exeter

Image: Mathias Harrer

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Structure

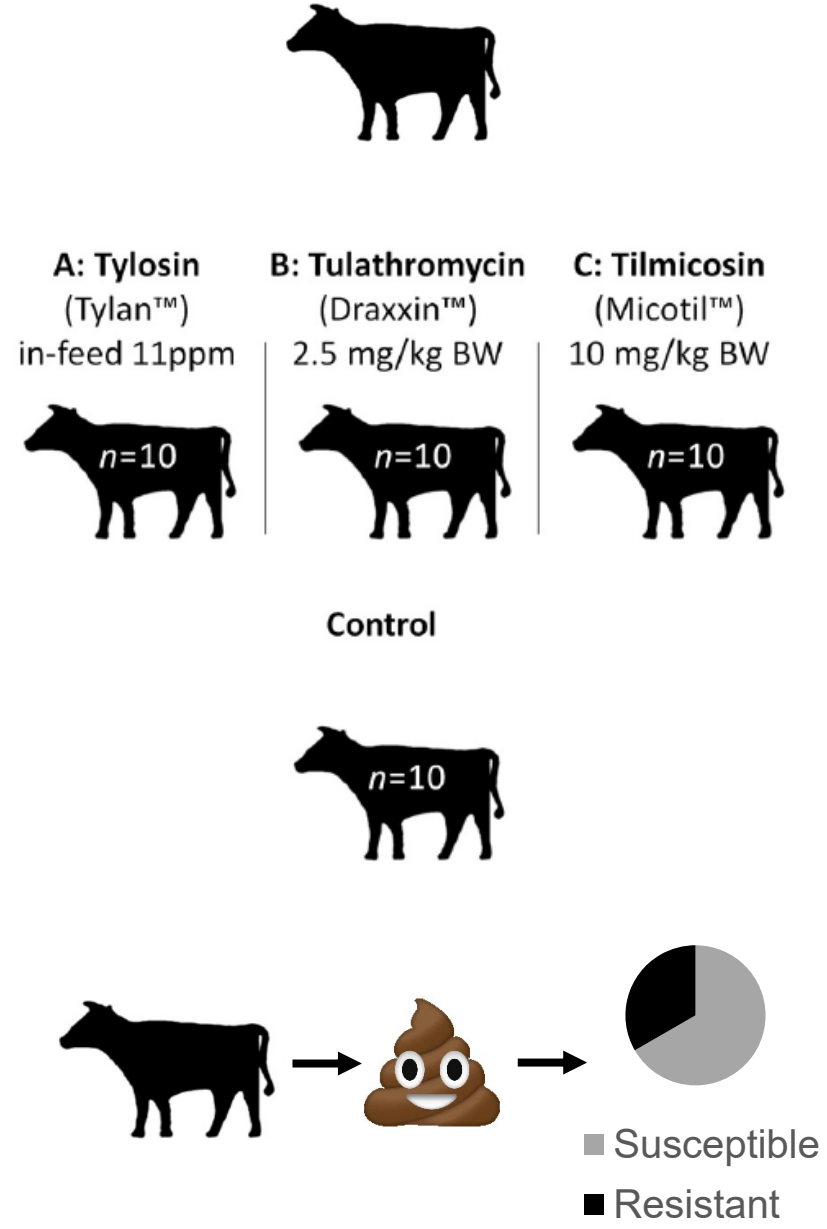
1. What the process of trying to obtain studies and data for modelling (systematic review) tells us about the knowledge base

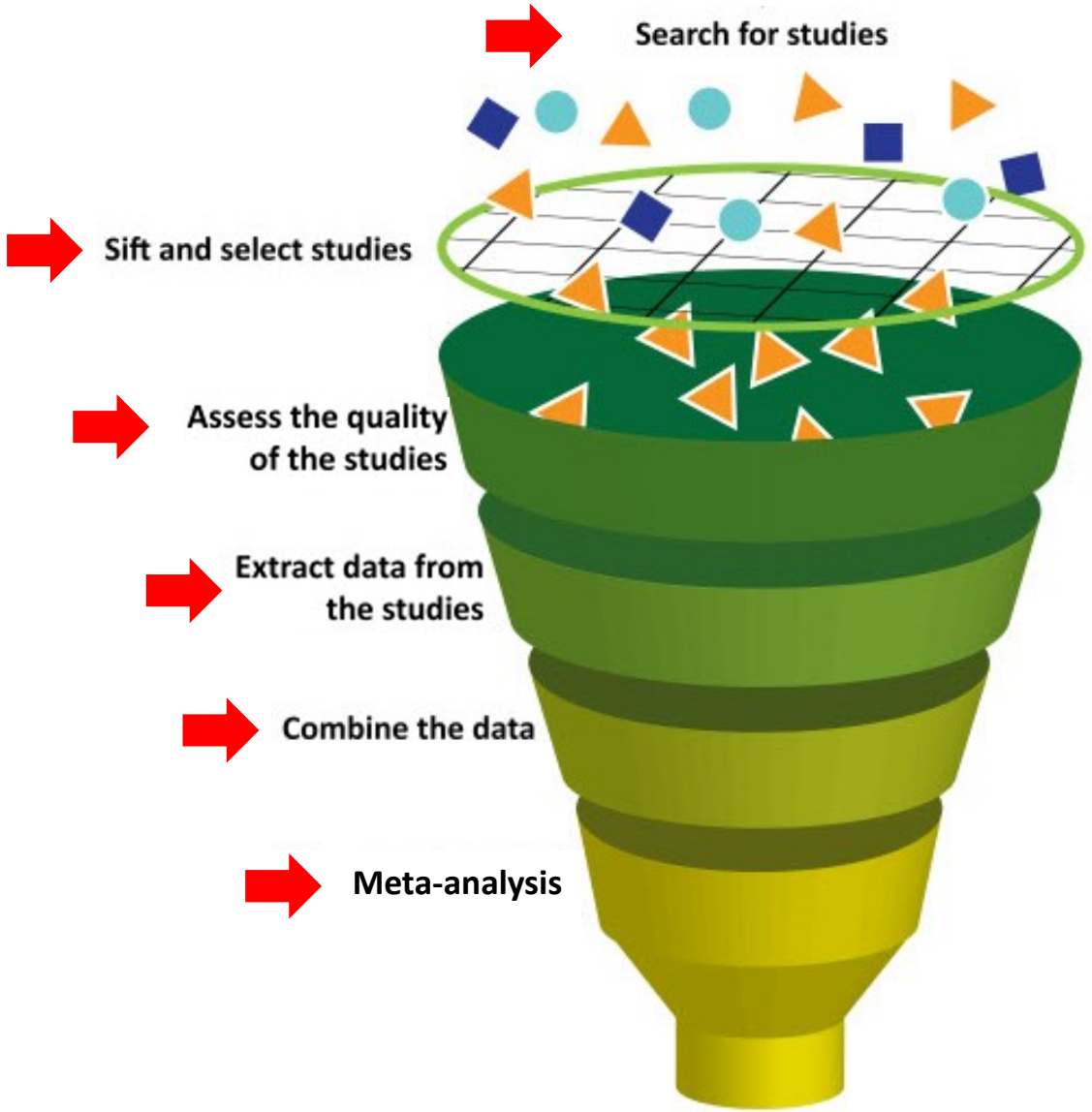
2. What the process of actually modelling the data from those studies (meta-analysis) tells us about the knowledge base

Knowledge	Knowledge gaps	Potential ways to fill knowledge gaps

Part 1:
What the process of trying to obtain studies and data for modelling (systematic review) tells us about the knowledge base

Does antibiotic use in beef cattle production drive antibiotic resistance?




Search for studies
Sift and select studies
Assess the quality of the studies
Extract data from the studies
Combine the data
Meta-analysis

The answer!

146

potentially relevant publications identified

– 114 excluded because didn't meet our criteria e.g. no/wrong control group

32 relevant publications identified **+ 5** new relevant publications published whilst we were conducting review

37 relevant publications identified

18 relevant publications with sufficient data

} High risk* of bias associated with these studies

*doesn't mean they are bad, mainly just badly reported

Knowledge

Knowledge gaps

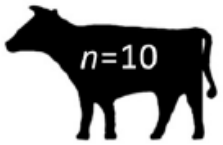
1. Lack of well-controlled studies
2. Unclear how reliable the more well-controlled studies are, due to poor reporting
3. Unable to make use of all the more well-controlled studies, due to lack of data sharing

Potential ways to fill knowledge gaps

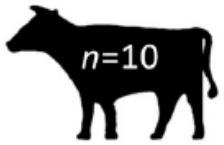
1. More studies!
2. Peer review and pre-registration of study protocols (e.g. Registered Reports)
3. Universities/research institutes, journals and funders rewarding and enforcing data sharing

Part 2:
What the process of actually modelling the data from those studies (meta-analysis) tells us about the knowledge base

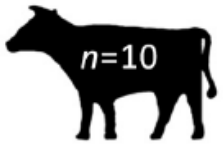
A: Tylosin
(Tylan™)
in-feed 11ppm



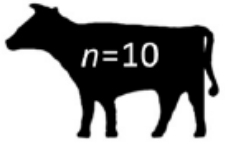
B: Tulathromycin
(Draxxin™)
2.5 mg/kg BW



C: Tilmicosin
(Micotil™)
10 mg/kg BW

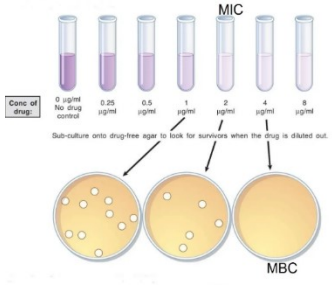


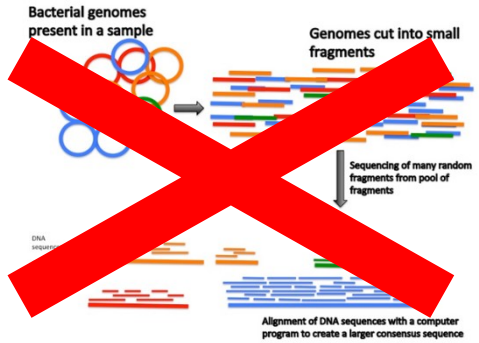
A: Tylosin
(Tylan™)
in-feed 11ppm

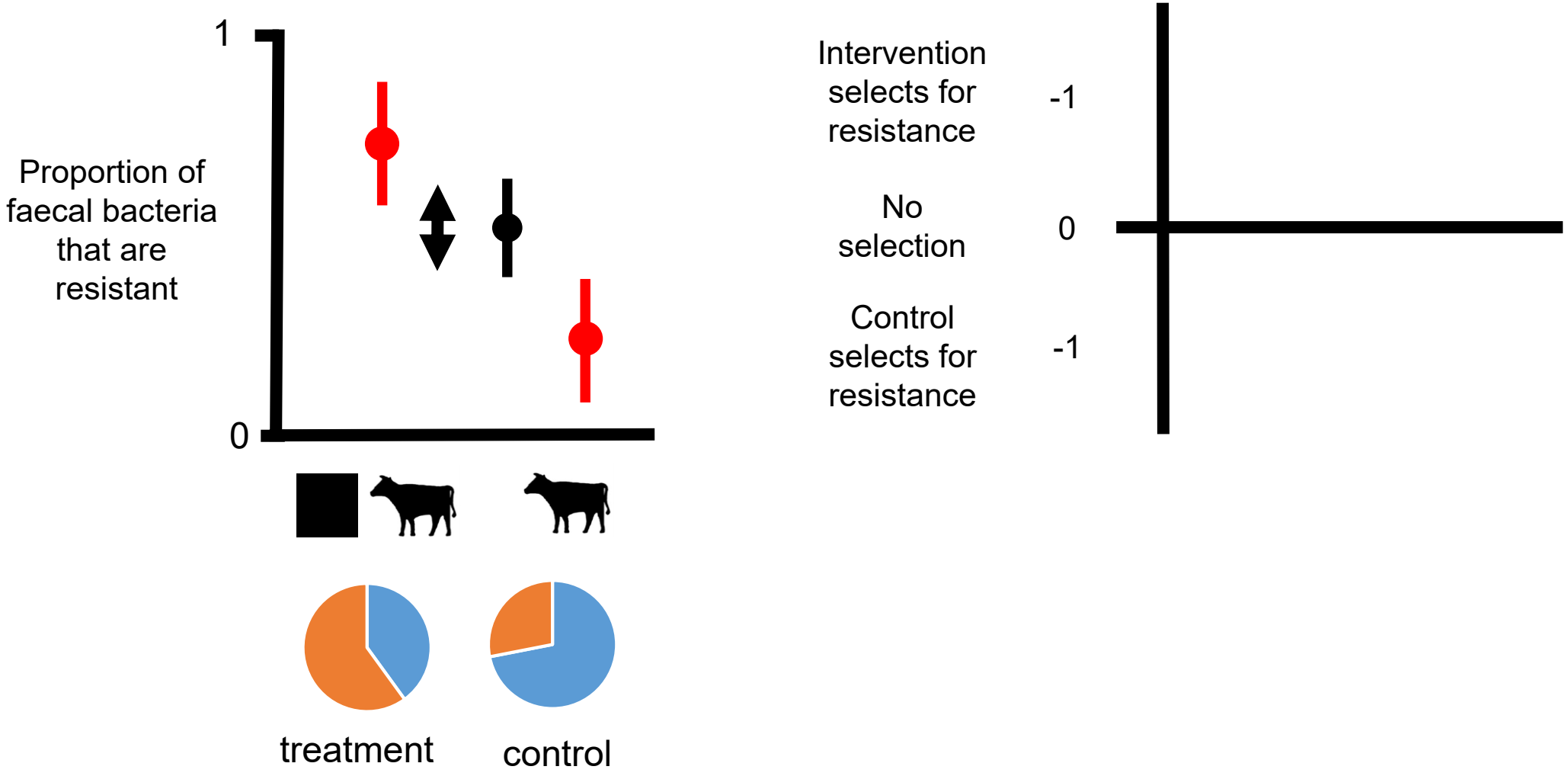


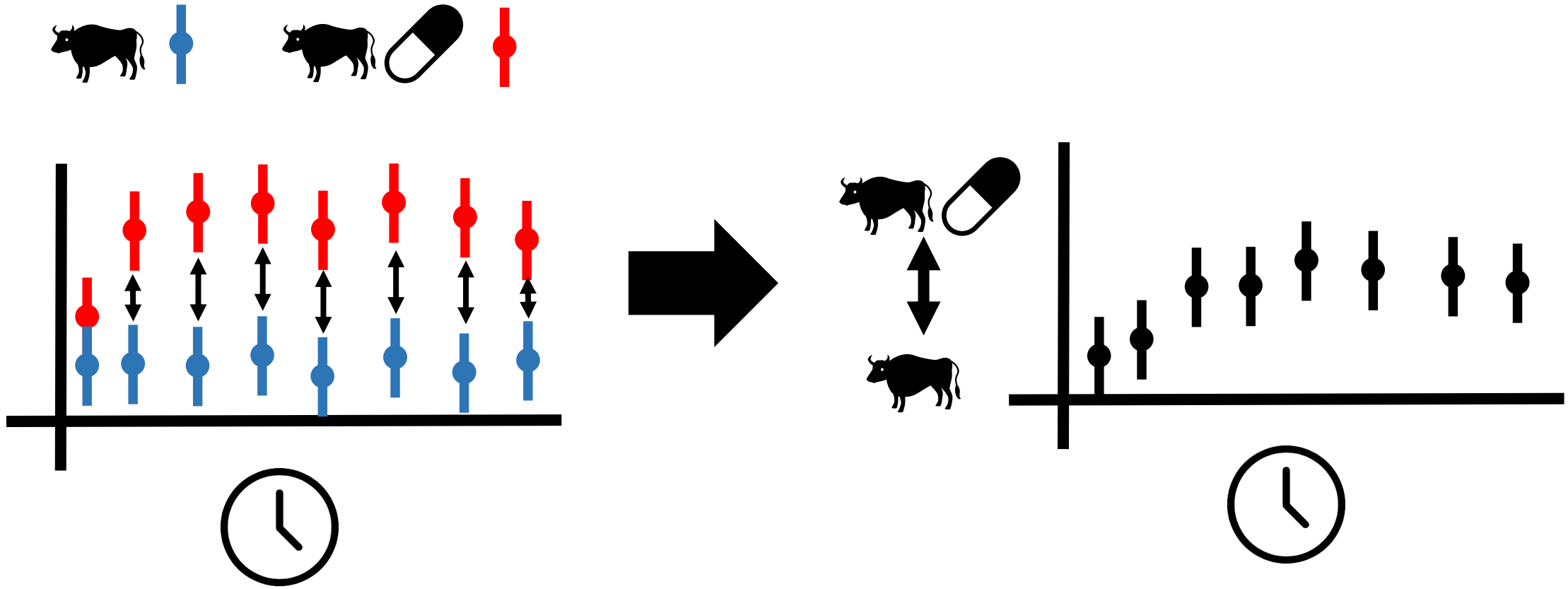
Tylosin
(macrolide)
resistance
measured

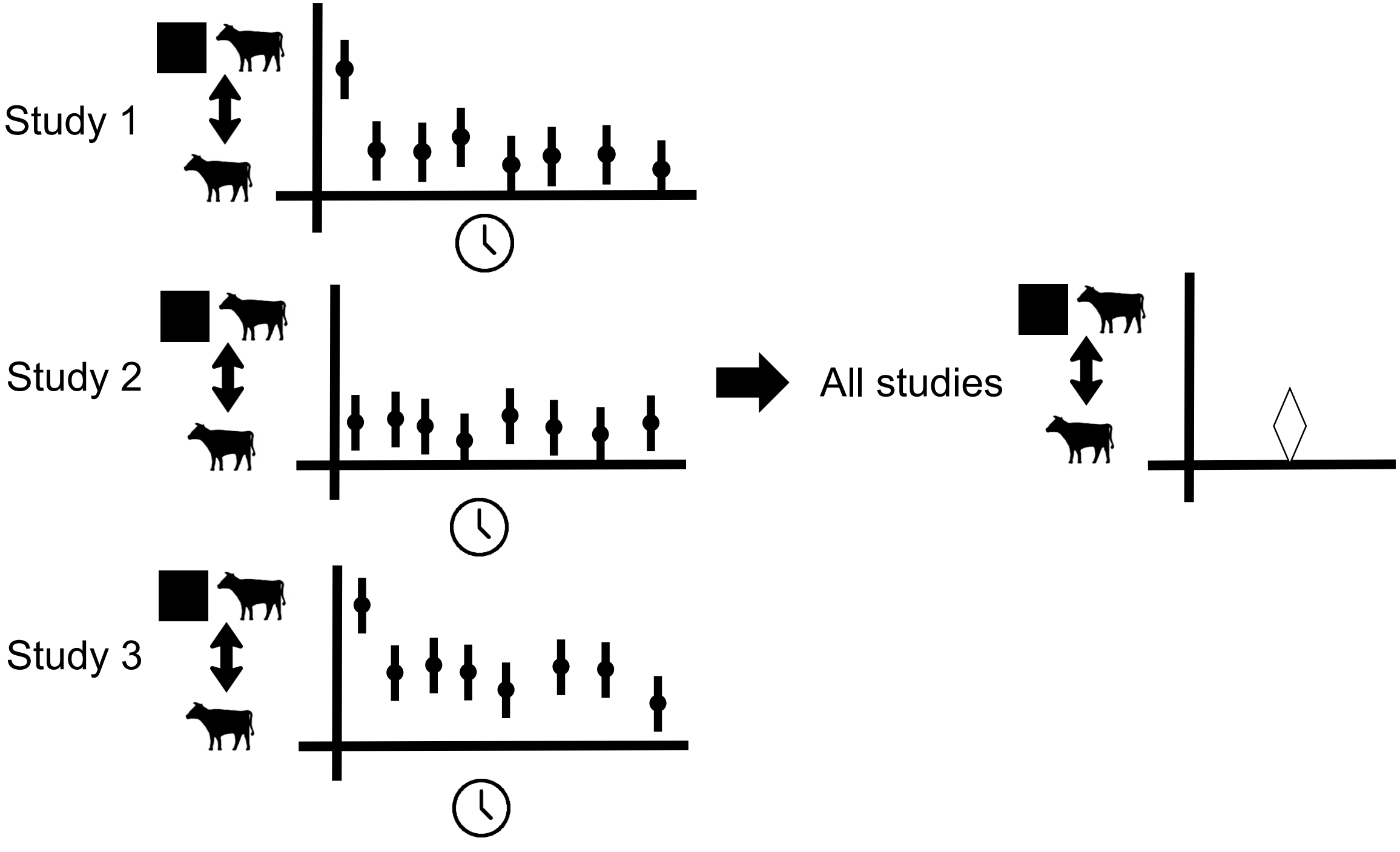
~~Ceftiofur~~
~~(cephalosporin)~~
~~resistance~~
~~measured~~



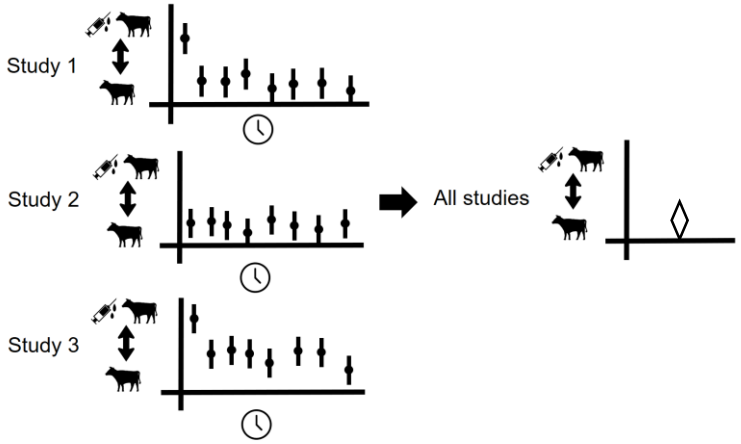



Proportion of faecal bacteria that are resistant
1
0
treatment
control
Intervention selects for resistance
-1
No selection
0
Control selects for resistance
-1

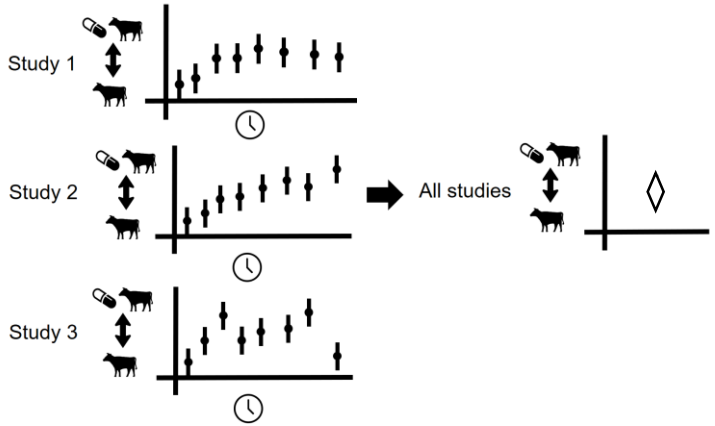



Study 1
Study 2
Study 3
All studies

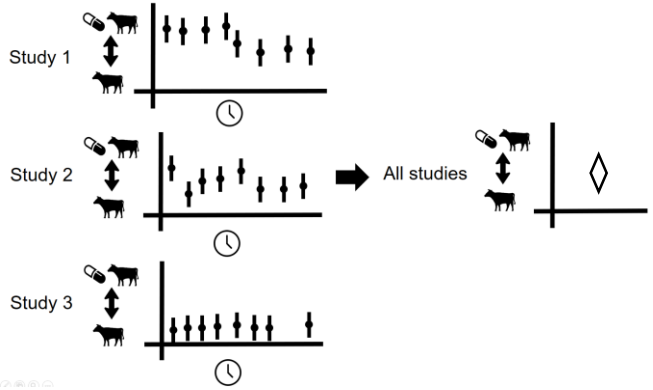
Injection



In-feed (during)

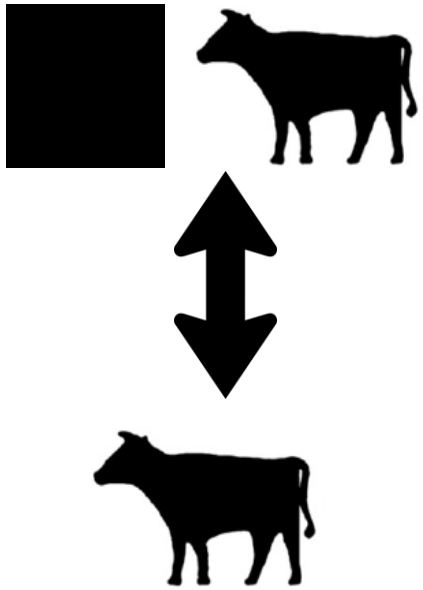


In-feed (after)



Calculated **overall effect size** separately for measurements taken after antibiotic injection, during the feeding of antibiotics and after the withdrawal of antibiotics from feed,
in order to make results more meaningful.

What did we find out?



Estimate

2

1

0

Study 1

Study 2

Study 3

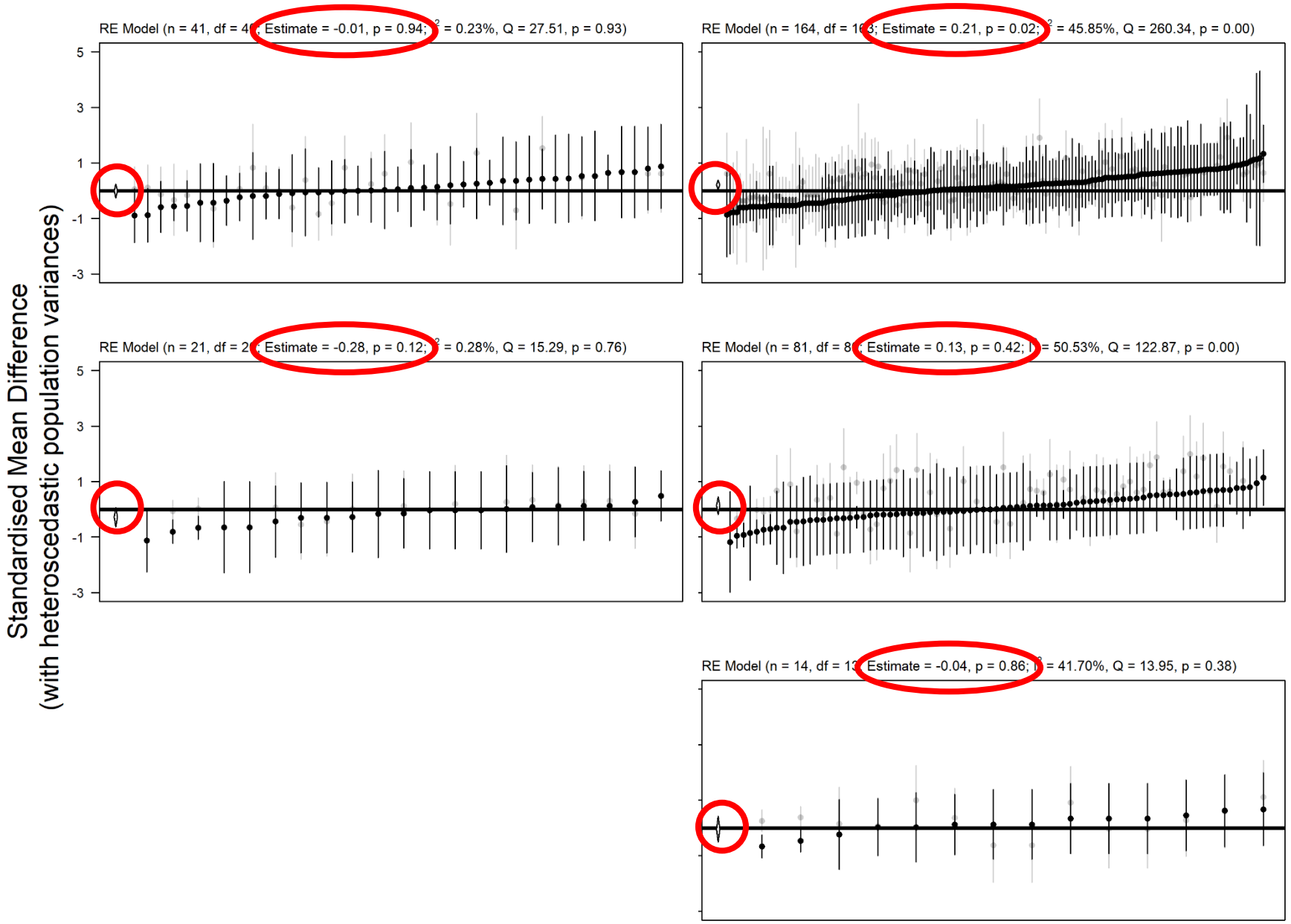
Pre-intervention

Post-intervention

Injection

In-feed (during)

In-feed (after)



Knowledge

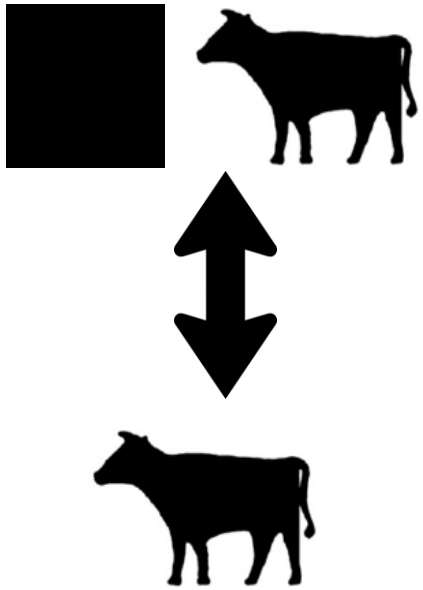
1. **Injecting antibiotics causes an increase in the % of resistant bacteria in faeces**

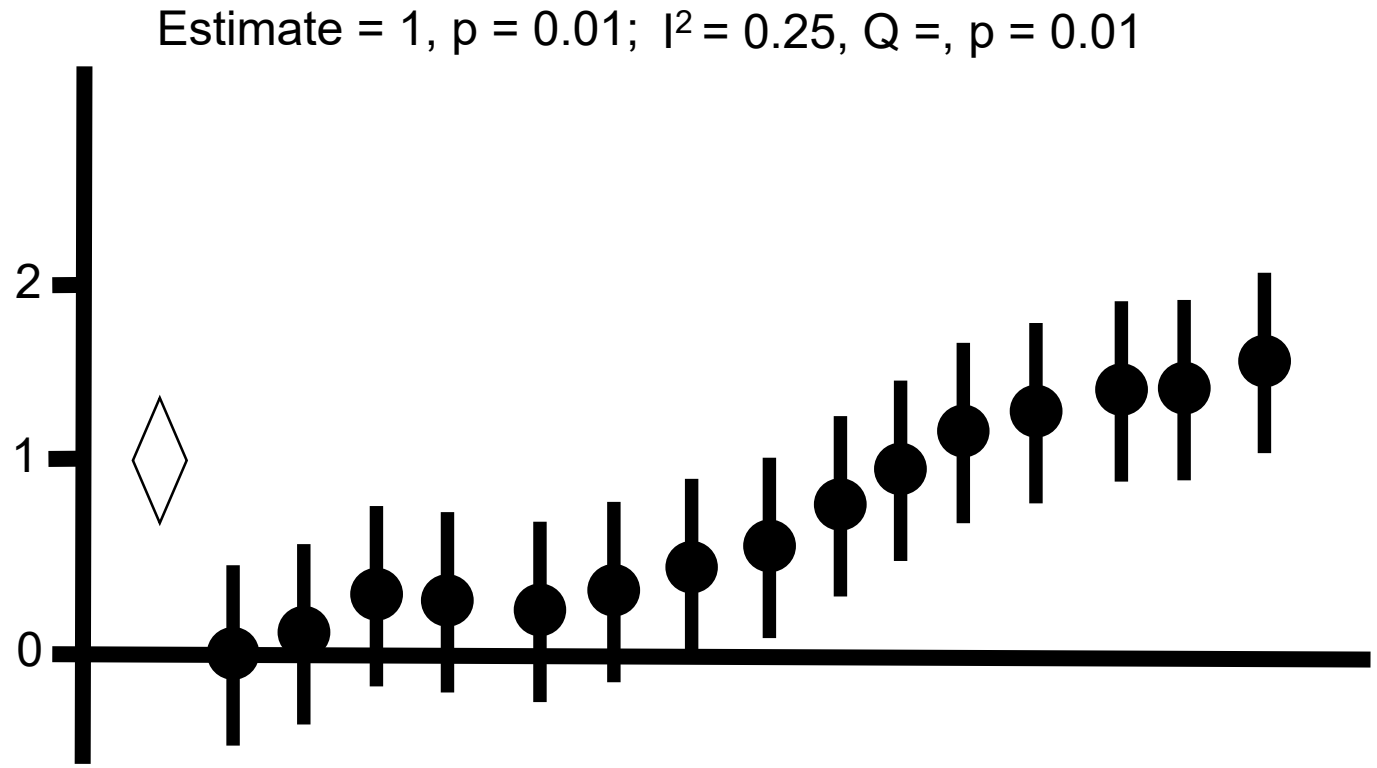
Knowledge gaps

1. Lack of well-controlled studies
2. Unclear how reliable the more well-controlled studies are, due to poor reporting
3. Unable to make use of all the more well-controlled studies, due to lack of data sharing

Potential ways to fill knowledge gaps

1. More studies!
2. Peer review and pre-registration of study protocols (e.g. Registered Reports)
3. Universities/research institutes, journals and funders rewarding and enforcing data sharing




Estimate = 1, p = 0.01; I2 = 0.25, Q =, p = 0.01
2
1
0

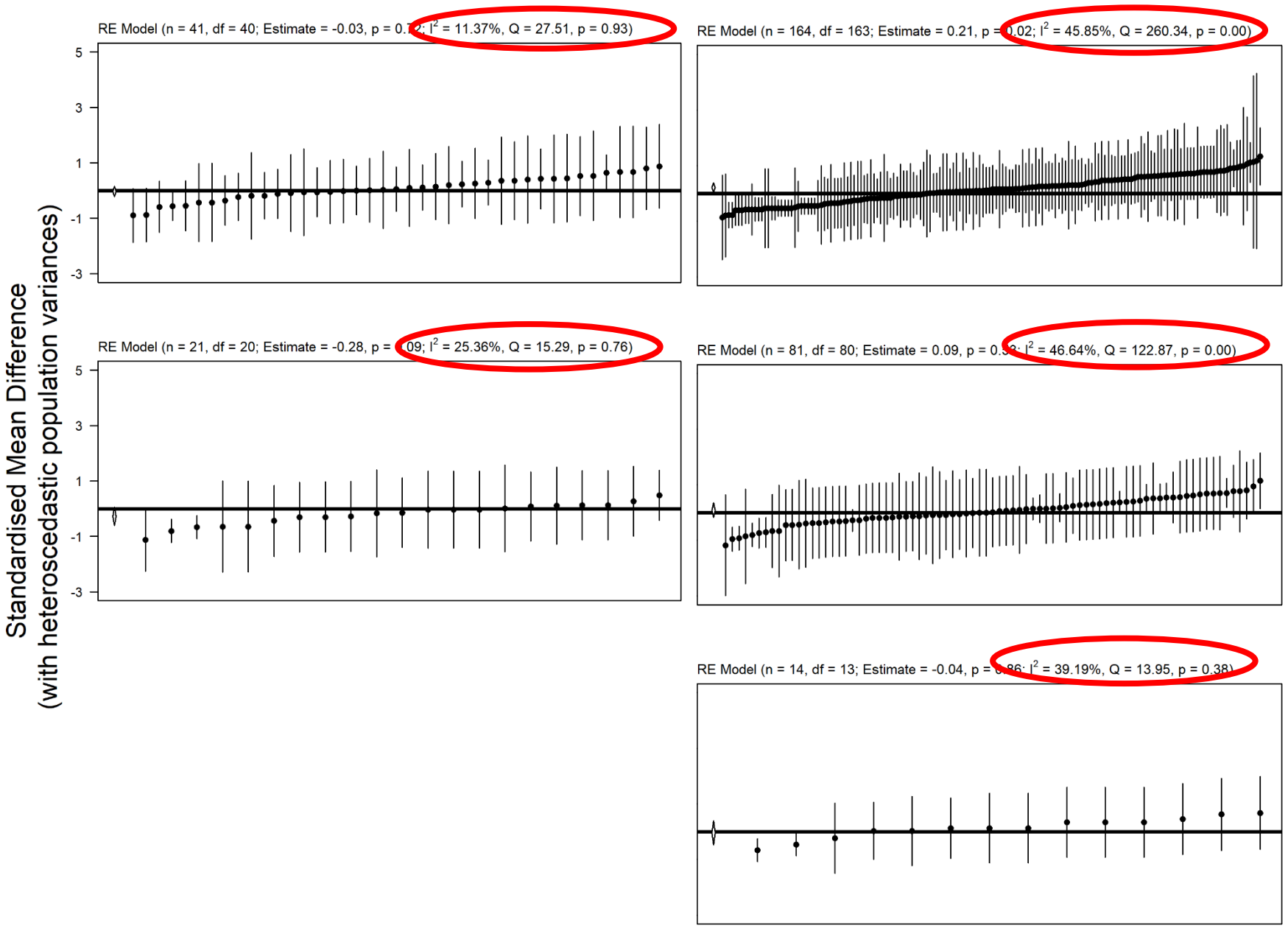
Pre-intervention

Post-intervention

Injection

In-feed (during)

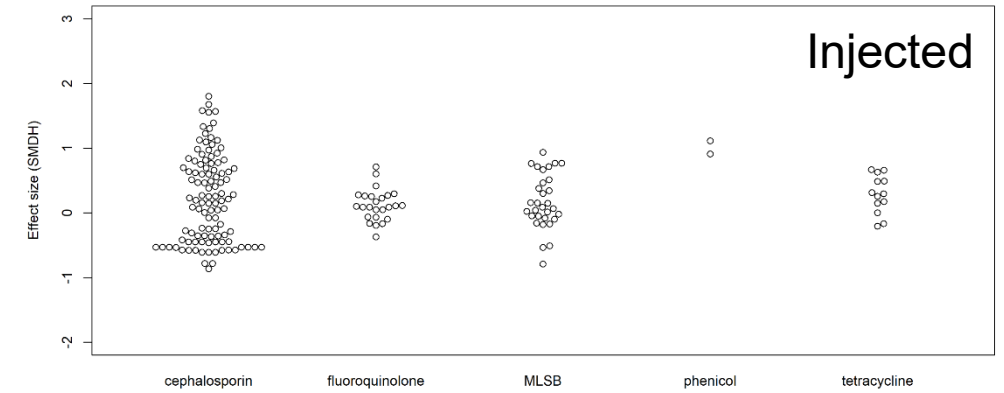
In-feed (after)

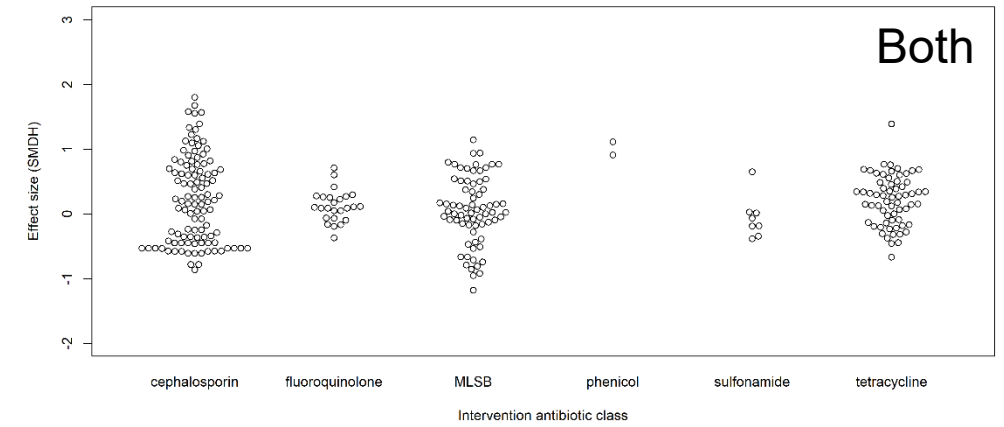


What might be driving this heterogeneity between studies?

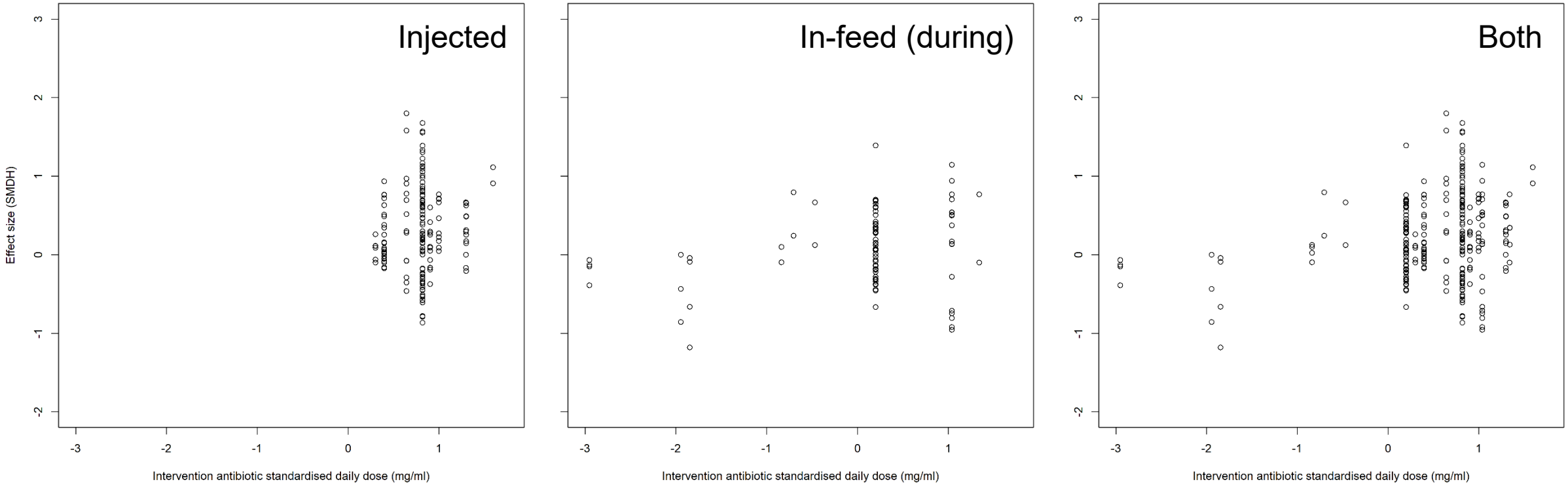
No detectable effects of antibiotic class…

may be due to lack of variation in classes used



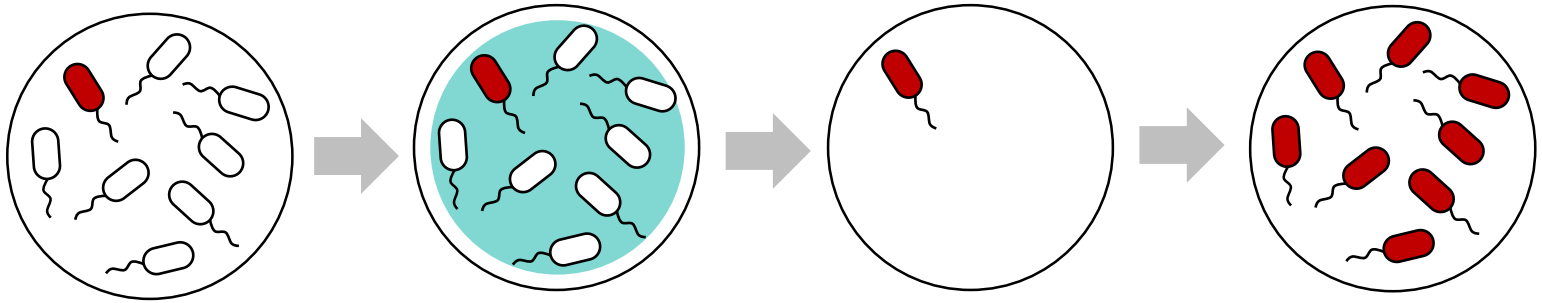


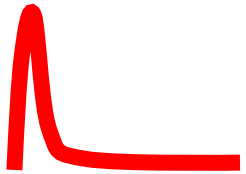
No strong effects of used daily dose (UDD) of antibiotic…



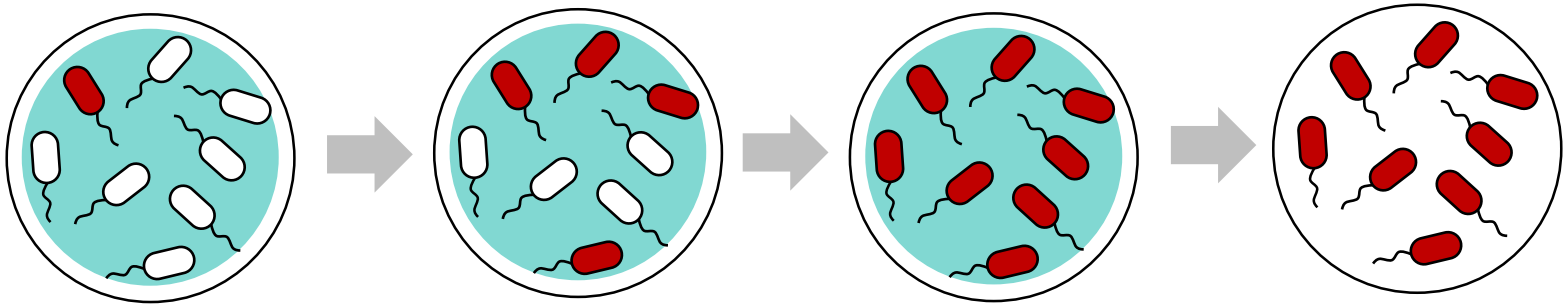
…may be due to lack of variation in doses used

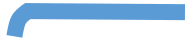
Injection

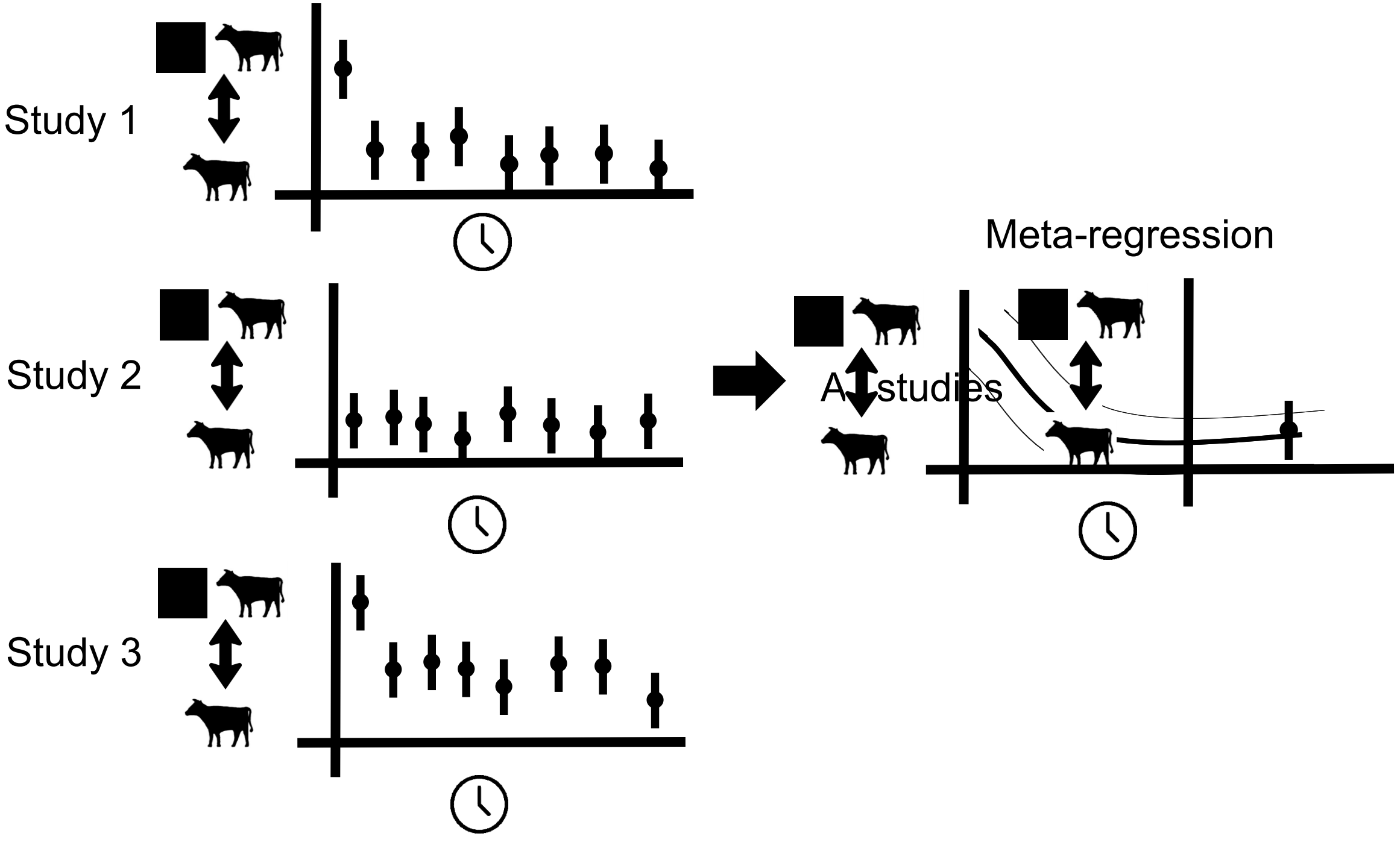




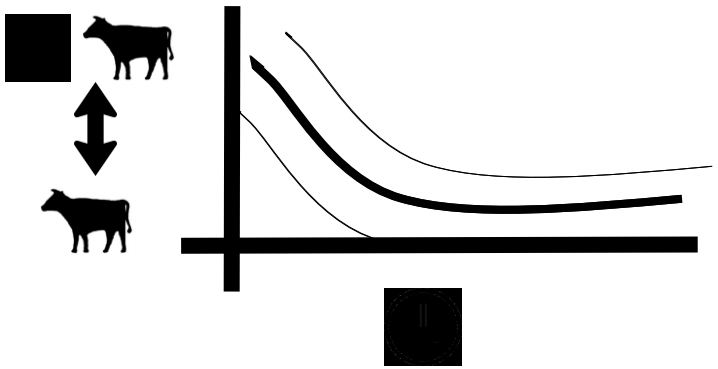
In-feed



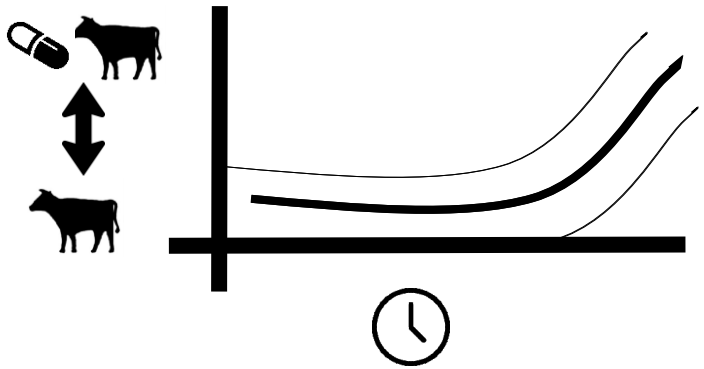



Study 1
Study 2
Study 3
Meta-regression
All studies

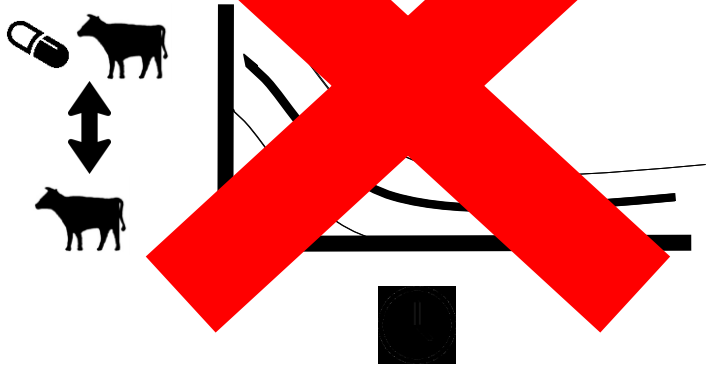
Injection



In-feed (during)



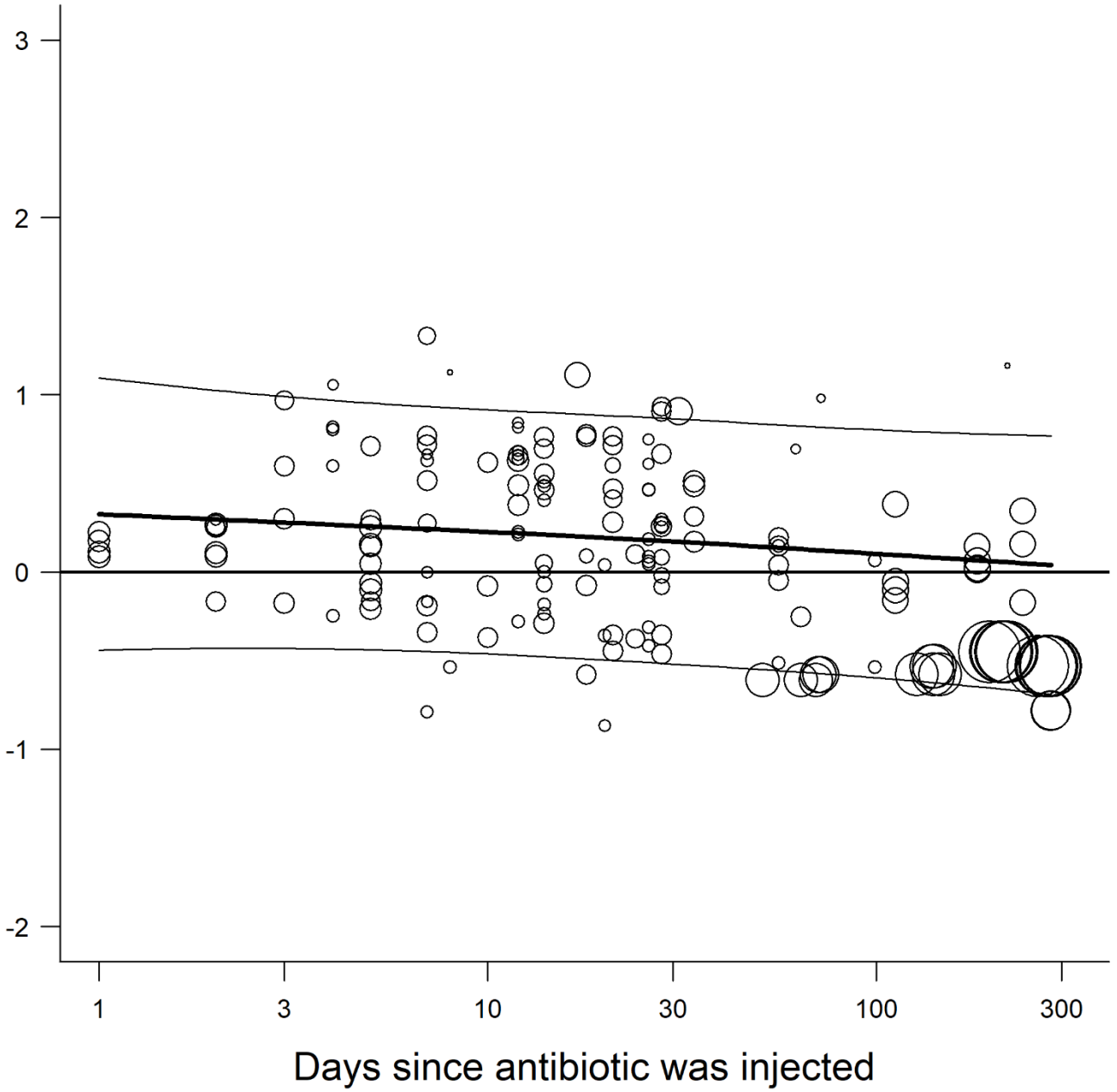
In-feed (a[illegible])



Does time of sampling explain the heterogeneity between studies?

For injected antibiotics, there is no significant effect of time since antibiotic was injected

…but lack of sampling at the head of this distribution (i.e. immediately after antibiotic injection)!



Knowledge

1. Injecting antibiotics causes an increase in the % of resistant bacteria in faeces

2. **No consistent effect of number of days since antibiotic was injected (time)**

Knowledge gaps

1. Lack of well-controlled studies

2. Unclear how reliable the more well-controlled studies are, due to poor reporting

3. Unable to make use of all the more well-controlled studies, due to lack of data sharing

4. **What is the size of the effect immediately after injection?**

Potential ways to fill knowledge gaps

1. More studies!

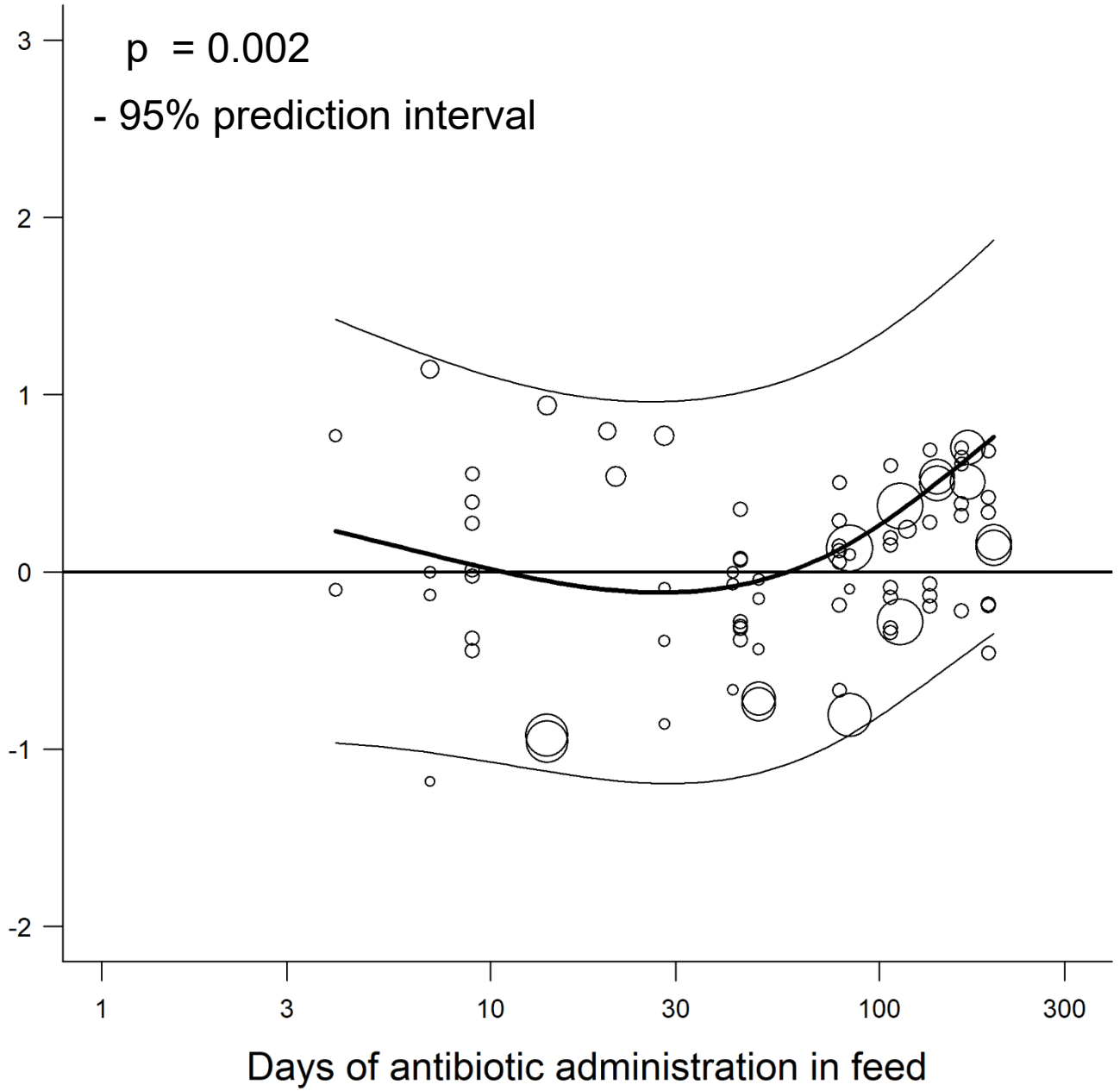
2. Peer review and pre-registration of study protocols (e.g. Registered Reports)

3. Universities/research institutes, journals and funders rewarding and enforcing data sharing

4. **More short-term studies on effects of injecting antibiotics**

During the administration of antibiotics in feed, there is a detectable (if modest) increase in the proportion of resistant bacteria in faeces with number of days on antibiotic feed

…but lack of sampling at the heads and tails of this distribution!



Knowledge

1. Injecting antibiotics causes an increase in the % of resistant bacteria in faeces

2. No consistent effect of number of days since antibiotic was injected (time)

3. **Feeding antibiotics potentially causes an increase in the % of resistant bacteria in faeces after hundreds of days**

Knowledge gaps

1. Lack of well-controlled studies

2. Unclear how reliable the more well-controlled studies are, due to poor reporting

3. Unable to make use of all the more well-controlled studies, due to lack of data sharing

4. What is the size of the effect immediately after injection?

5. **Does the effect of feeding antibiotics continue to increase past ~200 days on antibiotic feed?**

6. **How long does the effect of feeding antibiotics last after they are withdrawn from the diet?**

Potential ways to fill knowledge gaps

1. More studies!

2. Peer review and pre-registration of study protocols
(e.g. Registered Reports)

3. Universities/research institutes, journals and funders rewarding and enforcing data sharing

4. More studies sampling immediately after injecting antibiotics

5. **More studies sampling through the early and late stages of feeding antibiotics**

6. **More studies sampling after the withdrawal of antibiotics from feed**

Conclusions

1. Despite **problems with the quantity** and **questions around the quality** of scientific research in this area, we can still selection for resistance by antibiotic use in beef cattle production systems

2. **Improving future studies'** design, reporting and data availability may help further our understanding

3. But we should also think about ways to **make better use of past studies** (e.g. combined meta-analysis across livestock systems, using metagenomic data).

}

If you're interested in leading projects around these ideas (and maybe hiring someone on them…), **please come chat!**

Knowledge

1. Injecting antibiotics causes an increase in the % of resistant bacteria in faeces
2. No consistent effect of number of days since antibiotic was injected (time)
3. Feeding antibiotics potentially causes an increase in the % of resistant bacteria in faeces after hundreds of days

Knowledge gaps

1. Lack of well-controlled studies
2. Unclear how reliable the more well-controlled studies are, due to poor reporting
3. Unable to make use of all the more well-controlled studies, due to lack of data sharing
4. What is the size of the effect immediately after injection?
5. Does the effect of feeding antibiotics continue to increase past ~200 days on antibiotic feed?
6. How long does the effect of feeding antibiotics last after they are withdrawn from the diet?

Potential ways to fill knowledge gaps

1. More studies!
2. Peer review and pre-registration of study protocols
(e.g. Registered Reports)
3. Universities/research institutes, journals and funders rewarding and enforcing data sharing
4. More studies sampling immediately after injecting antibiotics
5. More studies sampling through the early and late stages of feeding antibiotics
6. More studies sampling after the withdrawal of antibiotics from feed

These results are robust to:

- Accounting for potential correlation between effect sizes from the same study
- Correcting for publication bias (not just driven by small, underpowered studies or older studies with big effects)
- Removing studies that we thought might have a disproportionate influence on the results (e.g. the lowest quality studies, observational/non-randomised studies)