

## Knowledge Synthesis in Animal and Veterinary Research Blog #3

By Lee Wisener on March 26, 2019

### Evidence hierarchy and the research continuum adapted for animal research and veterinary medicine

Evidence pyramid = evidence hierarchy  
Levels of evidence are based on the value of the evidence  
for making a clinical or policy decision

Valid means free from systematic bias

- ✚ All valid evidence has value.
- ✚ Some valid evidence has higher evidentiary value for decision making than other evidence.

The extent to which we can draw conclusions about the effects of an intervention depends on whether the data and results from the study/studies are **valid**.

**A study has 2 types of validity:**

- 1. External validity:** the extent to which the study is addressing the appropriate question (e.g. are the study findings applicable/generalizable to your question)
- 2. Internal validity:** the extent to which the study answered the question correctly (e.g. free from bias)

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.handbook.cochrane.org](http://www.handbook.cochrane.org).

**“Bias is a systematic error, or deviation from the truth, in results or inferences. Biases can operate in either direction: different biases can lead to underestimation or overestimation of the true intervention effect.”**

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.handbook.cochrane.org](http://www.handbook.cochrane.org).

- ✚ Hierarchies of evidence are controversial and will vary depending on the research question.
- ✚ Hierarchies of evidence reflect study designs and **NOT the biases from how the study was conducted** (for example, a poorly designed or executed [i.e. biased] clinical trial may have less value than a well-designed and executed cohort observational study for a particular intervention).

### Experimental studies

In experimental studies, we intervene in the study by deliberately applying the intervention [i.e. we allocate study subjects to one of at least 2 intervention groups (e.g. a treatment group and a control group)]. We observe the effect of our intervention on the outcome of interest, usually with a view to establishing whether a change in the outcome may be directly attributable to our action. Random allocation is an essential design component.

Two examples of experimental study designs are **laboratory experiments** and **clinical trials**.

From *Statistics for Veterinary and Animal Science*. 2006. Second Ed. Petrie A. and Watson P.

### Observational studies

These are also known as ‘natural experiments’ because *“we merely observe the animals in the study and record the relevant measurements on those animals. We make no attempt to intervene”* [i.e. the investigator does not allocate the intervention or exposure].

There are three main types of observational study designs: cross-sectional, case-control, and cohort

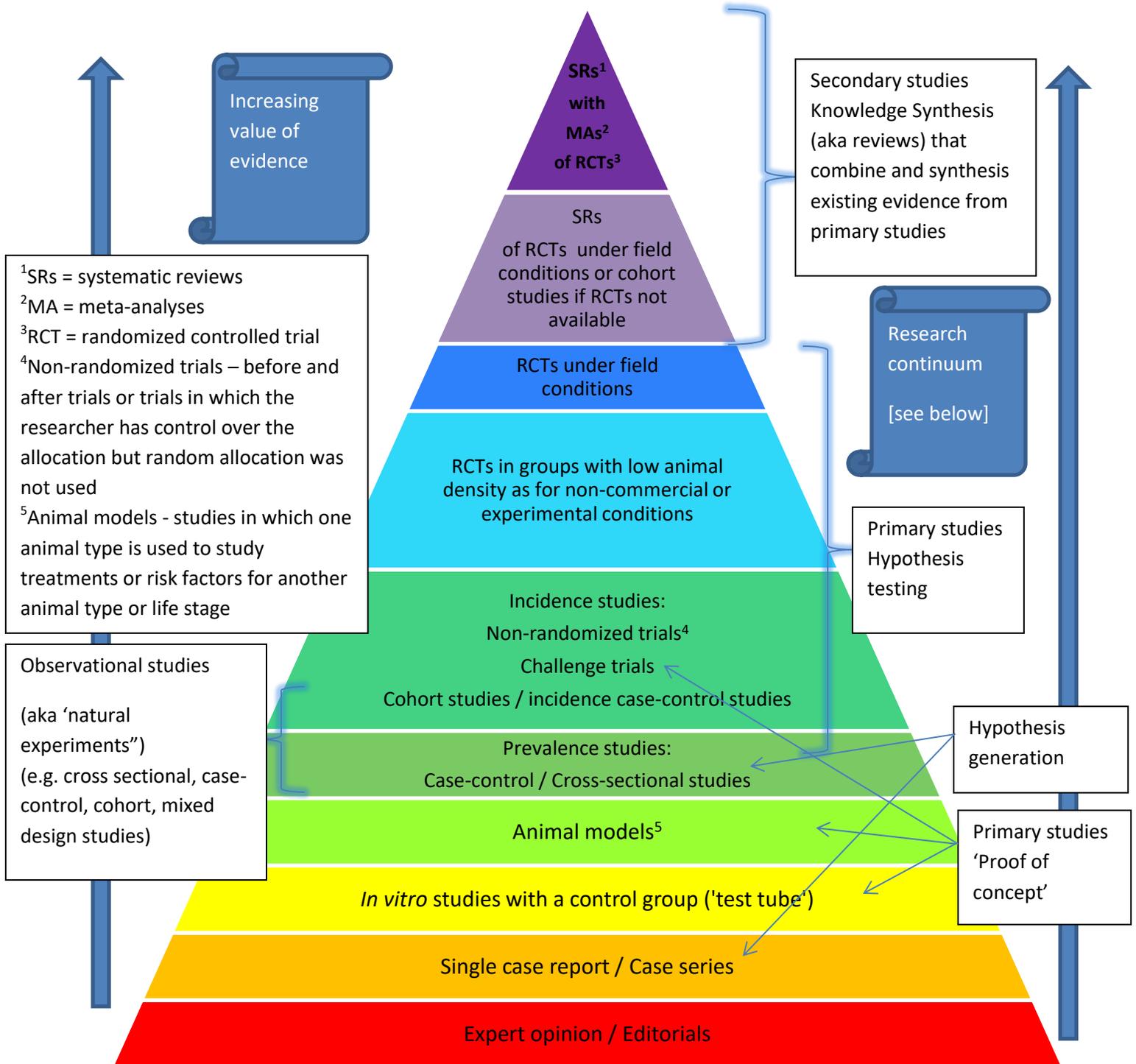
From *Statistics for Veterinary and Animal Science*. 2006. Second Ed. Petrie A. and Watson P.

## *Hierarchy of Knowledge or Evidence pyramid*

*Modified for animal research and veterinary medicine*

Pyramid shown below is for intervention type studies

Hierarchy of evidence



Proposed pyramid of evidence for animal research and veterinary medicine as presented by Sargeant et al., Sargeant, JM, et al., Study designs and systematic reviews of interventions: Building evidence across study designs. 2014. Zoonosis and Public Health 61 Suppl. 1, 10-17.

If we assume that the evidence is based on research that was designed and conducted without bias, the hierarchy of evidence is based on inherent bias or validity of various study designs and the validity of generalizing the findings to other groups/populations.

*“There is no consensus about the exact rankings of the various types of ‘evidence’, but the relative ranking of the major study designs is relatively consistent.”*

*“There are strengths and limitations of study designs commonly used in animal agriculture and veterinary research to assess interventions (preventive or therapeutic treatments)”*

Sargeant, JM, et al., Study designs and systematic reviews of interventions: Building evidence across study designs. 2014. Zoonosis and Public Health 61 Suppl. 1, 10-17.

## *Research Continuum*

*Modified for animal research and veterinary medicine*

In the research continuum, evidence generation may start with an unusual finding or idea that is described in the literature as a **hypothesis generating** study. This idea, which may lead to a proposed intervention, needs to be tested scientifically. **Hypothesis testing** studies [aka analytical studies] can evaluate the intervention through research stages that may start with preliminary ‘proof of concept’ studies for initial efficacy and safety evaluation, using *in vitro studies* and/or challenge trials, then randomized controlled clinical trials (RCTs) under experimental conditions followed by RCTs in the field under ‘real world’ conditions. Eventually, the information from RCTs can be combined into systematic reviews and if appropriate, meta-analyses (statistical combination of data from multiple studies) to determine if the intervention is effective across a variety of real world conditions.

1. **Hypothesis generating** studies: Research and evidence generation may start with an unusual finding reported in an outbreak **report** (e.g. a report of children visiting petting zoos who contracted a zoonotic infection such as *Salmonella* which resulted in diarrhea illness. A follow-up **survey** may have reported the same findings. These are descriptive in nature and do not have a control group. Alternatively, a **cross-sectional design observational** study may find that young school children with diarrrhea illness were more likely to have visited a petting zoo recently than children without diarrrhea.

2. **Hypothesis testing** studies [aka analytical studies]: These types can also be experimental or observational study designs.
  - ✚ An intervention may start with '**proof of concept**' studies such as an *in vitro* **experiment** [aka 'lab bench' or 'test tube' experiment]. One example would be to test plant extracts in a animal stomach digester model for reduced *Salmonella*.
  - ✚ Another '**proof of concept**' study may be an *in vivo* **challenge trial**. In challenge trials, not only is the intervention allocated by the researchers, but the induction of 'disease' is also under the control of the researchers. One example would be investigating probiotics to reduce *E. coli* O157 shedding in feedlot cattle being tested first in experimental beef calves intentionally infected with the pathogen during the trial.
  - ✚ Another example is a **cohort observational** study that follows children who visited the petting zoo at an agricultural fair and whose teachers had received local public health messaging about the zoonotic risks and compared them to a similar group visiting the petting zoo whose teachers did not receive the public health messaging to determine if the children whose teachers received the public health messaging developed fewer cases of zoonotic diarrhea.
  - ✚ Another example would be an **RCT** in which the intervention evaluated was the prevention of any food or drinks taken into the petting zoo by the children. In this example, the researchers would randomly allocate some children to NOT be allowed to take food and drinks into the petting zoo area (i.e. the treatment group children) and other children be allowed to take in food and drinks if they wished (i.e. the control group children). The researcher would then follow the children to compare which group had more incidents of diarrhea.
3. **Research synthesis**:
  - ✚ Combining studies into a systematic review (SR) provides additional value to the evidence on the effectiveness of an intervention.
  - ✚ There needs to be a sufficient number of studies that share enough commonality to be combined appropriately.
  - ✚ Studies conducted using designs of lower evidentiary value are not appropriate for a systematic review of an intervention under real-world conditions.
  - ✚ In general, RCTs are the best option for inclusion in a SR.
  - ✚ If RCTs are not available, then observational studies or challenge trials may be used though these may not provide as high evidentiary value as a single large well designed and executed RCT.

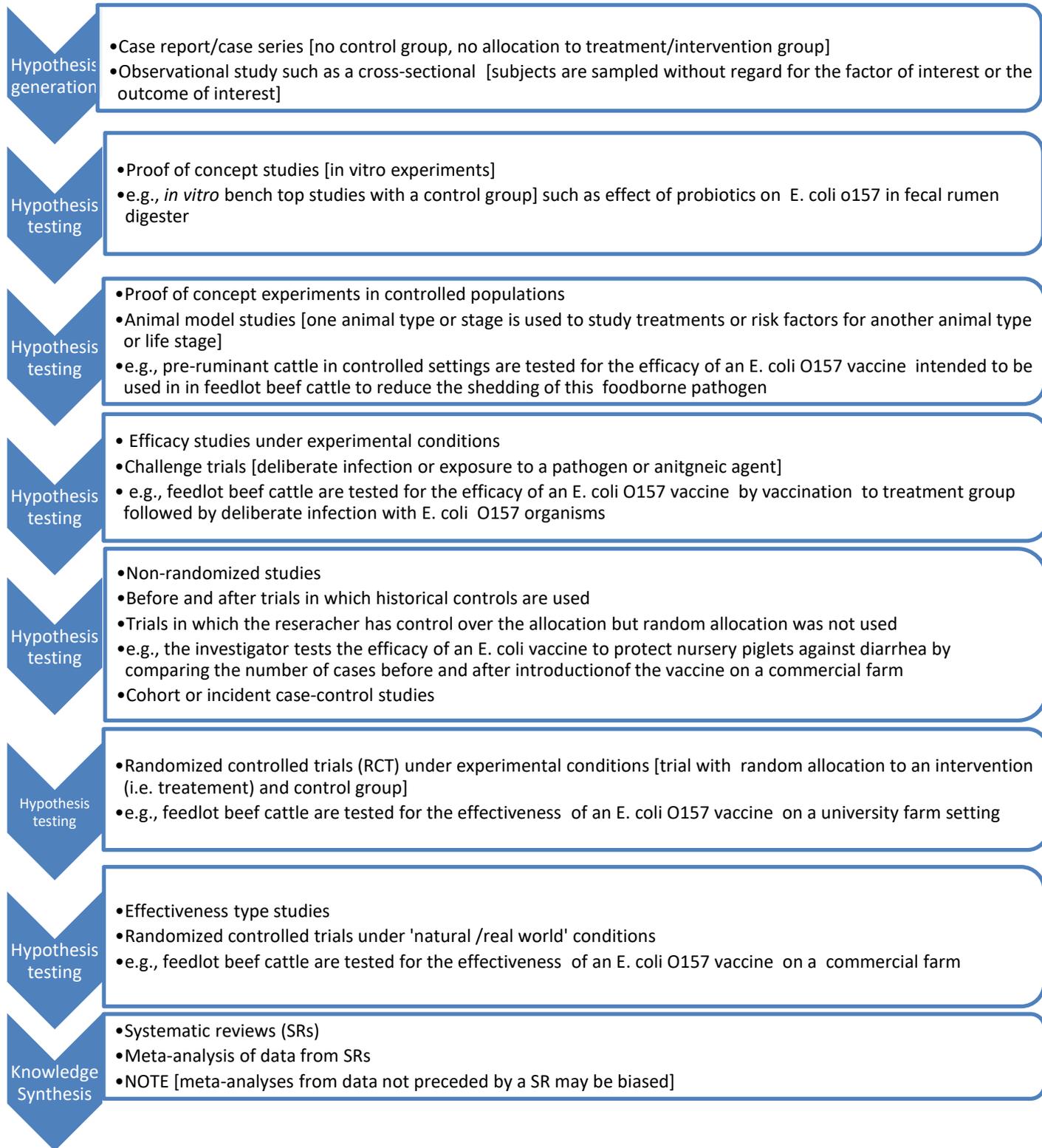
- ✚ For exposures that cannot be tested with an RCT, well designed and conducted cohort studies are preferred over other observational study designs.

*“The RCT is considered the ‘Gold Standard’ for evaluating efficacy of interventions and if there are well executed available for inclusion in a systematic review, that review may be restricted to only this design. In some instances, RCTs may not be feasible or ethical to perform, and there are fewer RCTs published in the veterinary literature compared to the human healthcare literature. Therefore, observational study designs, where the investigator does not control intervention allocation, may provide the only available evidence of intervention efficacy. While observational studies tend to be relevant to real-world use of an intervention, they are more prone to bias.”*

Sargeant, JM, et al., Study designs and systematic reviews of interventions: Building evidence across study designs. 2014. Zoonosis and Public Health 61 Suppl. 1, 10-17.

**All evidence** from primary AND secondary studies should be critically appraised for **internal** validity or bias.

Hierarchy of evidence



**Challenge yourself:** as you answer the question think about where these study design examples would fit on the evidence pyramid or in the research continuum

- In a challenge trial experimental beef calves were given probiotic (treatment group) or nothing (control group) then intentionally infected with *Escherichia coli* O157:H7. The probiotic group had reduced fecal shedding of the zoonotic pathogen *Escherichia coli* O157:H7 compared to the control group. Does that mean that the probiotics will reduce the shedding of this pathogen in feedlot beef cattle living on commercial farms?
- A systematic review and meta-analysis showed that feeding a high dose of probiotics to feedlot beef cattle favoured a reduction in shedding of *Escherichia coli* O157:H7. Does that mean that feeding probiotics will reduce beef contaminated with *Escherichia coli* O157:H7?
- A survey of dairy farms found that farms that fed probiotics to cows during their dry period [aka – non-milking period] had fewer new cases of mastitis [i.e. infected udder] when they resumed milking compared to farms that did not feed probiotics. Does that mean that the probiotics ‘prevented’ cases of mastitis on those farms?
- Probiotics were shown to help 12 experimental adult beagles recover from diarrhea. Does that mean probiotics will help all types of dogs of any age recover from diarrhea?
- One type of probiotic was shown to be an effective preventative treatment in reducing diarrhea of nursery pigs in a clinical trial. Does that mean all probiotic types will be equally effective?

NOTE: treatment group refers to the group that receives the treatment/intervention being tested while the control group receives no treatment, placebo, or a different treatment.

For additional information see:

Gott et al., Research into Understanding Scientific Evidence, Durham University School of Education  
[https://community.dur.ac.uk/rosalyn.roberts/Evidence/CofEv\\_Gott%20et%20al.pdf](https://community.dur.ac.uk/rosalyn.roberts/Evidence/CofEv_Gott%20et%20al.pdf)