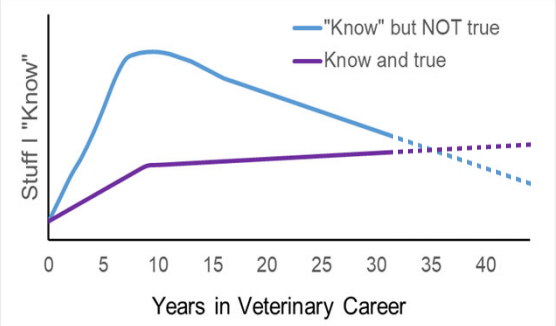
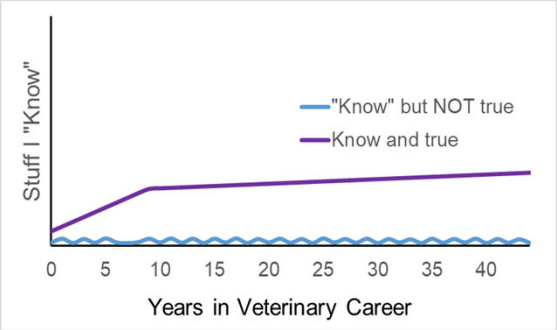
Investigating the Literature

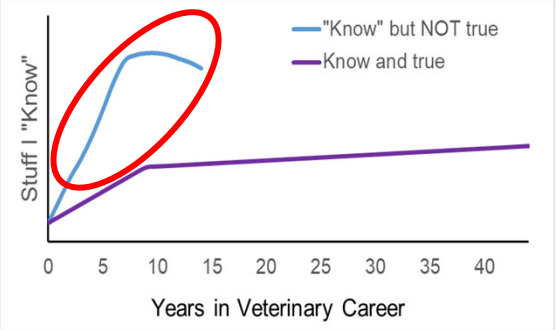
Larson's Veterinary Career



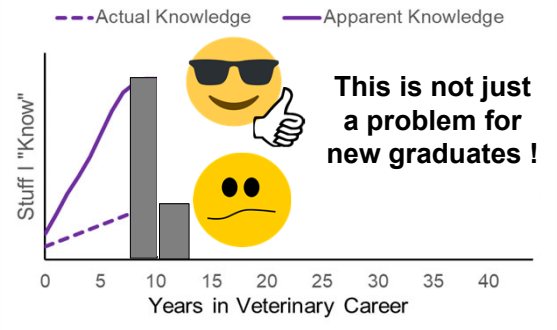
Good Goal for Veterinary Education?



How Do We Get Rid of This Stuff?



Maintaining Confidence In the Face of Accurate Self-Awareness



Going Faster Doesn't Mean You Will Arrive at the Truth Faster (Slow Down To Go Faster)

We (researchers and practitioners) need to "slow down so we can speed up".

Acting on studies that did not adequately control for bias or confounding or that were interpreted beyond the limits of the data and subsequently prove to be false or highly dependent on other factors will divert resources and policies in ways that are wasteful at best and harmful at worse (although I would argue that wasteful **is** harmful).

The longer it takes (years, decades, centuries) to discard conclusions that are not a true representation of the natural world – the more harm is done.

Curiosity is the essence of discovery

The opposite of curiosity is certainty

Certainty is the death of curiosity

Embrace a high (unachievable) bar for certainty

Veterinary Skills Needed to Evaluate Claims:

- **Sound understanding of biology / ecology**
- **Understanding risk of inaccurate conclusions**
  - **Random (chance) variation**
  - **Bias in how animals are selected or measured**
  - **Confounding the effect of one factor with the effect of another factor**
  - **Extrapolation from laboratory measurements or other species**

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  - Confounding the effect of one factor with the effect of another factor
  - Extrapolation from laboratory measurements or other species
- **Understanding of interactions that influence application of claims in different settings**
- **Ability to search for and retrieve high-quality studies (control for bias and confounding)**

EBVM Defined:

- *"The consistent use of current best evidence derived from published clinical and epidemiological research in management of patients, with attention to the balance of risks and benefits of diagnostic tests and alternative treatment regimens, taking account of each patient's unique circumstances, including baseline risk, co-morbid conditions and personal preferences."*

A dictionary of Epidemiology, 4th ed. Oxford Univ Press, 2001

Why do EBVM?

- Personal experience may be misleading
- Studies based on bench-top methods are often misleading (not whole animal – i.e. cell culture, tissue response, etc.)
- Randomized trials are required to validate results because predictions based upon physiology may be wrong
- Reading literature requires more than common sense to evaluate the evidence

But Aren't We Already Doing Science-Based Veterinary Practice?

- Define Science:
  - Not just being involved in a profession that is based on a "science" i.e. biology / veterinary medicine
  - Knowledge obtained and tested through the scientific method (Webster)
- If it isn't tested – it isn't science

But Aren't We Already Doing Science-Based Veterinary Practice?

- When veterinary practice is not based on science:
  - The statement has never been tested by means of a carefully documented controlled experiment that can be repeated by any other researcher.
  - The statement is extrapolated from one controlled experiment result to another hypothesis.

Keys for EBVM:

- Ability to efficiently and accurately search for best available evidence

Key for EBVM: Ability to efficiently and accurately search for best available evidence

PubMed - http://www.pubmedcentral.nih.gov/

CABI - http://www.cababstractsplus.org/veterinarymedicine/index.asp

Google Scholar – http://scholar.google.com

Keys for EBVM:

- Ability to efficiently and accurately search for best available evidence
- Basic understanding of criteria for determining strength of evidence

Key for EBVM: Basic understanding of criteria for determining strength of evidence

Levels of Evidence

- Some evidence is very strong (i.e. rigorously tested in the target species under natural conditions in experiments designed to prove a theory to be false)
- Some evidence is very weak (i.e. not tested)
- And some is intermediate

Levels of Evidence
The Hierarchy is Based On:

- The strength of evidence of causation
- The ability of the study to control bias
- The similarity between the study population and the population currently being considered in the clinical setting

Veterinary Medicine Levels of Evidence - Basic

Level of Evidence	Description of Evidence
1 "Fact"	• Systematic review of randomized clinical trials in the target species under representative conditions with naturally occurring disease that is free of worrisome variations in the directions and degrees of results between individual studies
2 Trustworthy Evidence	• Single, randomized clinical trial in the target species under representative conditions with naturally occurring disease with narrow confidence interval • Cohort study in the target species under representative conditions with naturally occurring disease
3 Supportive Evidence	• Controlled experimental trial with the target species and induced disease • Systematic review of case-control studies in the target species • Individual case-control study in the target species
4 Supposition	• Case-series in the target species • Poor quality cohort study in the target species (<80% follow-up) • Poor quality case-control study in the target species (<80% follow-up) • Well-designed clinical, experimental model, cohort, or case-control study in another species
5 Opinion	• In vitro research • Pathophysiologic rationale • Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

Need For EBVM:

- Teaching and practice based on rational extrapolation from basic sciences or uncontrolled observation is <u>not</u> science and does not lead to excellence in care for our patients and clients.

KANSAS STATE UNIVERSITY

Develop a clear and precise clinical question using the PICO method

↓

Use PICO terms from the clinical question as potential search terms for PubMed, CABI, Google Scholar, etc.

↓

Evaluate titles to select abstracts to read – select only titles relevant to clinical question

↓

Read abstract – discard articles not relevant to clinical question, give priority to articles with highest levels of evidence and study population most similar to the population that stimulated the clinical question

Read Abstract:

- Can determine if paper is relevant
- <u>Cannot</u> determine quality of the work
- If you commit to the paper after reading the abstract - you must read it <u>fully</u> and <u>critically</u>!

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Read article – <u>stop reading and discard</u> if allocation or selection of animals for treatment groups is biased or if clinical outcomes are not assessed identically for all animals

Bias & Confounding

- Issues of internal validity
  - This is important !
    - So you don't get fooled by **wrong** information from research studies due to bias or confounding

Bias & Confounding

- Issues of internal validity
- Bias
  - Systematic error (vs. random error) that results in mistaken conclusions regarding the relationship between the exposure (or explanatory factors) and the outcome
  - Random (non-systemic) errors are not considered to be bias – these errors are randomly distributed amongst groups/observations
  - Lack of bias → internal validity

Bias & Confounding

- Issues of internal validity
- Bias
- Confounding
  - The mixing of the effects of one risk factor with another
  - Identifying a spurious relationship between a risk factor and a disease that is due to the effects of a separate factor

Bias & Confounding

- Why is this important to understand?
  - To understand what research studies mean (and don't mean) – to be an educated consumer of research information
  - Clinical practice – To better understand the causes of disease and appropriate treatments
  - Research – To use appropriate study design, analysis, and interpretation

Bias & Confounding

- Why is this important to understand?
  - Bias and confounding can (and do!) distort study results and can lead to interpretations that are completely wrong!!
- Why does this happen?
  - Multi-factorial nature of disease
  - Lack of understanding of the roles of bias and confounding by researchers and clinicians

Bias & Confounding

- Challenge for researchers and health practitioners?
  - Obtain valid study results i.e. results that represent the **true nature** of the relationship between exposure and disease
  - This requires consideration of all possible errors due to bias and/or confounding

Bias & Confounding

- How to control for bias and confounding
  - Appropriate study design
  - Statistical analytic techniques
  - Understanding and accommodating for limitations (don't over-interpret!)

Bias & Confounding

- Take Home
  - **Beware!** When you read results from a veterinary study…an apparent link between a risk factor and a disease may be real, or just an anomaly of how the study was done.

Strategies to control bias:

Explicit enrollment criteria	• Limits selection bias at enrollment • Enables evaluation of the external validity of the study population
Randomization (random allocation of animals/pens/etc. to treatment)	• Limits allocation bias and confounding
Blinding	• Limits information bias
Stated null hypothesis Sample size justification Outcome used to determine sample size Number of withdrawals Number of outcomes reported	• Evaluate potential for analytical bias

Fatal Flaws

Selection Bias Risk

- Lack of appropriate assignment to treatment
  - e.g. lack of random allocation for randomized controlled trials; random selection from a pool of animals that meet the inclusion criteria for observational studies
  - Uneven numbers in treatment - unless specifically indicated (i.e. 2:1 ratio)
  - Indication that anyone influenced which animals were assigned to each treatment group

Fatal Flaws

Selection Bias Risk

- Lack of appropriate assignment to treatment
- Lack of a clear and consistent case definition for inclusion in the study
- Lack of appropriate 'match' animals in case-control and cohort studies due to inconsistent case-definition between treatment or inconsistent length or intensity of follow-up
- *A table should be included that reports important characteristics of the treatment populations prior to intervention so that their similarity can be assessed to assure the reader that selection bias did not occur*

Fatal Flaws

Selection Bias Risk

Information Bias Risk

- Lack of blinding of anyone who assesses study animals – particularly important for subjective assessments
- Lack of a clear and consistent case definition for outcome assessment
  - Different criteria used to identify treatment success (or other outcome) between treatments

Fatal Flaws

Selection Bias Risk

Information Bias Risk

Confounding Risk

- Complete confounding
  - If the all the animals in each treatment differ from all the animals in the other treatments in any way other than the treatment of interest

Fatal Flaws

Selection Bias Risk

Information Bias Risk

Confounding Risk

- Complete confounding
  - If the all the animals in each treatment differ from all the animals in the other treatments in any way other than the treatment of interest
- Uncontrolled partial confounding
  - Partial confounding occurs when animals with a factor that impacts the outcome are unevenly distributed between txs
  - Partial confounding can be controlled within the experimental design phase with blocking and in the data analysis phase by including the confounding factor as a covariate

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Identify the limitations of a relevant, valid study: incomplete outcomes of importance, narrow study population, inability to detect clinically important level of effect, interactions of interest not tested, etc.

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Accumulate relevant, valid studies that address clinical question and integrate the results by giving greater emphasis to studies with the greatest control for bias and confounding. Use high-quality systematic reviews and meta-analyses when available. Greatest confidence occurs when direction and magnitude of treatment effect is similar between studies and various study types and relevant study populations are included

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Think critically: gather information, evaluate information and stratify its strength, reflect on all the available information and evidence to identify what is known and what is unknown and how one's personal biases and perspective may influence the thought process, and finally, come to a clinical decision while identifying potential new evidence or information that if obtained would cause a change in the decision

Summary: Why use scientific literature in clinical decision making

- Doctors are expected to know and use the most trustworthy understanding of disease causation and intervention
- Biology / Medicine is very complex and complete knowledge is not possible
- No short-cuts – the scientific method is a slow, iterative process
- Our perspective on the scientific process does not have to align with our clients'

How should we read?

- Title
- Author(s)
- Abstract/Conclusions

RELEVANCE

- Materials and Methods
- Data / Supporting evidence
- Outcome(s)
- Conclusions

QUALITY

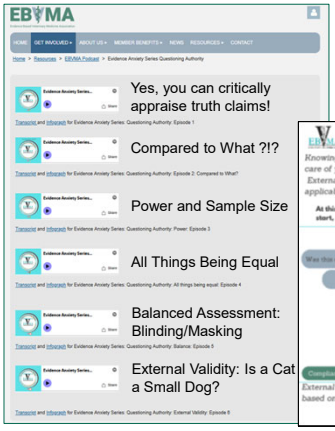
The Value of What We Read:

Quality versus Relevance

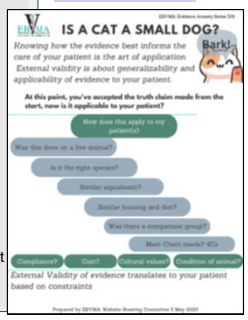
- Abstract:
  - Can determine if paper is relevant
  - Cannot determine quality of the work
  - If you commit to the paper after reading the abstract - you must read it fully and critically!

Critical Evaluation of the Literature

- Who is responsible for what you allow into your brain?
  - You are responsible !!
  - Protect your brain



https://www.ebvma.org/Evidence-Anxiety-Series-Questioning-Authority



Introducing **QUIT** - the **Q**uality & **U**ncertainty **I**ndicator **T**ool:

10 user-friendly questions for assessing veterinary treatment articles

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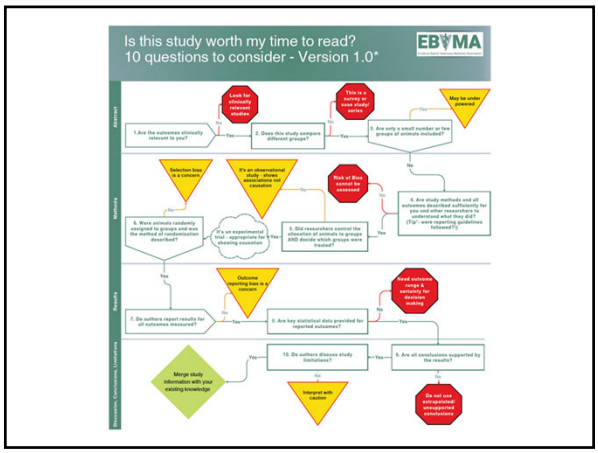
Keywords: Evidence Based Veterinary Medicine, critical appraisal, knowledge translation, EBVMA, Risk of Bias

Abstract:

Evidence based veterinary medicine (EBVM) was introduced almost three decades ago. The Evidence Based Veterinary Medical Association has promoted EBVM for 20 years, and yet it is still hard to do in daily practice. Practicing veterinarians make intervention decisions all day and the public expects they are made in consideration of the best available body of evidence. And therein lies the quandary. Keeping current isn't just a matter of staying on top of new research, it means being able to assess its value within the context of the existing body of evidence. It takes time to do this and time is always in short supply for busy practitioners. It would therefore be most efficient if practitioners had access to living systematic reviews of a wide swath of intervention questions but we're not there yet. In the interim, practitioners have to triage publications and do their best to assess and assimilate new studies accordingly. Appreciating this challenge, the EBVMA Board has collaboratively developed a user-friendly 10 question tool as an aid to help practitioners quickly assess the merits of new research. We named it QUIT, the quality and uncertainty indicator tool. QUIT is a living prototype and we invite feedback from all users.

Veterinary Evidence Summaries

- Systematic reviews
  VetSRev (database of veterinary systematic reviews)
  http://webapps.nottingham.ac.uk/refbase/
- Best Bets for Vets
  Evidence summary (CAT)
  https://bestbetsforvets.org/
- RCVS Knowledge Network
  Various resources
  http://knowledge.rcvs.org.uk/home/


Is this study worth my time to read?
10 questions to consider - Version 1.0*
EBMA
Abstract
Methods
Results
Discussion, Conclusions, Limitations
Look for ethnically relevant studies
This is a case report or case study/ series
May be under powered
1.Are the outcomes ethically relevant to you?
2. Does this study compare different groups?
3. Are only a small number or few groups of animals included?
Selection bias is a concern
It's an observational study - shows associations not causation
Risk of Bias cannot be assessed
4. Are study methods and all outcomes described sufficiently for you to understand what they did? (Tip*- were reporting guidelines followed?)
6. Were animals randomly assigned to groups and was the method of randomization described?
It's an experimental trial - appropriate for showing causation
5. Did researchers control the allocation of animals to groups AND decide which groups were treated?
Outcome reporting bias is a concern
Head outcome comp & certainty for decision making
7. Do authors report results for all outcomes measured?
8. Are key statistical data provided for reported outcomes?
Merge study information with your existing knowledge
10. Do authors discuss study limitations?
9. Are all conclusions supported by the results?
Interpret with caution
Do not use extrapolated/ unsupported conclusions