

## **Theriogenology and Developments in Epidemiology: *Future Opportunities?***

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**Abstract:** The concepts and methods of the branches of epidemiology, particularly clinical epidemiology, likely have much to offer the discipline of theriogenology. As with theriogenology, epidemiologic methods evolve when technological innovation enables new approaches to old problems. The recent emergence from clinical epidemiology of the evidence-based medicine paradigm in human medicine and the associated developments of systematic reviews and meta-analysis may present new opportunities for collaboration between the two disciplines.

Key words: analytical epidemiology, clinical epidemiology, evidence-based medicine, systematic reviews

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### **Introduction**

With evolving technology and continual change in the client industries, whether domestic pets or agricultural animals, new opportunities for productive collaborations between the disciplines of theriogenology and epidemiology are emerging. Thirty years ago, who would have thought that real time imaging of a fetus could be done using portable ultrasound technology, that camelids would become a species of serious interest to U.S. theriogenologists or that the scale of a large dairy being 300 cows would change to being 3,000 cows and still increasing. Since the announcement of the IBM Personal Computer in 1981, three decades later almost everyone has ready access to a previously unimaginable amount of computing power as the computing capability of many personal computers now exceeds that of most mainframe computers of earlier decades. With the development of the internet in 1983 and Tim Berners-Lee's development of HTML in 1989, the exchange of information between these distributed but interconnected personal computers has become both inexpensive and relatively easy. As a consequence, the amount of on-line information is exploding in all fields and now includes on-line bibliographic databases with links to on-line versions of journal papers, e-mail listserves and blogs for communication between remote colleagues. Whereas clinicians used to be the primary providers of specialized information to their clientele, now they are also functioning more in the selection, evaluation and interpretation of such information that is now directly accessible by that clientele. The traditional "push" flow of printed information, the provision of which was often driven by publication schedules of the providers, is changing to a "pull" flow, driven by the occurrence of an immediate "need to know" on the part of the user. Personal computer technology has enabled dairy herd record systems to move from Dr. Zemjanis's flip cards in the tin racks to cow-side PDAs (personal digital assistants) that interface by a wireless local network to personal computers located in farm offices, which in turn automatically upload data via the Internet to multi-herd databases for comparative analysis and flagging of exceptions needing management and consultant attention.

Meanwhile, the knowledge bases, methods and technologies of veterinary disciplines have continued to evolve, particularly as allied scientific disciplines, such as molecular biology, have emerged and made rapid advances. The purpose of this paper is to discuss developments associated with the discipline epidemiology that may be useful to theriogenologists,

concentrating on the more recent, to identify selected resources that provide entry points to these, and to consider emerging opportunities afforded by these developments.

### **Background on Epidemiology**

Epidemiology is the study of the distributions of diseases, more broadly of health conditions, and of their causes and associations in populations as classified by intrinsic attributes, such as genetics, age, gender and reproductive history, and extrinsic factors, such as housing, nutrition and environment. Over time, the branches of infectious disease epidemiology, descriptive or observational epidemiology, analytical epidemiology and clinical epidemiology have developed. Evolution of epidemiology is driven by the social cost of ill health, the causes of and risk factors for which need to be understood as a basis for developing and evaluating interventions to reduce their impact. Advancing technology provides new opportunities for acquiring data and the development of new methods for analyzing this data. A number of excellent epidemiology texts are available, examples of which are Dohoo et al.(18), Hulley et al.(41), Noordhuizen et al.(54), Rothman and Greenland (61), Smith (70) and Thrusfield (77), as well as more specialized materials, such as Ruegg (63), and a plethora of on-line materials.

The history of epidemiology is intertwined with the histories of science, medicine and technology. Infectious disease epidemiology is the classical epidemiology, being the study of epidemics; the dynamic factors involved in the transmission of infectious agents in populations and the natural history of disease, which is how a disease spreads through groups and how an individual case develops. Epidemiology began with Hippocrates, the "Father of Medicine", and his 400 B.C. writings such as "On Airs, Waters and Place" and "Of the Epidemics" (<http://classics.mit.edu/Browse/browse-Hippocrates.html>).

Descriptive epidemiology, the most basic form of epidemiology, is the description of the patterns of occurrence of health-related states or events in groups and their characteristics; answering the questions of "who?", "what?", "where?", and "when?". This branch began in the 1800's with John Snow, the "Father of Modern Epidemiology" and his intervention at the Broad Street Pump to prevent spread of Cholera in London based on his study of cases and controls (<http://www.ph.ucla.edu/epi/snow.html>). This work is most remarkable because it occurred before the germ theory of disease and the development of the Henle-Koch Postulates (1877) for assessing infectious causality.

Analytical epidemiology, the next major development, emerged in the late 1940's and is the development of study designs and the methods for their analysis to evaluate potential associations between risk factors or interventions and health outcomes in large heterogeneous groups. The need to assess drug and vaccine efficacy in large field populations, driven by the discovery of antibiotics and particularly the development of viral poliomyelitis vaccines, led to the development of the experimental study methodology of randomized controlled clinical trials. The need to assess associations between risk factors, some rare or with potentially long periods between the exposure and the outcome, for chronic and noninfectious diseases, particularly cardiovascular diseases and lung cancer, led to the development of the observational study methodologies of case-control and cohort studies. New biostatistical procedures such as multiple logistic regression, survival analysis and special procedures such as Mantel-Haenszel analysis were developed to analyze the data generated by these designs, facilitated by analysis routines coded in the FORTRAN programming language running on mainframe computers, a then emerging technology. Analytical methods continue to evolve as advancing computer technology makes widespread use of computation-intensive methods feasible.

One of the most important developments associated with the emergence of analytical epidemiology was the parallel development of Hill's-Evans Postulates, which are more generally useful for assessing cause and effect under broader circumstances than those to which the Henle-Koch Postulates are applicable.(26) Hill proposed his Criteria for Causation (1965) to

evaluate cause and effect relationships for non-infectious diseases, particularly the relationship between smoking and lung cancer. Based on Hill's criteria, Evan's Postulates (1976) provide a direct basis for developing testable hypotheses evaluated by executing an epidemiologic study based on the appropriate comparisons. Fulfilling the entire set constitutes very strong evidence for causality but, unlike the Henle-Koch Postulates, the failure to fulfill one or more particular criteria may not significantly weaken evidence for causality. On the other hand, strong negative evidence for particular criteria logically refutes causality while others provide only weak evidence for cause when fulfilled. These concepts can define a strong logical framework for establishing causation within a discipline, such as that of Guzelian et al. for toxicology (29).

Clinical epidemiology, a recently emerged branch of epidemiology (23,64), is the application of epidemiology to the clinical process, particularly clinical decision making on diagnosis, prognosis and treatment, and the evaluation of evidence for these, both patient-derived and from the clinical literature, for use in this decision making. Clinical epidemiology includes the methodology for appropriate evaluation of diagnostic and screening test performance in specific target populations and for interpreting test results on individuals and groups. Several current clinical epidemiology texts include Fletcher and Fletcher (24), Haynes et al. (36) and, for veterinary medicine specifically, Smith (70).

### **Emergence of Evidence-Based Medicine**

In the 90's the paradigm of evidence-based medicine (EBM) coalesced from clinical epidemiology, traditional journal clubs, and long standing efforts to establish efficient methods for clinicians to perform valid critical appraisals of the clinical literature.(12) The key was the recognition by educators at medical schools implementing problem-based learning curriculums that, in contrast to the traditional authority-based lectures and textbooks, answers to many important clinical questions were not supported by empirical evidence in the primary literature and that what evidence existed in such literature varied widely in strength. Also driving the development of EBM was the demand from government entities and other third-party payers that if different clinical procedures or drugs with the same objective differed considerably in cost, they wanted evidence that the higher cost option was justified by sufficiently higher efficacy.

In a landmark paper describing the implementation of EBM in a residency training program (3) (<http://www.cche.net/usersguides/ebm.asp>), the EBM Working Group stated "evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research." EBM was further defined by Sackett et al. (65) as "evidence-based medicine is a short-hand term for five linked ideas: first, that our clinical and other health care decisions should be based on the best patient- and population-based as well as laboratory-based evidence; second, that the problem determines the nature and source of evidence to be sought, rather than our habits, protocols or traditions; third, that identifying the best evidence calls for the integration of epidemiological and biostatistical ways of thinking with those derived from pathophysiology and our personal experience . . .; fourth, that the conclusions of this search and critical appraisal of evidence are worthwhile only if they are translated into actions that affect our patients; and fifth, that we should continuously evaluate our performance in applying these ideas." Further, "The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. By individual clinical expertise we mean the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice. . . . By best available external clinical evidence we mean clinically relevant research, often from the basic sciences of medicine, but especially from patient centred clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative, and preventive regimens. External clinical evidence both invalidates previously accepted diagnostic tests and treatments

and replaces them with new ones that are more powerful, more accurate, more efficacious, and safer."(66) (<http://bmj.bmjournals.com/cgi/content/full/312/7023/71>) This definition and the emergence of this paradigm in human medicine has not been without considerable controversy. (9,47,72)

Since the first publication of the phrase "evidence-based medicine" in the primary literature in 1992 (3), the number of bibliographic records containing the term has exploded. A bibliographic citation analysis from the Institute for Scientific Information covering the years 1992 to 2004 (available on-line (<http://garfield.library.upenn.edu/histcomp/index-cochrane.html>)) shows the linkages between the foundation publications. An April, 2006, search of the National Library of Medicine on-line database PubMed ([www.pubmed.gov](http://www.pubmed.gov)) with the specific phrase "evidence-based medicine" yielded 21,218 papers and a similar Google (<http://www.google.com/>) search yielded 7,670,000 websites. Because of the rapid evolution and integration of this paradigm into human health care and the desire by its developers to facilitate this process, the web is a major repository of EBM materials. The primary websites include the Oxford Centre for Evidence-based Medicine (<http://www.cebm.net/>), the University of Alberta Centre for Health Evidence (<http://www.cche.net/>), Evidence-based Decision Making (<http://www.evidencebased.net/>) and Netting the Evidence (<http://www.shef.ac.uk/scharr/ir/netting/>). A number of print and on-line journals focusing on EBM have appeared as well as EBM textbooks, such as Strauss et al. (73) and, for veterinary medicine, Cockcroft and Holmes (14). Recent papers discuss the implementation of EBM in veterinary practice, such as (13,21,39,40,62), the British Equine Veterinary Association is undertaking EBM-focused clinical research through its website (<http://www.beva.org.uk/index.php>) and is incorporating EBM into their two journals (46) and a veterinary group, the Evidence-based Veterinary Medicine Association (<http://www.ebvma.org/>), is forming.

Procedures and methods to support the practice of EBM are developing rapidly, particularly strengthening clinical study design and execution, improving the clinical literature reporting this research and improving the rapid critical appraisal and interpretation of this literature. These efforts include the CONSORT (Consolidated Standards of Reporting Trials) statement (2,49) (<http://www.consort-statement.org/>) to improve the reports, and indirectly the execution, of clinical trials, the STARD (Standards for Reporting of Diagnostic Accuracy) statement (6,7) to improve the reports of diagnostic accuracy studies and the MOOSE (Meta-analysis of Observational Studies in Epidemiology) proposal (74) as well as others (8,43). Because these standards are updated as serious weaknesses or problems are recognized through experience with their application, they are dynamic and, because their adoption is intended to be widespread, the identical reports of the updates are published in multiple journals under special copyright agreements. Although anonymous peer reviewed literature is likely considerably stronger than non-peer reviewed literature, the peer review process is not without its flaws (53,69) and employing it alone has been found insufficient to ensure strength of evidence. The fundamental problems are that the opportunity for the occurrence of bias, which is the systematic deviation from truth (17) at any point in the research process (45), is affected by errors and omissions in study execution and is inherently different between study designs (e.g., experimental vs. observational, prospective vs. retrospective) and the fact that certain types of clinical questions can only be addressed by inherently weaker study designs.(27) From another perspective, quality is "the extent to which all aspects of a study's design and conduct can be shown to protect against systematic bias, nonsystematic bias, and inferential error."(43) Although such standards are intended for use in human medicine and will require modifications to meet the circumstances of veterinary medicine, several veterinary journal editors have called for contributors and reviewers to apply such statements to future articles in those journals.(37,59) The structured abstract (4,35), intended to improve both quality and readability

of abstracts, is one of the first of these innovations and now is the form of about two-thirds of clinical report abstracts (52), including many in veterinary journals. Abstracts are critical because most often it is the only paper component busy clinicians read.(67) To assist readers in critical appraisal, some 25 Users' Guides to the Medical Literature appeared in *JAMA* along with many other similar publications in other clinical journals.

Because of the large number of primary scientific papers being published from active research areas each year across a wide range of journals, clinicians and others have long relied on secondary scientific reviews as an efficient means for updating. However, those developing methods for critical literature appraisal quickly recognized that no matter how strong the literature underlying the conventional narrative review process, it too often resulted in weak, biased and sometimes misleading reviews and, furthermore, that users unfamiliar with the primary literature could not detect these flaws.(51) To strengthen reviews, the systematic review process, focused on using scientific methods to identify, assess and synthesize information into reviews, is developing.(50) The QUOROM (Quality of Reporting of Meta-analyses) statement, a guide intended to improve the reporting of meta-analyses of controlled clinical trials, is in early stages of development (48) as well as one for reviews of prognosis studies.(34) The systematic review process also provides a formal means for incorporating the "grey" or unpublished literature, which is critical to reducing the generally positive publication bias of the primary literature.(15,56) Developing these statements is a continuing process as the challenges in improving these reviews are considerable (11,33,55,68,76) and the issues complex.(71) Developing in parallel with the methodology for systematic reviews is meta-analysis, the statistical methodology for combining the quantitative estimates from multiple studies.(75) Although meta-analysis has a long history (10), it is evolving rapidly as the statistical foundation for EBM but not without some controversy.(22) Examples of recent systematic reviews, some including meta-analysis, in veterinary medicine from a range of journals include Adkin et al.(1), Aragon and Budsberg (5), Craigmill et al.(16), Dohoo et al.(19,20), Fourichon et al.(25), Hirst et al.(38), Lopez-Gatius et al.(44), Rabiee et al.(58), Robert et al.(60), Trotz-Williams and Trees (78), and Westwood et al.(80). Hirst et al.(38) took the novel step of establishing a website to disseminate their review and associated materials but its status is presently unclear.

The Cochrane Collaboration (<http://www.cochrane.org/>) is a large international non-profit organization formed to develop standardized methods for systematic reviews, to establish the structures for performing and updating each review, to provide software and materials to support the review process, to provide a repository for the data and the reviews and to disseminate these.(28,79) A fifteen-year history of how the organization came into being is on-line at (<http://www.update-software.com/history/clibhist.htm>). The operations of the Collaboration are guided by ten founding principles, which are collaboration, building on the enthusiasm of individuals, avoiding duplication, minimizing bias, keeping up to date, striving for relevance, promoting access, assuring quality, continuity and enabling wide participation. The reviews are performed and updated by Cochrane Review Groups, of which there are currently fifty and which are comprised of individuals with an interest in developing and maintaining the reviews relevant to a particular health area, some 2,500 reviews being completed to date. These groups are supported by 11 Methods Groups that develop the methods for performing reviews. The extensive Cochrane Manual (<http://www.cochrane.org/admin/manual.htm>) is the principal procedural resource for these groups.

Moving full circle, the shift toward EBM in clinical practice is stimulating a shift toward evidence-based human (32) and veterinary medicine (30) educational practices, including the formation of the BEME Collaboration (best evidence medical education, <http://www.bemecollaboration.org/>) and the publication of BEME guides, such as (31). If a paradigm shift doesn't significantly improve patient care, it was likely a waste of scarce resources and education is a critical step in achieving that improvement.

## **Whither theriogenology?**

The discipline of theriogenology as well as veterinary medicine in general whole would likely benefit from greater incorporation of the evidence-based medicine principles and practices developing in human medicine as well as other principles from epidemiology. Shifting from the traditional authority-based knowledge paradigm to more evidence-based knowledge paradigm would likely benefit all stakeholders by increasing certainty about the efficacy of clinical diagnosis, prognosis, therapy and prevention practices. Those of sufficient efficacy could be supported to clients on the basis of empirical evidence. Those found lacking efficacy would be removed from the clinician's armamentarium and research on their replacements fostered. In the long term, the credibility of the profession would be maintained if not enhanced. The general status of evidence in the veterinary literature with regard to important clinical questions is essentially unknown but assuming that weaknesses similar to those observed in the human medical literature, which led to the EBM paradigm, are present with similar prevalences seems reasonable as a first step.

Veterinary medicine is fundamentally different from human medicine in several important respects, both positive and negative, beyond the fact that it serves multiple species rather than a single species. First, the allocation of animals to experimental study groups can occur under a much broader range of circumstances than for humans. For example, random allocation, rather than self-selection, to smoking and non-smoking groups is unlikely to ever occur in humans. Compared to humans, animals are frequently managed in groups (e.g., herds, kennels, stables) under relatively homogenous, controlled circumstances of housing, nutrition and other environmental factors that increase the strength of comparisons between individuals experiencing different levels of the factors of interest. Analytical methods have been developed to adjust for clustering effects when these must be taken into account to assure validity.

On the negative side, the profession and the resources available to support clinical research for the development of EBM resources are far smaller for veterinary medicine than human medicine. For example, the number of physicians with privileges at the University of Washington Medical School is greater than the number of veterinarians in the entire state of Washington. As noted by Keene (42), the entire membership of the oncology specialty of the ACVIM is approximately the size of the oncology division of a medical school with a regional cancer center. This suggests that to obtain similar results, a greater proportion of the individuals in a veterinary discipline would have to be engaged in the collaborations to generate evidence for evidence-based veterinary medicine than in human medicine. Unlike the human side, funding for such endeavors will likely be scarce, particularly for minor and non-economic species, for multiple reasons.

The supporting veterinary literature needed for developing EBM components, such as systematic reviews, is clearly not as plentiful as that for similar efforts in human medicine. Keene noted that during a period in which 60 studies relevant to a particular veterinary clinical question were published in the veterinary literature, 5,400 studies were published in the human literature for the equivalent human clinical question, almost a 100 to 1 ratio, and that many of these were based on inherently stronger study designs.(42) Aragon and Budsberg noted that although 28 studies contained data relevant to their clinical question, they classified none as containing level I evidence (randomized blinded controlled trials), 5 as containing level III evidence (uncontrolled case series) and 23 as level IV, the lowest strength of evidence. In a review of the field efficacy of bovine respiratory vaccines, Perino and Hunsaker (57) concluded "We are impressed with the small number of useful reports . . . while there are hundreds of reports in the literature, most suffer from one or more design flaws or limitations. . . it suggests that we may be making less than optimal recommendations on vaccine use because of a lack of clinically relevant information." They further concluded "it is time to critically evaluate vaccination as a management tool" In the United States, demonstration of field efficacy is required for

approval of human vaccines while only demonstration of laboratory efficacy is required for animal biologicals. Many authors of systematic reviews noted that the heterogeneity of study designs, missing variables and missing estimates of precision in the source literature caused problems in their review process and that the process took a great deal of time. A general impression is that investigators taking note of such observations in reviews can lead to stronger, more consistent clinical study design and execution and to a stronger literature base in the future.

The clinical sides of the veterinary medical disciplines have the most important role in a discipline's move to incorporate EBM. The first step is determining the critical questions regularly occurring at the veterinarian-patient interface for which an evaluation of the evidence through a systematic literature review is needed. A question may be critical because it involves a frequent procedure, such as vaccination, the risk of serious adverse outcome on an individual basis, such as rendering a valuable stud unfit for breeding, something about which more certainty is needed, such as the best preventive practice among several, is a nagging problem, such as detecting subclinical but chronic infections like Johne's, or is simply descriptive epidemiology benchmarking a species new to veterinary practice. When answering the critical question involves evaluating known alternatives and the literature is found lacking or inconclusive, the missing evidence can be generated by the design of a strong clinical study executed by clinicians during the normal course of delivering care to the particular species. To acquire sufficient number across the desired range of circumstances within a reasonable time frame and minimizing the burden of participation will often require the participation of clinicians at multiple locations. In other circumstances, establishing the case for traditional basic research focused on a specific question may be the most appropriate action. Computer-based communications technology has a critical role in networking remote clinicians participating in the processes of defining the critical questions appropriately, facilitating the systematic reviews and developing and executing the needed clinical research studies. To participate effectively and to maintain study quality, participating clinicians will need a basic understanding of epidemiologic research principles and methods, such as to the level of that contained in Hulley et al. (41). As this understanding will also benefit them in performing critical appraisals of the literature they read for their own clinical use, a logical move is to incorporate this knowledge requirement into the board certification process. Over time, such a requirement will establish a critical mass of boarded clinicians with the expertise to incorporate EBM into the discipline, having both discipline and clinical research knowledge beyond that of general veterinary medicine.

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