

# POPULATION MEDICINE NEWS

Epidemiology, Preventive Medicine, Public Health  
Production Medicine, Computer Applications in Vet Med

August 3, 1992 5(16)

## CRITICAL REVIEW OF UNCRITICAL REVIEWS

*Our profession would benefit if review article authors would more critically review the design and analysis aspects of cited field studies.*

The culinary metaphor was whimsical, but the efficacy-by-pseudoreplication recipe described in the July 6 issue of PMN was an accurate depiction of some efficacy trials reported in the veterinary literature.<sup>(1)</sup> Rather than being the result of a desire to circumvent good science, such studies seem to reflect a lack of appreciation of the dominant role of group effects (e.g., pen effects) in morbidity risk variation, because of this, the need to analyze at the same level at which one allocates. In a larger sense, the failure to understand and avoid pseudoreplication is a symptom of difficulties that we veterinarians have experienced in taking science from the orderly, controlled setting of the lab bench to the chaotic environment of the world where genuine efficacy must finally be measured. Our problems have sometimes been compounded by the failure of review article authors to critically evaluate design and analysis features in synthesizing their conclusions.

For example, consider a recent review of the literature regarding bovine respiratory syncytial virus vaccination which included the assessment:

*"Field trials with BRSV ' have been conducted. Most of these trials have been controlled studies, and results suggest the vaccine to be safe and efficacious."*<sup>(2)</sup>

Seven references were cited to support this conclusion of which one was a symposium proceeding, itself containing reports from numerous studies. Relevant to our present discussion, many of the cited studies appear to have used pseudoreplication. Furthermore, some of them contained egregious randomization errors in that the vaccinates and controls were markedly

dissimilar in weight or entering BRSV titer (controls being significantly more naive in one of the cited studies; a study which still failed to show a statistically significant morbidity or mortality advantage on the part of vaccinates-ref 3); some contained no statistical tests or other inferential tools (ie, P-values or confidence intervals); some used historical controls in conjunction with pseudoreplication, beginning with unusually high morbidity years to be used as unvaccinated controls; and some, in fact, showed little or no effect or even a negative effect. The authors of the report most worthy of the appellation "controlled study" (a near-model effort) concluded from their 5 separate trials: "Although the trend in these field trials was to a sparing effect of the BRSV vaccine, the small reduction in treatment rate may not justify the cost of the vaccination program."<sup>(4)</sup>

The word "suggest" from the above-quoted BRSV review did not, in this critical reader's judgment, adequately convey the exceedingly tenuous nature of any conclusions--positive or negative--that might properly be drawn. Yet, given the backdrop (*Compendium on Continuing Education*), the quoted statement was surely taken, by many readers, as de facto endorsement of a commercially available product by disinterested, thus objective, academic reviewers. We will likely see the review cited as authoritative in textbooks referencing sentences containing the words "many studies" and "well established efficacy."

In comparison to the literature in other biomedical sciences, the veterinary literature stands out for its lack of critical review of the design and analysis of cited articles in reviews and textbooks. Original articles and reviews in the animal sciences and in human medicine

## Continuing Education Programs, Fall 1992

### Bellingham

#### Best Western Lakeway Inn

October 21

Erich Studer and Mushtaq Memon: Should we be doing postpartum exams?

Mark Kinsel: Abortion epidemiology and diagnosis

\*

### Tacoma

#### Pierce College, November 14

Using the dry period to prepare for high milk production

Ruth Blauwiel: Balancing dry cow diets for high milk yields

Joe Harrison: The importance of silage quality in the health and function of the cow.

Steve Fransen: Walking the tightrope between high forage quality and maximal yield

\*

### Pullman

Food Safety from Farm to Table

Updates on practical aspects of food safety from the farm to the consumer. Topics include

Listeriosis, Campylobacteriosis, Salmonellosis Disease associated

with E coli O157, Foodborne diseases from aquatic animals,

Controversial role of the Food Safety Inspection Service, and

Consumer responsibilities in food safety.

\*

\*

For Bellingham and Tacoma programs, contact Christina Rockett: 509-335-7070

For Food Safety Program in Pullman, contact Dr. Virginia Hillers: 509-335-2970

are monitored by a vigilant group of numerant pundits who, though annoyingly anxious to dash off letters to the editor, encourage a more careful approach in the conduct and review of field research. Occasionally the veterinary profession benefits from the comments of our more numerant colleagues in related disciplines. An historically important example occurred when JL Gill of the Department of Animal Science at Michigan State University wrote a scathing letter to JAVMA regarding the use of pseudoreplication in an anthelmintic trial published in that journal.(5) Since Gill's letter, anthelmintic researchers appear to have walked a path of relative righteousness with respect to pseudoreplication.

Unfortunately, we are more often left to the devices of our own literature, a sanctum where design and analysis have been considered peripheral to scientific discovery and where review articles sometimes seem to be judged more by the poundage of their reference lists than by the intensity with which results and conclusions of the cited reports are scrutinized. Under these conditions, a strong product bias is inevitable since, as was demonstrated in the July 6 issue,(1) establishing efficacy is a trivial business when investigators are freed of the constraint of analyzing their data at the same level they allocate it (pseudoreplication).

The failure on the part of some researchers to provide for adequate design and analysis and the reluctance of reviewers to critically review the articles may stem from a feeling that, since statistical considerations are (thought) straightforward and of secondary importance in laboratory science, the same must be true for field research. It is noteworthy that, in the above quoted BRSV vaccination review, (2) far more space was dedicated to critically reviewing antigenic and immunologic aspects of vaccine development—concerns of laboratory science—than to efficacy of the product in the field. Which is more important to those who might read a publication called *Compendium on Continuing Education*?

Although errors such as pseudoreplication are common in laboratory experiments,(6) they have relatively

less impact under physically controlled, laboratory conditions. The P-value obtained from a trial using line bred mice in an environmentally controlled facility may not be greatly biased by counting individual mice as the experimental units even though allocation is done by cage or room. The same error repeated in a feedlot trial can, as demonstrated in the July 6 issue,(1) result in "statistical significance" in a majority of trials even when the true efficacy is exactly 0. The noise we would like to ignore and the signal for which we are searching are much closer in magnitude in the field than in the laboratory. Careful efforts are necessary to detect and measure any signal that exists and to avoid the illusion of one that does not exist. For our trouble we gain external validity and statistical power, study attributes seldom available to laboratory researchers evaluating practical issues such as vaccine efficacy.

Allocation by groups (e.g., pens) is not necessarily a design flaw. For communicable disease, sub-populations rather than individuals are the legitimate targets for vaccination programs, thus allocation by pen is appropriate for a feedlot vaccination study. Under this design, pseudoreplication would occur at the analysis stage only if each individual animal were considered an independent observation. In the words of 1 reference "In ANOVA terminology, it [pseudoreplication] is the testing for treatment effects with an error term inappropriate to the hypothesis being considered." (6)

Considerable work has demonstrated that much of the morbidity risk an individual experiences is due to pen effects. (e.g., ref 7) In other words the morbidity and mortality data from pen mates are strongly correlated. One hypothesis is that environmental and host factors directly influence exposure and resistance of individuals which, in turn, indirectly influence some aspect of infection dynamics in the pen, thus resulting in a broad distribution of pen morbidity with a long right tail (Fig 1 in July 6 issue). Though we do not yet have a full understanding of the reasons behind pen effect, we do not need such an understanding in order to conduct high quality vaccine trials. Beginning in the latter 19th century methods were developed, mainly by agricultural statisticians,

by which treatment effects could be isolated from the noise of all other sources of variation. The fundamental tools for this process, randomization and replication, are often misunderstood and misapplied by researchers (as in most of the supposedly "controlled" BRSV trials cited by ref 2) and must be carefully evaluated by reviewers.(6,8)

For the reviewer who wants to become better at critically reviewing the design and analytical aspects of research papers we recommend "Evolution of statistical design and analysis..." by Gill (8) and "Pseudoreplication..." by Hurlbert.(6) [Thanks to Dr. Carol Lichtensteiger for bringing the latter excellent reference to our attention]. Both of these papers discuss the practical design and analytical problems that researchers face and the historical development of tools to deal with them. Neither is mathematically intense. For review authors who do not desire to critically evaluate the design and analytical aspects of cited papers, we hope you will not be making any statements that might influence health policy decisions.

*References: 1. Sure-Fire recipe for efficacy; Pop Med News, 5(14), July 6, 1992. 2. Baker JC, Vellcer LF; Bovine respiratory syncytial virus vaccination: current status and future vaccine development. Compendium on Continuing Education 13: 1323-1335, 1991. 3. Morter RL, Amsutz HE; Effectiveness of vaccination of feedlot cattle with bovine respiratory syncytial virus. Bovine Pract 21:65-69, 1986. 4. Donkersgoed JV, Janzen ED, Townsend HG, Durham PJ; Five field trials on the efficacy of a bovine respiratory syncytial virus vaccine. Can Vet J 31:93-100, 1990. 5. Gill JL; Biased statistical analysis when the animal is not the experimental unit (letter). JAVMA 190:5-6, 1990. 6. Hurlbert SH; Pseudoreplication and the design of ecological field experiments. Ecological monographs 54(2): 187-211, 1984. 7. Martin SW, Meek AH, et al; Factors related to sickness and death in feedlot calves. Bovine Proc. 13:32-36, 1981. 8. Gill JL; Evolution of statistical design and analysis of experiments. J Dairy Sci 64:1494-1519, 1981.*

*POPULATION MEDICINE NEWS is produced by the Washington State University Field Disease Investigation Unit, Pullman, WA 99164-6610 (509-335-0711) and is supported in part by the WSU Cooperative Extension Service. Viewpoints expressed are not necessarily those of the University or its Administration. This newsletter may be copied by anyone. Editors: Dale Hancock and Susan Holler.*