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AN APPROACH TO META-ANALYSIS: POST-PARTUM GNRH AND THE REPRODUCTIVE PERFORMANCE OF DAIRY COWS

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La recherche scientifique s'est beaucoup développée ces dernières années. En conséquence, les revues bibliographiques jouent un rôle grandissant. Les revues traditionnelles s'appuient sur les connaissances d'un expert dans son domaine mais sont rarement organisées, objectives ou quantitatives. Cependant, la méta-analyse permet une recherche épidémiologique rigoureuse pour comparer des résultats d'études similaires, et autorise des estimations de résumés. La méta-analyse permet également de mesurer les biais dans les publications ou les études de qualité. Les résultats des méta-analyses sont faciles à comprendre et à communiquer. Communes en médecine et en sciences sociales, les méta-analyses sont rares en médecine vétérinaire et en agronomie. Ce papier présente une approche structurée des méta-analyses et en discute les bénéfices. Comme exemple, des essais testant les effets de la GnRH sur les performances reproductives de vaches laitières en post partum sont présentées. L'article conclut par une proposition de standardisation de la méthode méta-analyse dans le monde vétérinaire grâce à un système expert souple. On espère qu'un tel système pourra aider les chercheurs à conduire des analyses de qualité, et que ces analyses pourront être sensibles sur le réseau Internet et remises à jour régulièrement.

INTRODUCTION

A meta-analysis is a rigorous and objective means of reviewing scientific literature and providing a valid quantitative summary of the results of similar studies. Meta-analytic methods initially focused on the synthesis of combined estimates of effect and the evolution of various statistical models. Currently, however, the emphasis of most well conducted meta-analyses lies in investigation of the relative size and nature of *differences* observed between point estimates of effect reported by authors of similar studies: A concept termed *heterogeneity.*

While meta -analyses are now common place in the medical literature, fewer than half a dozen have been published in the fields of veterinary or agricultural research. In the current climate however, with a rapidly increasing volume of published trials and the funding for further research increasingly difficult to obtain, meta-analyses are likely to become commonplace.

In 1997, a meta-analysis of the effects of gonadotrophin-releasing hormone (GnRH) on the reproductive performance of post-partum dairy cows was published by this author (Beckett and Lean, 1997). Various points of this analysis will be used to illustrate general objectives and techniques. The discussion is necessarily brief and further information may be obtained from the author.

THE OBJECTIVES OF META-ANALYSIS

To provide a quantitative supplement to traditional literature reviews : Meta-analysis has evolved as a quantitative supplement to traditional scientific reviews and this usually remains the primary objective. While obvious benefits can be seen in utilising a specialist's understanding and experience within a given area, the completeness and neutrality of the work is not always guaranteed. Material may be included in the review on the basis of authorship, institution, or results, rather than as a result of study design or quality. Traditional reviews may also tend to highlight conflicts between the opinions of reviewers, in which trial results are at best tallied in a 'head count', without any further attempt to quantify the disparities or summary estimate treatment effects.

Numerous authors have reviewed and discussed the effects of GnRH on post-partum dairy cattle (eg. Ijaz et al, 1987; Drost and Thatcher, 1992; Britt, 1994). It has been this author's impression, however, that each of these placed a different emphasis on the results of particular studies, and that the only similarity between conclusions drawn from each review was a general reluctance to interpret the significance of, and reasons for, disparities between the results of the original authors. In meta-analysing the original studies that examined these effects, we were able to state clearly our literature search strategy, inclusion criteria and methods for extracting and comparing results. Any conclusions we made were based on this completely objective and transparent approach and did not reflect our personal opinions.

To identify and explore heterogeneity between the results of similar studies : Meta-analysis provides a means by which the results of a group of studies may be examined statistically, either overall or within subgroups of study design, quality or any other clearly identified grouping variable. In this way, meta-analysis allows us to decide whether the association between an exposure and outcome may depend upon characteristics of the studies in question, a concept commonly encountered in statistics and termed interaction, effect modification or *heterogeneity.*

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Determination of heterogeneity between subgroups identified *a priori*, or amongst the group of studies as a whole, is currently viewed as one of the most useful and valid outcomes of meta-analysis (Greenland, 1994). Heterogeneity may, however, be considered 'true' or 'unexplained'. In this situation, variation in effect size cannot be accounted for by clearly identified grouping variables and, although statistical models are available to facilitate the combination of disparate results, many authors warn that these are poor data summaries and may be counter-productive in the search for and quantification of causal relationships (Greenland, 1994; Olkin, 1994). True heterogeneity may be regarded as evidence for the need to investigate the intervention more specifically and, in this regard, is considered to be a positive outcome in meta-analysis.
Significant heterogeneity in the effect of GnRH on two of the five reproductive parameters commonly reported was one of the most notable conclusions drawn from our meta-analysis. Heterogeneity was resolved however by excluding the group of studies that enrolled cows with abnormal puerperia (those with calving difficulties, placental retention or other periparturient diseases) and it was interesting to note that when the remaining studies were combined, there was no significant treatment effect. This result suggested that, with reference to the two parameters concerned, any benefit obtained from treatment during the post-partum period may be restricted to cows with abnormal puerperia, and that this group should be examined more closely in further studies.

To increase the statistical power to identify a treatment effect : Meta-analyses are frequently used as structured overviews of similar studies in which costs and practicalities have limited sample size and precision and, therefore, the capacity to detect a significant or meaningful treatment effect. Meta-analysis provides a means by which individual studies of relatively low power may be combined statistically (where appropriate) to give both point estimates and confidence limits for measures of overall treatment effect.
It is interesting to note that virtually all published trials investigating the effects of GnRH on post-partum dairy cattle were conducted using a single research herd or a small commercial farm. Many of these did not report significant treatment effects for the reproductive parameters examined and explained this in part by noting the low statistical power. By using meta-analysis, we were able combine the results of similar trials and obtain sufficient power to base our conclusions on genuine heterogeneity, rather than sample size.

To investigate the possible role of Publication Bias : Publication bias refers to the tendency for 'positive' studies to be more likely to be reported than 'negative' studies, where a positive study is often considered to be a statistically significant result refuting the null hypothesis. The proportion of total relevant studies that are unpublished will vary with the nature of the research (larger and more expensive epidemiological studies tend to be more likely to be published - at least as abstracts) but may be as high as 22 percent (Dickersin and Berlin, 1992).
The effect of publication bias is generally to produce an anticonservative influence, the direction of which will depend on the nature (preventive or therapeutic) of the association considered. Various graphical and statistical techniques are available to assess the magnitude of publication bias that may be occurring in a meta-analysis, or to estimate the number of unpublished studies that would be necessary to significantly alter any combined effect estimates obtained.
Publication bias was suspected in the group of GnRH trials discussed above. Many of the studies were small and inexpensive field trials carried out in the environment of a commercial diary and, as such, failure to report uninteresting findings in a refereed journal was considered to be reasonably likely. In order to examine the possibility of publication bias, we constructed *funnel plots* (2-dimensional funnel-shaped plots of effect size against their standard errors which should, were publication bias present, show a deficiency in the lower left corner) and measured *Rosenthal's fail safe number* (the number of unpublished studies reporting no treatment effect that would be needed to alter the mean effect size). Unfortunately both these methods are guides only and are based on the assumption of a relatively large number of trials. We were able to state that publication bias was not likely to be a problem in the overall group of studies, but were not confident about interpreting the either graphical or numerical estimates derived from the smaller subgroups.

Economic analysis : An additional though not surprising facility of meta-analysis, is the use of summary estimates in cost benefit type analyses. These are obviously analogous to analyses that may have been carried out using the results of single trials yet, if the procedure is rigorously followed, should continue the benefits of increased precision and multi-study validity discussed above. Unfortunately we were not able to demonstrate any significant effect of GnRH from the studies identified and could not therefore consider an economic analysis.

To define new research questions : It has been suggested that a meta-analysis should be carried out as a pre-requisite for any scientific research grant. While this may not always be practical, the point remains that a well conducted meta-analysis will highlight areas of disparity between studies, with further research needed in instances where this disparity cannot be resolved by considering plausible subgroups of design, quality or other clearly identifiable grouping variables. On a similar note, a *cumulative meta-analysis* may be conducted to determine whether further research is likely to make any real difference to combined estimates. This procedure is simply a repeated analysis on a chronological basis, progressively including more studies. The result is typically that of a series of increasingly narrow confidence intervals centering around an increasingly stable pooled estimate of effect. Where this estimate is demonstrably stable and reasonably precise, further studies of that design may not be warranted. It has been shown that many recent expensive trials and epidemiological studies in the medical literature have contributed little to combined estimates based on studies conducted up to that point and, as such, may not have been a particularly efficient use of resources.

We concluded from the meta-analysis of trials examining the efficacy of GnRH, that further research was needed to examine the effect of this treatment on the subgroup of cows with an abnormal puerperium. A retrospective cumulative meta-analysis suggested that this need could have been identified after fewer than half of the clinical trials had been carried out.

AN EXPERT SYSTEM FOR META-ANALYSIS

One of the principle threats currently facing meta-analysis is the production and publication of poor quality analyses, or abbreviated data summaries which pass under the guise of meta-analysis. In either case, it is this author's opinion that readers will quickly begin to view this essentially simple but rigorous study design as a technically difficult and dubiously reliable exercise. While the usual retort would be to recommend that statisticians conduct the analyses, it is my belief that meta-analysis should be a readily accessible tool and a workable alternative or supplement to traditional literature reviews.

One obvious solution would be the construction of an expert system which walked the user through the process of conducting valid meta-analyses. Such a system could be accessed via the Internet and, in this way, would also serve as a comprehensive data base for clinical trials in animal science. Summaries and results of clinical trials could be entered directly by their authors through an interactive series of windows, or could be supplied in a generic format from refereed journals in the animal health fields. In all cases, full descriptions of the methods and results, together with the details of publication, would be available to anyone conducting an analysis or simply reviewing the literature.

The system itself would support meta-analyses of both continuous and categorical outcomes and would provide summary statistics, graphical representations, estimates for publication bias and an option for conducting cumulative meta-analyses. The system should ideally be maintained in an institution in which a person with interests both in this field and in expert systems is able to follow statistical developments, conduct additional literature searches where deficiencies have been recognised and periodically assess the validity of outputs. The system would in many respects represent an animal science equivalent to the Cochrane Collaboration, a body of medical epidemiologists who oversee the conduct and publication of meta-analyses in the medical and social science fields.

CONCLUSIONS

Meta analyses are not intended to replace either well conducted traditional literature reviews or "definitive" clinical trials but, rather, to provide a powerful, exhaustive and efficient means of objectively evaluating the results of similar studies. Meta-analyses are often quite simple and inexpensive to perform, and provide easily understood graphical and statistical summaries that may be used in designing or validating future research and establishing the likely direction, magnitude and precision of point estimates for the effect of interventions. In addition to and often complementing this role, meta-analyses provide an objective framework for examining differences observed between the results of apparently similar studies. These differences may reflect subtle disparities in study characteristics, or may indicate the need for further specific research.

In order to maximise the production and publication of high quality meta-analyses, this author advocates the construction of an expert-system-based application that could be accessed via the Internet. Such a system would also act, and be maintained as, a database for clinical trials in animal science and would substantially increase the efficiency of scientific development in many areas of veterinary and agricultural research.

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