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THE RELEVANCE OF ARTIFICIAL INFECTION MODELS FOR THE STUDY OF RESPIRATORY DISEASES IN FARM ANIMALS

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INTRODUCTION

Disease models have frequently been applied to the efficacy evaluation of novel therapeutic agents. This approach offers the advantage of increased control over the infection process as well as over environmental factors which contribute to the field condition, but which may confound the interpretation of results. The investigator also has the opportunity to use equipment and monitor response variables, which may be impracticable under field conditions. Models do have limitations and these include recognising that other facilitating factors form an integral part of the pathological process experienced under commercial production conditions. The design and application of a model is also relevant. Some models are designed primarily to reproduce a disease under artificial conditions, others have been designed with the goal of being able to assess the efficacy of a prophylactic or therapeutic agent in a relatively applied environment.

REVIEW

The use of artificial infection experiments is not a new concept. Reproduction of disease by experiment formed part of Robert Koch's postulates in the 19th century, when it was first proposed that diseases are due to infectious entities. The selection of animal models for research should be based upon the following considerations:

1. Appropriateness as an analogue
2. Reliability of the model
3. Benefit over study of natural infection
4. Mechanism of infection
5. Experience of investigator
6. Limiting confounding factor
7. Number of animals involved & ethical implications
8. Contribution to current knowledge base
9. Cost

Evidently experiments which can provide an insight into the interaction of therapeutic compounds with ongoing pathology and an active immune response are highly relevant to the eventual applied use of a therapeutic agent. The option of direct infection allows greater quantification of doses administered and the morbidity which can be set at 100%. This considerably reduces the number of animals required to generate a statistically satisfactory data package. It can be seen that the estimates of sample sizes required are much smaller, than would be required to detect similar differences where the prevalence is set at 50%.

Table I

Estimation of sample sizes needed to detect differences in prevalence in groups of animals with disease prevalence levels of 50% & 100%. (e.g. a=0.05 and the power of the test (1-b)= 0.8)

Difference to detect	Sample size required where prevalence in one group is 100% (one sided test)	Sample size required where prevalence in one group is 50% (two sided test)
1%	309	39251
5%	61	1566
10%	30	388

Table II

Example of morbidity encountered using 3 different infection mechanisms in pigs involving *Actinobacillus pleuropneumoniae*

Infection mechanism	Morbidity (as evidenced by clinical signs)
Endobronchial inoculation	100 % in 12 hours (60 animals)
Intra-nasal spray	67% in 24 hours (100 animals)
Seeder model	25% in 24 hours (120 animals)
Natural infectious outbreak (typical)	5-30% in 24 hours

DISCUSSION

When using experimental infection as a part of the efficacy evaluation of a product, it is vital to pay a great deal of attention to design. Models should always be selected for their reliability, this is best done by either taking a historical view of past performance (i.e. repeatability of results) or running confirmatory pilot studies in advance of the definitive evaluation.

Artificial infection models are particularly well suited to investigating the efficacy of a therapeutic compound against one or a specific set of infective agents. They also facilitate the collection of high quality data, and may help to reduce the overall number of animals used in the process of efficacy trialing therapeutic products.

Models provide a useful tool, allowing us to 'bridge', from *in vitro* to field studies. There is scope for their increased use in product development.

REFERENCE

Reeve-Johnson L. (1997). Use of experimentally induced diseases in the development and evaluation of therapeutic agents. The Veterinary Record (in press).

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