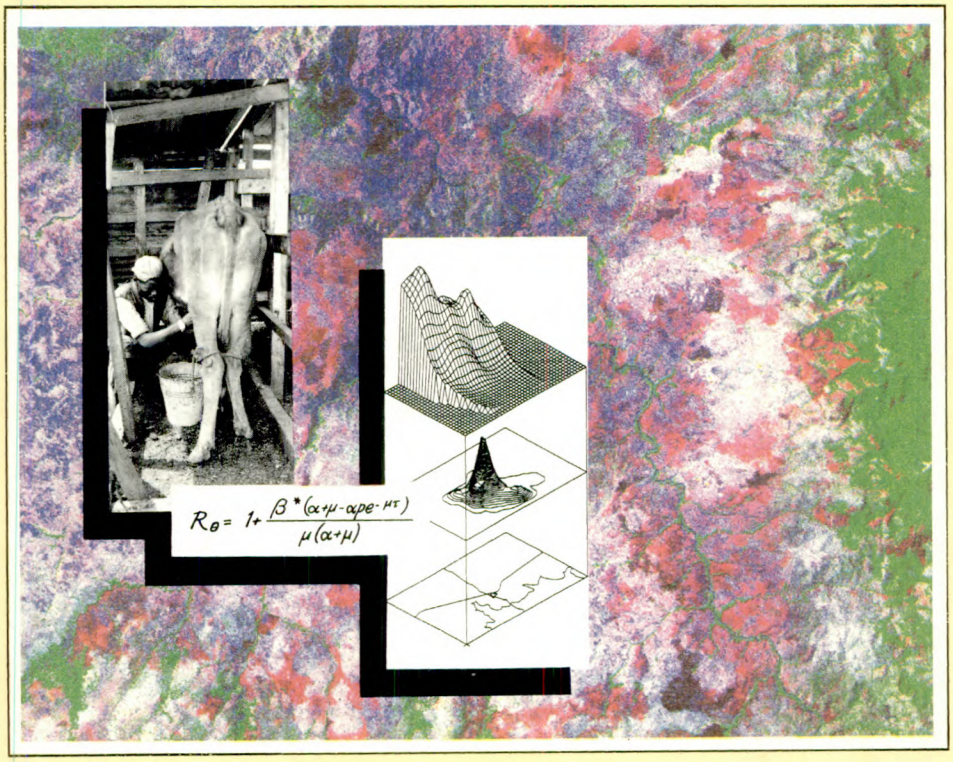
MODELLING VECTOR-BORNE AND OTHER PARASITIC DISEASES



PROCEEDINGS OF A WORKSHOP ORGANIZED BY ILRAD IN COLLABORATION WITH FAO

ILRAD • NAIROBI • KENYA

23–27 NOVEMBER 1992

MODELLING VECTOR-BORNE AND OTHER PARASITIC DISEASES

PROCEEDINGS OF A WORKSHOP ORGANIZED JOINTLY BY THE INTERNATIONAL LABORATORY FOR RESEARCH ON ANIMAL DISEASES AND THE FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

HELD AT ILRAD, NAIROBI, KENYA

23–27 NOVEMBER 1992

Edited by
B.D. Perry
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THE INTERNATIONAL LABORATORY FOR RESEARCH ON ANIMAL DISEASES
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The International Laboratory for Research on Animal Diseases (ILRAD) was established in 1973 with a global mandate to develop effective control measures for livestock diseases that seriously limit world food production. ILRAD's research program focuses on animal trypanosomiasis and tick-borne diseases, particularly theileriosis (East Coast fever).

ILRAD is one of 18 centres in a worldwide agricultural research network sponsored by the Consultative Group on International Agricultural Research. In 1993 ILRAD received funding from the African Development Bank, the United Nations Development Programme, the World Bank and the governments of Australia, Belgium, Canada, France, Germany, Ireland, Italy, Japan, the Netherlands, Norway, Sweden, Switzerland, the United Kingdom and the United States of America.

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Contents

Foreword

Modelling means different things to different people. Interpretations include the graphical representation of concepts or processes, such as organograms and flow charts, the statistical manipulations of data to determine associations (or the lack of them) between factors and the mathematical expression of dynamic processes. All three of these examples can be validly applied to diseases, both animal and human. But which types of models fit which types of problems, and what are the problems which lend themselves to modelling? Modelling science is relatively young and although the answers to these questions might be clear and straightforward to a few people, they are not clear to many, including those working in infectious diseases and in the modelling sciences themselves. Many biological scientists tend to be put off by the equations and by the abundance of assumptions; many modellers on the other hand are fearful of the complexities of biological processes, and how these conflict with the ability to represent processes numerically. Successful use of modelling therefore requires an integration of these different skills and understandings, and it was in search of such interdisciplinary integration that this workshop was conceived.

The International Laboratory for Research on Animal Diseases (ILRAD) is conducting basic strategic research on the improved control of livestock diseases and traditionally attempts to address research issues through experiments. As such, the use of mathematical models to screen hypotheses and question the validity of experimental results has not featured strongly. Recently, ILRAD has been paying increased attention to the impact of its research on enhanced livestock productivity and here, given the paucity of data in many subject areas, the use of modelling appears intuitively more valuable. It was thus decided to hold a workshop to explore both of these areas, bringing together ILRAD scientists, with statements of their research goals, and experienced modellers prepared to display and discuss their wares. In the early stages of developing plans for the workshop, it was learnt that the Food and Agriculture Organization (FAO) was intending to embark on a similar project, exploring the potential use of models to better deliver technologies to improve animal health and productivity to the field. The workshop objectives of the two organizations, ILRAD and FAO, were then rationalized and united as follows:

1. To present the perceived modelling requirements of ILRAD and FAO.
2. To review the modelling procedures appropriate to meet these requirements.
3. To identify relevant approaches.
4. To determine the database requirements for the development of such modelling approaches.
5. To explore potential collaborations.

Formal sessions covered the six major subject areas, namely vector and helminth population dynamics, parasite transmission, host-parasite interaction, parasite variation and polymorphism, effect of disease control programs and modelling systems. Within each session, the perceived requirements of ILRAD and/or FAO were presented and then examples of appropriate developed models presented. Further sessions provided examples of the application of modelling to vector-borne and other parasitic disease control, and

considered the database and training requirements. This proceedings provides a comprehensive report of all scientic sessions, and of the discussions and recommendations which ensued.

We wish to thank the many people who assisted in running of the workshop, and in the preparation of the proceedings. In particular, we thank Dr. Rob Eley and Mr Kepher Nguli for taking charge of the logistic arrangements for the workshop, Miss Lucy Kirori for preparing the manuscripts and Mr Peter Werehire for laboriously typesetting and proof reading the entire volume.

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Opening address

A.R. Gray
Director General, ILRAD, Nairobi, Kenya

On behalf of ILRAD, I wish to welcome you to Nairobi and to this workshop on the modelling of vector-borne and other parasitic diseases convened by ILRAD in collaboration with the Food and Agriculture Organization of the United Nations. We are delighted to see so many of the people involved in modelling activities and their applications gathered in one room to help us and FAO better apply quantitative methods to achieving our respective goals.

We particularly welcome this opportunity to work together with FAO, the largest coordinator of global animal disease control, and laud the initiatives taken to combine our resources in the development of this workshop.

Why are we interested in modelling? The strategic nature of research carried out at ILRAD has required an understanding of immune mechanisms in cattle and of parasite antigens, and ILRAD has become a recognized centre of excellence in these areas. Our interest in modelling was fostered particularly by the need to similarly understand the complex dynamics of the diseases we work with in the field, and to develop methods to see the control measures that we and others are working on, successfully applied under the multitude of different conditions prevailing in Africa and elsewhere.

Our first exposure to modelling techniques was thus in the area of epidemiology and we developed valuable collaborations with the University of Strathclyde, the Imperial College in London and the Australian National University. We then went on to apply modelling to help us predict the economic impact of diseases and their control, and again we have developed a productive collaboration with Texas A & M University to help achieve this. These experiences have led us to understand that modelling may help us understand other processes on which we are working, such as immune response, parasite polymorphisms and resistance to chemotherapeutics and anthelmintics, for example. They also led us to believe that the fast rate of development of modelling techniques and their better application to research problems warranted a review of the state of the art as applied to vector-borne diseases, to allow us to critically evaluate where, when and how they could best be used by ILRAD in a strategic research mode.

The workshop program covers a wide field, but you will notice that there is ample time for discussion, during which I hope you will roll up your sleeves and consider critically both the problems being presented by ILRAD staff, and the philosophy and examples presented by the modellers themselves. This is a unique opportunity, for ILRAD, for FAO, and for the modellers, to present and exchange ideas that will lead, we hope, to the production of recommendations relevant to us all as to how to proceed.

I wish you all a very successful, enjoyable and productive workshop.

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INTRODUCTION

The contribution of modelling to our understanding of infectious diseases

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ABSTRACT

Study of infectious diseases requires an ecological perspective: understanding of the biology of the host and pathogen (and intermediate hosts) is essential to comprehension of the transmission of infection and consequently patterns of disease. The veterinary and medical perspective of infectious disease is directed largely at the consequences of infection to the individual host, and tends to overlook the importance of population-level transmission processes. This paper will emphasize the value of modelling in development of understanding of population level issues in infectious disease control by reference to a variety of cases where this approach has led, and may lead in the future, to insights not as easily available to other approaches.

The quantitative approach is likely to become increasingly important in infectious disease epidemiological research and infection control. This is due to the increasing role of economic considerations in infectious disease control. By way of illustration, we can consider the industrialized and nonindustrialized regions of the world, between which the epidemiology and control of infectious disease differs markedly.

In developed countries, infectious disease is typified by either low incidence of disease or largely self-contained outbreaks. This is mainly due to resources available to vaccinate large proportions of the populations, the infra-structure available for continuous monitoring of infection, and the generally improved nutritional and health status of potential hosts. In these regions, the aim is to produce control strategies that cost less to implement than the productivity gained by the intervention. In contrast, the developing countries continue to bear an enormous infectious disease burden. In these countries, the aim is more comparative—given limited resources, which infections should be targeted by which method.

Quantitative frameworks are essential for rational consideration of policy in either instance. However, this approach requires that the population and transmission dynamics of the infection are well understood and characterized before economic and logistic variables can be combined into a single framework to consider the cost and benefits of different control strategies. Use of mathematical models within economic frameworks has been hampered by the lack of understanding of detail of transmission dynamics. However, as understanding is increased, so the models become more realistic and reliable, and they can be used as a basis for design of control strategies. This point is illustrated by consideration of several different infections under different states of development.

Models of human helminths and human childhood viral infections have developed to the point where they have predictive value and can be combined with economic frameworks. In contrast, quantitative description of the transmission dynamics of HIV (and the consequent patterns of AIDS) is beset by inadequately described processes. In the latter case, models are useful for more qualitative predictions.

INTRODUCTION

This paper is intended as a brief review of the usefulness and pitfalls associated with mathematical modelling of infectious disease agents. Readers are referred to Anderson and May (1991) for a fuller and more detailed account of methods and applications to particular diseases. Infectious diseases require special consideration for two reasons. First, they involve the interaction between two separate organisms: the host and the infectious agent. Second, in contrast with non-transmissible diseases, the infection (and disease) of one host provides the source of infection (and disease) to other hosts. This latter effect is inherently non-linear, generating epidemics that show complex patterns with time. Consequently, dynamic models (e.g. differential equations and Monte Carlo simulations) are the tools most commonly used in the study of infectious diseases, in contrast to the statistical models used in non-transmissible disease dynamics.

Study of infectious diseases requires an ecological perspective: understanding the biology of the host and pathogen (and intermediate hosts) is essential to a comprehension of the transmission of infection and consequently of the patterns of disease (Anderson and Thresh, 1988; Anderson, 1990). The veterinary and medical perspectives of infectious disease are directed largely at the consequences of infection to the individual host, and tends to undervalue the importance of population level transmission processes. This paper will emphasize the value of modelling in development of understanding of population level issues in infectious disease control by reference to a variety of cases where this approach has led, and may lead in the future, to insights not as easily available to other approaches.

The strategy by which infectious disease is controlled is increasingly determined by economic considerations, and consequently the quantitative approach is likely to become increasingly important in infectious disease epidemiological research. By way of illustration, we can consider the industrialized and nonindustrialized regions of the world, between which the epidemiology and control of infectious disease differs markedly.

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of human helminths and human childhood viral infections have developed to the point where they have predictive value and can be combined with economic frameworks. In contrast quantitative description of the transmission dynamics of human immunodeficiency virus (HIV), and the consequent patterns of AIDS, is beset by inadequately described processes. In the latter case, models are useful for more qualitative predictions.

POPULATION *VERSUS* INDIVIDUAL PERSPECTIVE

Infectious diseases occur as a consequence of parasitism by one organism of another. Parasites (including all members of the *Protista)* and hosts are ecological entities which are subject to evolutionary pressures to maximize reproduction. Parasitism is one life-style that organisms have adopted. Consequently, the study of disease transmission and propagation is an essentially ecological subject and in order to understand the parasite it is necessary to consider its ecology in terms of the parasite's reproduction and survival. In this respect, the parasite's effect on the host (disease) is only relevant in terms of the repercussions that these have on the survival and reproduction of the parasite. This concept of considering the parasite's point of view is contrary to the education and training that the veterinary profession currently receives. In this subject, the emphasis is strictly on the host, the pathological effects of parasites and the cure of disease within single hosts. This is not intended as a criticism of the veterinary profession, which should be concerned with the wellbeing of individuals, but is intended to demonstrate that understanding of infectious disease transmission dynamics is not best served by the veterinary perspective alone.

As an example, consider helminth parasites. The usual pattern is for parasites to have a highly clumped distribution within the host population: most hosts have few or no parasites, while a few have many parasites (Anderson and May, 1991). A simple assumption is that the more helminth parasites that a host harbours, the more likely that host suffers disease (clinical signs of infection) and the greater the loss of production of that host. Figure 1a shows those two assumptions. These can then be combined to consider the herd (community) loss due to parasites, shown in Figure 1b, in terms of the production loss by degree of parasitism. The greatest individual loss occurs in those hosts with intermediate burdens (the curve is peaked). Individuals with intermediate burdens are individually less affected than those with the heaviest burdens, but this is outweighed by greater representation of intermediate burdens within the herd. Consequently, if the aim of control is to reduce disease within the herd, targeting those individuals with the highest burdens will not be as effective as targeting those with intermediate burdens as well, or even instead.

QUANTITATIVE APPROACH

A mathematical model of infectious disease agent transmission is a framework of ideas including individual level processes expressed in a mathematical formulation. Consequently, an understanding of the processes at the individual level is required, for example: mode of transmission, rates of reproduction, mortality and density dependence in reproduction, survival and establishment. When these are combined into population level

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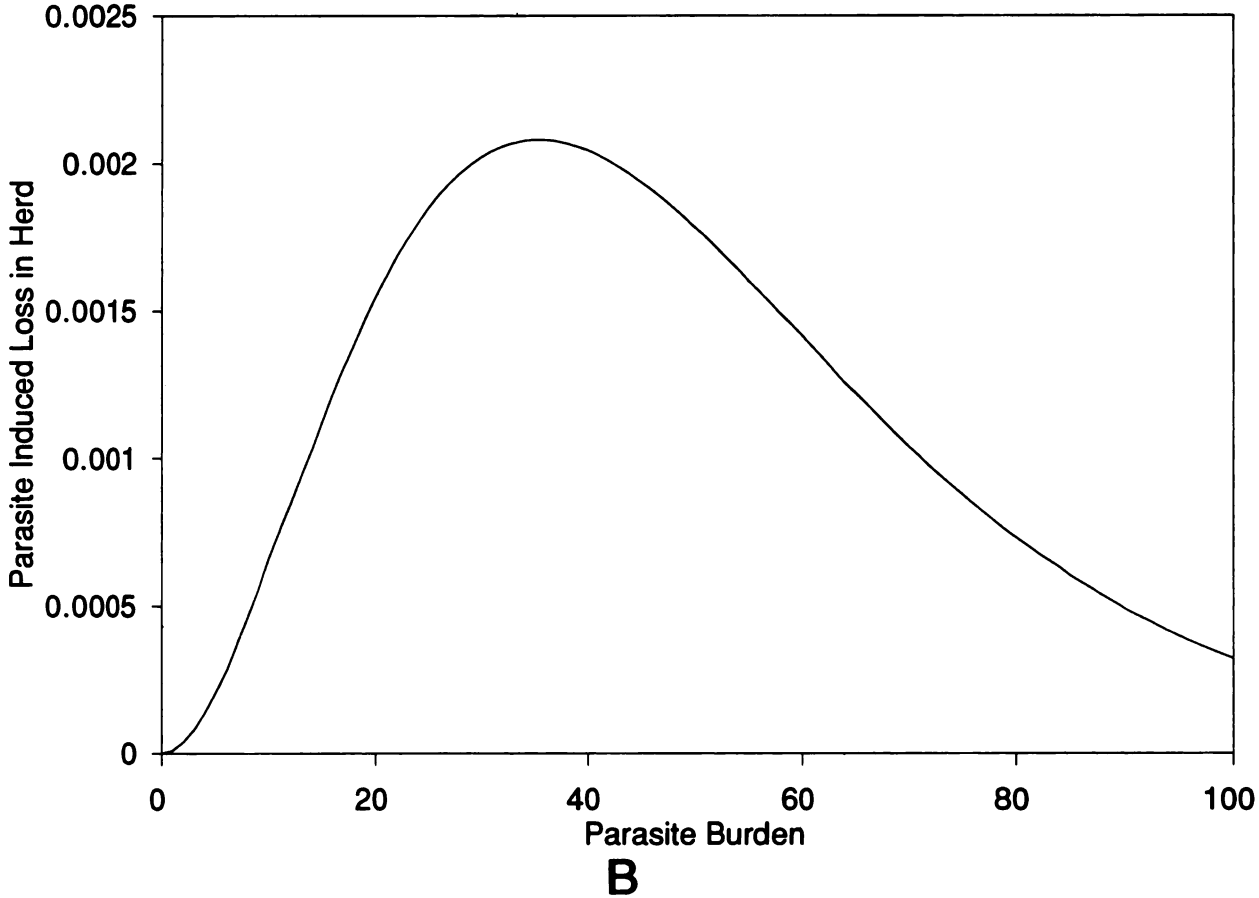

Figure 1. **(a)** shows two assumed relationships as functions of the parasite burden. The bars show the proportion of hosts with each parasite burden calculated from a negative binomial distribution with mean 20 and dispersion parameter, k, 1.0. The line shows the production losses of individual animals with each parasite burden: the greater the parasite burden the greater the loss of production from that animal. **(b)** shows the combination of the two relationships in **(a)** as a function of parasite burden. The line represents the product of the frequency with which a burden occurs and the production loss associated with that burden, and is therefore the production loss associated with each parasite burden in a herd.

models, their amalgamation can produce counter-intuitive results, as a result of the non-linear nature of the individual processes. The comparison of individual and herd production losses illustrated above (Figure 1) serves as an example of this. Once such understanding of the population dynamics exists and a framework has been developed, it can be used in several ways.

STATIC EVALUATION OF HELMINTH DISEASE

The simplest use is to examine the population effects of disease. M.S. Chan, D.A.P. Bundy, G.F. Medley and D. Jamison (manuscript under preparation) used the understanding of the population dynamics of human helminth infections to assess the health impact of these parasites at a global level. They considered six levels of heterogeneity within their framework. First was the distribution of helminths within communities, which shows surprising consistency across infected communities (Guyatt *et al.*, 1990). Second was the distribution of community level prevalences within geographical locations, which was estimated by collation of many observations of prevalences (proportion of individuals infected) within different communities. For example, the overall prevalence of infection within a country may be 50%, but there will be a distribution of prevalences such that some communities will have much higher prevalences, some lower and some will be uninfected. Third was the observed geographical heterogeneity on a country basis, such that some countries have higher overall prevalences than others. Fourth was the effect of age on the prevalence of infection. Fifth was the effect of age on disease. The health impact of infection was measured simply as the proportion of people with helminth burdens greater than some threshold value, and this phase value changes with age, such that younger children have a lower threshold. Sixth was the demographic heterogeneity in terms of the age structure of populations within different countries, which was used to convert the proportions into the numbers of individuals suffering disease. The results indicate that even with conservative estimates of the threshold and prevalence of infection, the number of people with deleterious health consequences of helminth infection is up to two orders of magnitude greater than previously estimated from case reports.

This is an example of the use of understanding of population level effects. It is not a dynamic model (there is no time component), but a static examination of the distribution of helminth parasites to assess their health impact. Realistically, this will never be estimable by any other means than a modelling approach, emphasizing the value of mathematical modelling. Further, it is necessary to measure the impact of infection to enable health policy-makers to prioritize resource allocation, and, as it must be done, is best done by those with some knowledge of the population biology of helminths.

DYNAMIC IMPACT ON HELMINTH POPULATIONS OF CHEMOTHERAPY APPLICATION

In order to extend this analysis of the effect of parasite burdens to the benefits that can be accrued from chemotherapeutic interventions, the models must contain some dynamic

component, i.e. the parasite population must change with time. Chemotherapy application reduces the helminth population (across all hosts) to a proportion of its pre-treatment level dependent on the treatment regime implemented. Following the application, the helminth population increases to recover its precontrol level. A framework incorporating this dynamic aspect plus the distribution of parasites required to estimate their health impact has been developed by Medley *et al.* (1993).

One of the problems with constructing the framework is the lack of knowledge concerning the mechanisms that generate the observed distribution of helminth parasites (Bundy and Medley, 1992). Chemotherapy will alter the parasite distribution, but during the period of helminth population expansion following chemotherapy, the original pre-treatment distribution of parasites is regained, and some mechanism must be postulated for this to occur. The simplest, most general mechanism that is consistent with empirical observation was used, but this illustrates that the biological and ecological processes must be understood to generate a population level model.

The most striking result obtained was the non-linear relationship between disease prevention and treatment effort measured as the proportion of people treated (coverage) and drug efficacy. This arises from the fact that increased treatment reduces the rate of establishment of worms across the whole host population (untreated as well as treated), so that those hosts that went untreated gained more benefit as the helminth population was reduced. The aim of this research is to incorporate economic and logistic costs of treatment in interventions. Without consideration of costs of treatment the most effective control program is to treat everybody all the time. Incorporation of costs allows different programs to be compared in terms of both the benefits gained (disease prevented) and the cost of that benefit.

QUALITATIVE *VERSUS* QUANTITATIVE PREDICTION

Mathematical models of infectious agent transmission provide quantitative results, i.e numbers. However, the reliability of the results is not dependent on the numerical precision to which they are quoted, but on the biological and ecological understanding that underpins the model. It is possible to generate mathematically-complex models that produce virtually worthless results because the biological assumptions are unfounded. Even if the biological assumptions and estimates of the parameters of the biological processes are perfect, there remain many problems in interpreting numerical results of mathematical models in terms of predictions. It is unlikely that models of infectious diseases will have the predictive power of, say, models of the solar system, given the degree of complexity and heterogeneity within biological systems. Consequently, it is very unlikely that models may be used to predict the parasite burden of individual hosts.

Returning to the example of the helminth control program model described above, it is again unlikely that such a framework will be able to predict accurately the quantitative effects of chemotherapeutic interventions. However, what is required of the model is that it provides the correct rank ordering of different programs, i.e. that it correctly predicts that program A will cost more and be less effective than program B. This type of quantitative prediction is perfectly feasible, and more robust than qualitative prediction.

VACCINATION AGAINST CHILDHOOD VIRAL DISEASES

Viral infections of childhood, especially measles, remain significant causes of morbidity and mortality throughout the nonindustrialized countries. Models of the transmission of these disease agents have developed significantly over the past decade to the point where they are used for quantitative examination of different vaccination policies (Anderson and Grenfell, 1986; Nokes *et al.*, 1990; Anderson and May, 1991). In developing countries there is difficulty in vaccinating children before they become infected. Live virus vaccines fail to provide protection if the child has significant levels of maternally-derived antibodies so that ideally it would be better to wait until this passive protection had waned (about one year) before vaccination. However, transmission may be high in these areas, so that if a significant proportion of children have lost maternal protection, they will become infected and suffer disease before one year of age. Consideration of different vaccine formulations that overcome the maternal protection to some extent and can be administered to younger infants has been usefully done within a model framework to assess the impact of such a change in vaccination policy (McLean *et al.*, 1991).

In developed countries, the problems are different. Vaccination coverage is generally at very high levels, and transmission is on the verge of being halted. Here, the problems are associated with epidemic outbreaks in groups of unimmunized people, and with vaccine safety. As transmission is reduced, so individuals are at considerably diminished risk of acquiring infection and suffering disease. Consequently, the number of people who suffer adverse effects due to the vaccine can outweigh those suffering the adverse effects of disease. This poses a dilemma in regard to the benefits of vaccination to communities and individuals. A quantitative analysis of the situation, in particular with regard to the use of more immunogenic vaccines with higher reactogenicity versus less immunogenic and reactogenic vaccines, can only be performed with the use of a transmission model (Nokes and Anderson, 1991). Models of this sort can only be used quantitatively when the epidemiological and biological details of transmission and infection are well understood.

DEMOGRAPHIC IMPACT OF AIDS

In contrast to the situation with childhood viral infections is the situation with regard to the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS). It was only in 1982 that this syndrome was recognized. The incubation time to AIDS (the length of time between infection with HIV and clinical diagnosis of AIDS) is very long (median about 10 years) and variable (Hendriks *et al.*, 1993). Consequently, although knowledge of the biochemical and immunological effects of the virus is growing rapidly, epidemiological knowledge is growing at a much slower rate. The longest cohort study has been following individuals since 1979, and the whole range of incubation periods has still not been observed. It is also not known what proportion of those infected will develop AIDS and over what time scale, nor the fate of those that do not develop AIDS.

Of particular interest with regard to the implications of the AIDS pandemic is the effect that it will have on the demography of developing countries, which are currently suffering the greatest prevalence of HIV infection (Anderson *et al.*, 1988; Anderson and May, 1991).

Because of the lack of epidemiological and biological knowledge, mathematical models of this situation cannot be considered predictive. However, they do serve to provide qualitative results. They indicate that if demographic impact is to be marked (for example to produce a reduction in population size), then this will be seen over a time scale of decades. They also highlight those epidemiological and biological variables that are most influential in determining the epidemic pattern, and therefore those variables that must be better understood if quantitative prediction is to be possible. The most important of these variables are the full incubation period distribution, the infectivity of individuals throughout the incubation period, and the patterns of sexual behaviour (the number of different sexual partners and how they are chosen with respect to their sexual behaviour).

CONCLUSIONS

Mathematical modelling is becoming increasingly recognized amongst those working on infectious diseases as a useful tool for researching the quantification of infectious processes. In the research arena, models provide a framework for the amalgamation of field and laboratory data and can be used to highlight those areas where more data and investigation are required. This process is likely to continue in the future, but perhaps the greatest growth will be in the area of designing control policy. As modelling science develops and the understanding of transmission dynamics of specific disease agents increases, epidemiological models will become increasingly useful within the context of health planning and disease prevention. Health policy-makers and resource managers already make use of quantitative techniques to assess costs of disease control programs, but all too frequently the epidemiological detail is missing. The coalition of these two areas is likely to be an important aspect of mathematical modelling of infectious disease epidemiology in the future.

Another area of growth is likely to be the development of models of the dynamic processes within individual hosts in contrast to the transmission dynamics between hosts. This is likely to provide insights into immunological, biochemical and genetic processes and hopefully to guide research to produce increased understanding of the mechanisms that govern host/parasite interactions at an individual level. At present, models in this area are largely speculative as the requisite biological knowledge is lacking, but as researchers in this area become more aware of the potential usefulness of mathematical modelling, so models will become more established in empirical observation (Schweitzer and Anderson, 1992).

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The modelling of vector dynamics in disease research

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The relationship between disease risk and vector challenge may be used for quite different purposes; to determine the amount of intervention (i.e. vector control) required to reduce disease by a certain amount, or to test the output of a full epidemiological model of disease transmission. The relationship is necessary and sufficient for the first exercise, but not for the second. If understanding the dynamics of disease transmission is our aim, we require precise information on the determinants of risk to vertebrates, the challenge by vectors and the relationship between the two.

Attempts are made to reconcile the rather distinct objectives of those who wish to control vector-borne tropical diseases and of those who wish to understand the transmission of such diseases through detailed epidemiological studies.

I begin with an overview of direct and indirectly transmitted diseases and conclude that the basic reproductive number of the latter is often considerably higher than that of the former. The implications for the spread and control of indirectly transmitted diseases are outlined. The equation for the basic reproductive number for vector-borne diseases shows that most of the components of importance are related to the vectors rather than the hosts. The study of vector populations dynamics therefore forms a vital part of vector-borne disease epidemiology.

A brief discussion of risk-challenge relationships shows that the vector modelling requirements will vary from one disease to another. For some diseases, such as malaria, the vector models need to concentrate on what happens at low vector densities, whilst for others, such as onchocerciasis, the higher vector densities are relatively more important. African animal trypanosomiasis appears to fall between these two extremes. Whilst we already know the major ingredients of models for vector (and other animal) species, the density-independent and density-dependent components have rarely been quantified. Models allow us to guess the relative importance of density dependence *vis-a-vis* density independence, and they even allow us to guess that certain stages of the vector's life cycle are more vulnerable to density-independent mortality than others. Here, therefore, it is not the models which are lacking, but the field data to test them.

Vector models eventually need to be integrated into testable models for disease transmission. Here we believe we understand the broad generalities of transmission, but not its details in particular situations. I suggest that we may borrow from insect ecologists, who faced an analogous problem many years ago, an analytical technique to be (re) named

'transmission factor analysis' (tfa) which will identify the causes of changes in the effective reproductive number of vector-borne (and other) diseases. This will both highlight areas where data are still lacking and act as an interface between those charged with controlling disease and those who believe that better control methods will only arise from a more thorough understanding of disease transmission.

The impact of modelling on animal disease control

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ABSTRACT

Over the last 20 years computer modelling has gone from being an esoteric interest of a few people (with little understanding by others of its value and application) to being a recognized tool both for research and policy formulation in animal disease and its control. As with most innovations in research method, acceptance and application of the technique has been patchy and slower than might have been hoped, but both the number of people using the technique and the range of practical application has grown rapidly over the last ten years. This paper reviews the techniques which have been used in computer modelling and the degree to which the method has received practical application. Examples will be provided of different types of models and their application.

The simplest models incorporating disease information have been at the level of individual farms. Most have been used to improve understanding of particular biological systems, to evaluate research directions and priorities and to provide improved 'rules of thumb' for advisers in their work with farmers. They have also been used quite extensively as teaching tools in order to allow students to gain experience of making complex decisions without influencing the real-life outcome.

Current farm-scale models are reaching the point where they are quite practical for individual 'innovator' and 'early adopter' farmers to use as decision support tools, and that is occurring to a growing extent. The key requirement in moving to this stage is that the models be integrated with health and production recording software and other programs already used by farmers. Most models have so far been strategic in nature, concerned with medium-term policy issues. A growth area is the use of specialized models in short-term tactical decision-making, to answer limited questions such as whether or not to apply a particular treatment to animals or plants, given the specific circumstances at that time rather than general expectations as to the future.

Regional and national models have received far greater practical use. A wide range of these 'policy models' have been developed to answer questions about individual diseases and countries, or to investigate other situations where modelling has specific application. The range of diseases and situations covered has been quite wide. Current developments include the integration of models with other precisely targeted software to form a complete decision-support system which can assist in the management of a farm or of a national disease control program.

INTRODUCTION

Over the last 20 years computer modelling has changed from being an esoteric interest of a few people (with little understanding by others of its value and application) to being

a recognized tool both for research and for policy formulation in animal disease and its control. As with most innovations in research methods, acceptance and application of the technique has been patchy and slower than might have been hoped, but both the number of people using the technique and the range of practical applications has grown rapidly over the last ten years. This paper will review the techniques which have been used in computer modelling and the degree to which the method has received practical application.

TYPES OF MODELS

The objective of modelling is to build a simplified representation of a complex system within the real world, in order to test procedures which would be too costly or impractical for various reasons to test on the real world system. Such models can include physical replicas, mental or conceptual models, mathematical representations which are solved by analytical methods, and representations within a computer which can be investigated by mathematical or purely computational methods.

The bulk of current modelling effort involves computer processing, although varied methods are used to carry out the modelling and produce results. Early computer models of livestock production and of animal disease (Morris, 1972) built between about 1965 and 1975 were all designed to run on mainframe computers, and could only be used by people with detailed technical knowledge of computer operation. A variety of modelling methods were used with varying degrees of success. As computing has moved to mini-computers and thence to personal computers, models have followed. They have become far more comprehensive and realistic, and in most cases far more accessible to non-modellers through the design of easily used interfaces for setting parameters and the development of more visual methods of presenting results. These now include spatial as well as temporal trends in disease occurrence, plus other relevant items such as economic consequences. Examples will be provided of different types of models and their applications.

There are two fundamentally different ways of representing disease processes in computer models. The first is deterministic, in which the processes built into the model are fixed by the coefficients set for each variable, and no biological variability is allowed for. Such models will always produce the same outcome for any given set of parameters and initial conditions. The second is stochastic or probabilistic, in which outcomes of at least some of the processes are obtained by drawing samples randomly from standard statistical distributions (binomial, normal, etc.), or empirical distributions based on field data. Such models produce different outcomes for each run, and it is necessary to run the model a number of times (commonly five, and in some cases as many as ten) in order to represent the range of likely outcomes and provide a reasonable estimate of the mean outcome. Deterministic models are faster to run, but it is more difficult to make them realistically represent the disease control issues of interest at a practical rather than a theoretical level. In some cases they are incapable of realism—for example in estimating the proportion of cases in which a disease would be successfully eradicated by a particular control strategy. They will always predict either success or failure under such circumstances—not a probability of success.

Both of the approaches have their uses, and the one chosen should depend on the nature of the problem and the kinds of answers required; deterministic models are valuable for deriving general principles, while stochastic models are applicable to analysing specific practical problems.

Differential and Difference Equation Models

The classical deterministic mathematical approach to analysing time-varying processes such as disease occurrence is through the formulation of differential equations (for continuous processes) or difference equations (for step processes), and using integration to predict the future values of the variable of interest. Over the years this has been a very fruitful approach for systems with relatively few important variables, provided that the equations describing the system were mathematically tractable (Anderson and May, 1981; Anderson, 1982). The approach is very valuable for deriving general principles about the behaviour of simplified 'representative' systems. As the model system being described is allowed to approach reality and hence increases in complexity, at some point for any system the set of differential equations becomes insoluble by standard mathematical methods.

Computer simulation is then normally used to solve the equations, in which case the approach becomes closer to other forms of simulation modelling, although the solutions derived are still deterministic. In some differential equation models certain of the coefficients have biological interpretations which are helpful in understanding fundamental systems dynamics. However again the insights offered through such coefficients tend to lose their clarity as model systems become more complex and approach closer to field reality. Some have argued (Onstad, 1988) that this general approach is inadequate to handle ecological systems modelling, because the coefficients are highly aggregated and not representative of true relationships and because the equilibrium solutions sought may be largely imaginary as far as real world systems are concerned.

Double and Triple Binomial Models

These models have been used by a few workers (Beal and McCallon, 1983) to describe animal disease processes, based on the fact that most disease transmission events are binomial in character, and it is possible to formulate epidemiological problems by means of these more complex binomial functions. However they have no clear advantage over other approaches and their use has not spread widely.

Markov Chain Models

These are well suited to the deterministic description of disease transmission processes, and can be formulated in terms that are mathematically manageable and realistically

handle infectious disease epidemiology (Kristensen, 1987; Carpenter, 1988; Dijkhuizen, 1989). They are not as well suited to other types of disease, such as parasitic diseases, where the issue of interest is the severity of disease rather than its presence or absence.

Other Mathematical Approaches

A wide variety of other specific mathematical techniques have found application in various specific instances for investigating disease, but in general they have been used because they fitted a particular special case and they have not found wide applicability.

Electronic Spreadsheet Models

Although electronic spreadsheets were originally designed as accounting tools, they have evolved into very powerful methods for representing many different types of quantitative problems, using the capacity to embed mathematical equations within individual cells of the spreadsheet. It is not difficult to build various forms of simulations within spreadsheet software, and this can be a good structure within which to formulate a disease model. If appropriate it can subsequently be converted to a standard computer program, but the development process will always benefit from the design work done within the spreadsheet format.

Although simple spreadsheet models are deterministic in nature, it is also possible to build stochastic models within a spreadsheet, using the random number generator built into current spreadsheets. This can be done from scratch, but it is now possible to use add-on modules such as the program @Risk, which integrates with selected spreadsheets and adds to them the capacity to run full stochastic simulations involving sampling on any one of about 20 statistical distributions, with automated processing of sequences of runs using both standard Monte Carlo procedures and the faster variant termed Latin hypercube simulation. Although such models are slower to run than those which are written in a programming language, the flexibility and speed of development and adjustment make them an attractive option for some modelling activities.

Monte Carlo Models

These use random number generators to sample from statistical distributions and hence create the sequence of events and results which form the model outcome. Each single outcome is a chance event (hence the gambling association which produced the name of the technique), but in current Monte Carlo systems where millions of such random number selections take place in a single run, the behaviour of the system is stable yet reflects the variability seen in real-world systems. By repeating runs five or more times with different random number seeds to start the process, estimates of natural variability can be made. The technique has advantages over analytical approaches in that it is far easier for non-mathematicians to understand and use, it can approximate much more

closely to the real nature of events and processes using a mix of analytical and empirical representations, and it can far better represent sequences over time and conditional probabilities. It does not however have the mathematical purity and same potential for providing conceptual insights which mathematical analyses can in some cases offer, nor does it automatically identify optimal parameter settings for disease control. However the optima it identifies through structured sensitivity analysis (Marsh *et al.*, 1987) are usually more realistic for practical applications than analytical solutions, so this is not a major disadvantage.

A Monte Carlo model is structured by defining the biological processes believed to be involved in the system of interest, and then creating a computer program which carries out a simulation of all the relevant processes in the time sequence believed to occur in reality. The structure of the model is based on the nature of the data resources which can be used to construct it and hence it is normally possible to get data for most aspects of the model from published research. Where an essential item is unavailable, a guesstimate is used and a decision made in the light of initial model runs whether field data collection will be necessary to refine the estimate.

Optimizing Models

For some disease control purposes, it may be useful to have a true optimizing procedure which mathematically finds the best combination of resource inputs to achieve the desired goal. Linear programming, parametric programming and dynamic programming have all been used in such applications. Dynamic programming is the most powerful of the techniques, but requires considerable mathematical understanding to apply and is not yet readily available as a package procedure on microcomputers. It is likely to find increasing use in the future as a goal-seeking tool in the definition of control policies in combination with more traditional simulation methods (Huirne *et al.*, 1992).

APPLICATIONS OF THE VARIOUS MODELLING APPROACHES

Each of the modelling approaches is gradually finding its niche in the spectrum of techniques, as modelling matures as a research tool. Analytical mathematical models are best suited to identifying central issues in relation to a particular disease and establishing broad principles concerning constraints to the effectiveness of alternative approaches to control. As the focus moves from principle to specific guidance on the detailed merits and risks of specific control measures, the mathematical methods reach a point where they cannot approach realism much closer than they have already done because the issues which determine differences between strategies are not capable of adequate representation within a tractable mathematical function.

Another factor is that the people who must make use of the information at the practical level must be able to understand and believe what has been done, and in most cases they have difficulty with mathematical approaches in which typically some of the variables and many of the coefficients do not translate into measurable items in the field situation.

Decision-makers are also very interested in the probability of failure, as well as the expected outcome, since a control policy which succeeds 'on average' may fail a substantial proportion of the time. A model which fails to make estimates of variability around expected outcomes is not very helpful in practice.

Thus as the investigation of a major disease problem moves from establishment of principles to field implementation of control policies, modelling support needs to move from deterministic to stochastic, and from a mathematically solved solution to a solution by repeated simulation with sensitivity analysis. The extent to which model parameters match items which are measurable in the field also becomes increasingly important. In selected cases optimizing rather than evaluative models can offer useful insights.

The point along this continuum where modelling stops is usually determined by money, as far as investment in research and evaluation models is concerned. If the problem is an easy one or not of great importance then a simple mathematical or spreadsheet approach may be adequate. If the problem is a biologically difficult one or is seen to be very important, then a larger investment in more detailed modelling may be justified, as a continuing aid to decision-making and to justification for the chosen research and control strategy. The selection of approach is always a compromise between ease and speed of development on one hand, versus realism and power to investigate approaches in detail on the other hand. The background of the modeller will also be very influential, with those from a mathematical background espousing the mathematical approach and those with a biological training seeking closer approximation to the reality they see in the field. Unfortunately there have been very few examples where the two approaches have been compared effectively in dealing with the same problem, so intuition rather than evidence largely determines the approach adopted.

We choose to use Monte Carlo modelling as our principal, but not our only modelling method. One of us (RSM) has a training both in veterinary science and mathematics, but exploration of various alternative approaches over a period of years led to dissatisfaction with the mathematical approaches as veterinary tools, and increasing reliance on Monte Carlo modelling. It is a very flexible technique which can readily be adapted to deal with quite diverse animal disease issues, and models can be formulated around existing knowledge and available data, rather than having to process the data to fit it to the requirements of a mathematically determined set of coefficients. With current computing techniques, it is possible to achieve high speed of model operation and prompt output of results, without sacrificing biological validity. Interactions between factors in complex biological systems are usually crucial in determining actual system behaviour, and Monte Carlo models can represent such interactions in a much more biologically realistic manner than alternative approaches. Because the model is formulated around current understanding of the particular problem, it is relatively easy to incorporate new knowledge as it becomes available. It is also much easier to represent biological heterogeneity, including spatial variability, through various procedures such as the use of multiple sub-models and linking models to geographical information systems. It is far easier to provide a model interface which is easy to use and requests information in a familiar form, and to explain to potential users what the variables are and how the model operates. As modellers at the applied end of the spectrum, we find that these advantages justify the additional development effort, and allow the models to be useful over a longer time period and a wider geographical area.

EXAMPLES OF MODELS

The simplest models incorporating disease information have been at the level of individual farms. A few such models have been applied for specific decision-making in the past, but most have been used to improve understanding of particular biological systems, to evaluate research directions and priorities and to provide improved 'rules of thumb' for advisers in their work with farmers. They have also been used quite extensively as teaching tools in order to allow students to gain experience of making complex decisions without influencing the real-life outcome. Most of the earlier models were used almost exclusively by their developers and close associates, because until recently the portability of models between computers and between different field environments has been low. With standardization of computer hardware this problem (which was previously a major issue) has virtually disappeared, all except a few models now being available on MS-DOS personal computers.

Farm models deal either with a specific disease within the farm, but without including a representation of the production system. Current farm-scale models are reaching the point where they are quite practical for individual 'innovator' and 'early adopter' farmers to use as decision support tools, and that is occurring to a growing extent. The key requirement in moving to this stage is that the models be integrated with health and production recording software and other programs already used by farmers. If they do not have to re-enter data they are more likely to use the program. Most models have so far been strategic in nature, concerned with medium-term policy issues. A growth area is the use of specialized models in short-term tactical decision-making (Jalvingh, 1993) and to answer limited questions such as whether or not to apply a particular treatment to animals or plants, given the specific circumstances at that time rather than general expectations as to the future.

Regional and national models have received far greater practical use than farm models, largely because typically only one or two people are needed to work directly with the model, and if important decisions were to be made they could devote sufficient time and effort to developing and then applying the models. A wide range of these 'policy models' have been developed to answer questions about individual diseases and countries, or to investigate other situations where modelling has specific application. The range of diseases and situations covered has been quite wide. Current developments include the integration of models with other precisely targeted software to form a complete decision support system which can assist in the management of a national disease control program (Morris *et al.*, 1992).

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ILRAD'S RESEARCH PROGRAMS AND THE MODELLING NEEDS OF ILRAD AND FAO

The Trypanosomiasis Program at ILRAD

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The International Laboratory for Research on Animal Diseases (ILRAD) has developed a research strategy for devising improved methods of trypanosomiasis control on the basis of four premises. First, control of both tsetse- and non-tsetse-transmitted trypanosomiasis will rely for the next decade on the use of the existing chemoprophylactic and chemotherapeutic compounds in livestock species and, where appropriate, on control of the tsetse fly vector. Second, trypanotolerance is an under-exploited trait which can potentially provide a particularly sustainable means of improving livestock productivity in both tsetse- and non-tsetse-infested areas. Third, development of new means of immunological or chemical control of trypanosomiasis will require continued research effort on parasite biology, host-parasite interactions and host immunology and pathology. Fourth, the effectiveness and sustainability of existing and new control measures will be enhanced by a better understanding of the epidemiology of trypanosomiasis. Among the objectives, those to be achieved in the shorter term are to:

- identify genetic markers of epidemiologically important parasite traits and to determine the limits and extent of genetic exchange occurring between trypanosomes in the field;
- determine the nature of immune cell activation and dysfunction during infection and to identify the parasite molecules responsible;
- determine to what extent defective bone marrow function contributes to the anaemia of trypanosomiasis and to identify parasite and host factors responsible for anaemia development;
- determine the critical factors in host-parasite interactions controlling *in vivo* parasite growth rates and host-parasite accommodation as it occurs in the carrier state;
- identify genetic markers of trypanotolerance in N'Dama cattle; and
- determine the epidemiological factors in representative field circumstances which are critical for productivity impacts and disease maintenance.

The longer-term objectives are to:

- determine the impacts of control measures on disease, productivity and profitability in representative and defined circumstances in selected study sites;
- develop decision aids for disease controllers to guide design of control strategies based on epidemiological, social, environmental and economic considerations;
- assess the vaccination potential of selected parasite antigens; and
- identify, isolate and characterize trypanotolerance genes in large and small ruminants.

It is envisaged that modelling may assist research progress in several areas. These are development of a more refined understanding of the epidemiology of trypanosomiasis, of

the host immune response and host-parasite interactions, and of parasite and host genetics. Further, it is likely that models *per se* will be essential components of any decision aids which the Program may develop in order to rationalize the disease control process.

Modelling needs of the Tick-Borne Diseases Program

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The goals of the Tick-Borne Diseases Program are the investigation of aspects of the biology of *Theileria* species as they relate to disease control; the development of parasite characterization reagents for epidemiological and immunological studies; the production of defined *Theileria* populations; the identification of antigens of *Theileria* and other tick-borne pathogens that may be used for vaccination or diagnosis; the development of vaccines against *Theileria* and other tick-borne pathogens of cattle based upon characterized antigens and delivery systems; and the evaluation of novel vaccines and the provision of support for tick-borne disease control by national and international organizations. The primary research focus is to develop a subunit vaccine for *Theileria parva,* the cause of East Coast fever of cattle, to replace an effective but difficult to apply infection-and-treatment method. The infection-and-treatment method is being adopted gradually throughout the eastern, central and southern African region in a complicated environment of tick-borne diseases where the traditional control method has been short-interval acaricide application to cattle. Future research will involve the development of novel vaccines for anaplasmosis, babesiosis and cowdriosis in collaboration with other laboratories working directly on the protective antigens of the causal organisms.

Models exist for the transmission dynamics of *T. parva* to and from cattle but we know little of transmission from reservoir hosts. ECFXPERT is a site-specific simulation model that can be used to predict changes in tick populations and the incidence of East Coast fever in response to environmental and management factors. This model requires further development to make it more useful under a wider range of circumstance as new data are generated. A large database has been assembled on tick stabilate-induced infections in cattle and its transmission to ticks which may contribute to model construction. The development of new reagents for more specific detection of parasites and antibodies in mammalian hosts and for assessing infections in ticks, together with new information on the biology of the parasites, will greatly improve the quality of epidemiological data for inclusion in such models.

Attempts have been made to model the dynamics of *T. parva* development in cattle but critical data, such as on the rate of multiplication of the parasitized lymphocytes, are not available. The kinetics of immune responses are being elucidated and will be critical data for model development. However the dose of infecting sporozoites is the major factor influencing the severity and outcome of infection. New vaccines are likely to be based upon sporozoite antigens that will block or reduce the number of lymphocytes infected,

and/or schizont antigens expressed on lymphocytes that will limit infected cell proliferation and arrest the development of the pathological effects. Animals immunized with a recombinant sporozoite antigen show variable responses to a standard challenge with an overall protection of 70%. The proportion of sporozoites escaping neutralization and establishing as schizonts determine the outcome of challenge. In field situations further differences may be introduced depending upon virulence of the challenge parasite and age, nutrition status and the relative susceptibility of the animal. Modelling in this area may assist in the design of new vaccines.

The development of new models or improvement of existing models should allow us to provide more accurate definition of tick-borne diseases, their vectors, the interplay between different pathogens, hosts and reservoirs, for epidemiological studies, maintenance of disease surveillance, monitoring disease spread or selecting target populations for different control measures. The development and application of models should also identify areas that require improved data or research effort for greater understanding of any one disease or disease interactions. It may be possible to model the impact of the introduction of new parasite types into defined parasite populations and to determine the influence of sexual recombination, now at the level of genetic markers but later at the immunogenic level.

The Socioeconomics Program and perceived modelling needs in the areas of epidemiology, socioeconomics and environmental impact assessment

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The Socioeconomics Program was initiated at ILRAD in 1987, and aims to identify the factors which govern the successful application of improved disease control measures for livestock disease, with emphasis on trypanosomiasis and theileriosis, and to assess the likely impact of improved disease control in economic, social and environmental terms in different locations and under different management conditions. The Program has four objectives, two of which (numbers 2 and 4 below) in particular lend themselves to the use of a modelling approach.

The objectives are to:

- identify the factors which are essential for the successful production, delivery and adoption of improved control measures for livestock diseases;
- determine the probable economic, social and environmental consequences of the application of improved control measures for tick-borne diseases and trypanosomiasis in different locations, production systems and agroecological zones of the world;
- support ILRAD's tick-borne diseases and trypanosomiasis programs in assessing the cost-effectiveness of alternative research options for the development of disease control technologies and be of use to international, regional and national livestock disease control programs; and
- quantify and predict the relative economic importance of the infectious and non-infectious diseases of livestock in different regions and livestock production systems in Africa and elsewhere, and the justification for their control.

Assessing the economic importance of diseases and the impact of disease control relies on the use of accurate data on the current distribution and occurrence of diseases, and on their effect under different conditions of livestock production economics. With the scarcity of such data with regard to tick-borne diseases in the African continent, the Program started by using existing models to predict the distribution of the tick *Rhipicephalus appendiculatus* as a surrogate for *Theileria parva* distribution data. Two models were used, CLIMEX and BIOCLIM, both run on interpolated climate surfaces for the continent. While reasonably effective in predicting current and potential distribution ranges, neither of these models effectively predicts tick abundance on livestock under different conditions, an important prerequisite to predicting the occurrence of the diseases they transmit. At

present, it is unclear whether other available models, such as T3HOST and ECFXPERT could be developed to fulfil this function.

An initial attempt has been made to model the dynamics of *Theileria parva* infection under very specific circumstances of endemic stability (see Medley, G.F., this volume), and this has shown that it is possible to predict incidence and case-fatality under these circumstances. It is important that this modelling approach be applied to other sets of circumstances to assess its value as a predictor of theileriosis occurrence under varying conditions.

Economic impact models developed by the Program have thus relied so far for their calculations on estimates of disease incidence taken from the literature from diverse studies carried out over the years, but they have made use of the developed distribution models in determining the proportion of cattle populations at risk using simple overlay techniques in a geographical information system (GIS). Two economics models have been developed. The first is a deterministic spreadsheet model that can be applied on a herd, on a national or regional basis, and calculates beef, milk, animal traction and manure losses due to morbidity and mortality associated with theileriosis. It also assesses the economic impact of control measures in terms of benefit-cost ratio (BCR). The second model is a stochastic farm-level simulation model which simulates the annual production and consumption aspects of a farm household over a ten-year period, and measures, in terms of BCR and other indicators, the effect of disease control programs at the farm level.

Both these economic models, and a third developed by Alexandra Shaw (A.P. Consultants, UK), are being tested under different conditions to assess their validity, and then refined and applied to both theileriosis and trypanosomiasis control. Their successful application to these and other diseases will depend on the accuracy of data on distribution, occurrence and effect of diseases. Although attempts have been made to model these indicators, none of the currently available models are developed to a stage that will allow their strategic application over widely differing circumstances.

A further challenge will be to extend economic impact assessments to include sociological and factor effects of control measures on the environment, particularly in the case of trypanosomiasis. In a new project just initiated, research will emphasize the potential implications of trypanosomiasis control on regional environments using modelling and GIS analyses, and drawing on results of field studies.

Modelling needs of FAO

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In attempting to define the modelling requirements of FAO in the control of vector-borne diseases and other parasitic infections, it may be appropriate to reflect on how disease control and the efforts of the Animal Health Service are integrated into the overall objectives of the organization.

The containment of livestock diseases is not the sole objective of FAO but merely a component in an effort to enhance livestock production, better land usage and agricultural resource management, which should result in the development of more profitable and sustainable production systems. Thus FAO's efforts are focusing on achieving among other things the following:

- Improvements in the efficiency of the production and distribution of all food and agricultural products.
- Improvement in the levels of nutrition and standard of living.
- Better conditions for the rural populations through employment and income generation.
- Natural resource conservation and environmental protection.

Considering these overall objectives on one side and the complex inter-relationship which exists between the hosts, the parasites, the environment, the production systems and the available economic resources on the other, integrated disease control has become extremely complicated and FAO realizes that only through an increased use of modelling can the amount of data involved be manipulated and made accessible.

Before entering into a brief description of FAO's needs in relation to modelling of the specific diseases which are on the agenda of this meeting, it should be emphasized that FAO is mainly an applier, a user of models and as such is only marginally involved in developing models through projects and research contracts with individual scientists and laboratories. FAO, therefore, is looking to this workshop for guidance in relation to the possible future use of available models, the potential for their immediate applicability in the field, possible adaptation and future prospects of developing user-friendly models.

Having established FAO's main objectives in livestock disease control and related development aspects, it may be relevant to consider the geographical areas and the main components in the development of sound control programs which should receive priority attention.

Without ignoring Asia and Latin America, ILRAD and to a large extent FAO have a major interest in animal disease control in sub-Saharan Africa and the demographic explosion in this area requires an urgent response to the increased demand for food production. Considering that the region in spite of possessing 20 percent of the world's

permanent pastures only produces 3 percent of the global livestock production, it appears that the potential for livestock development is present, justifying the allocation of resources into disease control in the region.

Data collection, collation, analysis and dissemination has always been a major activity of FAO, but it is still a major concern of the Animal Health Service that lack of data on animal and human populations, livestock movements, disease occurrence, production systems and many other components which is necessary for the development of sustainable livestock production systems still seems to be the single most important constraint for the development of disease control programs.

Improved data collection will enhance the potential for using modelling in the determination of the ecology of vectors and parasites and the epidemiology of parasitic diseases. FAO has a major responsibility with regard to data collection through projects and programs and collaboration with modellers and epidemiologists during the project preparation and implementation phases is essential in order to ensure the highest possible quality of data and results.

It is often assumed that following the establishment of the ecology and epidemiology of vectors and parasitic diseases, control programs can be developed. However, the information available on climatic, environmental and other factors may only cover part of the extensive variations in agro-ecological zones or sub-units of a production system and only through the use of models will it be possible to develop comprehensive disease control programs based on the obtained data and agricultural, environmental and socioeconomic components.

FAO would also welcome an increased use of models for the implementation and appraisal of disease control schemes as this would improve the monitoring of the dynamic changes of environmental and biological factors enabling the organization to rapidly adapt to the changes.

While there are specific modelling needs for all three groups of diseases which have been targeted by this workshop, the need may be particularly important in the area of the economic impact of these diseases and anthelmintic resistance which has reached emergency proportions in several areas of Latin America and Africa.

There is a growing awareness of the fact that FAO will have to rely on a multidisciplinary approach in the preparation of economically and environmentally sustainable production systems including parasitic disease control. Information is, however, often sparse in many areas regarding ongoing changes of the general ecology, patterns of crop production, disease pressures, resource availability, market forces and improved technology. Without this information it is difficult to define effective disease control programs, let alone strategies for sustainable farming, land usage and resource management. It is obvious that the availability of modelling technologies which will enable the user to assess the importance of these factors either in isolation or combined would constitute a unique tool for FAO and other international agencies and governments involved in the development and implementation of production systems, disease control and the study of market forces.

VECTOR AND HELMINTH POPULATION DYNAMICS

Tsetse vector population dynamics: ILRAD's requirements

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The International Laboratory for Research on Animal Diseases' (ILRAD) research on immunological methods for the control of African trypanosomiasis involves some work on parasite transmission by tsetse flies but none on tsetse population dynamics. However, ILRAD does have an interest in understanding the epidemiology of the disease and in assessing disease risk from tsetse flies in order to estimate the potential impact of a vaccine or other means of disease control which may be produced.

The disease incidence or prevalence and its seasonal variations in an area are determined primarily by the population dynamics of the tsetse fly vector. Trypanosome infection rates in tsetse species seem not to vary to the same extent as the apparent tsetse density and it is the latter which appears to be most responsible for determining the seasonal variations in disease risk or 'Tsetse challenge'. The relationships between tsetse population dynamics and the epidemiology of trypanosomiasis are discussed briefly, using data from the African Trypanotolerant Livestock Network (ATLN) which is coordinated by the International Livestock Centre for Africa (ILCA) in collaboration with ILRAD. These data show results achieved with minimal entomological input, employing standardized methods over a range of sites in Africa and collected over periods of seven years or more.

Seasonal changes in apparent density of tsetse are shown to be closely related to climatic parameters and also correlate closely with changes in disease prevalence in cattle. Attempts were made as early as the 1950s to predict changes in tsetse density from observed climatic parameters and to compare these predictions with field data. Climatic factors have their effects on tsetse population density through their effects on tsetse survival or mortality rates. These changes in survival rates may also affect the age structure of the population which in turn is related to the trypanosome infection rates in the tsetse population. Some models have already been produced to estimate mortality rates and to show the effects of seasonally varying mortality on tsetse population dynamics.

Although correlations between tsetse challenge and disease prevalence can be shown, the relationship is not precise due to complex interactions of the many factors determining tsetse challenge and the practical difficulties in obtaining accurate estimates of the variables and parameters involved. Such relationships may be demonstrated more easily in areas with marked seasonal changes in climate such as ATLN sites in Ethiopia or northern Cote d'Ivoire rather than, for example, in Gabon where the climate is less extreme and where there may be less marked seasonal fluctuations in tsetse populations due to climatic factors.

Climatic factors, in particular rainfall, temperature and relative humidity, have been shown to be important parameters determining tsetse distribution and population dynamics. The relationship between these factors and tsetse population dynamics is therefore a potential area for modelling and further development of existing models.

Tick vector populations dynamics: ILRAD's requirements

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The International Laboratory for Research on Animal Diseases (ILRAD) is primarily involved in developing improved methods for the control of tick-borne diseases; it therefore takes an active interest in research on tick vector population dynamics but does not lead research on this subject. It is realized that tick vector population dynamics is one of the main factors controlling the epidemiology of tick-borne diseases. ILRAD's focus, within the tick-borne diseases, has been research on the development of vaccines against *Theileria parva,* the cause of East Coast fever (ECF). Thus interest concentrates on the main field vector of *T. parva, Rhipicephalus appendiculatus.* The particular interests, in the population dynamics of this tick, are aspects of the biology which influences the epidemiology of ECF. This can be illustrated by some examples. The distribution of the tick vector controls the distribution of the disease and climatic models have been helpful in establishing the distribution of vector and parasite where hard data are not available. The distribution of the tick vector population is dynamic, changing continually in response to changes in climatic conditions as well as movements of hosts. The seasonality of the changes in tick vector population density plays a large role in the epidemiology of disease throughout its distribution. This can be well illustrated by the transmission of *T. parva* throughout the year in the Lake Victoria Basin compared with the seasonal occurrence of theileriosis in central and southern Africa (e.g. January Disease in Zimbabwe).

Strict seasonality of *R. appendiculatus* instars in central and southern Africa is controlled by behavioural diapause of the adult stage which results in univoltine population there and multivoltine populations further north towards the Equator. This is thought to be a survival strategy of the tick in the southern areas. Hence ILRAD is actively involved in research on diapause in tick populations to determine how this influences the epidemiology of ECF. Tick populations are difficult to quantify since the immature instars are small and the free-living stages on the ground are dispersed and difficult to sample. Therefore all data collected from site-specific areas, although useful, are all relative counts and hence these data are difficult to correlate with the epidemiology of theileriosis. An additional difficulty is the wide range of hosts of *R. appendiculatus* in all its instars; up to 35 host species, both domestic and wild mammals, have been recorded but only cattle, African buffalo *(Syncerus caffer)* and waterbuck *(Kobus* spp.) have been implicated as hosts of *T. parva.* These animals vary in their ability to act as hosts for ticks and in their resistance to tick infestations. Hence only ticks which have fed as larvae and nymphs on infected hosts play a part in the epidemiology of theileriosis. Hosts which are refractory to infection

actually cleanse the tick vectors of their infections when they are infested. These examples illustrate the complexities of modelling tick vector population dynamics to a level where it can be useful in simulating epidemiology of theileriosis.

Tsetse population dynamics

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The paper presented describes the twin approaches of biological and statistical modelling of tsetse populations dynamics and distribution in space and time.

The biological approach is dealt with briefly. The requirements are full demographic (i.e. life-table) data for the tsetse combined with complete climatic data during the course of the sampling program. Extensive predictions that arise from the intensive studies at any one site are given with a cautionary note that vector dynamics elsewhere may differ because of the vectors' differing responses to local climate (i.e. abiotic effect) and because of the differing guilds of natural enemies throughout the range of the species concerned (i.e. biotic effect).

The statistical approach initially chooses to ignore local variations in the tsetse's response to abiotic conditions and seeks to model a distributional range through multivariate techniques such as discriminant analysis. This technique therefore requires extensive information on the presence and absence of a species throughout a region, and climatic data on an equally extensive scale. Whilst this approach is still rather 'broad-brush' in comparison with the biological approach, it does provide some indication of the likely regional variation in abiotic constraints on the presence or absence of a species, and thus can be used to target field investigations either to regions which show a variety of abiotic constraints (for comparative studies on fly ecology) or to regions where there is a false prediction of fly presence (flies may in fact be present, but inadequately surveyed), or absence (if confirmed, such areas indicate an inadequate understanding of climatic or other constraints). Examples are given of the distribution of *Glossina morsitans* and *G. pallidipes* in Kenya and Tanzania. Discriminant analysis identifies different climatic and vegetational constraints for these two species.

The above studies form part of an epidemiological interpretation of changes in disease risk in space. Another important element is changes in risk through time. Here the situation is complicated by a variety of suggested possible mechanisms for epidemic outbreaks of disease, and an acute shortage of data to distinguish between them.

It is concluded that past data sets are inadequate for the needs of present models, because the data were gathered in an epidemiological vacuum, i.e. without reference to any theory being tested. Today we are in a position to decide which data to gather, and how best to test alternative theories of trypanosomiasis transmission. As in other fields, however, modelling has made more and more rapid progress in the last few years, whilst field studies have declined almost to the point of extinction.

Simulation of tick population dynamics

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ABSTRACT

The *Boophilus* Cattle Tick Simulation Model is a computer program that simulates tick population dynamics and the processes involved in transmission of *Babesia* parasites. Tick population dynamics arecontrolled by climate, density and type of cattle and pasture type. Transmission of *Babesia* parasites is determined by the levels of infective ticks and cattle and various epidemiological parameters. Simulations can be run for either *Boophilus microplus* or *B. annulatus* ticks and either *Babesia bovis* or *B. bigemina* parasites. BCTSIM provides a tool to study tick density thresholds associated with disease transmission. Control technologies for the tick vectors are included in the model for comparison of various control strategies in a given geographic area. With proper regard for the limitations of the model, BCTSIM can serve as a knowledge source for planning an operational control program. The accuracy of model predictions can be determined only after extensive use in conjunction with actual control operations and field research.

Models developed using this approach provide a flexible framework for addition of biological details and control effects. Disadvantages of this approach include the difficult and time consuming process of model construction and programing, maintenance of program integrity and the extensive data requirements which are generally inadequate. Advantages include the biological realism of simulation results and the generally unlimited ability to program and simulate control technologies and strategies.

INTRODUCTION

Computer simulation models represent a powerful tool for study of vector population dynamics and integrated control strategies. Simulations can provide a comparison of the effectiveness of an unlimited number of control scenarios that would be impossible to conduct in the field because of the time and expense required. Effective use of simulation research will allow field research to concentrate on validation of model results and evaluation of the most promising control strategies.

Computer models for analysis of tick population dynamics and control have been developed for *Amblyomma americanum, Dermacentor variabilis* and *Boophilus* cattle ticks. These models all use a deterministic, dynamic-life-table approach with key biological parameters controlled by climate (temperature, humidity and rainfall) and other variables such as host type and density, habitat type and photoperiod. Components to simulate transmission of Rocky Mountain spotted fever by *D. variabilis* and babesiosis by *Boophilus* ticks were included in these models. Control technologies in the models include various acaricide application procedures, release of sterile hybrid ticks, and manipulation

of hosts and habitat. Studies to assess the validity of the models and to compare various tick control technologies and strategies have been completed. The software for these models is written in Microsoft Professional BASIC for interactive operation on advanced microcomputer systems. The software design allows the models to be used for extensive simulation research and provides a useful demonstration and training tool.

For the purpose of this meeting I will cover details of only the *Boophilus* Cattle Tick Simulation Model (BCTSIM) because of the importance of this tick in Africa and because the model includes interactions between population dynamics and disease transmission within a cattle herd. This paper will review the major components and relationships in BCTSIM and discuss potential uses in development of control strategies.

SIMULATION APPROACH

Development and validation of the present version of BCTSIM are provided in Mount *et al.* (1991) and Haile *et al.* (1992). The model construction and simulation approach used for BCTSIM was the same as that used previously for other simulation studies on tick population dynamics, disease transmission and control strategies (Haile and Mount 1987; Mount and Haile, 1987, 1989; Cooksey *et al.*, 1990; Haile *et al.*, 1990).

The basic model structure allows simulation of the population levels of ticks and cattle in various age classes and stages of parasitic development. Interactions between susceptible and infective individuals in the tick and cattle populations can be quantified to simulate *Babesia* transmission.

A dynamic life table approach with weekly time steps is used to simulate tick population dynamics as influenced by climate and other variables. The major factors that influence tick population dynamics in BCTSIM are: 1) temperature-dependent development rates for eggs and for engorged females off the host, 2) fecundity rates for engorged females according to temperature and type of cattle, 3) density-dependent survival rates for ticks on the host varied by type of cattle, 4) survival rates for free-living stages of ticks regulated by type of habitat, temperature, saturation deficit and precipitation and 5) host-finding rates for larvae dependent on host density, temperature and off-host larval density. Epidemiological parameters and relationships in the model include the reduction in fecundity of infected ticks, rate of transovarial transmission, effect of cattle type and inoculation rate on infectivity of cattle, variation of infected cattle recovery rate with age of infection, inoculation rate and species of parasite.

Several general assumptions were required in construction of the model. These assumptions are: 1) that every bovine animal of one type is equally susceptible to *Boophilus* tick infestation, 2) that all cattle of the same type are equally susceptible to *Babesia* infection and 3) that infected ticks survive equally long as non-infected ticks. Although these assumptions are not totally realistic, they are consistent with our objective of modelling mean tick populations and levels of disease transmission.

SOFTWARE

The present version of BCTSIM is programmed in Microsoft BASIC version 7.1 (Professional Development System) for use on an IBM PC-AT or compatible microcomputer. A

colour monitor (EGA or VGA) is desirable because the program makes use of colour in screen displays and graphics. Simulation time is improved with an advanced computer system based on an 80486 microprocessor or an 80386 microprocessor with a math co-processor.

BCTSIM was written for interactive operation and presents various menu options to specify input files and variable levels. The program also was designed to select from various methods for viewing and saving simulation results. The primary choices required for each simulation run include geographic location, basic biological data file for a tick species, climate file, cattle density, type of cattle, type of pasture and species of *Babesia*. A selection also allows the addition of *Babesia* infection in engorged female ticks or in cattle. The program is designed to present one year of simulation at a time and presents a post-simulation menu at the end of each year. The simulation can be continued for as many years as desired with the option to change selected parameters between years.

Each climate file contains values for mean weekly ambient temperature (°C), saturation deficit (mb), and precipitation (cm) for one year. Climate files for a given location may contain actual weekly average data for specific years or historical data which is the average for a number of years. For some climate files, interpolation was used to generate weekly data from monthly data.

The basic biological data files for BCTSIM contain 52 parameters and coefficients that define the tick life cycle and relationships between biological and environmental variables. A separate biological data file has been created for each tick species, *Boophilus microplus* (Canestrini) and *B. annulatus* (Say). These files are accessible from the main menu of the program and allow rapid adjustment of data during model development and refinement. An additional menu selection allows a choice of either *Babesia bovis* (Babes) or *Babesia bigemina* (Smith and Kilborne) as the parasite species for simulation. Although not in a data file, this choice allows on-screen review and editing of selected epidemiological parameters. The model allows simulations for one tick and one parasite species at a time.

Choices for the initial tick population include introducing eggs on a selected week during the first simulation year or introducing a population distribution of overwintering ticks saved as a data file at the end (week 52) of a previous simulation run. After initialization, simulations can continue for as many years as desired, with the initial population for each successive year being a continuation of the population from the previous year. The final population of any simulation year can be saved as an output data file for use as a future initialization file.

The primary output from BCTSIM is a graphics plot, presented on the monitor, of the weekly population of ticks on the host and the level of infection in cattle during each simulation year. An optional output is an animated life cycle display with an alternate screen presenting weekly data on major parameters in the model. A post-simulation menu provides options for graphic plots of climate data and levels of all life stages for each week of the yearly simulation. This menu also presents a choice to view a text summary screen which includes the annual mean numbers of each life stage on the host/hectare, off-host larvae/hectare and standard females/host/day. Epidemiological results on the summary screen include infected numbers of ticks off hosts and on hosts per hectares, percentage infection of ticks, numbers of cattle (susceptible, infected and recovered) per 1000

hectares, percentage of calves infected by nine months of age, and average daily inoculation rates of calves and cows.

BCTSIM provides an option to calculate growth rate per generation *(R)* and generation time *(T)* from the model output for a given set of input parameters. The growth-rate option accumulates all eggs produced by adult females rather than transferring them to the first egg stage; therefore, the total number of eggs produced over time from initialization by a single cohort of eggs can be determined. The growth-rate option accumulates egg production for each week and is programmed to compare the 500% accumulation with the initial number of eggs for a calculation of *R*. The week of 50% accumulation of eggs is also identified as a measurement of *T*.

SIMULATION OF CONTROL

BCTSIM provides preliminary programing to simulate tick control by 1) acaricide applications to cattle and 2) release of sterile hybrid ticks. Interactive choices for acaricide applications include: 1) length of residual activity and effectiveness level for each week post-treatment, 2) number of treatments during the simulation year, 3) week of initial treatment and 4) treatment interval, weeks. For sterile hybrid releases, the present program assumes that hybrid larvae are released in pastures with menu choices for: 1) release level, number/hectare, 2) release interval, weeks, and 3) host finding effectiveness compared to wild larvae.

Extensive simulation studies on control strategies have not been conducted. This will be the subject of a future paper after refinement of the control sub-models and possibly further refinement of other aspects of BCTSIM.

The present program can be used to demonstrate control principles and the influence of the environmental variables on effectiveness at different geographic locations. The degree of control required to reach theoretical tick density thresholds for maintenance of *Babesia* in cattle or for inoculation of all new calves can also be analysed. Although eradication can be simulated in the model, confidence in a prediction of eradication in any given situation would be limited because of uncertainty concerning levels of input variables and the nature of a deterministic model with low numbers. Addition of stochastic elements to the model would improve realism with low numbers; however, the variables required for the additional complexity would increase the potential for errors and uncertainty. The overall confidence in eradication predictions would probably be about the same with either type of model. The most practical use of present models will involve relative comparisons of different control procedures to provide knowledge for planning and implementation of operational programs. Extensive experience with BCTSIM in conjunction with control operations and field research will be required to determine the predictive capability of the model.

RESEARCH NEEDS

Improvement in the predictive capability of BCTSIM can only be accomplished with additional refinement and validation studies. These refinements will require quantitative

field research on specific areas of the tick-host-disease system. This research includes detailed and long-term studies to measure the actual levels of tick density and parasite prevalence for comparison with simulation output. Other areas needing quantitative study include: 1) the effect of cattle type, age and previous exposure on death rates due to *Babesia* infection, 2) cross immunity between parasite species and tick species, and 3) effectiveness of new acaricides and control procedures. Additional effort and resources will be required for software design to improve interactive and 'user friendly' aspects of the program as refinements are incorporated into the model.

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Modelling of *Rhipicephalus appendiculatus* population dynamics

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ABSTRACT

Simulations models of *Rhipicephalus appendiculatus* population dynamics are driven by a direct cause-effect relationship between temperature and length of the development periods. The timing of cohorts of the various instars can be modelled accurately enough by this relationship, although it must not be forgotten that experiments to determine it were carried out at optimum relative humidities. Survival of the free-living stages is governed by one or more humidity parameters in the models. Accurate quantification of the relationship between survival and both intrinsic and extrinsic factors is as yet not feasible. Elucidating this crucial relationship deserves the necessary attention: there is little justification in using any of the existing models to test whatever hypothesis before survival can be predicted confidently in function of its regulating factors. The models attempt to simulate the need to synchronize the tick's life-cycle with seasonal variation in humidity: the ultimate factor determining the tick's phenology on the mammal host is to be found in the humidity requirements and tolerances of eggs and free-living unfed larvae. However, there is no indication that either eggs or larvae—or nymphae—possess the ability to delay development and/or questing.

Current evidence indicates that adult ticks have the ability to diapause, i.e. are able to feed at the correct time of the year to ensure that the required minimum level of humidity is available for the immature stages. Given the uncertainty over the exact mechanism(s) available to adults to achieve this synchronization, simulation models can play an important role in this area to offer guidance with respect to the required research. It can be anticipated that other factors will assume more and more importance as models are developed further. These variables include host-dependent factors (host resistance to ticks and host density), tick population density-dependent factors and tick body size. Apart from the fact that we are not in a position to quantify any of the above relationships, they also introduce a degree of 'memory' into the system, which together with the absence of any form of selection in the models should urge for great caution when running the models over a period of several years. Simulation models of African tick population dynamics are likely to remain pure research tools in the foreseeable future and their further development should proceed in close collaboration with research, accompanied by the development of a flexible interface, ideally allowing the user to change not only the levels of the variables but also the actual relationships.

Rhipicephalus appendiculatus is a three-host tick. Briefly, a replete adult female drops off the host and produces a single egg batch after a pre-oviposition period. The eggs hatch into larvae. The larvae harden off and start to quest on pasture. After having been picked up by a host, the larvae feed and drop off the host upon repletion and moult into nymphs. The nymphs cycle through an identical series of events, resulting in adult ticks. It is accepted that adults, in particular females, have the ability to diapause in order to regulate host finding and feeding, thus ensuring that the most vulnerable stages, namely eggs and larvae, are exposed to favourable climatic conditions.

The lengths of the various development periods (pre-oviposition, pre-eclosion, larval and nymphal moults) depend to a large extent on temperature alone (Branagan, 1973a; Tukahirwa, 1976; Punyua, 1984; Short *et al.*, 1989). Strictly speaking, unequivocal evidence does not exist for this direct cause-effect relationship. The laboratory experiments were carried out at optimum relative humidities, i.e. 85–87% (Branagan, 1973a) and 90% (Tukahirwa, 1976), and the field observations (Punyua, 1984; Short *et al.*, 1989) do not allow the inference of cause-effect relationships. Nonetheless, we assume that the direct, single-variable cause-effect relationship between temperature and length of development period is correct, or at least sufficiently accurate, to allow simulation of the life cycle of the tick. Thus, there is little justification to direct a major research effort to fine-tune the details of this aspect of the tick's life cycle. The various approaches to quantify the relationship between temperature and development periods should be compared and tested, as was done by Byrom (1990) for the method developed by King *et al.* (1988). Testing criteria should include predictive power and complexity of the algorithm, both in terms of computing efficiency and collection of the required temperature data.

The survival of the free-living stages as well as hatching and moulting successes are regulated by humidity. The principal effect of humidity, and thus the limiting factor in relation to the geographic range of the tick, is thought to be the survival of the most vulnerable stages, particularly the eclosion of eggs and survival of larvae for a period sufficient to allow host contact (Branagan, 1973b; Hoogstraal, 1978). The ultimate factors determining the probability of instantaneous survival include the microclimate and the physiological age of the tick (Branagan, 1973b; Punyua, 1985). It is at present impossible to quantify the microclimate experienced by the ticks and, therefore, recourse must be taken to macroclimatological parameters. It is still a matter of debate whether it is soil moisture or air moisture or both that best predict the survival curves of the different instars. Furthermore, it has not been resolved whether humidity operates dependent or independent of temperature, i.e. whether survival and success should be expressed as function of relative humidities or vapour pressure deficits (Tukahirwa, 1976). Lastly, it must not be forgotten that humidity interacts with the physiological age of the tick.

Resolving the relationship between intrinsic and extrinsic factors on the one hand and survival on the other should be given priority. There is no point in looking for any other fundamental parameters and relationships that might influence the tick's population dynamics if we cannot predict with a certain degree of accuracy survival rates as a function of external factors. The same remark holds for index models that attempt to predict suitability of a certain area in relation to the tick's requirements and tolerances.

Although the survival of the most vulnerable stages is probably the ultimate factor that drives the tick's phenology, neither eggs nor larvae appear to have the ability to delay respectively development and questing to synchronize the life cycle with seasonal variation in humidity. It is now accepted that this synchronization, if required, must be achieved by the adult ticks, namely by either quiescence or behavioural diapause or a combination of both. A current research effort is designed to settle the question of whether or not the ability to diapause is confined to southern African *R. appendiculatus* populations or present in all populations. At the same time such studies will provide a better understanding of the mechanisms involved in induction, maintenance and termination of diapause to allow further real-life and computer experiments.

Quantifying the various interactions between the mammalian host and the tick remains fraught with difficulties. Broadly speaking, there are two components in the overall effect of the host, namely host density and host resistance to ticks. Host density has a direct effect on pick-up rates of the various instars and thus, together with survival rates, on the population level. However, our current knowledge about this complex relationship is largely qualitative and mainly confined to the cattle host. The effect of host resistance is probably far more important. The main problem here lies in the fact that although we have a whole body of experimental evidence relating to host resistance (Chiera *et al.*, 1985a, 1985b; Fivaz and Norval, 1989; Jongejan *et al.*, 1989), variation in host resistance in a field situation both seasonal and otherwise cannot at present be quantified.

Results from studies in the Eastern Province of Zambia, possibly a transition zone between areas with multivoltine and univoltine *R. appendiculatus* phenologies, reveal a distinct seasonal variation in body size of nymphae and adults, indicating that adult ticks collected at lower altitudes are smaller than those found at higher altitudes. Body size can be assumed to be correlated to the maximum possible generation interval, taking into account the need for diapause where required. Additional support for a correlation between voltinism and body size has been obtained by A.S. Young and R.G. Pegram (unpublished results). Clinal and seasonal variation in body size adds additional complexity to the model because of the different development and survival rates, and this aspect may require further research. Any heritable variation in body size and diapausing behaviour may complicate matters even more, especially when considering that host resistance has a direct effect on tick body size. This leads to an inherent problem when modelling, namely that certain parameters are built into the model at the start of a simulation run and that these parameters are kept constant and fixed throughout the entire simulation. This is hardly natural and will inevitably lead to erroneous conclusions if the horizon of the simulation exceeds anything but a few years.

To conclude, a computer simulation model of *R. appendiculatus* population dynamics very likely remains a research tool in the foreseeable future because of the lack of quantitative data required for the formulation of the relationships between certain aspects of the life cycle and their regulating factors.

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Host density and tick dynamics: the case of the vector of Lyme disease

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ABSTRACT

To determine whether the abundance of deer and mice limits the abundance of deer ticks, we implemented a model representing the life cycle of these vector ticks using realistic parameter estimates taken from two field sites in coastal Massachusetts. The main inputs to the model were scanning capacity and host abundance. The equation for scanning capacity includes estimates of the density of questing ticks and applies an algorithm based on the density of ticks actually attached to hosts. In a site in which the abundance of mice varied from year to year, deer abundance remained constant, as did that of recently emerged larvae. When the density of mice was held at a level that corresponded to that in a year of exceptional mouse abundance, the ticks thrived. When such hosts remained scarce, tick abundance waned. A stable density of ticks accompanied an 'ordinary' density of mice. Deer abundance was reduced in the other site while mouse abundance fluctuated. Although deer density diminished by 3/4 to about 100, tick density continued to increase. Our simulations suggested that the critical threshold of deer abundance is eight animals. We conclude that the abundance of deer ticks is sensitive both to the abundance of mice and of deer.

INTRODUCTION

White-tailed deer serve as the main host for the adult stage of the deer tick *(Ixodes dammini)* (Wilson *et al.*, 1985), the vector of Lyme disease in eastern North America (Piesman *et al.*, 1979). Egg production follows successful feeding. The concept that deer are crucially important in the life cycle of these ticks is based on diverse kinds of evidence, including: (1) qualitative observations establishing that stable infestations of the tick are evident solely where deer are resident (Spielman, 1988), (2) geographical correlations between the density of larval deer ticks feeding on mice and the density of deer (Wilson *et al.*, 1985) as well as (3) removal experiments indicating that the density of these ticks on mice in a site diminishes following local removal of deer (Wilson *et al.*, 1988). Some subadult deer ticks also feed on deer, although they generally feed on mice or other small animals (Piesman *et al.*, 1979). The abundance of deer ticks critically depends upon that of deer.

The immature stages of this tick appear to feed mainly on mice. Adult deer ticks, however, never parasitize these hosts. This complexity renders it difficult to define the

density of hosts required for perpetuation of this tick. It may be that the density of both kinds of hosts determines the abundance of the tick.

To explore this hypothesis, we applied a mathematical model formulated to represent the life cycle of deer ticks (Sandberg *et al.*, 1992) and implemented it with actual parameter estimates based on field observations in two sites in coastal Massachusetts. In one site, the deer population remained constant while the mouse population fluctuated during the eight-year period of the study. In the other site, the mouse population fluctuated mildly while deer were removed by limited hunting. We used computer simulations to explore the effect of realistic changes in mouse and deer abundance on the population biology of these ticks.

Description of Study Site and Field Methodology

To explore the effect of mouse abundance on the dynamics of the deer tick population, we used data derived from the Nantucket Field Station of the University of Massachusetts, on Nantucket Island, Massachusetts. This 32-hectare shoreline site was studied regularly during the period 1985 through 1991. The vegetation comprised equally of grassy meadows separating stands of dense coppice that mainly included bayberry, blueberry and scrub oak. Voles were most abundant in the meadows and white-footed mice in ecotonal situations. Although shrews, cottontail rabbits and domestic animals were abundant there, few animals of other kinds inhabit this restricted site.

Observations were made monthly between April and October. Deer density was estimated by direct observation and that of mice by a minimum-number-alive estimate (Wilson *et al.*, 1988). The abundance of rodents was estimated by placing oat-baited live traps (Longworth Co, Abingdon, UK) in a permanent 7×7 grid in the field site. Each captured animal was marked by means of a numbered ear-tag. The minimum number alive method of estimating abundance was employed (Hilborn *et al.*, 1976). The abundance of feeding ticks was determined by visually inspecting each trapped animal and animals were promptly released. Ticks were removed for subsequent identification.

The study on the effect of incremental removal of deer on the density of the deer tick was undertaken in Ipswich, Massachusetts, on a 567-hectare coastal site maintained by the Trustees of Reservations. Much of the property is comprised of a 9 km long barrier island characterized by beach, dunes, salt marsh and woodland. Lyme disease affects numerous residents of nearby sites (Lastavica *et al.*, 1989). Mouse abundance and density of ticks feeding on mice was monitored as described. Deer abundance was reduced from an estimated 430 in 1983 to about 150 in 1991.

THE MODEL

Matrix Representation

Our present effort to apply a discrete mathematical model describing the life cycle of a particular population of vector ticks derives from a previously developed system of

Table 1. Blood-feeding success of adult deer ticks feeding in the study site during 1983–1984.

Month	No. of deer present	No. of adults /deer	Days of activity /attached	No. of fed adults
Oct	10	86	15/10 = 1.5	1,290
Nov	10	62	30/10 = 3.0	1,860
Dec	10	9	25/10 = 2.5	220
Feb	10	11	15/10 = 1.5	165
Mar	10	11	30/10 = 3.0	330
Apr	10	11	15/10 = 1.5	165

linked matrices constructed to represent the seasonal progression of the developmental stages of this tick (Sandberg *et al.*, 1992). A separate matrix was used to represent each month of the year in a manner that captured the various events that punctuate the annual cycle of this tick. The main input variables were considered to be host density and efficiency of host-finding (scanning capacity) for each developmental stage of the tick. The original model was constructed around a set of arbitrarily chosen, seasonally variable biological parameters that remained constant from year to year. The present effort is designed to represent conditions actually observed during 1984-1991 in the Nantucket field site.

Estimates representing feeding parameters of the tick population are entered as elements in a series of modified stage-structured matrices (Leslie, 1945; Caswell, 1989). The density of ticks present during each year is calculated as the product of the mathematical vector for the previous year and of the 12 transition matrices representing each month of the year in question:

$$\mathbf{X}(t+1) = \prod_{i=1}^{12} A_i \, \mathbf{X}(t)$$

where A represents an 11 × 11 matrix containing the monthly transition parameters and $\mathbf{X}(t)$ is the vector representing tick density during each of the 11 designated activity stages of the tick in year (t) (Sandberg *et al.*, 1992). These include: eggs, nonfed larvae, fall-fed larvae, spring-fed larvae, nonfed nymphs (first year), fed nymphs (first year), nonfed nymphs (second year), fed nymphs (second year), nonfed adults, fall-fed adults and spring-fed adults.

Parameter Estimation

The two main input parameters that are used in the matrices are derived from the sequence of field observations actually conducted in the study site, as well as certain supplementary

Table 2. Blood-feeding success of larval deer ticks feeding in the study site during 1984–1985.

Month	Kind of host	No. of hosts present	No. of larvae/ host	Days of activity/ attached	No. of larvae fed on deer	mice	other	total
Aug	deer	10	200	15/3 = 5	10,000			
	mice	173	20			17,300		
	other	104	3				1,560	28,860
Sep	deer	10	178	30/3 = 10	17,800			
	mice	345	18			62,100		
	other	104	9				9,360	89,260
Apr	deer	10	8	15/3 = 5	400			
	mice	173	1			865		
	other	0	—				0	1,265
May	deer	10	84	30/3 = 10	8,400			
	mice	173	8			13,840		
	other	0	—				0	22,240
Jun	deer	10	121	30/3 = 10	12,100			
	mice	242	12			29,040		
	other	0	—				0	41,140
Jul	deer	10	31	15/3 = 5	1,550			
	mice	276	3			4,140		
	other	35	0				0	5,690
Total					50,250	127,285	10,920	188,455

observations conducted elsewhere. One of these variables, host density, is determined by direct observation (of deer) and by mark-release-recapture (of rodents).

The other main input parameter is estimated indirectly. Scanning capacity of a particular stage of the deer tick, questing in a particular month after a particular kind of host, is comprised of the following elements. The first two components, tick density on hosts and duration of activity that month, are derived from field observations. The third, duration of tick attachment, is determined in the laboratory (Piesman *et al.*, 1979). Biological assumptions are required to estimate the fourth component in this formula, density of questing ticks. These assumptions are based on certain features of the seasonally discrete life cycle of this tick (Yuval and Spielman, 1990).

The developmental cycle of the stages of the deer tick proceeds as follows:

$$\text{Egg} \rightarrow \text{Larva} \rightarrow \text{Nymph} \rightarrow \text{Adult} \rightarrow \text{Egg}$$

Ticks feed once during each trophic stage of development before they moult to the next stage. The rigid seasonality of this feeding behaviour in the case of the deer tick punctuates its developmental cycle as follows: Eggs deposited in June and July hatch in August. Larvae abundantly quest for hosts in August through September and again in April through July. Nymphs abundantly quest in May through July, adults from mid-October through December and again in February through mid-April.

Density of feeding ticks is calculated, month by month, on the basis of the observed density of ticks per host and the observed abundance of that host. More than 4000 adult

Table 3. Blood-feeding success of nymphal deer ticks feeding in the Nantucket study site during 1985.

Month	Kind of host	No. of hosts present	No. of nymphs /host	Days of activity /attached	No. of nymphs fed on deer	mice	other	total
Apr	deer	10	22	15/5 = 3	660			
	mice	173	2			1,038		
	other	0	—				0	1,698
May	deer	10	72	30/5 = 6	4,320			
	mice	173	7			7,266		
	other	0	—				0	11,586
Jun	deer	10	34	30/5 = 6	2,040			
	mice	242	3			4,356		
	other	0	—				0	6,396
Jul	deer	10	6	30/5 = 3	360			
	mice	276	1			1,656		
	other	35	0				0	2,016
Aug	deer	10	1	30/5 = 6	60			
	mice	242	0			0		
	other	0	—				0	60
Sep	deer	10	4	30/5 = 6	240			
	mice	345	0			0		
	other	35	0				0	240
Total					7,680	14,316	0	21,996

deer ticks appear to feed on deer in the site each year (Table 1), of which half are female. We assume that each of these becomes engorged and produces 2000 fertile eggs. We further assume that all eggs hatch to produce an equivalent number of questing larvae. In this case, more than four million questing larvae would be produced in the site each year. The cohort of ticks that hatches in the fall of 1984 will provide the basis of our analysis. Some of these larval ticks will attach to available hosts, and all of these will feed to repletion in three days. Those that fail to find a host during the fall of that year will resume questing during the subsequent spring (Table 2). We assume that all such engorged larvae ultimately moult to the nymphal stage and that all seek hosts beginning in the spring of 1985. Some of these nymphs will attach to available hosts as the opportunity presents itself during the spring and summer of 1985 and of 1986, and all of these will feed to repletion in five days (Table 3). We assume that all nymphs that engorge in 1985 moult to the adult stage and that all will seek hosts beginning in the fall of the same year. Some of these adults will attach to available hosts, and all of these will feed to repletion in ten days (Table 1). All engorged adults ultimately oviposit beginning in the summer of 1986. In this manner, the population of deer ticks completes its developmental cycle.

The density of questing deer ticks is estimated by combining the results of the monthly field observations with derivations based on these assumptions. The calculation begins with the assumption that about four million newly hatched larvae began to quest early in August of 1984 (Table 4). The activity of this cohort of ticks is followed until they mature to the adult stage and ultimately oviposit. We calculate the number of larvae questing at

Table 4. Seasonal abundance of questing deer ticks in the Nantucket study site, calculated by subtracting the observed number of feeding ticks in each stage (from Tables 1–3) from the number assumed to be present at the end of the previous month. This display represents the cohort that hatched as larvae in 1984.

Months	No. of larvae		No. of nymphs		No. of adults	
	questing	fed	questing	fed	questing	fed
1984						
Aug	4,030,000	28,860				
Sep	4,001,140	89,260				
1985						
Apr	3,911,880	1,265	188,455*	1,698		
May	3,910,615	22,240	186,574	11,586		
Jun	3,888,375	41,140	172,092	6,396		
Jul	3,847,235	5,690	164,097	2,016		
Aug			162,820	60		
Sep			162,745	2,610		
Oct					21,996	1,290
Nov					20,706	1,860
Dec					18,846	220
1986						
Feb					18,626	165
Mar					18,461	330
Apr			70,335		18,131	165
May						

*Includes 70,335 ticks from th Previous season.
Underscoring denotes groups of questing ticks containing individuals that engorged in a previous stage and emerged to quest at the designated month.

the beginning of each month by subtracting the calculated number of larvae that fed during the previous month from the number estimated to be questing during that month. In the event that no larvae were found on hosts during a particular month, we assume that diapause prevented questing activity. The number of questing nymphs and adults is calculated similarly. Larvae that engorge during the summer season are assumed to moult and to recommence questing as nymphs during the following season. These rules dictate the manner of calculating scanning capacity.

Scanning capacity of these ticks is calculated for a particular stage of the tick seeking a host in a particular month. That of an adult in October, for example (Tables 1 and 4), is:

$$(86 \times 15) / (10 \times 21{,}996) = 0.005865$$

which is the probability that an adult tick may attach to a deer. Thus, only 1 out of 171 adult deer ticks that are present in the site in October would find a host. A similar calculation is repeated for each of the other stages of the tick, for each month and for each kind of host. Scanning capacity is calculated and averaged over each of the 8 years (1984–1991) for which data are available.

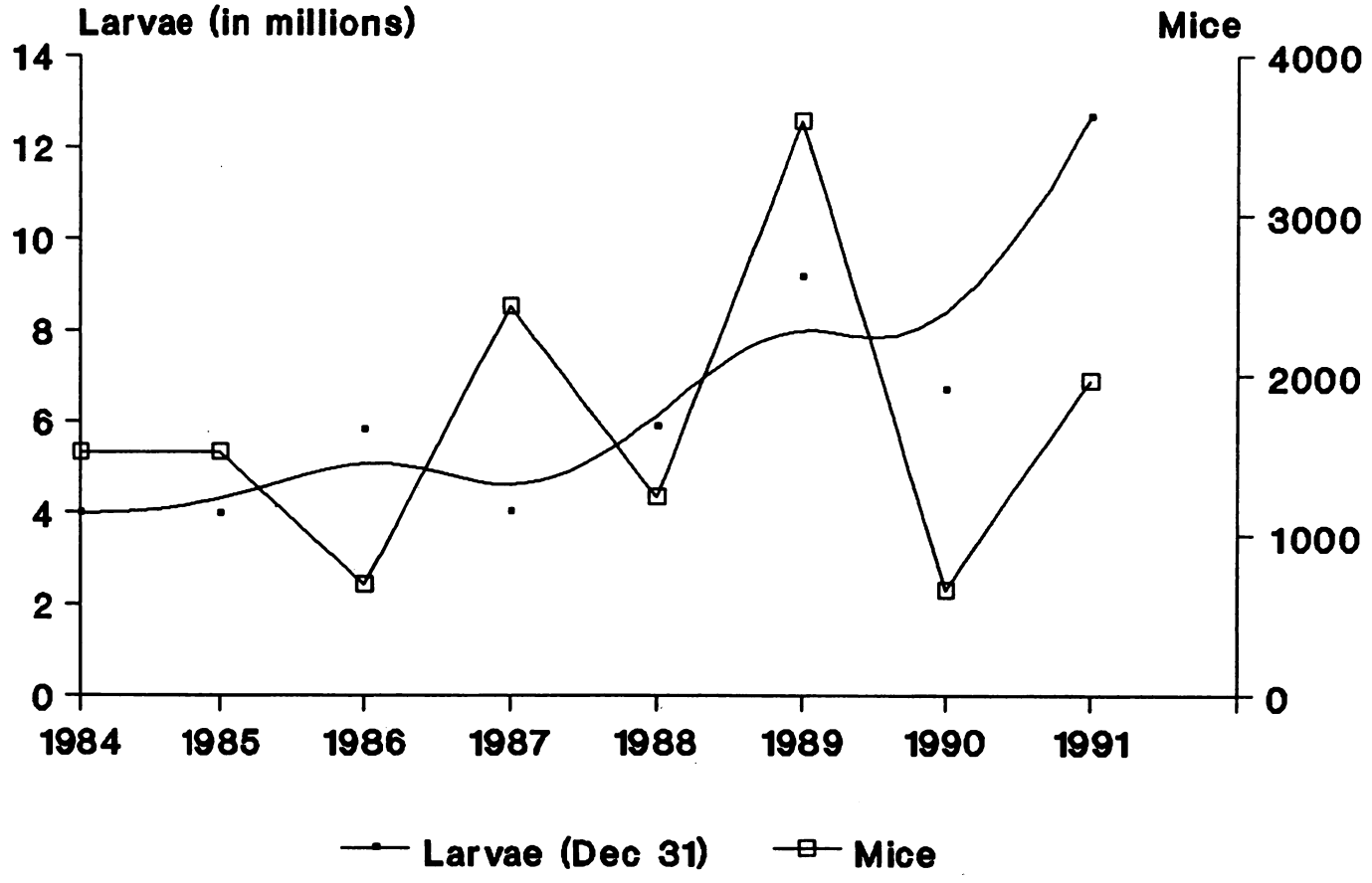

Figure 1. Changes in the observed abundance of mice present in the field site and simultaneous changes in the abundance of larval deer ticks predicted for the first of December for each year of the study.

Implementation of the Model

To implement the model, two programs are constructed; one for calculating scanning capacity and the other for vector density. For convenience, both employ computerized spreadsheets (Lotus 1-2-3).

The program for scanning capacity is based on the set of data summarized in Tables 1–4. Because scanning capacity is calculated for each month of the year, a column in the spreadsheet is designated for each month. The rows receive the observed data on host and tick density as well as the equations for calculating scanning capacity. The output of each columnar calculation is placed in designated positions in the appropriate matrix, thereby enabling us to obtain numerical values when matrices are multiplied.

In constructing the program for tick density, difference equations represent matrix multiplication. The columns represent density of the various stages of the vector for each month of the year. Vector density during each month depends on density during the previous month and on a transition parameter that represents feeding, moulting or death of the tick. In this manner stage-specific vector density is calculated for each of the designated months of the year.

RESULTS

Preliminary to our attempt to determine whether the abundance of mice may be critical in perpetuating the vector of Lyme disease, we analysed the pattern of annual variation in mouse abundance in the study site. Mouse abundance fluctuated annually, with a six-year rising trend between the years 1984 and 1989, followed by a two-year pattern of decrease (Figure 1). The abundance of mice varies from year to year in the study site.

We then determined whether the abundance of ticks may vary in parallel with the observed variations in the abundance of mice. Abundance of larvae during midwinter was chosen to represent the dynamics of the tick population because this phase of tick development directly reflects reproductive activity and is subject to few environmental variables. Abundance of questing larvae closely follows that of mice, generally lagging by a one- or two-year interval (Figure 1). The abundance of newly emergent larvae varies with the abundance of mice.

In order to examine the effect of a surfeit of hosts on the abundance of newly emerged larval deer ticks, we determined how many would develop if their rodent hosts remained as abundant as they were in an exceptional year. The year 1989, which was such a year, was chosen as the standard of such excess (Figure 1). The simulation was based on a model constructed so that one female deposited a clutch of 1000 fertile eggs in a site that had previously been devoid of ticks. Tick density increased exponentially, with a doubling time of 1.06 years (Figure 2). When hosts for the subadult stages of this tick are exceptionally abundant, the tick population increases rapidly and continuously.

We then determined how an exceptional paucity of hosts may affect the abundance of newly emergent larvae. Because mice were particularly scarce in the study site in 1990, that year was chosen as the standard of host scarcity (Figure 1). The simulation began, as in the previous simulation, with the deposition of a clutch of 1000 fertile eggs in a site that

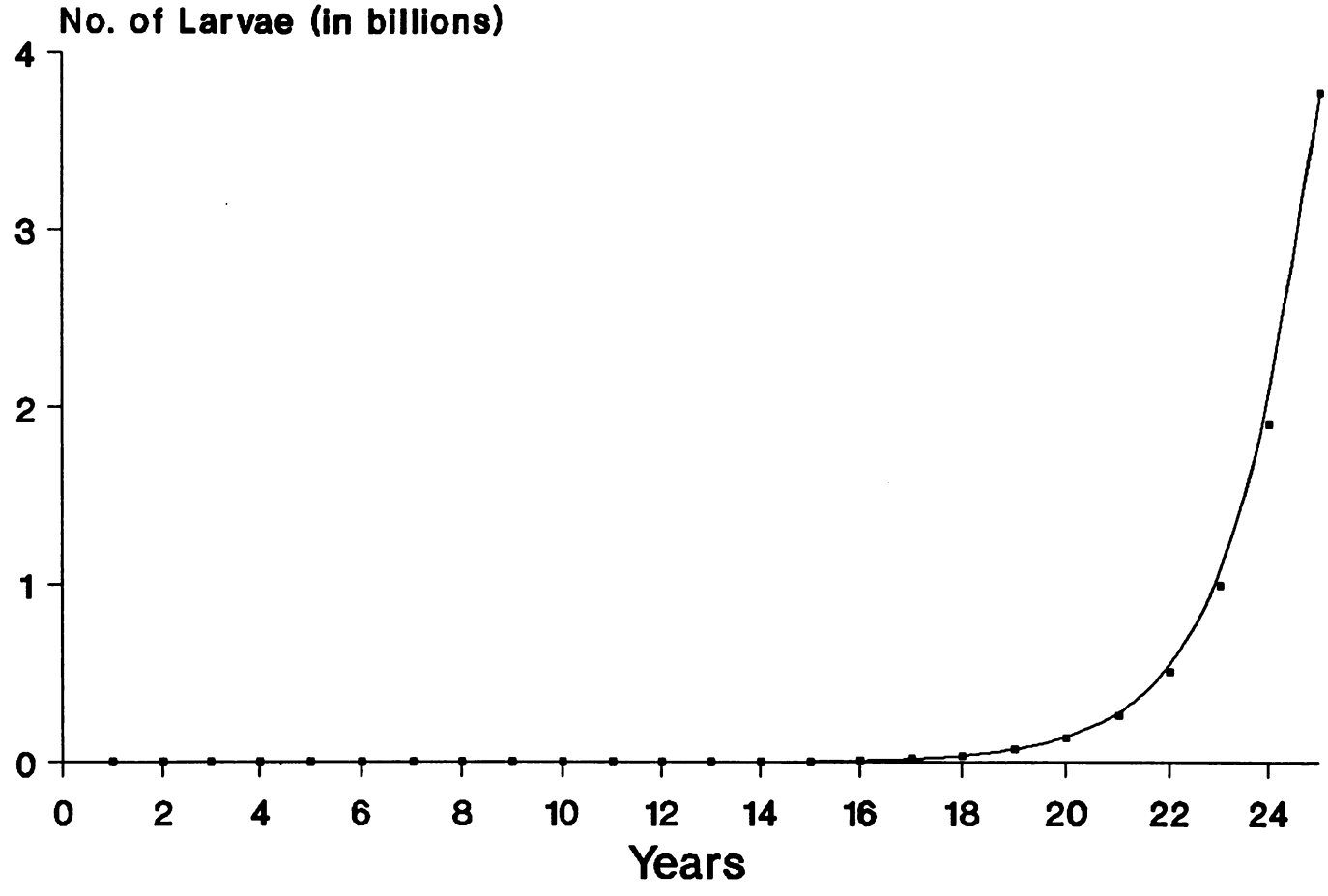

Figure 2. Increase in the simulated abundance of larval deer ticks assuming that mice continuously remained exceptionally dense (as observed in 1989).

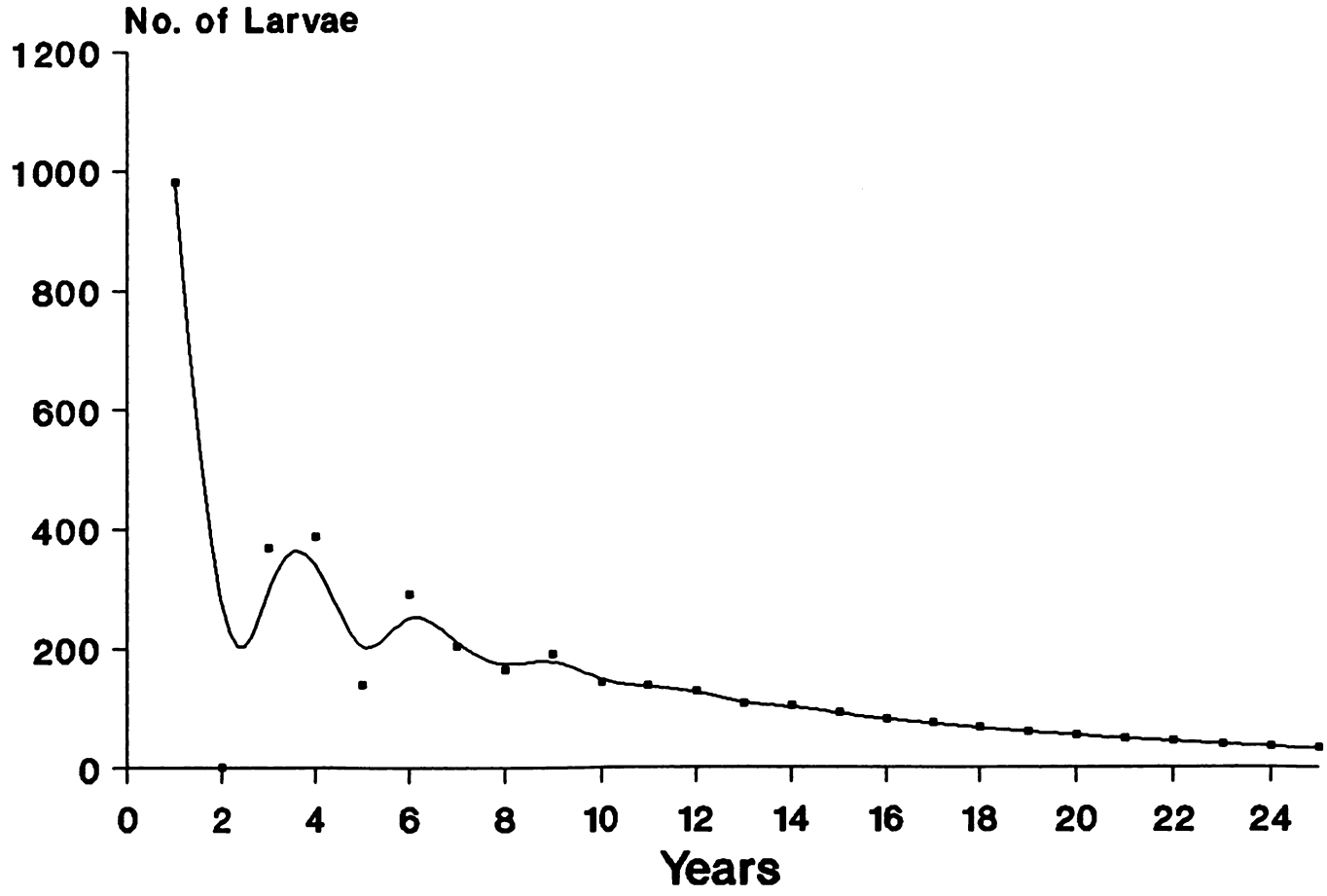

Figure 3. Decrease in the simulated abundance of larval deer ticks assuming that mice continuously remained exceptionally scarce (as observed in 1990).

had previously been devoid of ticks. Tick density waned and ultimately disappeared (Figure 3). Under these conditions of exceptional mouse scarcity and a continuing presence of ten deer, deer ticks might become endangered.

To determine whether a particular level of mouse density may result in a stable density of ticks, we applied a similar process using the data of 1986, a year in which the density of mice noted in the study site somewhat exceeded that in the designated year of paucity, 1990 (Figure 1). After 1000 eggs were 'deposited in the empty field' of the study site, the tick population decreased and oscillated (Figure 4). Tick density ultimately stabilized at a density that was about half that of the first year of the simulation. Indeed, a stable density of ticks appears to accompany an 'ordinary' density of mice.

Finally, we compared the relative contributions of mice and deer to the abundance of deer ticks. Mouse density corresponding to that observed in 1985 was chosen for this simulation because this level seemed 'typical.' This year's abundance of mice in the study site (Figure 1) permitted simulated tick abundance to rise exponentially, with a doubling time of 2.7 years (Figure 5). We simulated removal of one deer from the site and, by graphical interpolation, found the density of mice required to maintain tick density at the original level (Figure 5). Under these conditions, an increment of 30 mice compensates for the absence of one deer.

DISCUSSION

The dynamics of populations of deer ticks depends largely on host availability. Only a minute portion of the tick population proceeds from stage to stage, mainly due to a failure to find hosts (Sandberg *et al.*, 1992). Longevity of these ticks seems to be closely programed in nature; a questing larva does not live longer than 11 months, a nymph 14 months and an adult 8 months (Yuval and Spielman, 1990).

The observed series of seasonal punctuations in the life cycle of these ticks insulate development from prolongation or abbreviation due to short-term weather conditions (Yuval and Spielman, 1990).

Successful development of a tick depends upon its scanning capacity. Although various ticks move toward their hosts (Semtner and Hair, 1975), deer ticks appear to 'quest' passively (Daniels *et al.*, 1989). The ability of a tick to scan for a host, therefore, depends upon the nature of the terrain and the ability of the tick to resist drying. These variables are reflected in our parameter values.

Host abundance similarly affects the ability of a tick to find a host. Mouse density varies in a complex manner (Adler *et al.*, 1984). They begin to reproduce in the spring and continue to increase until fall. This temporal coincidence facilitates feeding activity of deer ticks by matching maximum questing activity of larvae, which eclode in August (Yuval and Spielman, 1990), with maximum availability of their hosts. Few alternative hosts are endemic to this isolated island on which our analysis focuses. Years of relative mouse abundance tend to follow years of scarcity. This alternation buffers the abundance of deer ticks because the same cohort of ticks generally experiences both extremes in their different subadult stages of development which spans two years or more. Multi-year cycles also occur. The five-year cycle frequently observed in populations of these white-footed

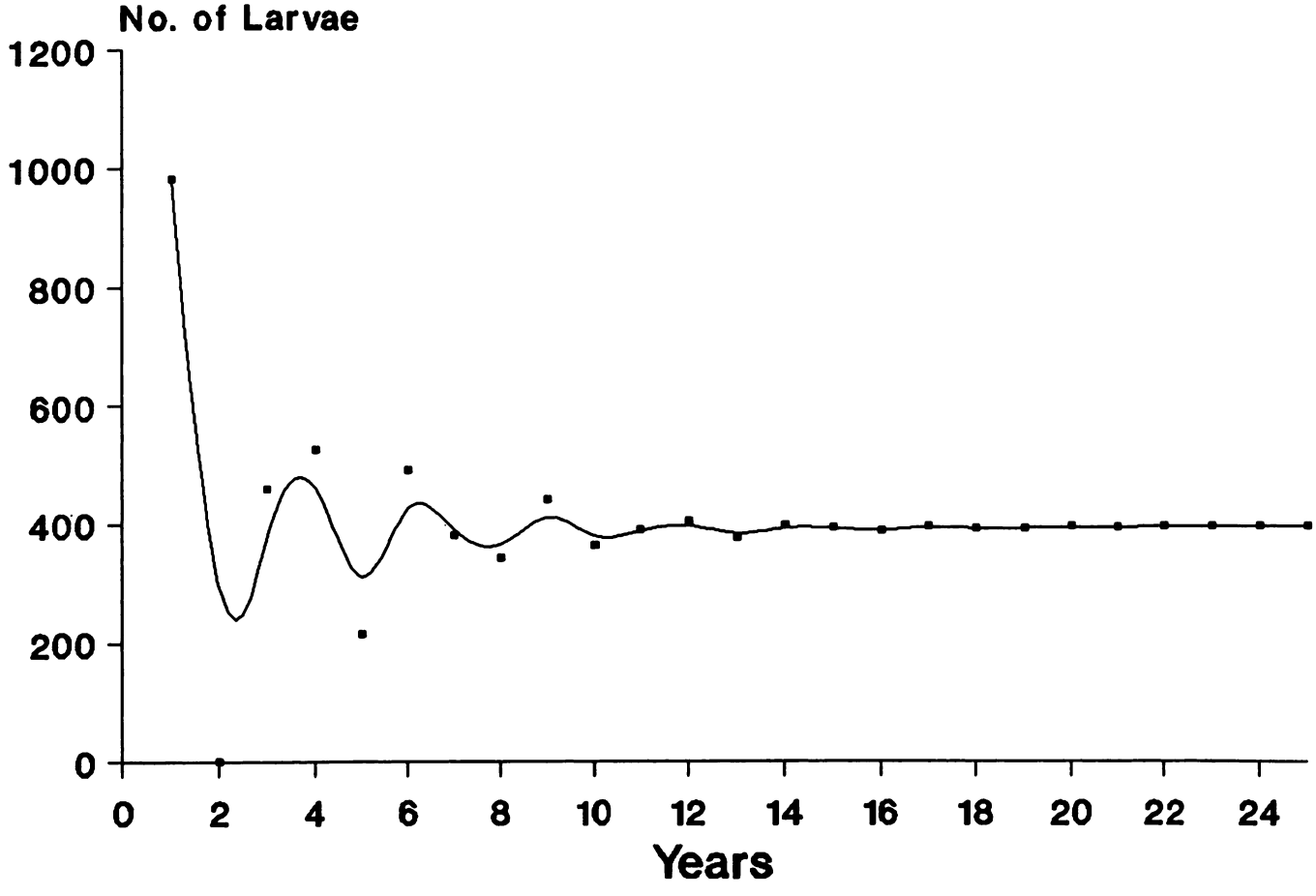

Figure 4. Stabilization in the simulated abundance of larval deer ticks assuming that mice continuously remained moderately scarce (as observed in 1986).

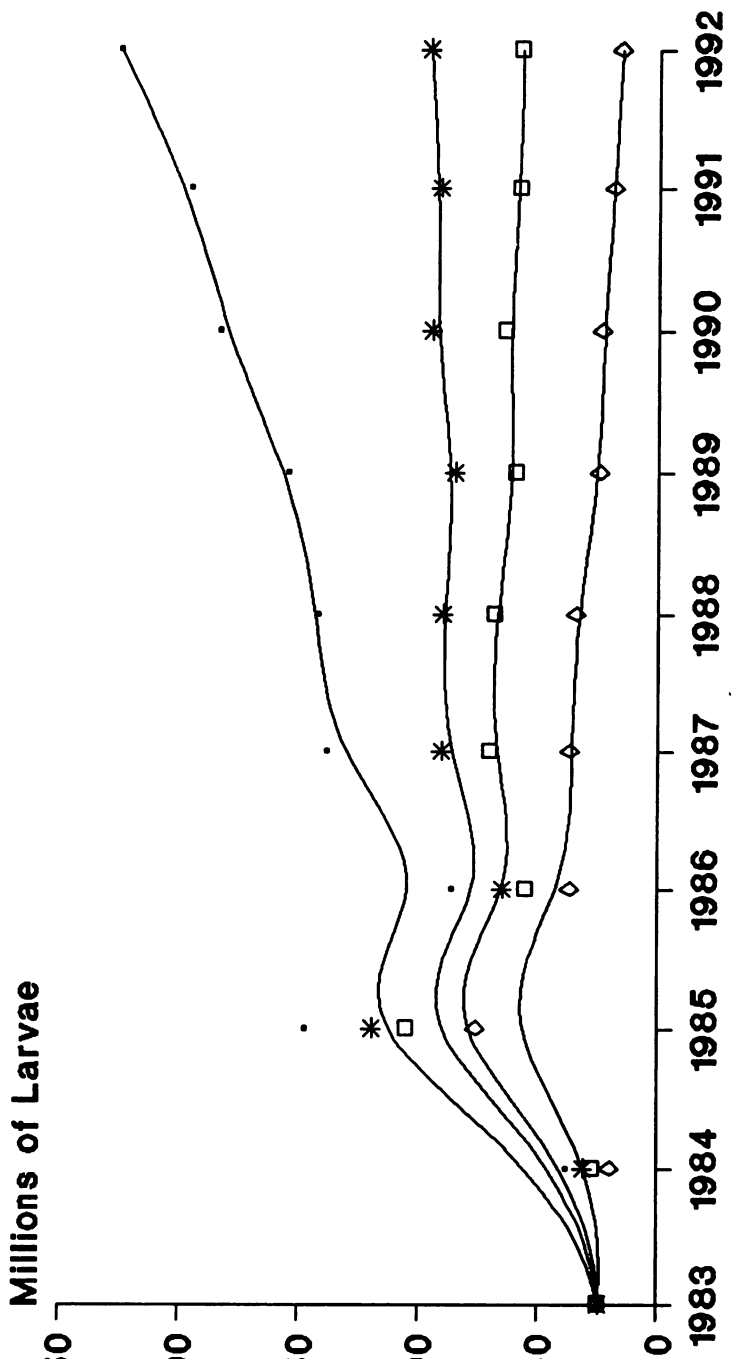

Figure 5. Increase in the simulated abundance of larval deer ticks calculated on the assumption that mice continuously remained moderately dense (as observed in 1985); then calculated as though 1 deer were removed; then calculated as though 30 mice were substituted for that deer.

mice (Adler *et al.*, 1984; Krohne *et al.*, 1988) is consistent with the pattern observed in our study. The matrix structure of our model incorporates all of these crucial and temporally variable relationships.

The derivation of scanning capacity combines estimates of potential turn-over of ticks on hosts and on efficiency of host-finding (Sandberg *et al.*, 1992). Although separate calculations are made for each stage of the tick questing during each month of the year, our simulations are based on average estimates spanning the eight-year period of observation. Estimates of the abundance of questing ticks are required for directly calculating the scanning capacity of ticks in a particular site. Because field observations are not available for direct estimation of this parameter, our estimates are based on an algorithm that uses the density of feeding ticks on hosts as one of its major inputs.

The density of feeding ticks is more easily determined in the field than is that of questing ticks. Questing deer ticks generally are sampled by sweeping vegetation with a section of fabric intended to represent a surrogate host. Such an operation, however, is fraught with uncertainty; only a tiny fraction of the population can be sampled; rarely at night or in the rain and never from sequestered sites such as a mouse's nest. Indeed, the distribution of questing larval deer ticks clumps closely around the site in which a gravid female had deposited her eggs (Daniels *et al.*, 1989), and questing larvae are far more abundant than are ticks in any other stage of development. Questing nymphal deer ticks are even more difficult to sample by means of a cloth flag because some variable portion of the population appears to emerge and quest within the nest of the host of the previous stage (Mather and Spielman, 1986). The number of questing ticks resident in a site vastly exceeds those that can be sampled on a flag or that actually succeed in finding a host and that are seen on hosts.

The presence of numerous deer generally is regarded as prerequisite to an abundant infestation of deer ticks (Spielman, 1988). Qualitative observations have established that stable infestations of the tick are evident solely where deer are resident; correlative observations demonstrate a relationship between the density of larval deer ticks feeding on mice and the density of deer (Wilson *et al.*, 1985); and experimental evidence demonstrates that destruction of resident deer was followed by the virtual elimination of these ticks (Wilson *et al.*, 1988). We now demonstrate that the abundance of mice also contributes to the abundance of these ticks and define a situation in which a paucity of mice eliminates the tick infestation. Under certain circumstances, one deer may be the equivalent of 30 mice.

This report constitutes the first representation of the population dynamics of the vector of Lyme disease in an actual endemic site. Our use of a sequence of assumptions combined with observational data makes it possible to construct an algorithm for calculating the density of questing ticks in the study site. We conclude that the abundance of deer ticks is sensitive to the abundance of mice and that these ticks may fail to perpetuate when mice are as scarce as they were in the field site in two of the eight years of observation.

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Modelling helminth population dynamics

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ABSTRACT

The population dynamics of the common helminth parasites of cattle and sheep have been the focus of much study over the last three decades. The dynamics of the accessible free-living stages is well understood, but there is still considerable uncertainty concerning the processes which regulate and control parasite numbers in the ruminant host. For example, it has long been supposed that resistance to *Fasciola* infections in cattle develops between the sixteenth and twentieth week after infection and is manifested in the rejection of established flukes. On the other hand, recent reanalyses of experiment infections show that the mortality of established flukes is essentially constant over this period and the supposed sudden rejection of the parasite burden is, in fact, illusory. In the case of the trichostrongylid gastrointestinal nematodes, there is a plethora of hypotheses concerning the causation of the observed changes in parasite burden during single- or trickle-infection experiments. Since these results are very similar irrespective of the parasite-host combination under study, it seems likely that eventually a single hypothesis should be able to account for all the observed patterns. It is suggested here that the proportion of ingested larvae that becomes established declines in sigmoidal fashion and that the mortality of established worms increases to some asymptotic value as the host's experience of infection increases.

Investigations of the population dynamics of helminth infections are useful in that they lead to mathematical models that can be used to design and communicate rational strategies for parasite control. Examples of such models include the UNIVERSE model for *Trichostrongylus* infections in sheep and PARABAN, a model for the common gastrointestinal parasites of cattle.

INTRODUCTION

This paper will deal with some recent empirical models for the population processes that occur in the parasitic phase of the life cycles of the common liver fluke, *Fasciola hepatica,* and several of the gastrointestinal nematode parasites of cattle and sheep. It will be argued in both cases that changes in the rate of parasite establishment provide the best explanation of observed patterns of infection. It will also be argued that density dependent regulation of parasite fecundity, though important in certain species, is by no means ubiquitous amongst the parasites considered here. Finally, the paper will address the problem of aggregated parasite distributions and the different extent to which these have to be taken into account in models of fascioliasis and parasitic gastro-enteritis.

The models described below deal exclusively with parasites of veterinary importance. Nevertheless, they owe a substantial debt to models that were first elaborated in a medical context and so we begin with a brief survey of the history of helminth models in general.

A BRIEF HISTORY OF HELMINTH MODELS

There are numerous mathematical models for the population biology of parasitic helminths (cestodes, trematodes, nematodes) of medical and veterinary importance. Most of these models are built according to a formal structure that evolved in a series of papers by Kostitzin (1934), Macdonald (1965), Tallis and Leyton (1966), Gordon *et al.*, (1970) and Nasell and Hirsch (1972).

Between 1965 and the early 1980s, the principal focus was on parasitic helminths causing disease in humans (e.g. nematode infections—Anderson, 1979b, 1980a, 1982, 1985; Anderson and May, 1982, 1985a; Anderson and Medley, 1985; Dietz, 1982—trematode infections—Hairston, 1965; Sturrock and Webbe, 1971; Lewis, 1975; Cohen, 1977; Barbour, 1978; Anderson and May, 1979a; Coutino *et al.*, 1981—and cestode infections—Ghazal and Avery, 1974; Keymer, 1982). A copious theoretical literature accumulated over the same period. This literature dealt in particular with the representation and understanding of the processes that regulate and control parasite abundance (e.g. Leyton, 1968; Crofton, 1971; Bradley, 1972; Bradley and May, 1978; Anderson 1976, 1978, 1979a, 1979b, 1979c, 1980a, 1980b, 1982; Anderson and Gordon, 1982; Anderson and May, 1978a, 1978b, 1978c, 1979a, 1979b, 1982, 1985a, 1985b; Anderson and Medley, 1985, Smith, 1984a).

From the mid 1970s onward, more and more of the models dealt with helminth infections of veterinary importance. Some early examples include Gettinby (1974), Gettinby *et al.* (1974), Hope-Cawdery *et al.* (1978), Williamson and Wilson (1978), Thomas (1978), Gettinby *et al.* (1979), Gettinby and Paton (1981), Smith 1982, Wilson *et al.* (1982), Paton and Gettinby (1983), Paton and Thomas (1983), Paton *et al.*, 1984. These studies and those that followed depended in large part on methodologies that evolved during the mid 1960s and early 1970s in the course of modelling helminth infections in humans and on models of physiological development first elaborated in the zoological literature in the mid 1950s (Grainger, 1959; see also Gettinby and Gardiner, 1980 and Gardiner *et al.*, 1981).

The most recent phase of modelling parasitic diseases of veterinary importance has seen a burgeoning literature on models for nematode infections of ruminants in cattle and sheep. For example, there are at least five models for *Haemonchus contortus* (Tallis and Donald, 1964; Tallis and Leyton, 1969; Leyton, 1968; Gordon *et al.*, 1970; Tallis and Donald, 1964; Smith, 1988, 1990; Coyne, *et al.*, 1991a, 1991b; Coyne and Smith, 1992; Leathwick, 1992), four for *Ostertagia circumcincta* (Paton and Gettinby, 1983, 1984; Paton and Thomas, 1983; Paton *et al.*, 1984; Paton, 1987; Gettinby *et al.*, 1989; Callinan and Arundel, 1982; Callinan *et al.*, 1981; Smith and Galligan, 1988, Smith, 1989), two for *Ostertagia ostertagi* (Gettinby *et al.*, 1979; Gettinby and Paton, 1981; Grenfell and Smith, 1985; Smith *et al.*, 1986, 1987a, 1987b; Grenfell *et al.*, 1986, 1987a, 1987b) and one for *Trichostrongylus colubriformis* (Barnes *et al.*, 1988, Dobson *et al.*, 1990a, 1990b, 1990c; 1990d; Barnes and Dobson, 1990a, 1990b). Over the same period, there was a parallel surge in the development of mathematical models for cestode and trematode infections of sheep (Mizraji *et al.*, 1980; Hernandez *et al.*, 1983; Correa *et al.*, 1983; Gemmell *et al.*, 1986a, 1986b, 1987; Roberts *et al.*, 1986, 1987; Meek and Morris, 1981; Smith, 1982, 1984a, 1984b, 1984c).

Broadly speaking, the early veterinary helminth models were conceived as tools to help predict damaging disease outbreaks. There was considerable emphasis on the effect of

weather on the development of the free-living stages of each parasite species because it was believed that climate held the key to the epidemiological patterns observed in the field (Gettinby *et al.*, 1974, 1979). This, together with the fact that the free-living stages were often more accessible than the parasitic stages, engendered a gigantic literature (not dealt with here) on the development and mortality of the free-living stages. As a result, by the early 1980s, modelling the demography of the free-living stages of any parasite was limited only by the availability of appropriate data. The methodology was well established and has since been subject to relatively few refinements.

During the 1980s, veterinary helminth models became much more like medical helminth models in that they were more concerned with the efficacy of proposed parasite control strategies. The utility of the early predictive models lay in the extent to which they could exactly predict pasture larval contamination at specific sites. They assumed that if one knew what the pattern of pasture larval contamination was likely to be, one would also know how best to apply anthelmintics. The more recent models and, indeed, modified versions of the predictive models, embody the view that the most efficient use of anthelmintics remains to be determined and that models can be instrumental in guiding that decision. At first modellers were interested only in what had to be done to keep parasite burdens low; later, several of the models were modified to address the question how can one keep parasite burdens low and simultaneously impede the spread of anthelmintic resistance (Gettinby *et al.*, 1989; Barnes and Dobson, 1990b; Smith 1990). This increasingly ambitious purpose meant that the model elements dealing with the parasitic phase became more sophisticated. Unfortunately, there was much less information on the demography of the parasitic stages of helminths of veterinary importance than there was on the free-living stages and veterinary models differed from one another not so much in the mathematics of their construction (which was fairly standard) but in the nature of the host-parasite interactions that were actually modelled. For example, there are (still) at least two competing hypotheses concerning the regulation of trichostrongylid infections in ruminants: the 'threshold' hypothesis first suggested by Dineen *et al.* (1965), Dineen and Wagland (1966) and Wagland and Dineen (1967) and the competing 'turnover' hypothesis developed in a series of papers by Michel (1963, 1969a, 1969b, 1970). Variants of both hypotheses can be found in all the existing trichostrongylid models. Nor is there any agreement on the processes which regulate *F. hepatica* infections in cattle. For example, Doyle (1972) argued that calves given a single infection of *F. hepatica* metacercariae will begin to reject the flukes between 20 and 24 weeks after infection, whereas Hope-Cawdery *et al.* (1977) stated that the fluke survivorship curve following a single infection was a simple exponential decline indicating a constant attrition of flukes throughout the course of the infection.

THE PARASITIC PHASE OF THE LIFE CYCLE OF *FASCIOLA HEPATICA*

The Problem

Fascioliasis is the cause of serious production losses worldwide. Often considered in the context of ovine infections, where production losses are directly, but non-linearly, related

to intensity of infection (Hawkins and Morris, 1978), modelling fascioliasis has proved to be a relatively simple task. In sheep there appears to be no significant acquired immune response to infection: parasite numbers are regulated by a severe density dependent constraint on parasite fecundity and density dependent, parasite-induced host mortality (Smith, 1982). Modelling bovine fascioliasis, on the other hand, has proved to be much more problematic. In the Americas, where bovine fascioliasis is more important than ovine fascioliasis, the infection accounts for millions of dollars of lost profit annually. In North America, bovine fascioliasis is endemic in the gulf coast region and north western regions of the USA and in eastern Canada (Malone *et al.*, 1982; Bouvry and Rau, 1986). In the Caribbean, bovine fascioliasis has been a serious long-term problem in Cuba, Jamaica and Puerto Rico (Frame *et al.*, 1979; Bundy *et al.*, 1983). It occurs also in many South American countries (Ueno *et al.*, 1982; Griffiths *et al.*, 1986). Precise estimates of the scale of the production losses are difficult to come by. Many studies are methodologically flawed because they fail to consider the cost and production consequences of attempting to control the infection (Morris, 1969). One of the most thoughtful though is the study by Bundy *et al.* (1983) on the losses incurred in Jamaica between 1979 and 1980. They estimated total annual losses of over two million (Jamaican) dollars for a national herd of about 300,000 animals. Anthelmintics directed against bovine fascioliasis can bring about profitable increases in production (Genicot *et al.*, 1991) but over an area as geographically diverse as North and South America the optimum treatment strategy is often by no means obvious. One solution is to construct a model that is sensitive to details of climate and management and, in particular, accurate with respect to its representation of the population of flukes within the host. This last is particularly important because most common flukicides are not equally efficacious over all age classes of flukes. Unfortunately, as mentioned above, there is no consensus on what happens in the parasitic phase of the life cycle in cattle.

A Model for the Parasitic Phase

The outcome of the well known single infection experiments by Doyle (1971, 1972) dominated much of the subsequent literature on the dynamics of the parasitic phase of the *F. hepatica* life cycle in cattle. Doyle found that most of the fluke burden was rejected between weeks 20 and 24 after infection. Hope-Cawdery *et al.* (1978) disagreed and suggested that the 'decline in the numbers of fluke in the liver follows an exponential decay curve' but offered no supporting data. An opportunity to discriminate between these conflicting claims arose during the construction of a mathematical model for bovine fascioliasis intended to assist in the design of effective anthelmintic strategies in the Americas. A survey of the literature revealed a number of studies in which calves had been infected with 1000 metacercariae and the flukes counted at varying intervals after infection. Combining these data produced a survivorship curve spanning 400 days (Figure 1).

The compilation showed that there is no reason to reject the simpler hypothesis that the survivorship curve was indeed exponential and that fluke mortality was constant throughout the course of the infection. In other helminth infections, parasite mortality following single infections is non-linearly related to the number of infective stages administered at the outset. Although such a model has been fitted to the data in Figure 1, there is no

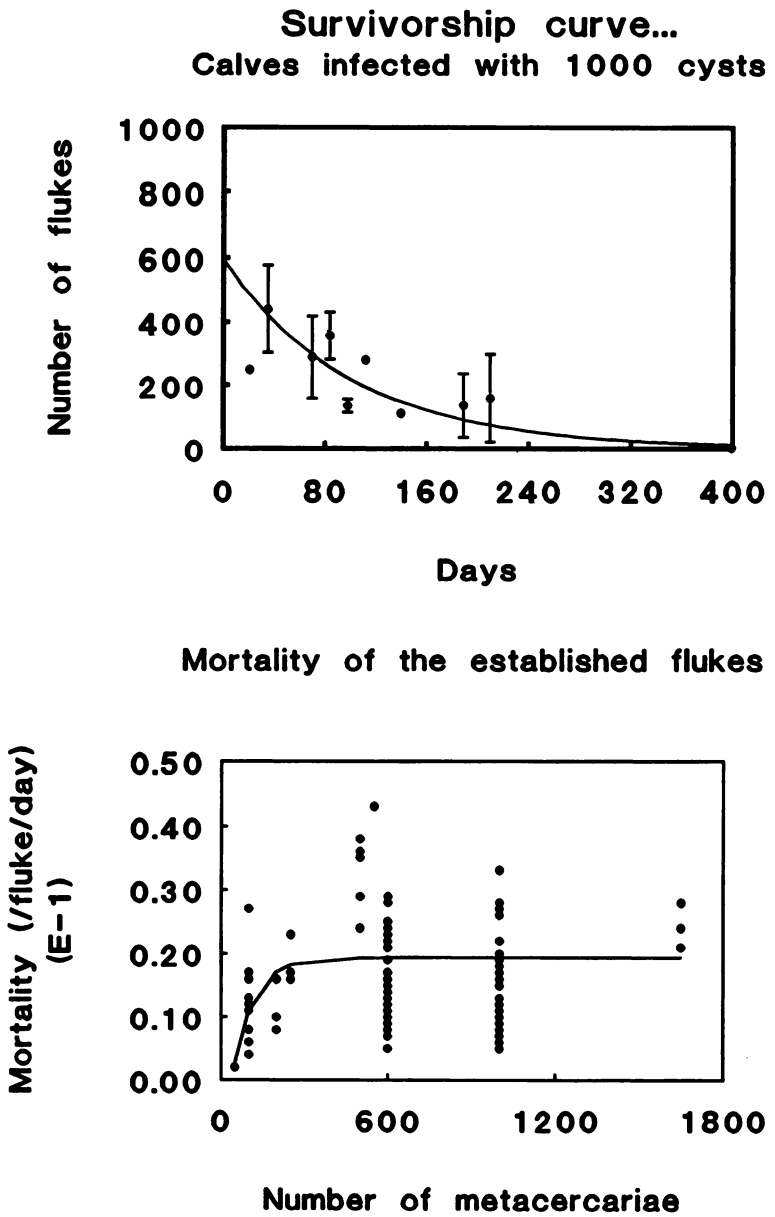

Figure 1. Upper axis: the survivorship curve of *Fasciola hepatica* in calves infected once only with 1000 metacercariae. Lower axis: the average mortality of established *F. hepatica* in calves infected once only with varying numbers of metacercariae (data from Pomorski, 1980; Wensvoort and Over, 1982; Kendall *et al.*, 1978; Furmaga *et al.*, 1983; Malone *et al.*, 1984; Herlich, 1977; Flagstad *et al.*, 1972; Dargie *et al.*, 1972; Dickson, 1964; Oldham, 1985; Hope-Cawdery *et al.*, 1978).

convincing evidence that fluke mortality varies in this way. However, challenge experiments clearly show that calves can develop an acquired resistance to infection with *F. hepatica* and the question arises how is this resistance expressed? Doy and Hughes (1984a) make a convincing argument that resistance to reinfection in cattle occurs at around the time when the juvenile flukes attempt to penetrate the liver. The evidence is twofold. The lack of liver damage in immune challenged animals suggests that very few flukes enter the liver capsule (or are killed soon after). On the other hand, there is no significant difference between the numbers of flukes recovered from the body cavity of newly challenged immune calves and newly challenged susceptible animals. Because juvenile flukes are already penetrating the liver capsule in large numbers four to seven days after excystment (Doy and Hughes, 1984b), it seems that resistance to further infection is expressed very early in the developmental phase of each cohort of flukes.

Doyle (1973) demonstrated that this resistance to challenge infection takes some time to develop. He found no significant resistance to infection in calves infected seven weeks previously, but substantial resistance in calves infected with the same number of parasites 12 weeks previously. The simplest function describing this pattern of change in the proportion of flukes gaining access to the liver is a declining sigmoidal curve of the form $e^{(a+bi)}/(1+e^{(a+bi)})$ (where a and b are constants and i is the infection rate). The parameters of such a curve were estimated by a non-linear least squares method (Berman and Weiss, 1978) from trickle infection data in Van Tiggle (1978). Van Tiggle infected calves with between 50 and 400 cysts per day. The rate of change in the proportion of flukes gaining access to the liver capsule varied with the daily rate of infection (Figure 2a). The steepness of the curves was determined by parameter b, which was inversely proportional to the infection rate (Figure 1b). When the complete model for the parasitic phase of the *F. hepatica* life cycle in calves was then tested against results of the trickle infection experiment (20 cysts per day) reported by Burden *et al.* (1978) it was found to slightly overestimate the observed burdens (Figure 1c). Reinspection of the relationship between parameter b and infection rate indicates that it may be curvilinear rather than linear as shown (Figure 1b). If this were the case, backwards extrapolation of the curve in Figure 1b to give the appropriate value of parameter b would give a much better fit to the data in Figure 1c.

THE PARASITIC PHASE OF THE LIFE CYCLE OF THE COMMON TRICHOSTRONGYLID NEMATODE PARASITES OF CATTLE AND SHEEP

The Problem

There are over a dozen different models for the parasitic phase of trichostrongylid gastrointestinal nematode parasites of cattle and sheep. What each of these models has in common with the others is that it represents a hypothesis about what happens to the parasites after the ingestion of the third larval stage and there appear to be almost as many hypotheses as there are models. Some workers suggest that this multiplicity of frameworks represents a real level of diversity between the different species of trichostrongylid nematodes. This is a view which Smith (in press) has contested suggesting instead that a single model adequately accounts for the observed dynamics in all of the common species. There are

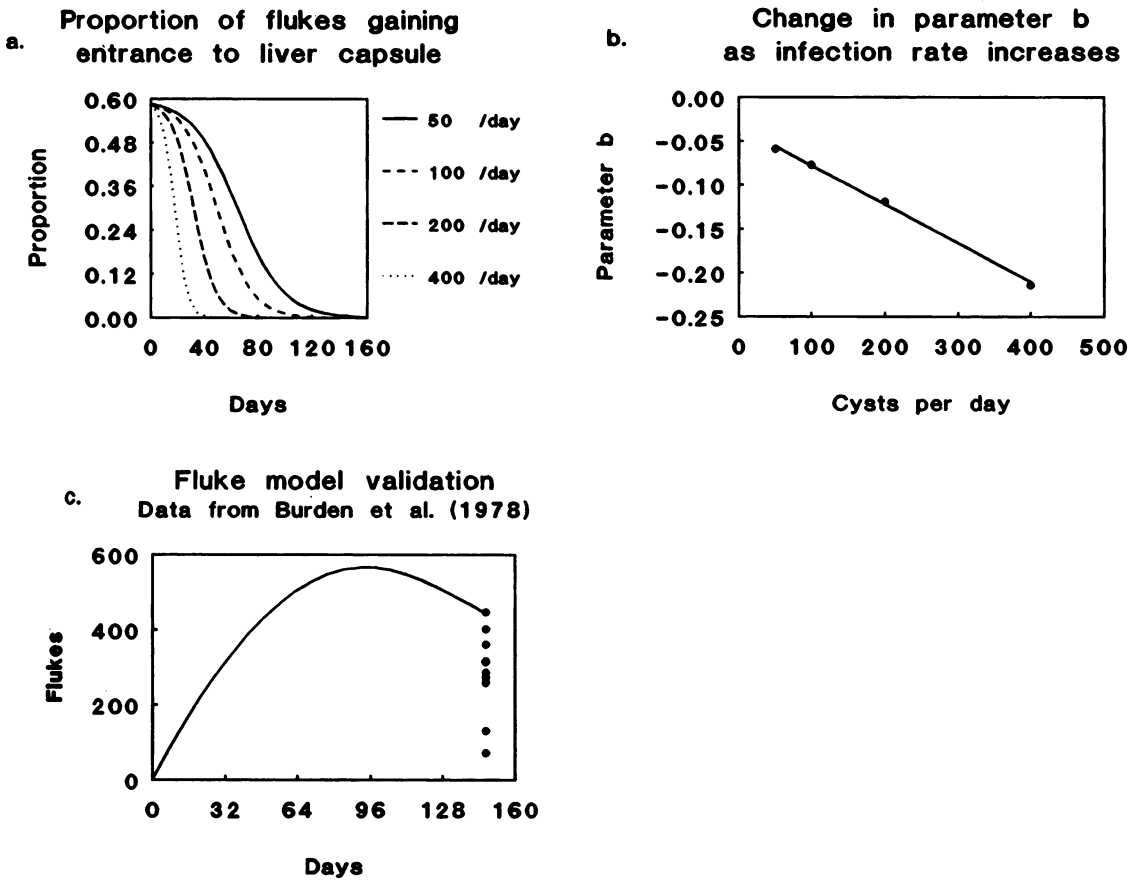

Figure 2. a) The proportion of flukes becoming established in the liver parenchyma at intervals during a trickle infection (estimated from data in Van Tiggle, 1978). **b)** Variations in the parameter b in trickle infection experiments involving 50 to 400 cysts per day (estimated from data in Van Tiggle, 1978). **c)** Predicted (solid line) and observed (●) fluke burdens in which calves were infected with 20 metacercariae each day (data from Burden *et al.*, 1978).

practical as well as biological implications in this suggestion. Natural infections are usually mixed species infections and, since no trichostrongylid species is ubiquitous in the cattle- and sheep-producing regions of the world, the mix of species changes from place to place. It would be far simpler if it were indeed true that a single model framework would work for all the species of interest (one species being differentiated from the rest merely in terms of the numerical values assigned to the constants that determine development and mortality rates). Such a framework would have universal application anywhere in the world.

A Model for the Parasitic Phase

There are two pieces of evidence that a single framework is appropriate for all the common trichostrongylid species. First, the qualitative outcome of trickle and single infection experiments is always the same irrespective of which species is used. Second, a single model framework has been shown to account adequately for the observed patterns in all the instances it has been tested (Smith, in press). The important features are these. Established nematodes (fifth stage worms) die at a rate which varies with the hosts' experience of infection. Parasite mortality increases non-linearly with exposure, but only up to a point. After that point it remains constant irrespective of any further exposure (Figure 3). In the most sophisticated versions of the model the mortality of the fifth stage worms declines in the absence of further exposure (Coyne, 1991), but the basic model works very well in the absence of this refinement provided its use is restricted to prebreeding hosts (Smith and Guerrero, 1993). Meanwhile, the proportion of newly ingested third stage larvae that become established in their predilection sites declines with time (Figure 3).

The pattern of immune exclusion occurring in the first 24 hours after the infective larvae have been ingested follows a declining sigmoidal curve in the same manner as the fluke model discussed above but, unlike the fluke model, it has so far proved impossible to demonstrate that the rapidity of the decline varies with the host's experience of infection (Smith, in press).

OTHER REGULATORY PROCESSES

Parasite-Induced Host Mortality

When an infected host dies its parasite burden dies with it. If the probability of host death increases with the intensity of infection, parasite mortalities due to that cause are density dependent and potentially regulatory. Parasite-induced host deaths in sheep infected with *F. hepatica* are still an important mechanism by which populations of flukes are regulated (Smith, 1982). For example, in the Rio Grande Do Sul in Brazil, acute fascioliasis causes mortality rates of 15–20% (500–800 sheep per flock, Ueno *et al.*, 1982). In the case of ovine fascioliasis, the relationship between host mortality rates and current parasite burdens is relatively easy to discern. That does not seem to be true of *F. hepatica* in cattle or trichostrongylid infections in cattle or sheep. Anecdotal reports suggest that liver dysfunction associated with chronic bovine fascioliasis may be implicated as an accessory

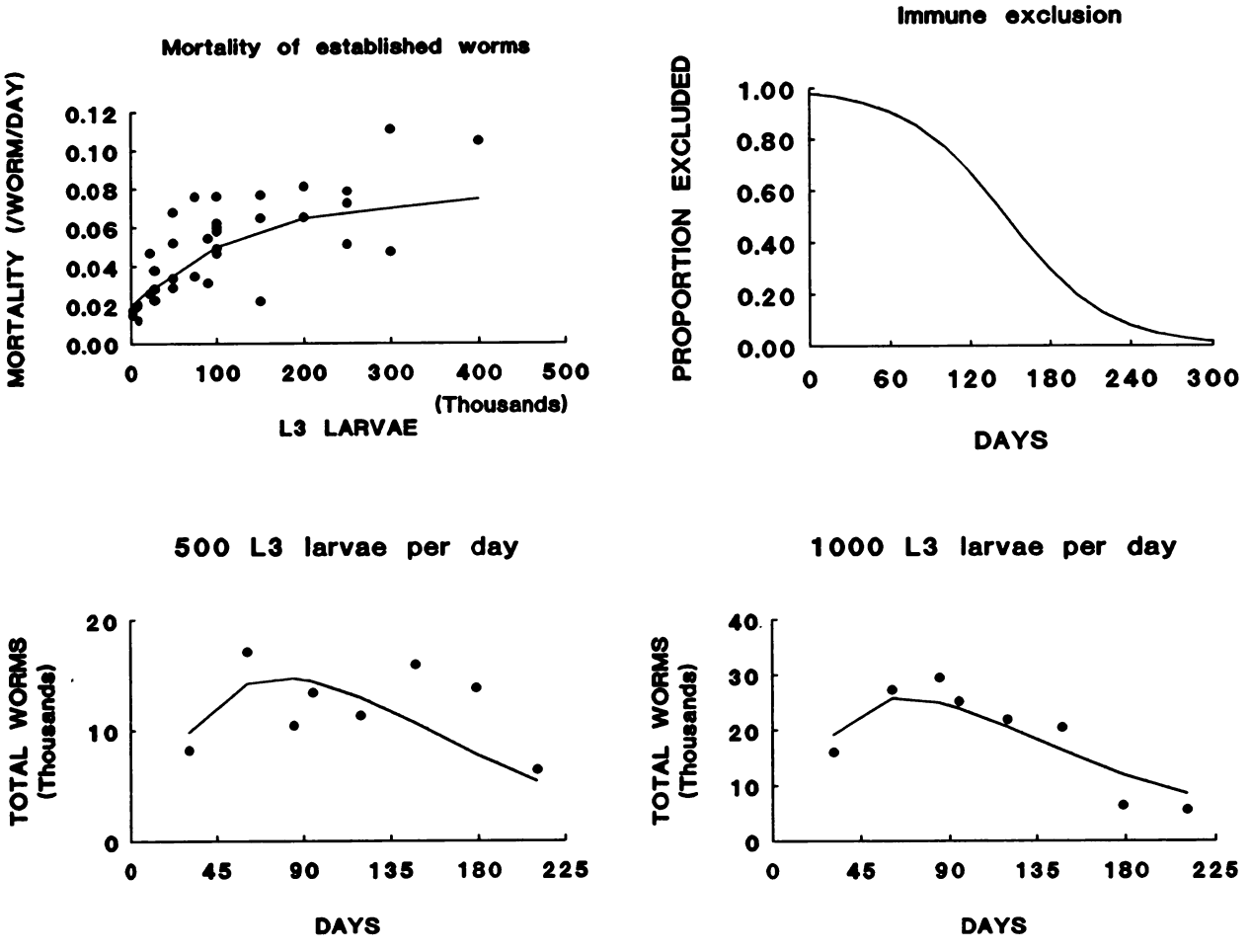

Figure 3. Upper axes: population processes regulating the abundance of *Ostertagia ostertagi* in cattle (Smith, in press). Lower axes: observed (solid line) and predicted (●) worm burden in calves infected daily with either 500 or 1000 larvae per day (data from Michel, 1969a).

factor in cattle deaths (Bundy *et al.*, 1983) and acute fascioliasis in calves may be fatal, but I can find no systematic investigation of the relationship between fluke burden and host mortality rates in cattle.

Similarly, there seems to have been no systematic attempt to examine parasite-induced host mortality in trichostrongylid infections. Such information that exists is generally inconsistent. Deaths attributable to natural infections with trichostrongylid parasites have been reliably reported (Anderson *et al.*, 1969; Al Saqur, 1982) but in order to get information on worm burdens at time of death we have to turn to experimental infections. In the case of bovine parasites, administration of over 300,000 L3 larvae either in a single dose or as the culmination of smaller doses has frequently caused the deaths of a proportion of the calves (Michel, 1963; Herlich, 1959, 1962) but neither the proportions affected nor the worm burdens at time of death show any between-study consistency. Parasite-induced host mortality is a feature of only one of the models of trichotrongylid biology published to date. Barnes and Dobson (1990a) utilized the 'lethal level' concept of Crofton (1971) to mimic sheep deaths due to *T. colubriformis* infections. They assumed that parasite burdens could be best described by the negative binomial distribution and 'killed' any hosts having an estimated number of 50,000 or more adult worms based upon the presumed value of k for the flock (where k is the exponent of the negative binomial distribution).

Regulation of Fecundity

There is good direct evidence that the fecundity of *F. hepatica* is regulated in sheep (Smith, 1982) and reasonable inferential evidence that the same thing happens in cattle (Van Tiggle, 1978). The regulation of trichostrongylid fecundity is much less clear cut. Michel (1969b) believed that the constraints on the fecundity on *O. ostertagi* in calves were so formidable that one could expect the same fecal egg output irrespective of the actual worm burden. This was to overstate the case, but Smith *et al.* (1987a) were able to show that *O. ostertagi* fecundity was significantly smaller in hosts infected for extended periods with large numbers of parasites. Paton (1987), quoting work by Jackson and Christie (1979) and Gibson and Everett (1978), argued that the fecundity of *T. circumcincta* was similarly regulated. However, other analyses indicated that constraints on the fecundity of this parasite were probably feeble at best (Callinan and Arundel, 1982; Symons *et al.*, 1981; Gibson and Parfitt, 1977; Smith and Galligan, 1988). The cautionary paper by Keymer and Slater (1987) made workers more critical about what constituted evidence for density dependent regulation of fecundity. For example Coyne *et al.* (1991b) reinvestigated claims for constraints on the fecundity of *H. contortus* infections in sheep (e.g. Roberts and Swan, 1981; Coyne *et al.*, 1991b). They measured parasite fecundity in natural and experimental infections and in neither case was there any need to invoke regulatory processes to explain observed patterns of fecal output (Figure 4). Furthermore, G. Smith (unpublished work) has been unable to find evidence that fecundity is regulated in bovine infections of *C. oncophora* or *T. axei*.

This kind of investigation is complicated by a number of factors. The actual measurement of fecundity (eggs/female worm/day) requires that both eggs and female worms can be counted accurately. These parameters are often estimated based upon assumptions about

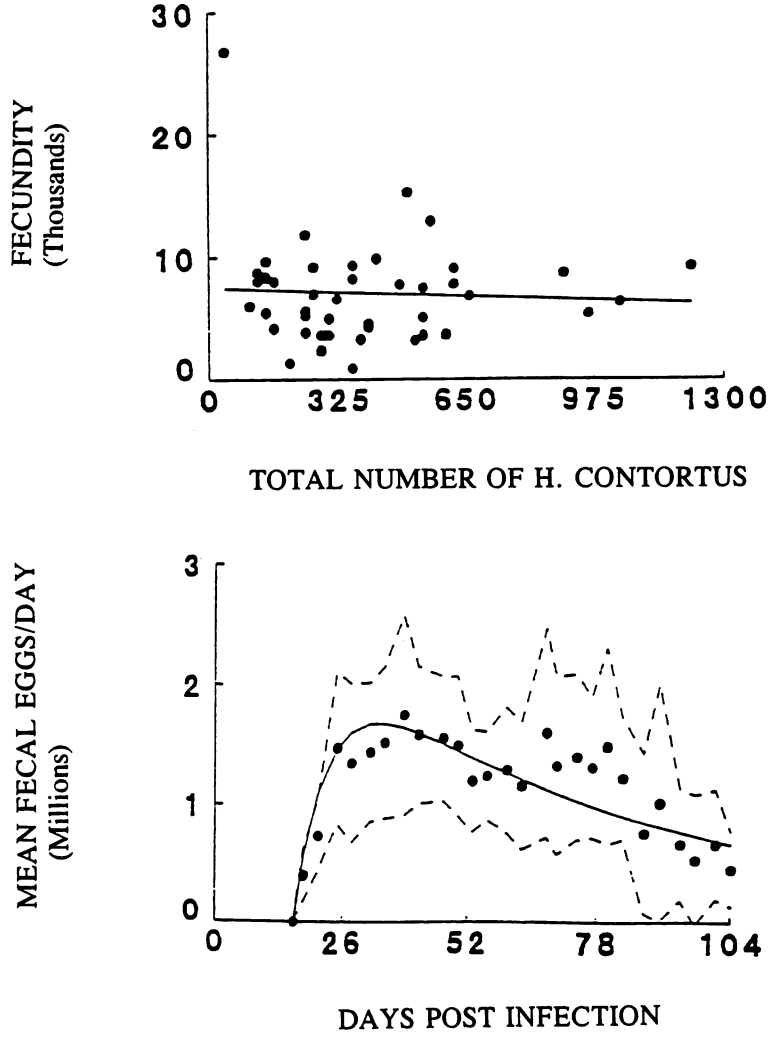

Figure 4. Fecundity of *Haemonchus contortus*. Upper axis: The relationship between estimated fecundity and total worm burden. Lower axis: The predicted (solid line) and observed (●) mean total output of eggs per day; the dashed lines show the 95% confidence limits for the observations. (Redrawn from Coyne *et al.*, 1991a).

recovery rates, sex ratios and amount of faeces produced per day in growing animals. Furthermore, it is necessary to be able to identify mature (egg laying) worms. Fecundity is normally calculated on the assumption that all fifth stage female worms are mature, but this is not the case and in the initial stages of an infection measured levels of fecundity are frequently less that actual levels because immature fifth stages predominate. Some models take explicit account of this maturation phase (e.g. Barnes and Dobson, 1990a; Coyne *et al.*, 1991a, 1991b) in order to lend verisimilitude to frameworks that are meant to be used by non-modellers. While the realistic patterns so obtained inspire confidence

in lay users, it is debatable whether the increased complexity in model format is worth the small improvement in overall model performance.

THE SIGNIFICANCE OF PARASITE FREQUENCY DISTRIBUTIONS

In a single host the severity of the constraint depends simply on the intensity of infection. However, in a community of hosts, the constraints on survival and fecundity summed over the whole parasite population depend upon the frequency distribution of parasites per host. Parasite frequency distributions are frequently aggregated. Such distributions are conveniently described using the negative binomial frequency distribution. This distribution is completely characterized by two parameters: the mean of the distribution and an exponent, k (the degree of aggregation being inversely proportional to the value of k). Aggregated parasite distributions enhance the ability of regulatory processes to maintain parasite populations at or near their equilibrium level but incorporating parasite frequency distributions in realistic models of parasite population biology is fraught with difficulty. Indeed, it is not always possible to incorporate parasite frequency distributions and the question arises as to whether this compromises model performance. Smith and Guerrero (1992) investigated this problem with respect to models of trichostrongylid population dynamics. They found that trichostrongylid populations are aggregated but that the estimated value of k for such populations is usually greater than one. Unlike helminth parasites of wildlife, where many hosts may escape infection altogether, helminth parasites of domestic species maintained at the highest possible stocking rates are usually found in high number in every host (Figure 5). Although the variance to mean ratio in such cases is invariable much greater than unity, indicating an aggregated distribution, the estimated values of k tend to be one or greater. Smith and Guerrero (1993) went on to show that when the degree of aggregation is such that $k > 1$, the results of a trichostrongylid model which recognizes parasite frequency distribution are insignificantly different from the results of a model which ignores parasite frequency distributions (Figure 5). It is not known whether this happy state of affairs is likely to apply to bovine fascioliasis.

Smith (1982) estimated the value of k for flukes in sheep flocks and found it varied over a range of values from very much below one (in which case the distribution must be recognized by the model) to values very much above one (in which case the distribution can be ignored). There are almost no studies of bovine fascioliasis which provide sufficient information to estimate k but a group of naturally infected calves autopsied by Nansen (1975) had a mean fluke burden of 82 and an estimated value for k of 2.5 (G. Smith, unpublished data).

SUMMARY

This paper presents a rationalization of the population processes occurring in the parasitic phase of two of the most important classes of helminth parasites infecting domestic cattle. Both *F. hepatica* and the common trichostrongylid gastrointestinal nematode parasites seem to be principally regulated by events early in the infection process. This is of clear

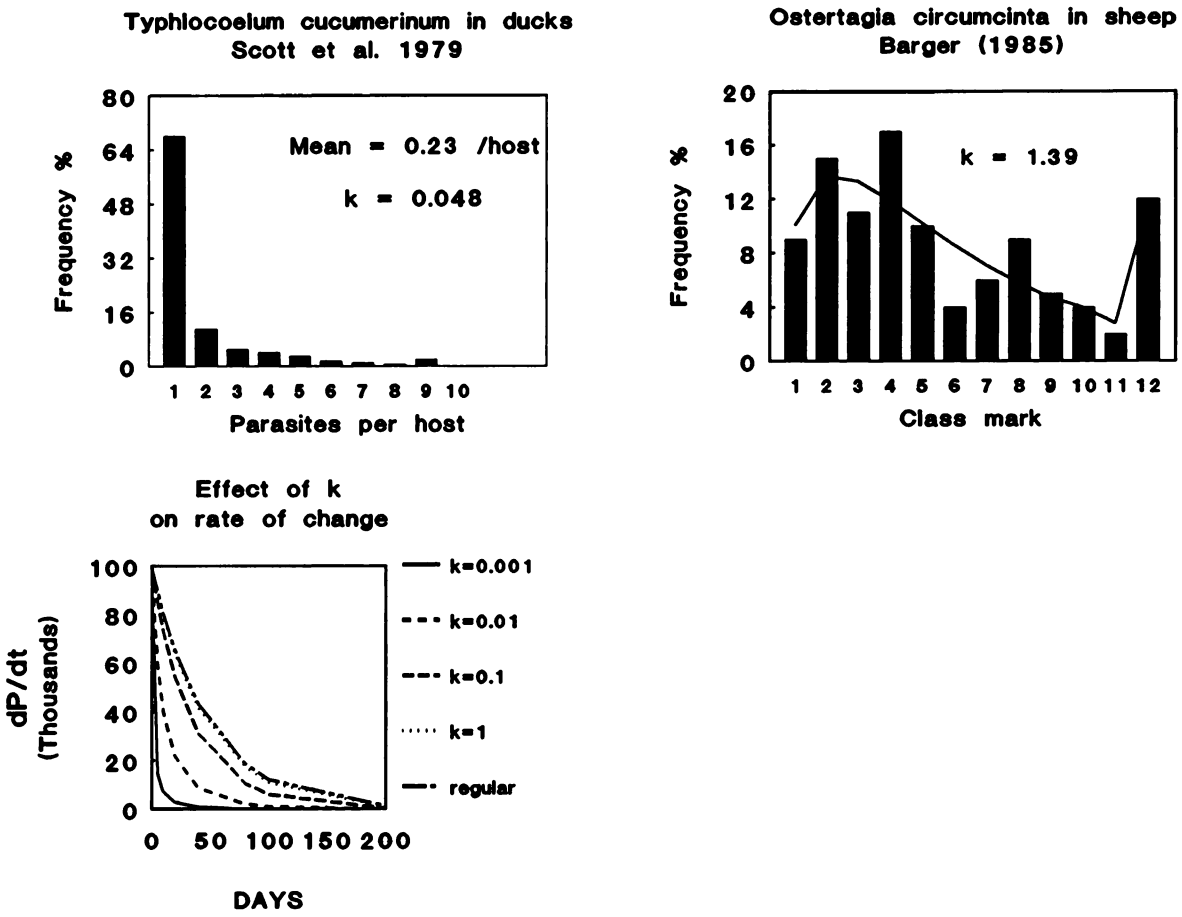

Figure 5. Upper axes: distribution of helminth parasites in wildlife and domestic host species respectively. Lower axis: the effect of parasite aggregation on the rate of change in the number of parasites (dP/dt) in a model assuming that parasite mortality was a function of the rate of infection in any given host. There is no significant difference between the trajectories of a model in which k is 1 and a model in which it is assumed that all hosts contain exactly the same number of parasites ('regular'). (Redrawn after Smith and Guerrero, 1993).

benefit to the host because it is subsequent invasive events that give rise to the pathology usually associated with the infections (e.g. parenchymal migration in the case of *F. hepatica* and emergence from the mucosa in the case of the trichostrongylids). It is not yet clear what is the role of other potentially regulatory processes. Parasite-induced host mortality occurs in both cases but its importance is unknown. Fecundity appears to be regulated in some of these parasites but not in others. Whether there is some systematic relationship between the regulation of fecundity and the survival of the free living stages has yet to be considered. It appears that modellers can gratefully relinquish the burden of trying to write tractable formulations incorporating empirical descriptions of parasite distributions, at least in the case of the trichostrongylids. Whether this is true of bovine fascioliasis remains to be seen.

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Session discussion

A general principle and requirement in vector research is to predict the distribution and abundance of the vectors in order to determine the disease risk in a population. It is important to identify both the set of factors which predict disease risk and the set which determine the population dynamics if the goal is to control diseases *per se*. The number of factors varies for different diseases but the overall opinion was that few variables are often responsible for the majority of the variance; such is the case for factors affecting the distribution of tsetse fly populations, where two or three variables account for most of the variance.

Concern was raised with regard to the availability of reliable data sets. Older data sets often were not developed with the needs of modelling in mind, and the negative effect of this is enhanced by the fact that fewer field projects are initiated to collect new data these days, reducing the possibilities of establishing new, reliable and useful data sets. It was proposed that literature reviews may supply certain initial data sets which, in combination with well designed field research for collection of information on outstanding questions, could contribute to better model development. It was generally agreed that models need to be validated and the lack of data sets is a severe constraint for testing the validity of the rather advanced vector models available.

The use of models to predict distributions of tick vectors was discussed and the importance of identifying the appropriate variables for inclusion in these models was debated. Climatic data are clearly crucial, and their availability and resolution, both as long-term average and real time data, are improving. Other factors likely to be important but yet to be fully evaluated in models include physiological age of ticks, host resistance to ticks, diapause and the role of wildlife hosts.

A factor which has not been considered important in the current tick and helminth vector models is the phenomenon of 'overdispersion' and it was pointed out that little is known about this. The distribution of different levels of parasitism within a population will determine levels of disease and economic loss, and overdispersion, in which low numbers of individuals carry high parasite burdens while the majority of the population carries low burdens, is likely to affect these significantly. The possible contributory roles of genetic and behavioural factors to overdispersion were discussed.

PARASITE TRANSMISSION

Transmission of *Theileria:* ILRAD's requirements

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The International Laboratory for Research on Animal Diseases (ILRAD) carries out active research in this area being an essential part of the epidemiology of theileriosis, and thus may be able to generate information essential to the disease modeller. Attempts have been made to quantify the transmission processes for *Theileria parva* but results have shown that it is complex. Many of the processes involved in transmission are multifactorial; generally, they can be divided into those driven by the host, the parasite, tick and the environment. These factors do not necessarily operate in isolation. ILRAD's attempts to quantify some of these processes are illustrated as follows. A large database has been assembled on the laboratory infection of cattle by *T. parva,* related to the infections of feeding ticks and this has been extensively analysed. However, until recently it had not been possible to quantify the relationship between the infective stage of the parasite for the tick, the piroplasm, to the resulting levels of infection in the tick. This made the ILRAD requirement for the production of ticks with predictable infection levels difficult. It is evident that the vectorial capacity of ticks varies with the instars, the sex and the population of ticks. Furthermore, in any tick population examined, overdispersion of *Theileria* infection has been detected; a small proportion of the tick population becomes infected or highly infected with *T. parva.* Factors controlling the infectivity of *T. parva* populations and the susceptibility of tick populations are under investigation.

The mechanism by which cattle are infected with *T. parva* by feeding ticks is also being investigated with a view to the development of control strategies for the disease, particularly in designing novel vaccines. The survival of *T. parva* within the tick can be quite different under varying climatic conditions. A complication, both in cattle and ticks, is that one individual may be harbouring more than one species of *Theileria.* New methods for differentiating species within cattle and ticks are being developed. The nature of the host population, in their susceptibility to infection by *T. parva,* is important and needs further quantification. Progress on the *in vitro* feeding of ticks may allow study of transmission of *Theileria* without complication of the host factors. It is hoped that new data generated from these studies will be useful in the developing and improving of transmission models of *T. parva* infection which in turn may lead to better understanding of the epidemiology of theileriosis. However, there are very few longitudinal studies of cattle available in site-specific situations. Data on such site-specific situations has been shown to be useful in modelling the transmission of *T. parva* and therefore ILRAD's research efforts should be directed to support site-specific studies in different epidemiological zones. ILRAD can be beneficial in the way of encouraging national programs to use the right techniques and the right approaches to provide the relevant information to disease modellers.

Transmission of trypanosomes: ILRAD's requirements

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The epidemiology of animal trypanosomiasis in tsetse-infested areas of Africa involves the relationship amongst the four biological factors, namely trypanosomes, reservoir hosts, tsetse flies and livestock, operating within the physical environment, which determine the distribution and frequency of the disease in livestock populations in the endemic regions. Certain changes in this dynamic interaction may result in an epidemic of trypanosomiasis in livestock. The epidemiology of animal trypanosomiasis is therefore a complex ecology since it involves two types of mammalian hosts, i.e. species of wild animals and livestock, which differ with regard to their reservoir potential for trypanosomes and the level of susceptibility to *Trypanosoma vivax, T. congolense* and *T. b. brucei* stocks, and a diverse tsetse species having a somewhat different range of hosts and with differing vector competence for different stocks of the three parasite species.

The transmission of trypanosome infections to livestock by tsetse flies is but a component of this complex cycle of transmission, and hence it cannot be regarded as an independent entity. Yet, it might be possible to formulate an accurate predictive model of this essential component. To achieve this goal, ILRAD's efforts need to be directed towards research, in at least two trypanosomiasis endemic areas, one in East and the other in West Africa, to quantify the following factors: tsetse species present in the identified areas, their distribution and abundance; vector sex ratio, their feeding interval and survival rate; infection rates in tsetse by *T. vivax, T. congolense, T. simiae* and *T. b. brucei;* incidence of mixed trypanosome infections in the vectors; trypanosome transmission coeficients, from tsetse vectors to the mammalian hosts and vice versa; species of wild mammals present, their distribution, abundance and their possible trypanosome reservoir potential for tsetse; proportion of tsetse bloodmeals from different species of wild hosts; size of the livestock populations; proportion of tsetse bloodmeals from livestock; and incubation period, infectiousness and immunity in the mammalian hosts of tsetse to the three pathogenic trypanosome species. This study will probably lead to a better understanding of the relationship amongst the involved biological factors, and hence provide the basis for formulation of the model of transmission of trypanosome infections to livestock by tsetse flies.

Models for *Leishmania* transmission

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ABSTRACT

Discussion in this paper is restricted to the problem of using models as a basis for estimating the absolute transmission rate of leishmaniasis, in particular the basic reproduction number, R_0.

I begin by noting that it is beguilingly simple to adapt, in principle, the theory of mosquito vectorial capacity to phlebotomine sandflies, and to other insect vectors. However, vectorial capacity is rather intractable in practice, whatever system it is applied to. There are two reasons why this is so, with two consequences.

The first reason is that the basic formula, originally used in malariology, is structurally deficient. For example, it does not account for heterogeneous contact rates between vectors and hosts (non-random biting rates), or parasite-induced mortality of vectors. Second, several of its parameters, such as vector mortality, are very difficult to estimate. There has been practically no effort to assess the confidence limits associated with published estimates of vectorial capacity, and many such estimates are not to be trusted.

The first consequence is that we need to be clear as to when vectorial capacity and related formulae are actually useful. I argue that effort will be expended more efficiently, and that conclusions will be more robust when such formulae are used to answer well-focused, comparative questions.

Second, if absolute estimates of transmission rate are needed, they will be more credibly obtained by adapting methods which have been developed for directly-transmitted infections. I give one example where the formula $R_0 \equiv 1/s^*$ (where s^* is the equilibrium fraction of host animals susceptible) has been modified and applied to visceral leishmaniasis in dogs. I also describe the real difficulties involved in applying even such a simple formula to a parasitic infection, which are mainly to do with distinguishing between infection and infectiousness. The argument leads, in a tantalizing way, to the conclusion that the usual method of identifying animals to be treated or culled could result in effective disease control, but without having permitted an accurate assessment of the magnitude of the problem in the first place.

INTRODUCTION

Macdonald's (1957) malaria model is one of the best-known of all mathematical models of infectious diseases. One product of Macdonald's work was a definition of the basic case reproductive rate, R_0, for a disease transmitted by a mosquito-like vector. R_0 is the average number of secondary cases which arise from each primary case when infection is introduced into a population consisting almost entirely of susceptibles. It is thus a mean maximum rate of spread of infection through a community. According to Macdonald:

$$R_0 = ma^2bp^n/-rlnp \quad (1)$$

where m is the number of mosquitoes per person, a is the daily biting rate of a female mosquito on man (as opposed to other hosts on which bites are wasted from the viewpoint

of *Plasmodium),* b is the probability an infectious mosquito actually transmits infection when biting, p is the daily mosquito survival rate, n is the time taken for plasmodia to mature to infectious sporozoites in mosquitoes (the extrinsic incubation period), and r is the daily human recovery rate from infectiousness. To focus the minds and hence the activities of entomologists, Garrett-Jones (1964) extracted all the transmission components of R_0 as the vectorial capacity, C,

$$C = ma^2bp^n/-lnp \quad (2)$$

C is the number of secondary cases which arise from the bites taken by all mosquitoes on one infectious person in one day. Equations (1) and (2) have been enormously valuable in identifying the relative importance of the different components of transmission. A classic argument used by MacDonald was that, since p is raised to the power n in the numerator, and appears in the denominator too, C (and thus R_0) ought to be particularly sensitive to changes in vector survival rate. He made this proposition just as the appropriate tool became available to test it: DDT was hugely successful as a residual insecticide, even in many areas which were highly endemic for malaria.

But this is a qualitative argument. There are two main difficulties with using these formulae quantitatively. The first is that they are structurally deficient. The second is that most of their components are very hard to measure. These difficulties exist whether we are interested in mosquitoes and malaria, sandflies and leishmaniasis, or tsetse flies and trypanosomiasis (Dye, 1992). Thus, although this paper is primarily concerned with leishmaniasis, we can illustrate these general difficulties in the next two sections by drawing on examples from malariology too.

STRUCTURAL DEFICIENCIES OF THE VECTORIAL CAPACITY EQUATION

The following are four of the many assumptions made by equations (1) and (2).

1. All mosquitoes feeding on a person carrying infectious parasites actually acquire infection. The probability that any vector picks up parasites from an infected host is in fact much less than one, and needs to be represented by including another parameter, say c, which has a value between zero and one (Nedelman, 1984).

2. Vectors bite hosts at random. This is almost never the case: for example, some people live nearer to breeding sites than others, and mosquitoes tend to bite adults rather than children because they are bigger (Port *et al.,* 1980). The consequences of non-random host choice are that R_0 will always be bigger than expected under the assumption of random biting (Dye and Hasibeder, 1986; Hasibeder and Dye, 1988).

3. Individual members of a vector population behave in a uniform way. There is growing evidence for genetically determined differences in host choice within mosquito populations, for which there must be epidemiological consequences. For example, V. Petrarca and J.C. Beier (cited by Coluzzi, 1992) have shown that the distribution of karyotypes among *Anopheles arabiensis* which have fed on man is different from those which have fed on animals.

4. Survival rate of vectors does not vary with age. Clements and Paterson (1981) have reviewed the evidence for both *Anopheles* and *Culex* mosquitoes and concluded that

survival rate commonly declines with age. A graph of log numbers of individuals (captured by whatever method) against age is often not a straight line (indicating constant survival rate), but a curve with increasingly negative slope (Figure 1).

DIFFICULTIES OF PARAMETER ESTIMATION

Among the components of equations (1) and (2), we focus on four problems of getting m, a and p from field data.

1. Man-biting rate. m is the number of vectors per person. Absolute vector density is very difficult to measure indeed. For example, different methods of interpreting mark-release-recapture data often give substantially different estimates of vector population size (Sheppard *et al.*, 1969). One solution is to measure m and a together in the product ma, which is the daily vector biting rate per person. In malariology, this has been done by trained bait-collectors spending entire nights, in shifts, inside and outside houses. In general, the results probably get close to the true mean biting rate. In recent years, the procedure has been euphemistically renamed the 'man-landing catch', but this does nothing to reduce malaria as an occupational hazard. Consequently, many research workers have now stopped using main-baited catches, especially in areas where the parasites are drug resistant. The alternative is to use traps, such as CDC miniature light/suction traps, which can at least record *proportional changes* in vector biting rate.

2. Vector survival rate. The pattern suggesting age-dependent survival seen by Clements and Paterson, and described above, has also been seen in a population of the sandfly *Phlebotomus ariasi* (Figure 2). But in this case we know that the shape of the curve actually reflects dissection error rather than survival rate falling with age (Dye *et al.*, 1987). Do the mosquito data suffer from the same problem? A second difficulty is the assumption that parasites have no impact on vector survival rate. There is much laboratory evidence, now supported by field data (e.g. Lyimo and Koella, 1992), showing that parasites such as *Plasmodium* can significantly reduce vector survival. Of course, all field estimates of survival rate are obtained by working with the entire vector population, in which the prevalence of infection is generally very low.

3. Vector host choice. Parameter a in equations (1) and (2) includes the probability that a mosquito takes any of its bloodmeals on man. In malariology, this probability is measured by the Human Blood Index (HBI). Although HBI is simply the proportion of all bloodmeals taken on man, it is hard to measure because representative samples are needed from all mosquito resting sites (Garrett-Jones *et al.*, 1980). That is, we need to be able to catch with the same efficiency in cattle pens, animal burrows, and vegetation etc. Since different sampling methods need to be used in these different circumstances, catches will rarely be comparable.

4. Vector biting rate (or the interval between bloodmeals, i). This is the other component of parameter a. It can be measured in mark-release-recapture experiments, but accuracy is often limited by low rates of recapture (Dye *et al.*, 1991). A second technique, developed for mosquitoes but applicable in principle to other vectors too, uses time series analysis, and the fact that all parous mosquitoes found in a population at time t must have been produced by all female mosquitoes at time t-i. The cross correlation coefficient between

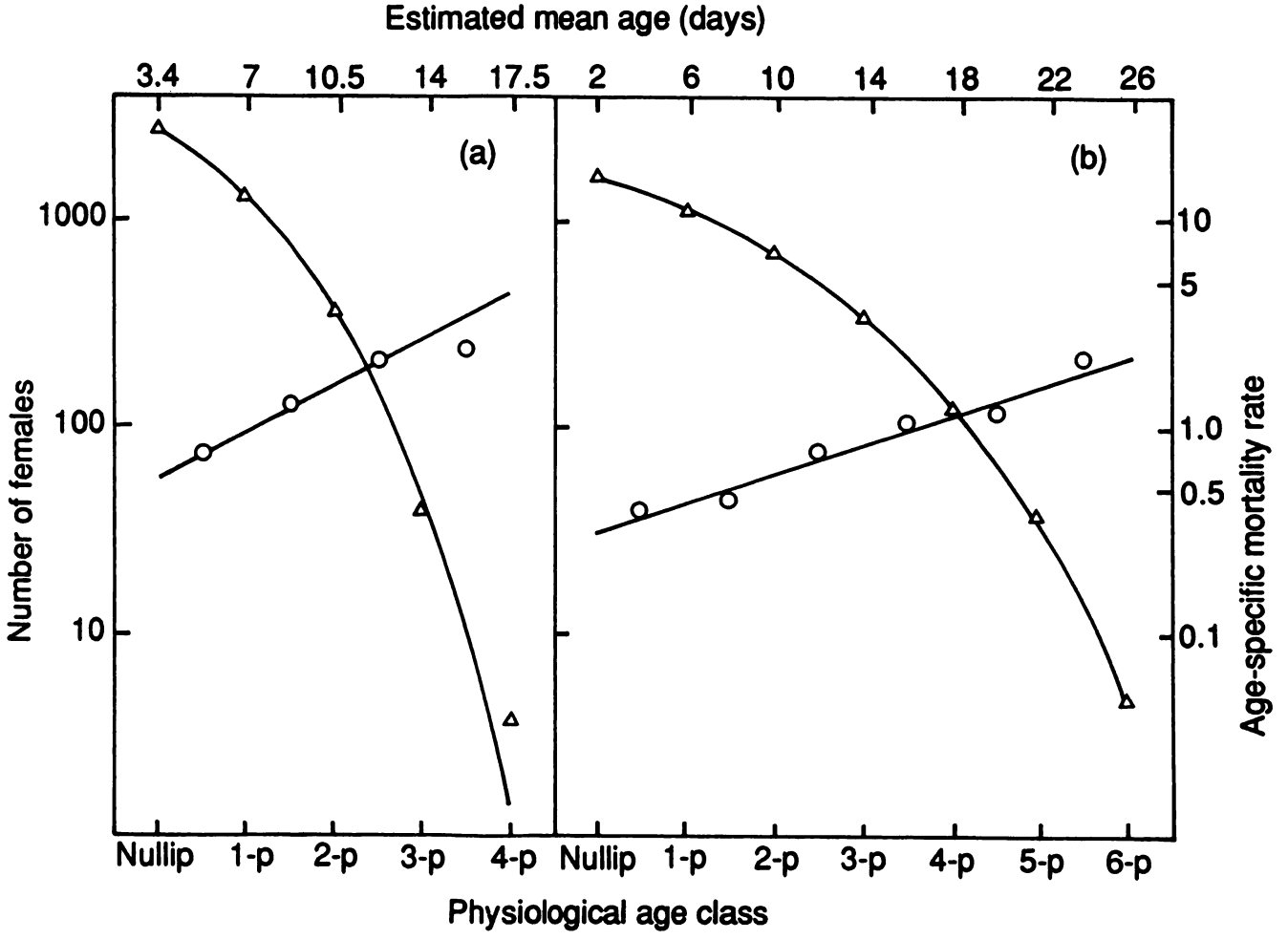

Figure 1. Log numbers of field-captured female mosquitoes (triangles), plotted as a function of calendar and physiological age (parous number), together with estimated age-specific mortality rates (per ovarian cycle, circles). (a) *Culex quinquefasciatus*, (b) *Mansonia uniformis*. These data, obtained by counting follicular relics in ovaries, suggest that mortality rate increases with age. From Clements and Paterson (1981).

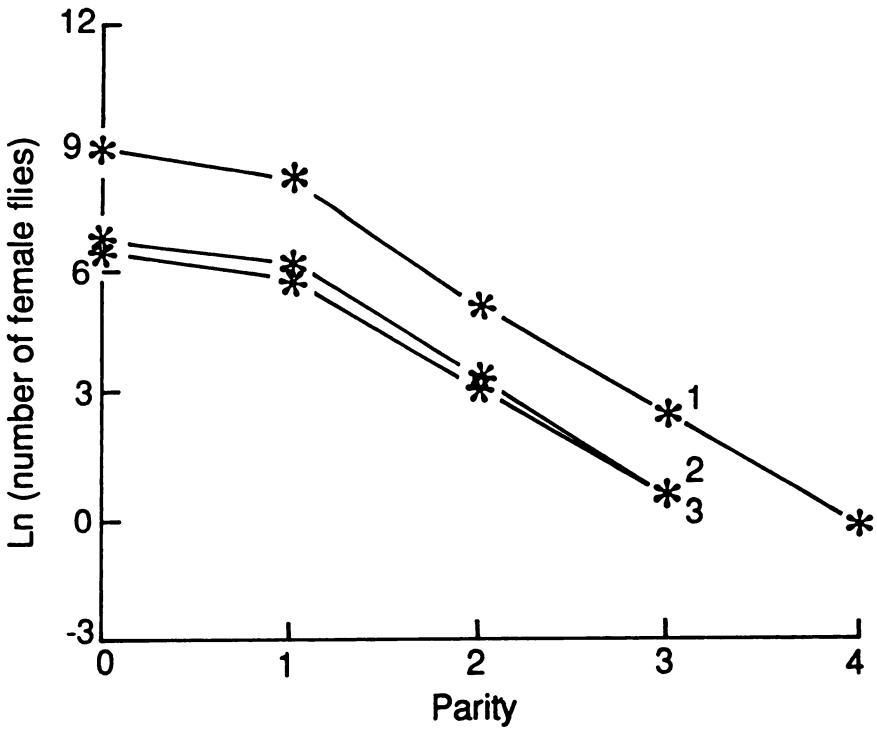

Figure 2. Log numbers of *Phlebotomus ariasi* sandflies plotted against ovarian age, for three sites in the Cévennes, France. The curves are non-linear because of dissection error; they are not evidence that mortality increases with age. From Dye *et al.* (1987).

the parous time series and that for total females should reach a distinct maximum when the lag is i days (Birley and Rajagopalan, 1981). In practice, a distinct maximum is not always found (Charlwood *et al.*, 1985). Underlying this technique is the further assumption that vectors are gonotrophically concordant, that is, they take one bloodmeal in each gonotrophic cycle. In fact, many bloodsucking insects take several bites during each cycle. The number of hosts an individual bites before acquiring enough blood to mature one batch of eggs may depend on the frequency with which feeds are interrupted.

Considering structural deficiencies and the problems of parameter estimation, the emergent conclusion is that equations (1) and (2) cannot easily be used to estimate the absolute transmission rate. The recommended alternative is to use entomological indices of transmission, like the vectorial capacity, in a comparative way. One example is given in the next section.

COMPARATIVE ANALYSIS

Transmission-blocking vaccines are a potentially important method of malaria control. Anticipating the experiment, Saul *et al.* (1990) developed a method of estimating the

probability that a mosquito acquires infection at each bite, K. This is the quantity which would be reduced by vaccination. Their estimate is given by:

$$K = D_b(1-P_f)/[QP_f(1-D_b)] \quad (3)$$

in which D_b is the proportion of vectors infected in each biting catch, P_f is the probability of surviving each feeding cycle, and Q is the proportion of feeds taken on humans, the Human Blood Index discussed above. Parameters Q and P_f are the most difficult to measure accurately; D_b is made more accessible by the availability of immunoassays.

A useful index of vaccine efficacy would be the ratio v = K (after vaccination)/K (before vaccination). But if this is all we need then we note that Q and P_f are unchanged by vaccination, that $1 - D_b \cong 1$, which gives $v \cong D_b$(after vaccination)/D_b(before vaccination). Thus a robust estimate of v can be obtained by measuring just one relatively tractable parameter. Notice too that biases in D_b are unimportant, provided they are identical before and after vaccination. There may be occasions on which we need to know actual K's before and after vaccination, but we certainly do not always need to know them.

ABSOLUTE ESTIMATES OF *LEISHMANIA* TRANSMISSION RATE?

The principal message of the previous sections is that measurements of transmission should depend on few, tractable parameters. If we do wish to estimate R_0, there are more direct methods than that given by equation (1). One such is due to Dietz (1975) and to Anderson and May (1991) who have shown for directly transmitted viral infections that, if L is the life expectancy of the vertebrate host and A the average at which infection is acquired, then $R_0 = 1 + L/A$. Where $L >> A$, $R_0 \cong L/A$. This formula has a simple, intuitive interpretation. On average, $R_0 > 1$ is required for an epidemic to occur. The ratio L/A just says that an epidemic will occur provided hosts live long enough, on average, to get infected.

We can adapt this formula for canine leishmaniasis (due to *Leishmania infantum* or *L. chagasi)* but in doing so must account for the fact that this is a disease for which death, rather than immunity, follows a durable period of infectiousness. The result is (C. Dye and G. Hasibeder, unpublished data)

$$R_0 = 1+[L_t+P_dL_i(1+E_f)]/A \quad (4)$$

Here P_d is the probability a dog survives the latent period, L_t is the expectation of the latent period, L_i is the expected duration of infectious life, and E_f is the expected number of bites taken by an infectious fly. Estimation of R_0 for canine leishmaniasis by this route is therefore rather more awkward than for common childhood viral infections, and we move to an alternative.

There is a second simple but useful formula, also derived for stably endemic, directly transmitted infections in homogeneously mixing communities: $R_0 = 1/s^*$, where s^* is the fraction of hosts susceptible to infection at equilibrium. Modifying this for a vector-borne disease like leishmaniasis gives $R_0 = 1/(s^*u^*)$ (Dye *et al.*, 1992; Hasibeder *et al.*, 1992). Here, u^* is the fraction of vectors which are uninfected at equilibrium, but this is approximately equal to one, and in practice may be ignored.

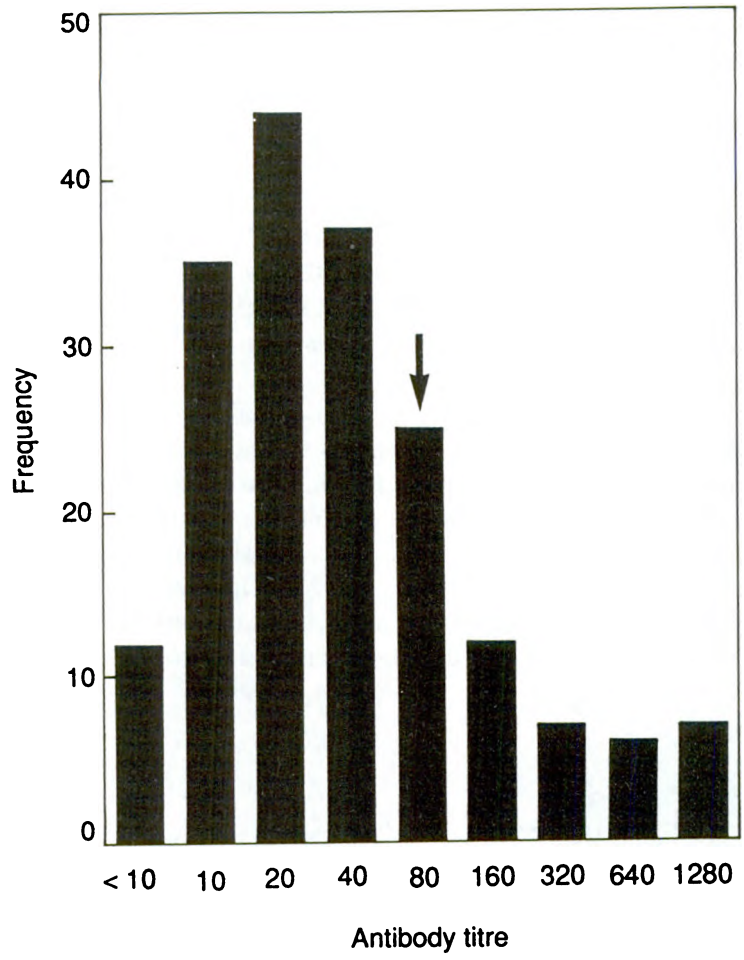

Figure 3. The frequency distribution of antibody titres obtained from a population dogs on the island of Gozo, Malta. Sera were subjected to IFAT for *L. infantum*. The distribution is unimodal, giving no suggestion that one frequently used cut-off point (arrowed) decisively separates infected from uninfected animals. From Dye *et al.* (1992).

Less easily dismissed is the question of non-homogeneous biting rates by sandflies. As already mentioned, mathematically convenient homogeneous biting rates are the exception rather than the rule. Assuming that a single population of sandflies bites at different rates in different patches of dogs, we get

$$R_0 = (\Sigma n_i \lambda^2{}_i)/(u^* \Sigma s^*{}_i n_i \lambda^2{}_i) \quad (5)$$

Now we have n_i dogs in the ith patch. The λ_i's are, conveniently, the relative (rather than absolute) magnitudes of the forces of infection (instantaneous incidences) on dogs in different patches.

Serology is the usual method of estimating both s and λ. However, the data are commonly hard to interpret. For many parasitic infections, frequency distributions of antibody titre are unimodal, showing no clear cut-off point between dogs which have been infected and those which have not (Figure 3). In a recent study of canine leishmaniasis on the Maltese island of Gozo, we explored the consequences of choosing three different but plausible cut-off points for ELISA, IFAT and DAT (Dye *et al.*, 1992). As expected, estimates of λ were rather insensitive to the choice of cut-off point. More surprisingly, they were insensitive to the assumption of homogeneous biting rates. But estimates of R_0 varied from 1.6 to 11.1. The difference is extremely important: the lower estimate suggests that eradication could be achieved if the vector population were reduced by 38%, whereas the upper implies that a reduction of 91% would be needed.

To investigate further the performance of serological tests in leishmaniasis epidemiology, we have attempted to calculate sensitivity and specificity of IFAT during a longitudinal study on a cohort of 50 dogs in southern France (Dye *et al.*, 1993). A combination of clinical signs and the success of efforts to isolate parasites were used as a 'gold standard', albeit an imperfect one. Figure 4 shows that, following infection during the transmission season in June and July, sensitivity took as long as eight to nine months to reach a satisfactory 80%, and this was maintained for just two months. Evidently, the IFAT will commonly underestimate infection rate in cross-sectional studies.

CONCLUSIONS

The vectorial capacity has been a hugely important concept in medical entomology. As well as providing ammunition for advocates of control by adulticide, it also been used in 40 years of teaching to make plain the components of transmission by mosquito-like vectors. Quantitative application of formula (2) has, however, been less successful. The formula has important structural deficiencies, and its parameters are hard to measure accurately. Consequently, medical entomologists should not use it to measure absolute transmission rate. They should use it as a starting point for answering particular comparative questions. The index of relative vaccination success described above is one example. Others are (Dye, 1992): What is the most important vector in an area? What best explains geographic and temporal variation in the incidence of infection? Why did vector control have no impact on the prevalence of infection? Which of two alternative control methods is likely to have the greatest impact on prevalence?

But not all the important quantitative questions in epidemiology are comparative ones. Mindful of the difficulties of getting R_0 via the vectorial capacity, we have tried to adapt two, more direct methods for canine leishmaniasis. One of these leads to a relatively simple formula which requires accurate estimates of incidence rate only. But even this simple formula is hard to apply in practice because serodiagnosis of *Leishmania* infection is an imprecise science. Our limited success in estimating absolute transmission rates underlines the general theme of this paper: in quantitative epidemiology, comparative questions are far more tractable.

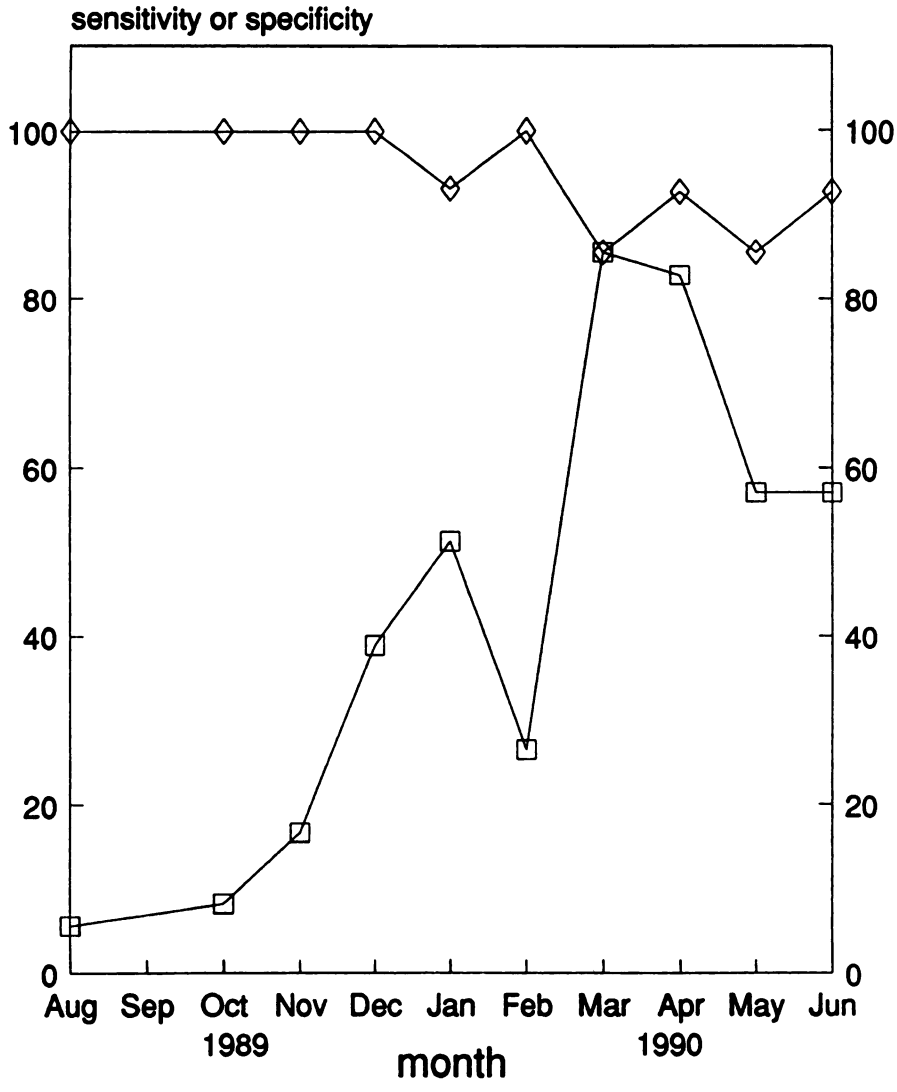

Figure 4. Sensitivity (squares) and specificity (diamonds) of IFAT for *L. infantum* in a cohort of 50 dogs over 11 months following the 1989 transmission season. Sensitivity took eight to nine months to reach a maximum of around 80%. From Dye *et al.* (1993).

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The transmission dynamics of *Theileria parva*

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ABSTRACT

This paper describes a quantitative framework which allows epidemiological field observations to be analysed and used to examine the transmission dynamics of *Theileria parva.* Initially the situation in endemically stable areas (characterized by continuous activity of the tick vector, *Rhipicephalus appendiculatus)* is considered, as this allows consideration of transmission at a stable equilibrium. The data used are: 1) the rate at which cattle are infected; 2) the prevalence of infection of ticks; 3) the rate of infection of ticks fed on 'carrier' cattle (i.e. cattle that have been exposed to infected ticks and survived the initial infection).

A dynamic compartmental model of cattle infection is described. It incorporates five stages of cattle infection: susceptible (uninfected), incubating infection, clinically diseased cattle that will survive, clinically diseased animals that will die from infection and cattle that have survived the initial infection ('carriers'). Estimates of the rates at which cattle move through the model are taken from the literature. Initially, the rate of infection is taken from the field estimate and the model is shown to characterize the infection within a cohort of calves born into an endemically stable area.

The model is adapted to include a transmission term that describes the rate of infection of ticks by cattle. Using the model and data estimates above, the dynamic stable equilibrium is characterized. The model is used to demonstrate three conclusions. First, that 'carrier' animals must be responsible for the majority of tick infections. Second, that reduction in tick density only reduces the prevalence of infection in cattle appreciably when the effective tick feeding rate is reduced to about 20% of its equilibrium level. Third, that the creation of 'carrier' animals by infection and treatment immunization does not alter the equilibrium perceptively as the majority of animals are 'carriers' already.

This model requires extension in several areas. First, the biology of 'carriers' and their infection of ticks requires more study: carrier infection may be as a consequence of continual exposure and sub-clinical infection or as a consequence of survival of the original infection in immunologically privileged sites. The details of this interaction will have considerable impact on the transmission dynamics. Second, the model should be extended to seasonal areas, which will require explicit consideration of the tick population dynamics.

INTRODUCTION

Theileria parva, an apicomplexan parasite, is the aetiological agent of East Coast fever (ECF) in cattle, and is transmitted by the ixodid tick *Rhipicephalus appendiculatus* (for a review of the epidemiology of *T. parva* see Norval *et al.,* 1992). East Coast fever is an important disease of cattle in sub-Saharan Africa. It has been responsible for major epidemics in the past century (Norval *et al.,* 1992) killing millions of cattle. Epidemics remain possible today when control methods are ceased, or the infection is introduced into previously uninfected areas. The economic losses to theileriosis are considerable

(Mukhebi *et al.*, 1992) and the effect of *T. parva* is to substantially reduce the productivity of cattle in Africa, both in terms of food and monetary value, and prevent the unconstrained introduction of improved breeds of cattle.

The transmission of *T. parva* is complex. The mammalian hosts of the infection are many, and there is considerable genetic diversity within populations of *Theileria* spp., complicating the classification of the parasite. *Rhipicephalus appendiculatus* is a three-stage tick (larva, nymph and adult) which feeds three times during the life cycle on a variety of different mammalian hosts. Each species in this complex has its own biology, much of which is poorly understood. This paper continues a process of clarification of this situation with the eventual aim of developing models that are useful in the design of control programs against ticks and the infections they transmit. In order to be able to make some progress, it is necessary to make some gross, simplifying assumptions about the population dynamics.

This preliminary work focuses on the epidemiological state referred to as endemic stability. Within such areas there is a high level of infection in both cattle and ticks, but with little mortality from infection due, in the main it is thought, to the genetic constitution of the hosts, which have been subjected to *T. parva* infection for many generations (Perry *et al.*, 1992). The details of the model framework and its analysis can be found in Medley *et al.*, (1993). Here I confine myself to outlining the biological assumptions contained within the model, the results and the possibilities for developing the model. I also consider two aspects that were not discussed previously: the interaction of two control policies (tick control and immunization by infection and treatment) and the possible influence of host age.

DESCRIPTION OF MODEL

The model is based on the division of the cattle population into five distinct categories (Figure 1). Calves are born susceptible to infection at a rate equal to total mortality in order to keep the host population size constant. On infection, cattle begin incubating the disease, the period of which lasts 15 days. During this period they are not infectious, but the infection is developing. After incubation, animals move into one of two acute disease stages, which corresponds to the onset of clinical symptoms. The division of the acute disease state into two groups is to make the model tractable, rather than being a biologically based assumption. One of these groups dies from the infection, with an average survival time of four days from onset of disease. The other group recovers with an average time of 15 days between onset of disease and recovery. On recovery, the animals enter an immune or carrier state, where they remain for life.

Estimates of the parameters described above were taken from the literature. The only parameter for which an estimate does not exist is the rate of infection. Data were taken from Moll *et al.* (1986) which describe the number of infected calves by age out of a cohort of 31. As endemic stability is assumed (i.e. there is no change in the transmission dynamics over time), age is synonymous with time. The estimate of the constant rate of infection was 0.016 per day, corresponding to a mean time from birth (= exposure to infected ticks) to infection of 63 days. The analysis showed that the rate of infection was age-dependent,

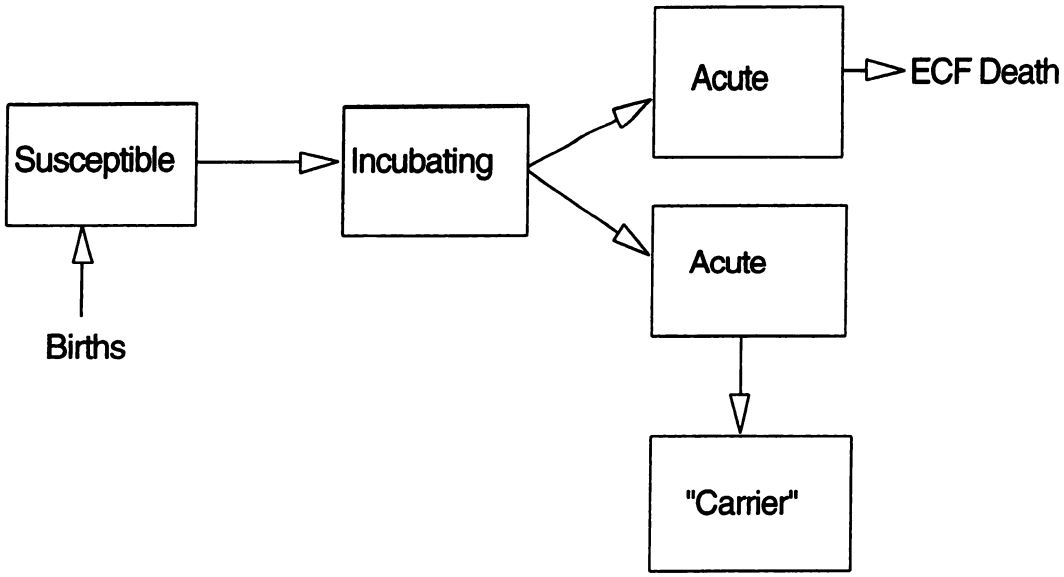

Figure 1. Diagrammatic representation of the model used. Each box represents a disease state of cattle that can be assessed immunologically and/or parasitologically.

but the current model is not age-stratified, so this result was not used in the model. The combination of the estimate of the rate of infection and the structure outlined above and in Figure 1 is a description of the infection and disease status of a cohort of animals in an endemic area.

Figure 2 allows a comparison of the observed data and the model results. As the rate of infection is estimated from the same data shown in the figure, it is to be expected that the rise in infection with schizonts is well modelled. However, the correspondence with the development of piroplasms and the development of immune/carrier state is due to the model structure and assumptions. It would appear that the model provides a good description of the progress of infection through a cohort of cattle in endemic areas.

We can use the estimate of the rate of infection to gain some insight into tick activity. The rate of infection is the product of the rate at which ticks feed, the probability that a tick is infected and the probability that infection is passed from an infected tick to a susceptible host. Moll *et al.* (1986) give a direct estimate of the probability of a tick being infected as 0.0227 (95% confidence interval: 0.015–0.033). If we assume that an infected tick has a high probability (90%) of passing the infection to the susceptible host it feeds on, then the number of tick feeds per day is 0.78. Equivalently, there is a successful tick bite every 1.28 days on cattle in the endemic area. This prediction could be tested empirically to validate the assumptions within the model thus far.

The model is developed to become a dynamic description of *Theileria* transmission, with the infection rate in cattle being dependent on the infection in ticks, which in turn is governed by the infection in cattle. Three of the cattle infection states (Figure 1) are allowed to be infectious: both acute disease stages and the immune/carrier state. This is

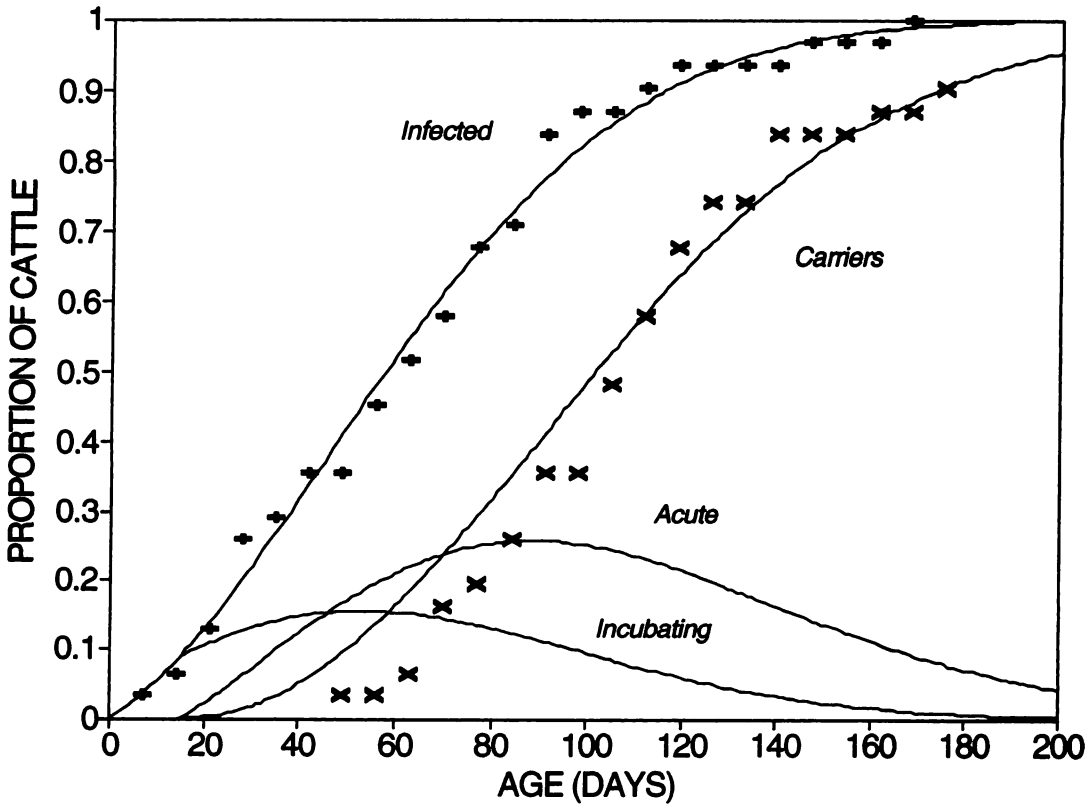

Figure 2. Results of the cohort model with age-related rate of infection estimated from data given by Moll *et al.* (1986) (see Medley *et al.*, 1992). The remaining parameters were taken from the literature (text and Figure 1). The figure shows the expected proportion of animals in each infection state compared with the observed state from Moll *et al.* (1986). The faster rising points (+) are the observed appearance of schizonts, and the lower points (x) are the first appearance of piroplasms. The infected curve includes all those animals not susceptible.

done to appraise the influence that a carrier state has on the transmission. By carrier state, I denote cattle that have survived a primary infection as carriers. They are able to infect ticks (with some probability), but do not exhibit any clinical signs of disease. The assumption here is that their infectious status is maintained by continuous infection derived from the primary infection. However, it may be that these animals require continual infection to remain infectious. The effect of this will require further investigation. Throughout their life cattle are subject to mortality at a rate which corresponds to a life expectancy of four years at birth. This value was estimated from demographic data of cattle in an endemically stable area (Moll *et al.*, 1984; Medley *et al.*, 1993).

There is one dynamic equilibrium within the model, whereby the number of cattle entering each infection state is equal to the number leaving within a specified time period. I assume that this dynamic equilibrium is the state at which endemically stable areas are. The equilibrium results can be used with the rate of infection estimated above and the

published estimates of progression through the infection classes (Figure 2) to assess the transmission potential of *T. parva* within the endemically stable area. The basic reproductive rate, R_o, is the most convenient parameter for encapsulating this potential (Anderson and May, 1991). In this case, the most appropriate definition of the basic reproductive rate is the number of infected ticks that would arise after one cycle of transmission if one infected tick were placed in completely susceptible populations of ticks and cattle. The value of the basic reproductive rate is 23, and the expected proportion of animals in each infection state is given in Table 1. When transmission occurs in parallel (i.e. there are three disease states in cattle transmitting infection simultaneously), then the basic reproductive rate can be separated into the components representing the contribution of each state to the overall transmission: the carrier state is the most important in terms of transmission, accounting for 95% of infection in ticks.

Table 1. Proportions of cattle in each infection class (Figure 1) calculated from the model. Note that the two acute compartments have been summed.

Infection Status	Equilibrium Proportion
Susceptible	0.043
Incubating	0.01
Acute	0.01
Carrier	0.937

There are field- and laboratory-based estimates for all the parameters in the model except the infection rate of ticks fed on animals in the acute disease state. Given the estimates of the overall tick infection rate (0.0227, 95% confidence interval: 0.015–0.033) and the proportions of cattle in each disease state derived from the model, the infection rate to ticks of each disease state of cattle is constrained. Young *et al.* (1986) estimated the infection rate of ticks fed on carrier animals to be 0.023 (95% confidence interval: 0.016–0.030). The surprising result is that the infection rate of cattle undergoing acute infections is not strongly determined within the model structure (Medley *et al.*, 1993). The best estimate of the infection rate to ticks of acute cattle is 10%, but values of 0.0% and 100% are compatible with the two observations and their confidence intervals. The reason for this is the comparison between the length of time that cattle reside in each infection state. The average time from commencement of overt clinical signs to recovery is of the order of 15 days, whereas the carrier state is probably lifelong. Consequently, the total number of ticks feeding on acutely infected cattle compared to carrier cattle at any one time is very small (15 days/4 years), and their infection rate is largely inconsequential in endemically stable environments.

Thus far, the model has concentrated on the results generated by considering the stable equilibrium condition. However, it is also instructive to consider the dynamics of infection, when the populations are not at the stable equilibrium, but change over time until that equilibrium is attained. The dynamic analysis is important because, first, it may give clues

to the important processes in non-endemically stable areas (e.g. where tick activity is seasonal) and, second, the introduction of control is a perturbation that changes the stable equilibrium, and the populations must change to re-attain the new equilibrium with control.

Control of theileriosis currently rests on two methods: reduction in the density of vectors by intensive use of acaricides, and immunization. Immunization, achieved currently by simultaneously infecting cattle and treating with chemotherapeutics to prevent acute disease, was shown to be effective almost two decades ago (Radley *et al.*, 1975). Following immunization, cattle are in the same infection state as cattle recovered from natural infection: they are immune to further disease, but able to support infections transmissible to ticks. These two control methods alter the population dynamics of the vector and infectious agent in a manner which is not easily predicted, and in addition their influence on transmission is opposite: tick control reduces the rate of infection and immunization creates infectious cattle.

SUMMARY OF RESULTS

The Carrier State

The major result of this work has been to demonstrate the importance of the carrier state in transmitting *T. parva* in areas which are endemically stable. The vast majority of infected ticks are derived from feeding on carrier animals. This can also been seen by comparing the infection rate of ticks in the field (2.27%) with the infection rate of ticks fed on carrier animals (2.3%). The infection rate of cattle showing acute clinical signs during their first experience of *T. parva* infection (the only parameter within the model for which there are currently no estimates) is undetermined.

Tick Infection Probabilities

The dynamic properties of the model can be evaluated by tracking the dissemination of infection through a population of susceptible cattle following the introduction of a single infected animal. The epidemic pattern is largely determined by the infection rate to ticks of cattle with acute clinical signs of infection. When this parameter is 1 (all ticks become infected), the epidemic is very peaked and susceptible cattle become infected quickly. When this parameter is 0 (no ticks become infected), then the dissemination of infection to susceptible cattle is dependent on carrier animals infecting ticks at a low rate, and is consequentially much slower. The net effect is that high infectivity of acute cattle produce a pronounced epidemic with morbidity and mortality confined to a short interval. As infectivity of acute cattle is reduced, then the epidemic becomes more extended and total mortality is reduced. The current understanding is that acutely infected cattle have a high rate of transmission to ticks, perhaps of the order of 70% (A.S. Young, personal communication). This understanding is in line with observed outbreaks of East Coast fever which have been characteristically associated with high morbidity and mortality in a short time (Norval *et al.*, 1992).

Tick Control

This model is further used to evaluate the effect of different control measures on the transmission of *T. parva*. *Theileria parva* transmission can be halted by sufficient reduction in the feeding rate of the tick vector. The tick feeding rate required for eradication is the reciprocal of the basic reproductive rate, 0.034, which translates to an average time interval between successive tick feeds of 30 days. Figure 3 shows the effect of tick control on the equilibrium average at infection. With no tick control (relative tick feeding rate unity) the average age at infection is 63 days, and as the tick feeding rate is reduced, so the average age at infection rises. A reduction in tick feeding rate by half only increases the average age at infection to 130 days, and the feeding rate must be reduced to 16% of precontrol to increase the average age at infection to one year. Likewise the relationship between the proportion of animals infected with *T. parva* shows non-linear relationship with a significant reduction not observed until the tick feeding rate is reduced to 20% of

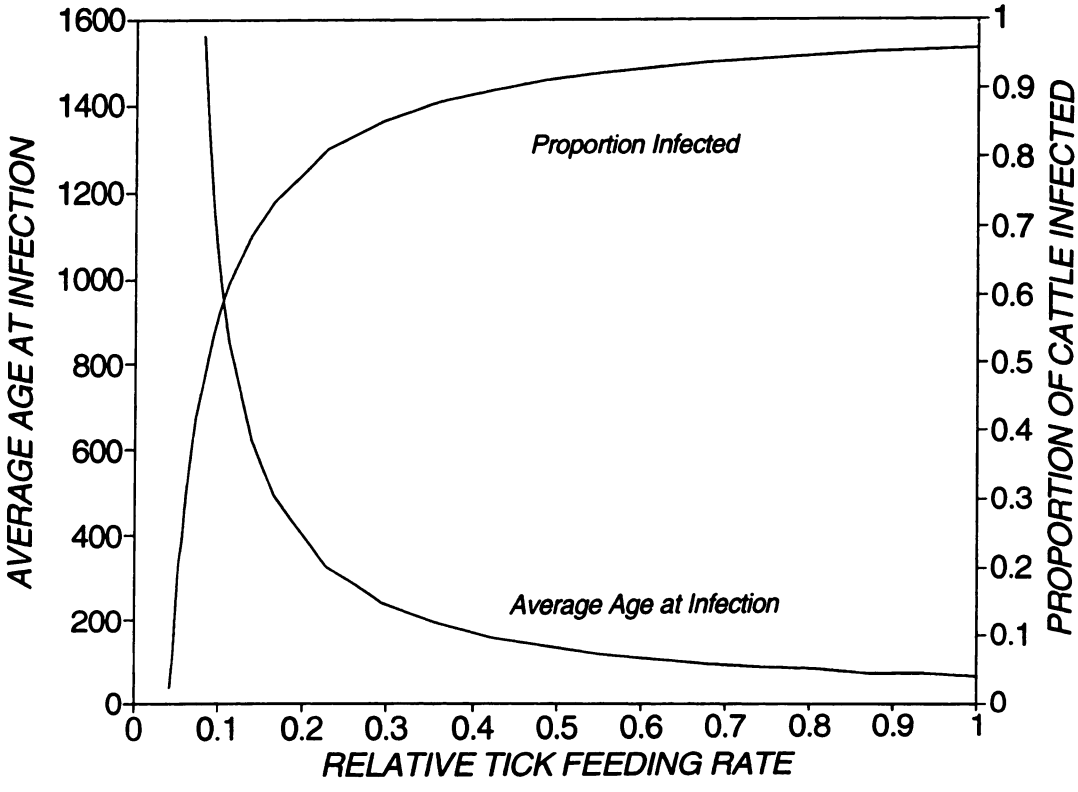

Figure 3. The equilibrium average age at infection and proportion of hosts infected with *T. parva* as functions of the relative tick feeding rate. These results are calculated taking the tick feeding rate estimated from the endemically stable area (0.78) as unity, and comparing the rate of infection when this is reduced by reduction in the tick population by acaricidal control.

its equilibrium rate. The non-linearity arises because as tick control is more intensively applied the infection rate in cattle is reduced and less cattle become infected, thus reducing the infection rate in the surviving ticks. This pattern explains why tick control has not been effective in reducing *T. parva* prevalence unless very intensively applied.

The dynamic pattern of tick control is stable, with the overall level of infection reduced to the equilibrium shown in Figure 3 according to the level of control. The new equilibrium is attained over a period of about three years and is related to the life expectancy of carrier animals. The equilibrium in the presence of control is such that the proportion of susceptible cattle is increased. If tick control is ceased, the return to the precontrol equilibrium emulates the results observed for the introduction of *T. parva* into a susceptible population. The more acutely infected cattle are available to ticks, the faster subsequent dissemination of infection throughout the susceptible cattle population. The precontrol equilibrium is re-attained within months of the cessation of control.

Immunization

Immunization has little direct effect on the dynamics of *T. parva* transmission in endemically stable areas. As the majority of cattle in these areas are carriers already, immunization reduces morbidity and mortality in direct proportion to the amount of immunization, but does not change the rate of infection to unimmunized animals. The dynamic changes following the commencement of an immunization program are very stable with the new control-derived equilibrium being attained within a year. On cessation of the control program, the pre-control equilibrium is re-attained on the same time-scale.

The value of the control-derived equilibrium is dependent on the infection probabilities of cattle to ticks. If tick infection relies more on cattle with acute clinical signs, and therefore less on carrier cattle, then immunization will have a more beneficial effect as it reduces the proportion of cattle with acute clinical signs, and consequently reduces the prevalence of infection in the ticks. This effect is, however, relatively marginal.

Tick Control and Immunization Combined

Tick control and immunization are commonly instituted in combination. The interaction between these two control methods is interesting as they have opposite effects. Tick control generally reduces the infection rate in cattle, consequently reducing infection to ticks, and further reducing infection in cattle. Immunization artificially creates infection, thus maintaining infection in ticks, and maintaining the tick-derived infection rate in unimmunized cattle. The major effect of the combination is that tick control reduces natural infection rates, thus increasing the average age at natural infection (Figure 3), and so making immunization more effective. Increasing the average age at infection increases the 'window' between birth and tick-derived infection during which immunization must occur to be effective.

Figure 4 shows the stable equilibrium situation for the combination of the two control policies. The graph charts the disease-induced mortality rate (per host per day) for different

tick control intensities from no control (1) down to control which eradicates the tick (0) for five different immunization efforts (measured as the average age at immunization in days from 200 down to 25). Note that complete eradication of the tick is required to eradicate infection when immunization is operating, but that without control there is a tick density below which transmission cannot be sustained. The major effect is that even relatively modest immunization efforts do not allow the non-linear pattern in tick control alone to develop. The effect of tick control is linearized, so that even less successful tick control policies are effective in reducing mortality. This is explained as tick control enhances the effect of immunization by increasing the average age at infection, and so makes immunization easier. The relative costs of each policy and the intensity with which they are applied would determine the best policy in terms of cost/benefit.

Figure 5 shows the same relationship, but now charting disease-induced mortality as a function of immunization effort for different tick control intensities from no control (100% of precontrol feeding rate) down to 5% of precontrol tick feeding rate. The pattern can be explained by comparison with Figure 3. With no tick control, the average age at infection

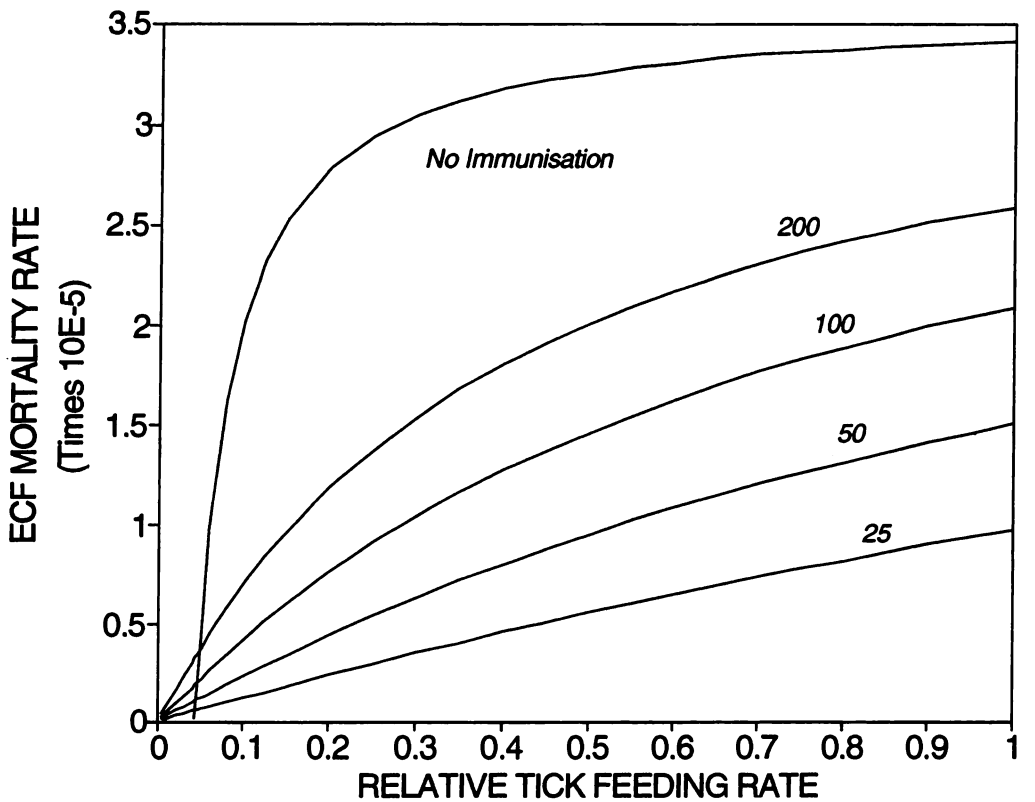

Figure 4. The effect on *T. parva*-related mortality of simultaneous immunization and reduction in tick feeding. The lines are the instantaneous disease-induced mortality rates (per host per day) as a function of the relative tick feeding rate (as in Figure 3) for five different immunization strategies from no immunization down to an average age at immunization of 25 days.

is approximately 60 days, but reducing the tick feeding rate to 50% increases the average age at infection to approximately 130 days (Figure 3), and it is at this point on Figure 5 that immunization becomes more effective, in that a slight increase in immunization effort reaps a higher reward in mortality reduction.

The dynamic introduction of a combined policy can be readily understood. Immunization prevents the creation of a large pool of susceptible animals. Consequently, at the cessation of control an epidemic is prevented in contrast to the situation with tick control alone.

DISCUSSION

This paper has extended the results derived from a model described in a previous paper (Medley *et al.*, 1993) by considering the interaction of two control methods for *T. parva*, namely, reduction in the tick feeding rate and immunization by infection and treatment. The type of model used (a deterministic compartmental model based on ordinary differential equations) is useful for preliminary investigations. It allows robust analytical solutions, which can lead to general conclusions. In this case, we can use the model results

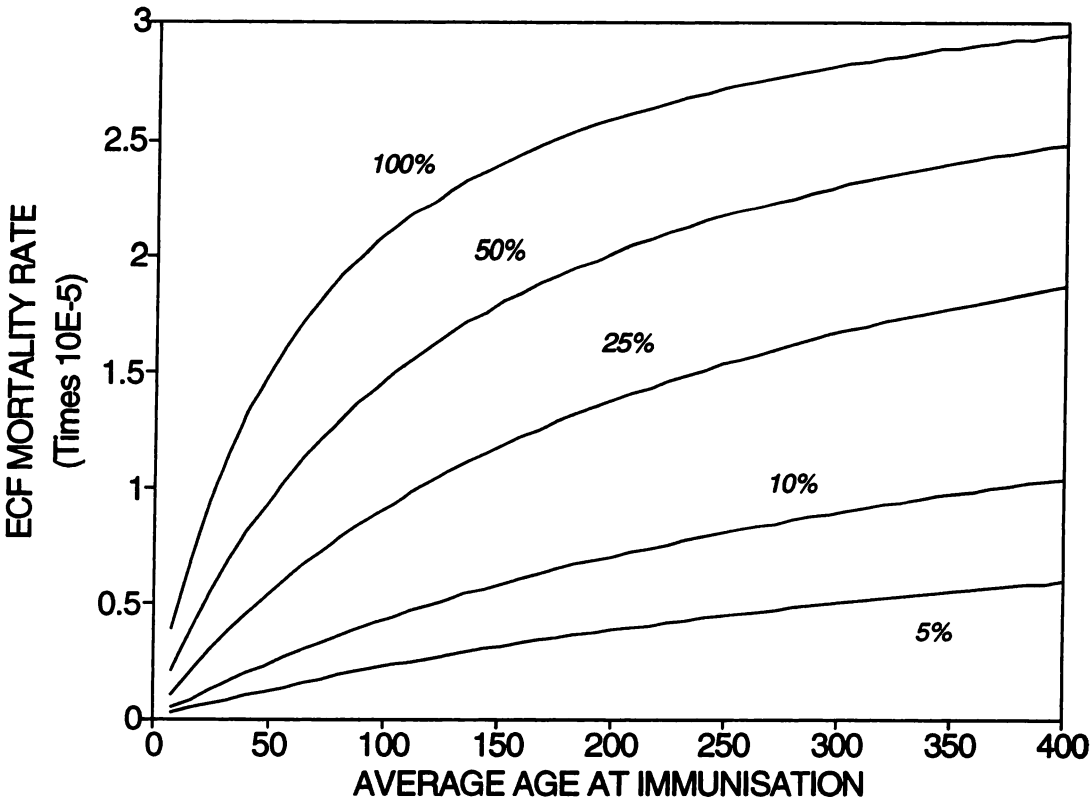

Figure 5. The same relationship as drawn in Figure 4, but the different lines show the disease-induced mortality as a function of the immunization effort for five different tick feeding rates relative to precontrol from 100% (= no tick control) down to 5%.

to demonstrate the importance of carrier animals in endemically stable areas, but also show that in areas that are not stable, the importance of infection to ticks by animals suffering acute clinical signs. Immunization by infection and treatment does not alter the pattern of infection in endemically stable areas, but reduces death due to East Coast fever in a simple fashion related to the effort given to control. Reducing the tick feeding rate (by acaricide application or grazing management) does not have a significant effect until very low feeding rates are achieved, i.e., until the tick population is virtually non-existent. However, reducing the tick attachment rate does increase the average age at which cattle experience tick-borne infection, thus making immunization easier (in terms of increasing the age over which immunization may successfully be given). While these conclusions are robust within the assumptions of the epidemiology of *T. parva* in endemically stable areas, they may not be directly applicable to areas that do not fulfil these criteria, and several mechanisms may act to alter this pattern.

First is the effect of host age. As the median age at infection in endemically stable areas is of the order of 60 days, we have not assumed that there is any effect of host age on progression of disease. However, this may not be the case. The mammalian immune system continues to develop after birth, and it is likely that the age at which an animal first experiences *T. parva* will to some extent determine the outcome of the infection. In particular, the proportion of animals that develop a carrier state and the proportion of animals that die from the infection are both likely candidates for modulation by host age. In areas of seasonal tick activity, and therefore seasonal transmission, the cattle will tend to be older when they first experience infection than in areas with transmission all the year round. The same will be true when the tick population is reduced by some control measures. Obviously, more information on the biology of the effect of host age at infection is required to enable its impact on the transmission dynamics to be quantified. In particular, the use of immunization to create carrier cattle in areas of seasonal transmission may have counteractive effects.

Second is the influence of the tick that infects an animal. A tick carrying *T. parva* infection has one or more acini infected within the salivary glands. The distribution of infection amongst adult ticks is highly skewed, with most ticks being uninfected, most of those infected having a single acinus infected, and only a very small number having more than one acinus infected. It is already accepted that the greater the number of acini infected on the infecting tick, the more serious the clinical consequences of infection to the host. Further, the distribution of infection in ticks is likely to be influenced by the infection in the infecting host. Thus not only will the proportion of ticks infected by feeding on acute rather than carrier animals be higher, but also the distribution of intensity of infection may be altered.

Third is the effect of tick stages. Most of the epidemiological work to date has been concerned with the adult tick (that becomes infected as a nymph). However, the nymph (infected as a larva) can also transmit infection, but little is known about the prevalence or intensity of infection in nymphs, largely as a result of the difficulty in counting and collecting this stage in the field. It may be that infection from a nymph can induce different clinical consequences of infection than infection from an adult tick, and, again with respect to transmission dynamics, it is the disease-induced death and the development of the carrier state that are most important in this context. Larvae and nymphs feed for a much shorter

time than adult ticks, but most acaricide application programs are designed to kill adult ticks and not prevent larval infection and nymphal transmission.

Finally are the effects due to the interaction between cattle and ticks. It is well accepted that cattle can mount a strong and effective immune response to *R. appendiculatus* that is acquired after past exposure to the ticks. What is not clear is the consequence of this response on the infection rate both to and from ticks. While the acquired immune response may reduce the feeding effectiveness and thereby reducing transmission to ticks, it may also result in increased concentrations of the lymphocytes at the biting site, facilitating their infection by *T. parva* sporozoites and increasing infection from ticks. Further the disease and clinical symptoms of animals suffering acute infections coincide with a reduced immune response, perhaps increasing the proportion of feeding ticks that become infected from acutely diseased animals.

A quantitative framework (mathematical model) is useful in two respects. First is allows observations on fairly disparate areas of research to be brought together in one structure. Thus, it is possible to evaluate the effect of transmission by carrier cattle within the context of all aspects of transmission. Second, the effects of interventions on the transmission dynamics may be counter-intuitive and non-linear, which suggests that only by examining the numerical details will the full ramifications of interventions be appreciated. The construction of the model also highlights the most important areas with respect to both future research and intervention possibilities.

The modelling approach adopted by Medley *et al.* (1993) and in this paper is powerful in that it can generate general principles. However, that generality is gained by adoption of the smallest possible number of assumptions required to generate the observed patterns. Before the results can be confidently applied, these assumptions require validation, and the importance of factors omitted, such as those outlined above, must be ascertained. As with all scientific methods, the current model has generated more questions than have been answered. However, the model does provide a good research tool in that it establishes a qualitative understanding of the transmission dynamics and produces a quantitative framework, both of which are essential for development of planned control policies. As more detail is incorporated into this model framework, so the model will become more useful in detailed design of the quantitative aspects of control policies, their effect on production, and their economic implications.

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Spatial factors in the assessment of trypanosomiasis challenge

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ABSTRACT

The severity of the trypanosomiasis problem in a particular location is traditionally assessed in terms of the challenge index—the product of apparent density of tsetse, or trap catch per day, and infection rate—which is assumed to be proportional to the force of infection. However this index masks variation in the force of infection between herds and among individuals within herds. It is also not necessarily comparable between sites since the relative abundance of tsetse to hosts may vary. We have studied the spatial distribution of herds of livestock in relation to tsetse and calculated an index of challenge based on the ratio of vectors to hosts. This index is strongly correlated with estimates of the force of infection calculated from the incidence of infection in susceptible zebu cattle; and it provides information on heterogeneity in exposure of different herds to tsetse. We argue that spatial distribution of vectors to hosts is a prerequisite for the application of epidemiological models of vector-borne diseases to real field situations.

INTRODUCTION

Trypanosomiasis challenge is traditionally estimated as the product of some measure of tsetse abundance and infection rate (i.e. the proportion of tsetse with mature infections). For example, the African Trypanotolerance Livestock Network of ILCA and ILRAD uses biconical trap catch per day × infection rate (Leak *et al.*, 1988); this measure may be modified by including the proportion of tsetse blood meals taken from cattle (Leak *et al.*, 1990). A challenge index such as this is a straightforward and inexpensive value to estimate in the field, which gives an indication of the risk of trypanosomiasis infection. Rogers (1985) found that the log of the challenge index was roughly linearly related to the Berenil index. The challenge index is assumed to be proportional to the force of infection, λ, which is defined as the number of potentially infective bites per animal per day (Smith and Rennison, 1958). If λ is constant during time t, $1-\exp(-\lambda t)$ is the risk of trypanosomiasis infection to susceptible animals in time t. $1/\lambda$ is the average interval between potentially

infective bites received by the host, and the average waiting time to first infection in susceptibles.

This challenge index suffers from two drawbacks: firstly, it is proportional to λ only if the relative abundance of hosts, and the exposure of cattle to tsetse, are constant. The inclusion of proportion of cattle feeds in the index only partially addresses this problem, since differing preferences by tsetse amongst the varying range of alternative hosts, plus spatial heterogeneity in contact patterns at different sites, still affect the estimate. If these vary, estimates of the index will not be comparable between locations. Secondly, the index gives no indication of variability in λ amongst individual animals, herds, or livestock species. Theoretical studies have indicated that for several systems heterogeneities in transmission rate can also have important consequences for the rate of spread of disease; recent field studies have addressed this issue for schistosomes (Woolhouse *et al.*, 1991), but it has not previously been undertaken for trypanosomiasis.

In this paper we examine the importance of space utilization by N'Dama cattle (T.J. Wacher and W.F. Snow, unpublished data; Rawlings *et al.*, 1994) in relation to tsetse distribution in determining the challenge rate to village herds in two study sites in The Gambia. The results are discussed in terms of the ratio of tsetse numbers to host numbers, which is referred to as tsetse exposure. The central objective is to measure the extent to which exposure to tsetse varies with spatial factors at the level of herd and season, and to compare this with the naive estimate from the challenge index in routine use which assumes uniform distribution of cattle and tsetse, as well as uniform infection rate amongst tsetse. Data on tsetse infection rates are available in the current study (Rawlings *et al.*, 1990), but not at a scale of resolution adequate to determine spatial and temporal variation, so this factor has not been used in our estimate of exposure.

METHODS

Field work reported here was carried out at two study sites in The Gambia, Keneba and Niamina East (Figure. 1). At each place cattle ranging and ecological studies were carried out in conjunction with livestock censuses, warthog transect counts and tsetse population studies. At each location a small herd of sentinel zebu cattle was maintained in order to provide an independent estimate of force of infection.

The unit of measurement for cattle range use was the daily grazing trail of one animal from selected herds, mapped by grid references taken every five minutes throughout the day. This was done on 8–20 days for each study herd in each four-month season. The sum of grid references falling within each 500×500 m grid unit of the study area provides an estimate of the space utilization distribution for each herd, which is weighted according to the number of animals in that herd.

Stock censuses and warthog transect counts were carried out monthly. Other wild hosts of *G. m. submorsitans,* while known to be present, were seen so infrequently that no population density estimates were possible, and they are not taken into account in analysis.

A small herd of 10 sentinel zebus was established for one year during the study period at each site, bled weekly and treated with Berenil when infected with trypanosomiasis

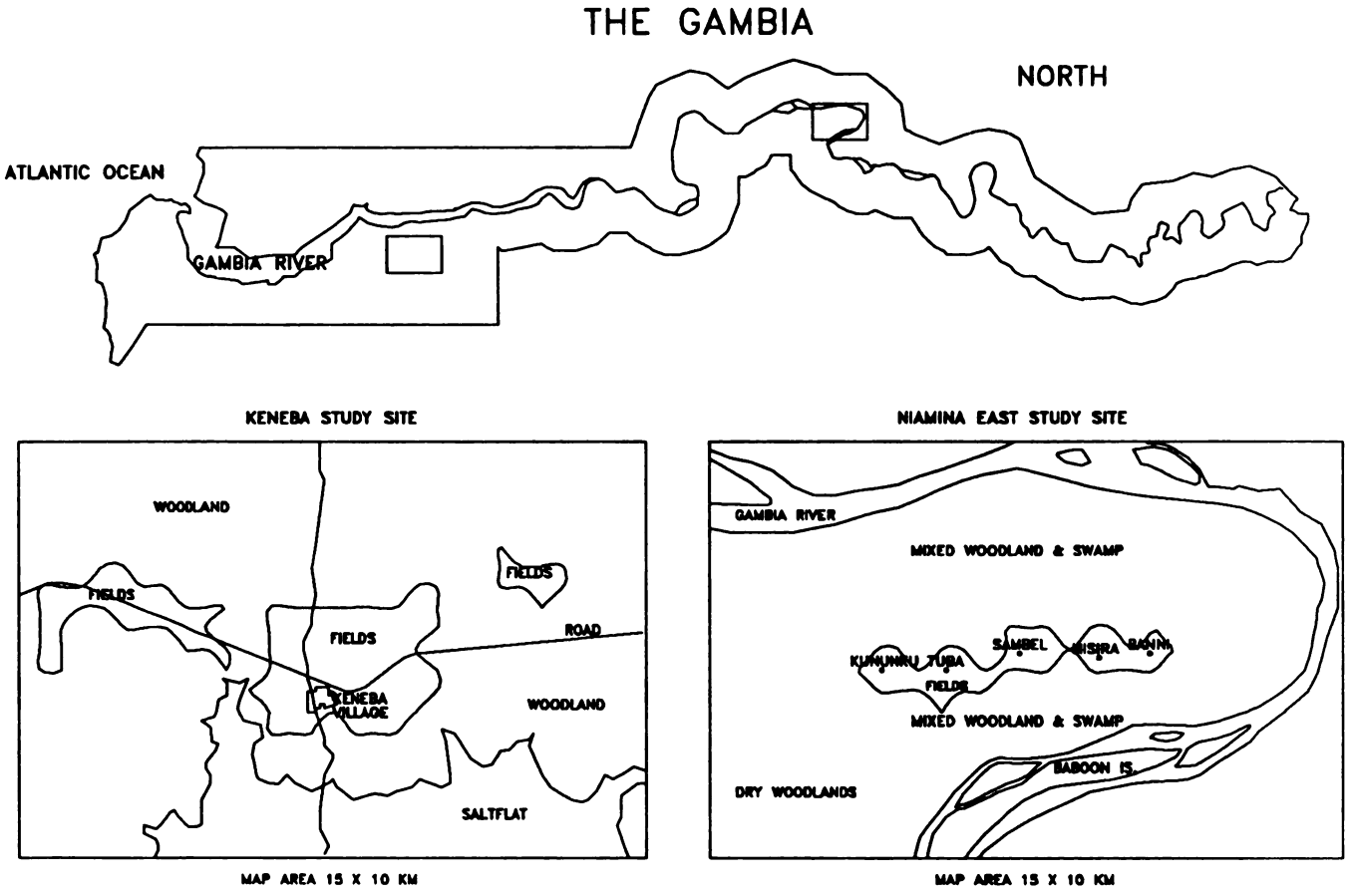

Figure 1. Map of The Gambia, West Africa, showing the location of Keneba and Niamina East study sites within the country, which is approximately 300 km long. The location of study villages and habitats are shown in detailed 10 × 15 km insets of each site.

(Claxton *et al.*, 1992). These data were used to provide an estimate of the frequency with which cattle received fresh infections.

Tsetse populations were monitored at each site by semi-systematic arrays of modified F3 blue box traps (Green and Flint, 1986), set for three days each month. A mark-release-recapture experiment was conducted to provide an estimate of trap efficiency. Trap catch data were converted to absolute densities of flies using this estimate, and the results interpolated using an inverse distance squared function in the program SURFER (Golden Software Ltd.) to convert point estimates to a regular 500 × 500 m grid.

These data were analysed to examine the effect of spatial heterogeneity on the vector to host ratio over each season. Analysis proceeded by calculating for each cell of the 500 × 500 m grid the ratio of tsetse to all hosts (composed of all cattle herds, small stock and warthogs) and for each herd summing the contribution of each cell weighted by the proportion of grazing time by that herd at that location. This spatially weighted estimate of tsetse/host ratio was compared with the 'crude' estimate which was derived from the simple ratio of total number of tsetse and total number of hosts in the study area.

The analysis assumes that spatial and temporal scale factors in recording intervals were appropriate, that all members of the herds used the seasonal ranges in an equivalent way and that range use was constant throughout each season. It was also assumed that warthogs were evenly distributed in woodland and scrub habitats and effectively absent elsewhere.

RESULTS

Cattle and Tsetse Distributions

The patterns of spatial and temporal distributions measured in this system at Keneba are summarized in Figure 2. These maps illustrate the data sets that were used to calculate exposure and show the seasonal changes between tsetse distribution and abundance and cattle grazing range. They indicate that at Keneba cattle range utilization was heavily focused on the village; through the early dry season of 1988, all village herds exploited the fields around the village and woodland areas to the south, while tsetse were relatively abundant in the woodlands to the north. Through the late dry season, village cattle made use of the field areas surrounding the village and began to exploit the woodlands to the north, where the tsetse population collapsed. In the wet season, village cattle were herded into the woodlands to the north of the village, keeping them out of the planted crops, when the tsetse population began to show signs of recovery.

Stock Censuses

The combined results of censusing the major host animals showed that domestic stock were more numerous than warthogs in both study sites, with the exception of the wet season period at Niamina East. The village herds at Keneba showed a marginal increase in numbers through the study period, but the site was affected by the substantial increase in cattle overall through the introduction of large numbers of ITC-owned cattle.

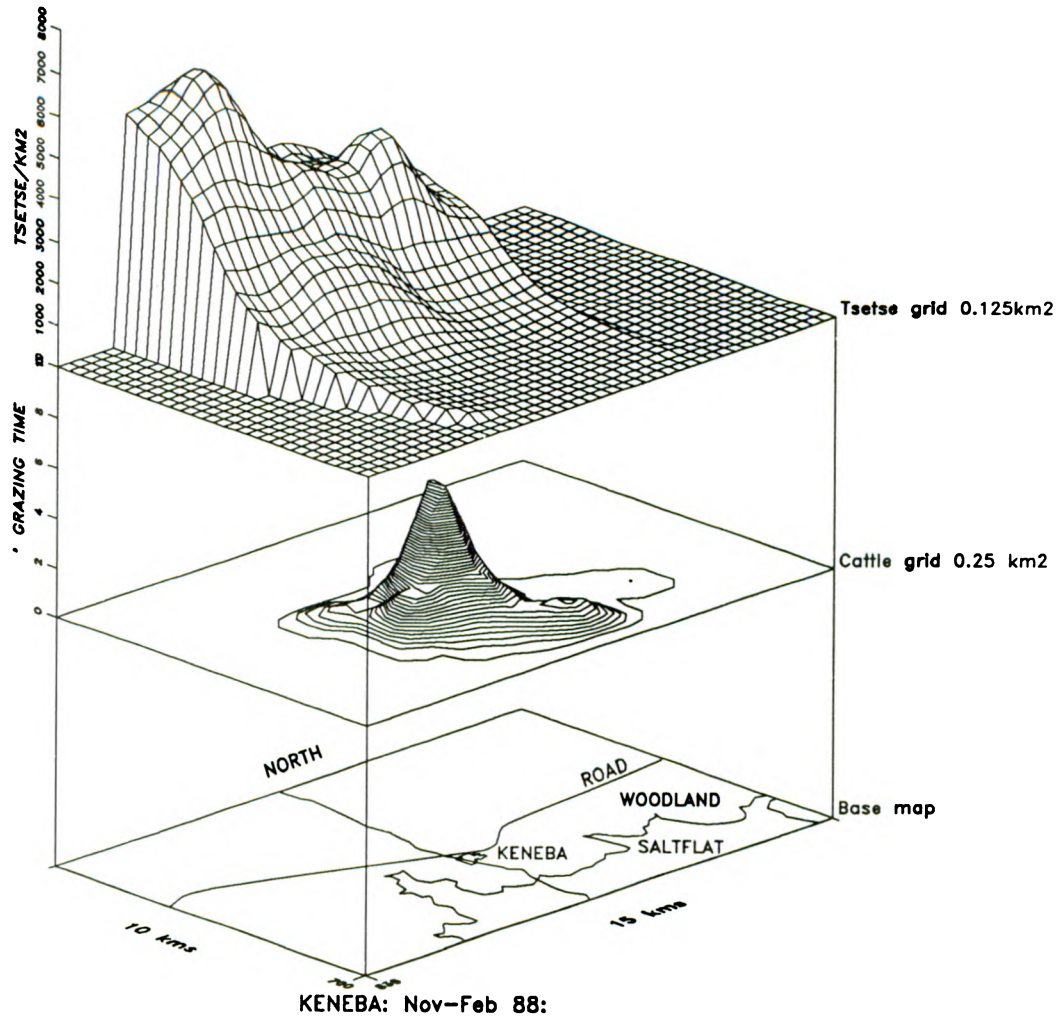

Figure 2 A

The Niamina East site was characterized by a small, stable number of resident cattle, annually augmented by an influx of dry season migrants taking advantage of the swamp grazing (T.J. Wacher and W.F. Snow, unpublished data), resulting in an approximately 20-fold annual variation in cattle stocking density. Transect counts for warthog at Keneba indicated an overall annual average of 11/km^2.

Tsetse Exposure

The estimated number of tsetse per head for each study herd of cattle at each study site over one year are shown in comparison to the 'crude' estimate (which assumes spatially homogeneous cattle and tsetse distributions) in Tables 1 and 2. Results at Keneba, suggest

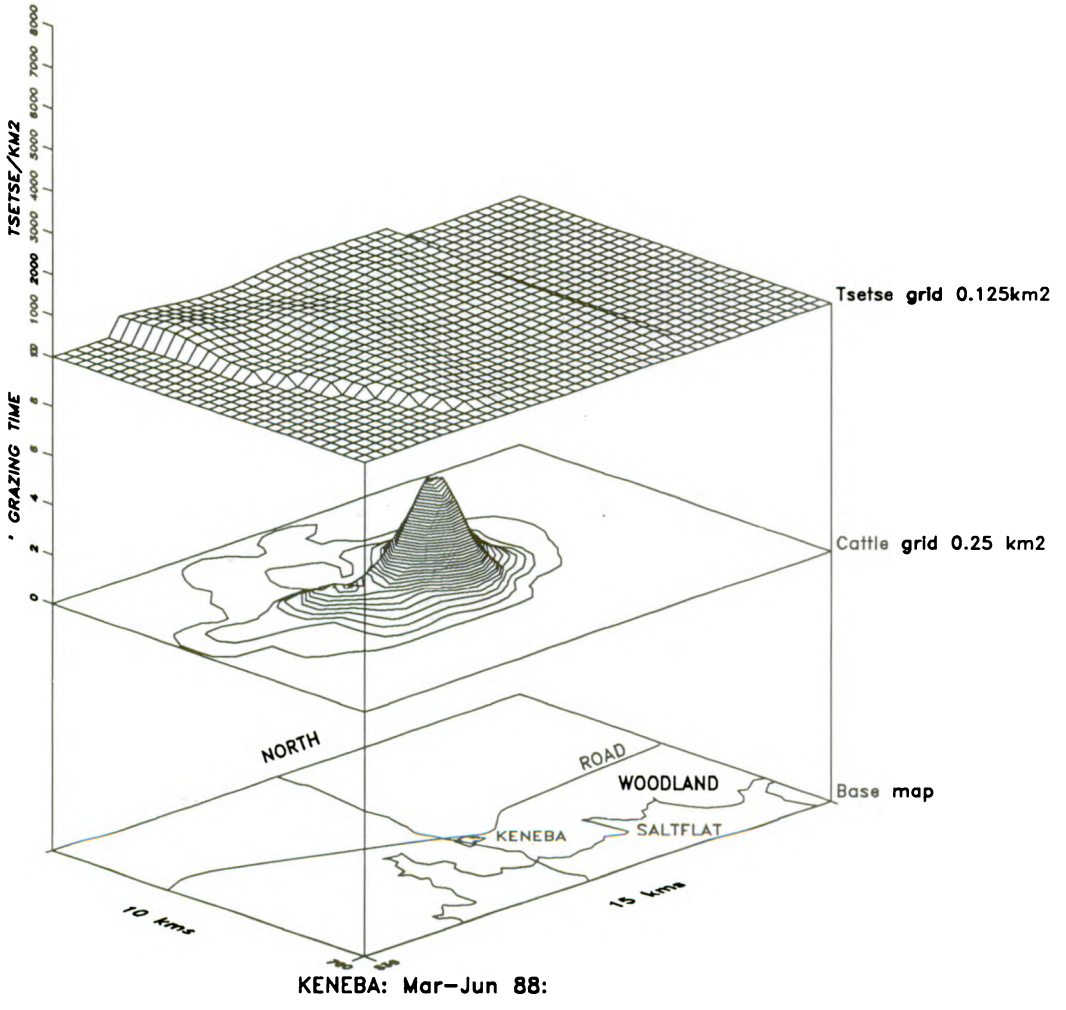

Figure 2 B

that tsetse exposure may have varied for individual herds by a factor of up to five or more from the crude estimate and by a factor routinely between 5 and 10 fold, occasionally much more, between herds living in the same village, once variation in range utilization has been taken into account. In early dry season of 1988, for example, Herd 3 received at least seven times the tsetse exposure of any other herd (Table 1). Herd 4 at Keneba achieved an exposure level consistently below the crude estimate; this was the ITC-owned group which in the study period reported spent a high proportion of time in a cleared field area near the village.

At Niamina East a similar order of variation (up to seven-fold) in tsetse exposure was indicated between individual herd values and the crude estimate. Between-herd variations were less extreme than at Keneba, though still frequently in the vicinity of a factor of five to seven.

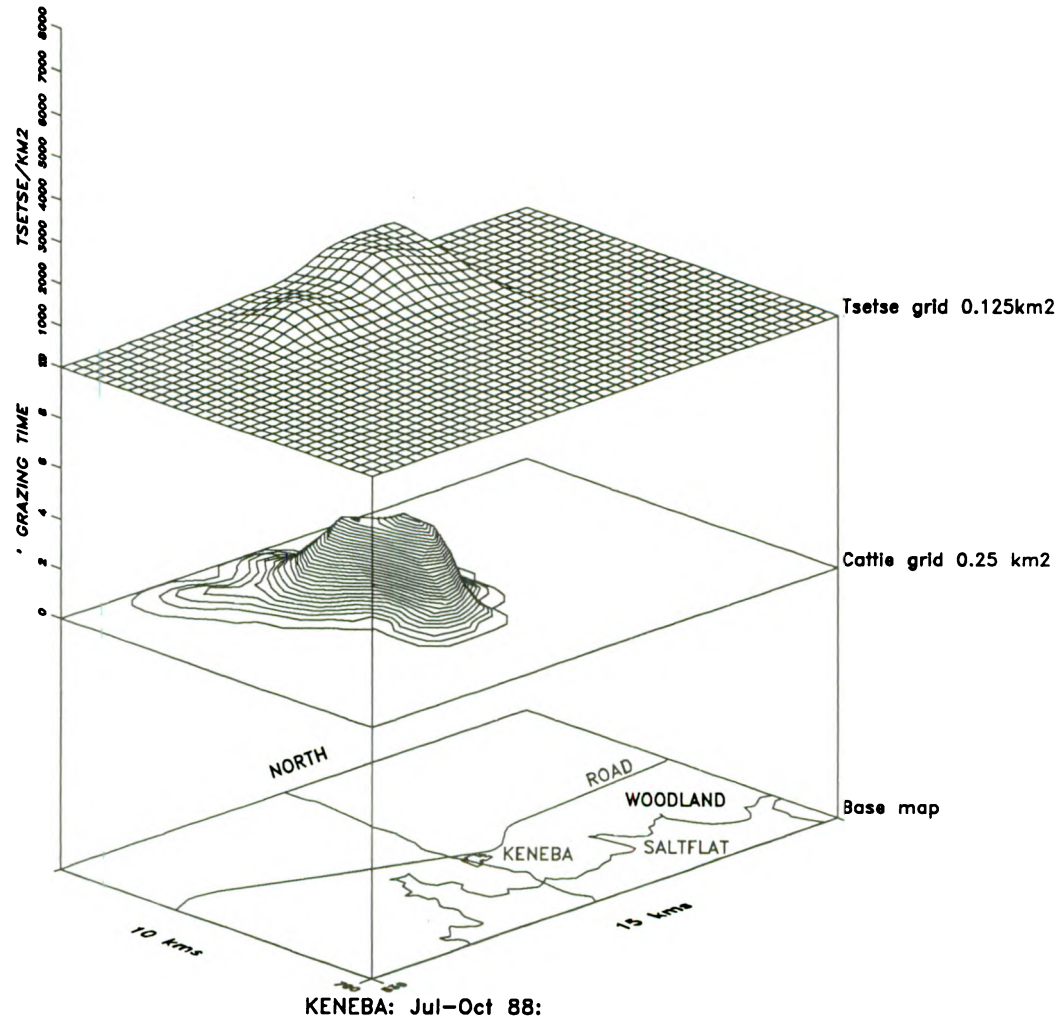

Figure 2 C

Figure 2. Detail of Keneba study site showing tsetse distribution (top layer) and grazing distribution of village herds combined (middle layer) over the site map in a) early dry season, b) late dry season and c) wet season 1988. Note that in analysis the grazing distribution is further broken down to the range of each herd separately for comparison with the tsetse map.

Herd 3 at Niamina East, based in the village of Misira (Figure 1) was estimated to suffer particularly heavy tsetse exposure. Although this herd suffered the greatest exposure, it did not experience the greatest number of tsetse within its range. The extreme values estimated are due to a combination of the small herd size (only 18 animals), and the fact that they spent time grazing on a rice field closely bounded by a locally increased density of tsetse in an area little used by other herds.

Table 1. Estimated numbers of tsetse/head experienced by village-managed N'Dama cattle from four different herds at Keneba, The Gambia, over three seasons. Note that the crude estimate refers to the number of tsetse/head over the whole study site, while the values below indicate the number of tsetse/head for each herd after taking into account herd movement and tsetse distribution.

	Early dry 88	Late dry 88	Wet season 88
Crude	4.7	3.3	1.0
Herd 1	3.6	6.5	1.8
Herd 2	3.8	4.9	3.6
Herd 3	28.8	3.6	4.7
Herd 4	1.0	0.7	0.04

Sentinel Herds

Comparison of the mean tsetse catch per trap per day for each season with the estimated force of infection to the sentinel zebu herds at each site shows a non-significant positive relationship (Table 3). The catch per trap per day (CTD) acts as a more convincing index when corrected for total number of hosts available in each season. The relationship between our estimate for tsetse exposure and the force of infection shows good correlation and the highest proportion of the variance is accounted for when comparing the force of infection in zebus with the estimated tsetse/head experienced by those zebus.

Table 2. Estimated numbers of tsetse/head experienced by village-managed N'Dama cattle from three different herds at Niamina East, The Gambia, over three seasons. Note that the crude estimate refers to the number of tsetse/head over the whole study site, while the values below indicate the number of tsetse/head for each herd after taking into account herd movement and tsetse distribution.

	Early dry 88	Late dry 88	Wet season 88
Crude	158.9	59.2	204.7
Herd 1	83.2	32.8	269.6
Herd 2	139.6	42.0	322.5
Herd 3	432.6	88.1	1159.0

DISCUSSION

In this paper we report data on the spatial distribution of tsetse and their hosts and have calculated an index of exposure of livestock to tsetse attack based on the ratio of the two. This index is validated by demonstrating close correlation to the force of infection independently assessed in studies of susceptible sentinel zebu herds. The index suggests that individual herds based at the same village or in the same general areas may

Table 3. Correlations between estimated force of infection in sentinel zebu herds and mean catch per trap per day (CTD), corrected for number of hosts, and the estimate of exposure, which incorporates grazing space utilization in relation to tsetse population distribution.

	r^2	F ratio	pdf
Mean CTD	48.0	4.61	>0.051
Mean CTD/head	88.3	37.0	<0.011
Exposure of zebus	97.6	203.26	<0.0011

experience a 5 to 10 fold, sometimes greater, variation in the degree of exposure to tsetse challenge.

The order of magnitude in this variability was similar at two sites despite considerable differences in stock management conditions at each location. The relative density of hosts was lower at Keneba; exposure was also much lower. Domestic stock numbers were essentially stable from season to season at Keneba, but through the course of this study the expansion of ITC-owned herds affected this pattern. The seasonal migration of cattle at the Niamina East site provides strong confirmation that host numbers should be a component of challenge index, if such an index is to provide a comparable measure under all conditions and related to the force of infection.

The use of herd movement data to assess the range utilization distribution of domestic stock has also involved a number of explicit assumptions, most notably that all members of a herd use the described seasonal ranges in an exactly equivalent way. Variation in range use by individual cattle within the same herd can only be considered once repeated tracking of the same sample of animals have been carried out. This was not done in the current study, since it was initially decided that sampling from the full pool of adult females in the herd would give a more accurate picture of overall herd ranging than a small subset that might include unknown individual biases in movement patterns.

The data have been used in a way that assumes the cattle ranges are used in a constant manner by each herd throughout each seasonal period. In practice this is unlikely to be so; a herd will on occasion spend several days visiting one area, before graduating to a new zone. There is thus potential for considerably different outcomes in real tsetse exposure according to the interaction of spatial patterns in tsetse and hosts and the relative timing with which this occurs.

For the warthog data, it has been necessary to assume a uniform distribution within the woodland and fallow habitats. This is unlikely to be a good estimate, and other mammalian hosts for *G. m. submorsitans* have been ignored altogether. This is an area of significant neglect, since the data clearly reveal that the periods of seasonal peak in tsetse numbers do not necessarily coincide with high overlap between cattle and tsetse. Hence in periods of maximum tsetse abundance it is clear that tsetse-wild host dynamics are of great importance and merit more detailed attention; warthogs *(Phacochoerus aethiopicus)* are a major host of *G. m. submorsitans* in The Gambia (Snow and Boreham, 1979; ITC Entomology Program, unpublished data). Similarly, the methodologies developed here can

be adapted to other livestock categories, notably small stock, but also groups subject to distinctive management regimes, such as draft animals.

The review of assumptions and simplifications involved in making these estimates of exposure has shown that the analysis used is likely to have given a conservative estimate of the real variability in individual exposure, since it was necessary to treat individuals as if details of their behaviour, beyond the spatial variability measured, was uniform. In practice this is unlikely to be true.

It is likely that the type of heterogeneity reported here will prove to be characteristic of most, if not all, situations involving tsetse-transmitted trypanosomiasis in Africa. The general consequences of such heterogeneities in host exposure for vector-borne disease transmission systems are known to result in an increase in the estimated transmission rate of the disease (Dye and Hasibeder, 1986). A full understanding of the dynamics between parasites and hosts, particularly mechanisms by which trypanosome species sustain their populations, will only be achieved when the importance of the spatially heterogeneous patterns of tsetse-host contact are considered in models which are being developed to describe the epidemiology of African animal trypanosomiasis.

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Session discussion

TRANSMISSION OF *THEILERIA*

The transmission model developed by Drs Medley, Perry and Young was considered to be a useful first step in the development of more comprehensive models which represent the transmission of *Theileria* spp. throughout Africa. It was agreed that such models could be of great value in enhancing the knowledge on the epidemiology of *Theileria* infections and for testing the effects of different control interventions.

Some of the areas which require further studies in order to generate data sets necessary for the development of such models were:

- The relative roles of acute infections of clinical cases, and low level infections of carrier animals, in maintaining a source of infection to cattle and as a cause of different tick infection rates under different epidemiological situations.
- The maintenance of *T. parva* infections within different populations.
- The relative roles of larval to nymphal transmission and nymphal to adult transmission.
- The seasonality of tick populations and *T. parva* transmission, as influenced by the occurrence (or lack) of diapause in *R. appendiculatus* populations at different latitudes.
- The relative role of wildlife in maintaining tick populations and *T. parva* infections in ticks.

It was proposed that studies using *in vivo* feeding of ticks could result in a greater insight into factors which control the transmission of *T. parva* by ticks. There was general support for the idea that other methods of modelling *Theileria* transmission should be considered, including matrix analysis, and that models developed for other parasites such as malaria should be evaluated as to their relevance to *Theileria*. The lack of specialized data sets, particularly those derived from longitudinal studies of calf populations under different epidemiological conditions, were considered a constraint for the development and validation of models.

TRANSMISSION OF TRYPANOSOMES

The possibility of strengthening decision-support systems for the development of control programs for tsetse-transmitted trypanosomiasis in livestock through modelling weighing the four options, namely tsetse control, chemotherapy (including chemotherapeutic and chemoprophylactic agents), trypanotolerance, and vaccines (when they become available) was discussed.

A potential area where modelling could be applied is in trypanosomiasis-endemic areas where trypanosusceptible cattle breeds exposed to tsetse challenge and under constant trypanosomiasis risk may develop a degree of trypanotolerance. For example, in eastern Africa the Orma Boran breed has been shown to be relatively trypanotolerant compared with other zebu cattle.

It was stressed that when studies of the spatial distribution of tsetse vectors and zebu cattle were designed, all the important variables involved in the transmission of trypanosome infections to cattle, such as the disease status, reservoir hosts, the tsetse flies and livestock, should be included in order to generate reliable and appropriate data sets for modelling. It is important that such studies are conducted in several trypanosomiasis endemic regions of Africa. The resulting data may serve to validate or modify the existing models of the transmission of trypanosome infections to livestock by tsetse flies. Such models will provide a useful basis for the identification of optimal control interventions for tsetse-transmitted trypanosomiasis in livestock in different epidemiological situations.

HOST-PARASITE INTERACTION

Possible application of modelling methods to bovine immune responses to *Theileria parva*

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Theileria parva is a haemoprotozoan parasite of cattle that gives rise to an acute and usually fatal lymphoproliferative disease. The life cycle of the parasite is complex and involves stages in the ixodid tick *Rhipicephalus appendiculatus* as well as the bovine host. Cattle become infected following the inoculation of sporozoites by an infected nymphal or adult tick. The severity of the disease has been shown to be related to the quantity of sporozoites inoculated. Sporozoites rapidly enter lymphocytes, where they develop to schizonts in the cytosol. It is this stage of the parasite that is responsible for the major pathology associated with the disease. Schizont-infected cells divide in an apparently uncontrolled manner and invade a variety of non-lymphoid tissues, disrupting their function. A striking feature of the disease is an extensive lympho-destruction, which is not confined to parasitized cells. This results in a net depletion of circulating lymphocytes, which is exacerbated by the invasion of the bone marrow by parasitized cells. Further disruption of immune function is believed to result from the elaboration by infected cells of powerful immune modulators. A significant component of the disease is therefore the result of perverted host immune mechanisms.

It is generally accepted that survival of an infected animal is dependent on successful control of the schizont parasitosis. Considerable research effort has been focused on the identification of those immune mechanisms that protect immune cattle. Immune animals almost invariably exhibit a transient schizont parasitosis before resolving infections, suggesting that protective mechanisms are directed at the schizont-infected cell. A number of observations have indicated that parasite-specific class I MHC-restricted cytotoxic T lymphocytes (CTL) are responsible for eliminating challenge infections in immune cattle. However, this activity is not detected in a significant number of immunized animals during the resolution of infection. It is likely that these alternative responses are mediated initially by CD4+ T cells with possible input from other effector populations. These possibilities are currently being explored.

It is clear that immunity to a parasite that infects and subverts the immune system presents a considerable problem to the modeller. The exact nature of the mechanisms responsible for protection remain to be defined, and although much information is available in this area it is not clear whether it constitutes a sufficient basis for a model. Nonetheless, a number of parameters have been defined that relate to the interaction between the parasite and the bovine host. The quantity of sporozoites inoculated has been correlated with the severity of disease, and the number of schizont-infected cells required

to produce fatal disease has been reasonably defined. In addition, immune responses to a defined antigen of the sporozoite surface have been shown to provide 70–100% protection. These findings might be incorporated in preliminary models to provide estimates of the possible impact of new vaccines.

Immune responses and pathogenesis of bovine trypanosomiasis

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Trypanosome infections in cattle usually result in a chronic disease, characterized by anaemia, leukocytopaenia, immunosuppression and cachexia. The parasites live in the bloodstream and evade immunological control by continuously varying their surface glycoprotein coat. Antibody to the surface-exposed epitopes of the variable surface glycoprotein coat (VSG) mediates the removal of a particular variant, but new variants expressing antigenically different VSGs appear throughout the infection. In cattle, following tsetse-fly transmitted infections, a fluctuating parasitaemia is observed, with several variants expressed at any one time. Some breeds of cattle such as the N'Dama *(Bos taurus)* have evolved the ability to control both parasitaemia and anaemia. The control of these two traits does not appear to be linked. Trypanotolerant cattle remain more productive in trypanosomiasis-endemic areas than *B. indicus* breeds (such as the Boran), but can succumb to the disease when exposed to very high challenge or stress.

ILRAD's immunopathology program aims to elucidate the mechanisms of trypanotolerance and to identify trypanosome antigens which cause either protective or pathological responses in infected cattle. These antigens will be used in the design of novel vaccines which elicit protective anti-parasite immune responses or to block pathogenic responses.

Results from studies on immune responses following *T. congolense* infections have shown that N'Dama cattle produce higher levels of IgG_1 antibodies to invariant antigens (specifically, a trypanosome cysteine protease and a heat shock protein) and variant antigens; they have earlier and higher T-cell proliferative responses and their monocytes secrete higher levels of costimulatory cytokines (IL1/IL6) early in infection compared to trypanosusceptible cattle. A population of IgM antibodies which bind to non-trypanosome antigens has been identified in Borans but not in N'Damas. This population of antibodies also binds to trypanosome VSG, suggesting that they are polyspecific in origin. Studies are currently under way into differential epitope recognition and antibody avidity between the two breeds. There appear to be no differences between breeds in the titre or isotype of antibody specific for the surface-exposed epitopes of VSG. Both N'Dama and Boran cattle experience a profound macrophage-mediated immunosuppression in the lymph nodes early in infection. The antigen which induces this suppressor activity has been purified and is being characterized. Also a massive increase in the numbers of $CD5^+$ B cells and in serum IgM levels has been described in all infected cattle. It has been suggested that the $CD5^+$ B-cell response is the result of a T-independent response to VSG.

The primary pathological feature of bovine trypanosomiasis is anaemia. The drop in red cells is due to the removal of both mature and immature erythrocytes by cells of the mononuclear phagocytic system (MPS) in the spleen and bone marrow. Results from *in vivo* and *in vitro* experiments suggest that erythrophagocytosis is higher in Borans than N'Damas. Data have also been obtained which indicate that in addition to the massive removal of erythrocytes by the MPS, there is insufficient red blood cell replacement into the circulation. Analysis of erythroid progenitor colonies in bone marrow from trypanosusceptible cattle has shown that there is a suppression of both early (BFU-E) and late (CFU-E) progenitor cells early in infection. As the infection progresses the CFU-E progenitors recover, but the numbers of BFU-E's remain depressed.

In summary, we have accumulated a database in which differences in the pathological consequences of trypanosome infection have been quantified in trypanotolerant and trypanosusceptible cattle. Other factors which affect the outcome of disease are being addressed, such as the role of specific cytokines or the direct pathogenic effects on host molecules, cells or processes, of certain trypanosome antigens. Can we use the data we have to develop models to test the effect of altering variables such as aberrant cytokine production or the failure to develop T-dependent antibody responses? Can we test how these different immunological and haematological processes interact to affect the outcome of disease? Is it possible to model the interactions between innate host factors versus specific immune responses in control of parasite growth and the role of the immune and erythroid responses in the control of pathogenesis?

Modelling of host-parasite interactions and their influence on the course of infection in tolerant and susceptible animals

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Trypanosomes which undergo complete cyclical development are capable of controlling their growth rates at different points within their life cycle. In the tsetse fly vector, mature metacyclic forms, which are infective for the mammalian host, are non-dividing. When an infected fly takes a blood-meal from a mammalian host, the infective metacyclic forms which pass into the host begin to differentiate into actively dividing bloodstream-forms. These actively proliferate in the vascular system. Studies on *Trypanosoma brucei brucei* in rodents have shown that when an infection has matured, the trypanosomes are capable of undergoing a differentiation event to become non-dividing. These non-dividing forms can be cleared by the host immune system through recognition of the surface coat of the parasite. The clearing of a wave of parasitaemia allows trypanosomes which have a different surface coat, generated through a process termed antigenic variation, to become established in the vascular system. The mechanisms of antigenic variation by which trypanosomes evade the host immune system are well documented. At present, there is no information available on how growth of the parasite is controlled, although there is evidence to suggest that a decrease in growth rate can allow the host to control and eliminate the infection. The available information on infections in trypanotolerant and trypanosusceptible cattle suggests that trypanotolerant breeds control the infection, at least in part, by reducing parasite load in the first wave of parasitaemia, with subsequent waves showing marked reductions until the infection is eliminated. Susceptible animals show only slightly higher parasite load in the first wave but are incapable of controlling subsequent waves. Immune dysfunction is evident in the susceptible animals following the first wave of parasitaemia but not in the tolerant animals.

The consensus opinion at present is that the control of parasitaemia occurs prior to the first peak of parasitaemia and prior to control of parasite numbers through immune recognition of parasite molecules. We believe that there must be signalling between the host and parasite, between parasites and between parasite and host which influence the course of the infection. In exotic breeds these signals are clearly wrong, and an unchecked trypanosome infection eventually results in the death of the animal. We wish to understand how these signals work on parasite proliferation in order to identify the signals and the parasite surface receptors they bind to. In the establishment of an infection and in the first wave of parasitaemia, the differences in parasite numbers could be due to control of parasite growth rates (e.g. cell division cycle) or death rates (e.g. programmed cell death).

We are not sure whether either of these possibilities would influence the modelling of an infection and whether it is important, or even possible, to determine experimentally which of the two is occurring. Towards the peak of the first wave of parasitaemia there is an immune response elicited by the host against the surface coat of the parasite which eliminates that antigenic type from the bloodstream and allows re-invasion of the vascular system with parasites having a different surface coat. At this time, susceptible animals start to display immune dysfunction whereas tolerant animals do not.

A further feature of parasite-host interactions is 'carrier status' in which trypanosomes are not detectable in the vascular system of the host, but if the host is subjected to stress the parasites actively proliferate and often kill the host. It has been suggested that in carrier status, parasites might sequester to 'privileged' sites in the host where they can avoid immunological attack. Again, we would like to know how parasite numbers are controlled in carrier status and what triggers apparent active proliferation following stress in the host. Can carrier status be accounted for by assuming that the parasites are in a dormant state and non-dividing or that they are dividing normally but dying off more quickly so that the numbers do not reach detectable levels in the blood? Should we be establishing whether there are host factors controlling this state?

Potential applications of modelling in the bovine genome project

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Trypanotolerance, the heritable ability of some cattle to remain productive in the face of trypanosome challenge, offers a sustainable means of reducing the impact of trypanosomiasis on productivity. Trypanotolerant cattle are relatively few in number and intensification of their breeding and dissemination is required. Introgression of trypanotolerance into susceptible cattle types is also a possible approach to production of improved cattle fitted to the humid and subhumid tropics.

Approaches to the improvement and dissemination of trypanotolerance genes would benefit from the availability of markers. Ultimately, with cloning of the genes, it will become possible to attempt production of transgenic trypanotolerant cattle designed to be productive under trypanosome challenge.

The bovine genome project is attempting to find genetic markers of trypanotolerance. The genetic basis of trypanotolerance is not well understood and there are, theoretically, an almost unlimited number of possible genes involved with any number of possible interactions. It is known to be a highly heritable trait and crosses between trypanotolerant N'Dama cattle and susceptible Boran cattle show an intermediate level of tolerance. The approach to identifying genes and estimating their number is to construct a large set of genetic markers which will be applied to a population segregating trypanotolerance. There are two possible areas where modelling could make a valuable contribution.

MODELLING THE GENETIC CONTROL OF TRYPANOTOLERANCE

A model could set up a given number of genes on a given number of chromosomes, each of which makes a given contribution to the phenotype and which interact in a given way. What then would be the expected outcome of breeding a trypanotolerant animal with a trypanosusceptible animal and then either back crossing or inter crossing to construct the second generation? Such a model would allow the estimation of the number of animals required for such an experiment and assist in the interpretation of its outcome. There is essentially no data available to assist in the construction of such a model. It would amount to a purely arbitrary, but highly useful, examination of the consequences on the resultant phenotype of a genetic mechanism of arbitrary complexity.

MODELLING MARKER DISTRIBUTIONS

The bovine genome has been estimated to contain up to 3×10^7 polymorphisms, all of which are potential markers. The technique of random amplification of polymorphic DNA (RAPD-PCR) allows access to an effectively unlimited number of markers and makes possible the search for genes controlling traits of interest in outbred populations. However, if a given number of animals has a given set of alleles at each marker locus, what fraction of markers will give a spurious association between a marker and genes controlling the trait of interest? A modelling approach could address this question by defining one or more populations of a given number of individuals. This definition must include the possibility of multiple alleles at each locus and a range of allele frequencies as well as allowing for population-specific alleles or allele frequencies. There are some data available which will allow the estimation of likely levels of heterozygosity and allele frequencies. Unfortunately, these are largely based on protein polymorphisms and may not be applicable to RAPD markers. However, this again amounts to a theoretical study which needs little support in hard data. It will allow the establishment of the 'worst-case' conditions under which such an approach would fail and thus allow investigations to be designed to test whether or not these conditions occur in reality.

Use of mathematical modelling for elucidating trypanotolerance: preliminary considerations

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ABSTRACT

African trypanosomes, the causative agents of sleeping sickness in humans and related diseases in livestock, escape immune destruction by sequentially altering the antigenic composition of their surface coat. Since the repertoire of the surface coat antigens is quite extensive, it is assumed that African trypanosomes are invulnerable to vaccination.

In a previous work, a mathematical model was presented for the interactions between the antigenically varying parasite and the humoral immune response in the naive host. Ability of the model to retrieve real-life parasitaemia profiles is crucially dependent on two assumptions: i) that antigenic variation involves an intermediate, possibly very brief, episode in which the old and the new antigens are simultaneously expressed on the parasite's coat; and ii) that the double expressers that vary in the antigenic composition of their coats also vary in their susceptibility to the immune response. Experimental evidence supporting these assumptions are warranted for further development of the model and for examining the prospects of anti-trypanosome vaccine. Now the model is extended to allow for different types of immunity. We see how parasitaemia profiles that characterize different host species or intra-specific variation in trypanotolerance can be retrieved if we vary the parameters of specific antibody response.

Since antigenic variation in African trypanosomes involves very intricate dynamics on the molecular, cellular and cell population levels of the parasite and the host immune system, it is highly likely that important features of parasitaemia are determined by currently undetected factors. It is for the investigation of these complex dynamics that we employ the tool of mathematical modelling, aiming at identifying the crucial subprocesses in the system. Updated information about details of inter-specific differences in the immune response to trypanosomiasis in general, and in affinity maturation in particular, is essential for improving the predictive ability of the mathematical model.

INTRODUCTION

African trypanosomes are protozoan parasites transmitted by the tsetse fly to people and wild and domestic animals in Africa. Infection in domestic livestock results in weight loss, impaired immune responses, and haematopoietic and reproductive disorders. However, a few breeds of livestock that are indigenous to Africa, such as the N'Dama cattle *(Bos taurus)* of West Africa, are able to tolerate trypanosomes well and, in many

cases, appear to suffer no ill effects from infections. This property, shared by many of Africa's wild ruminants, is known as *trypanotolerance*. The more common livestock breeds, in which trypanosomiasis readily develops, such as zebu cattle *(Bos indicus)*, are referred to as *trypanosusceptible* (e.g., Murray, 1987).

Understanding trypanotolerance seems to be a necessary step in the development of control methods for these diseases. Thus, a series of experiments was carried out in which N'Dama and a zebu breed called Boran were infected with *Trypanosoma congolense* and parasitaemia was monitored in the two infected breeds. Initially, the N'Dama and Boran showed similar levels of parasitaemia, but as the infections progressed, high numbers of

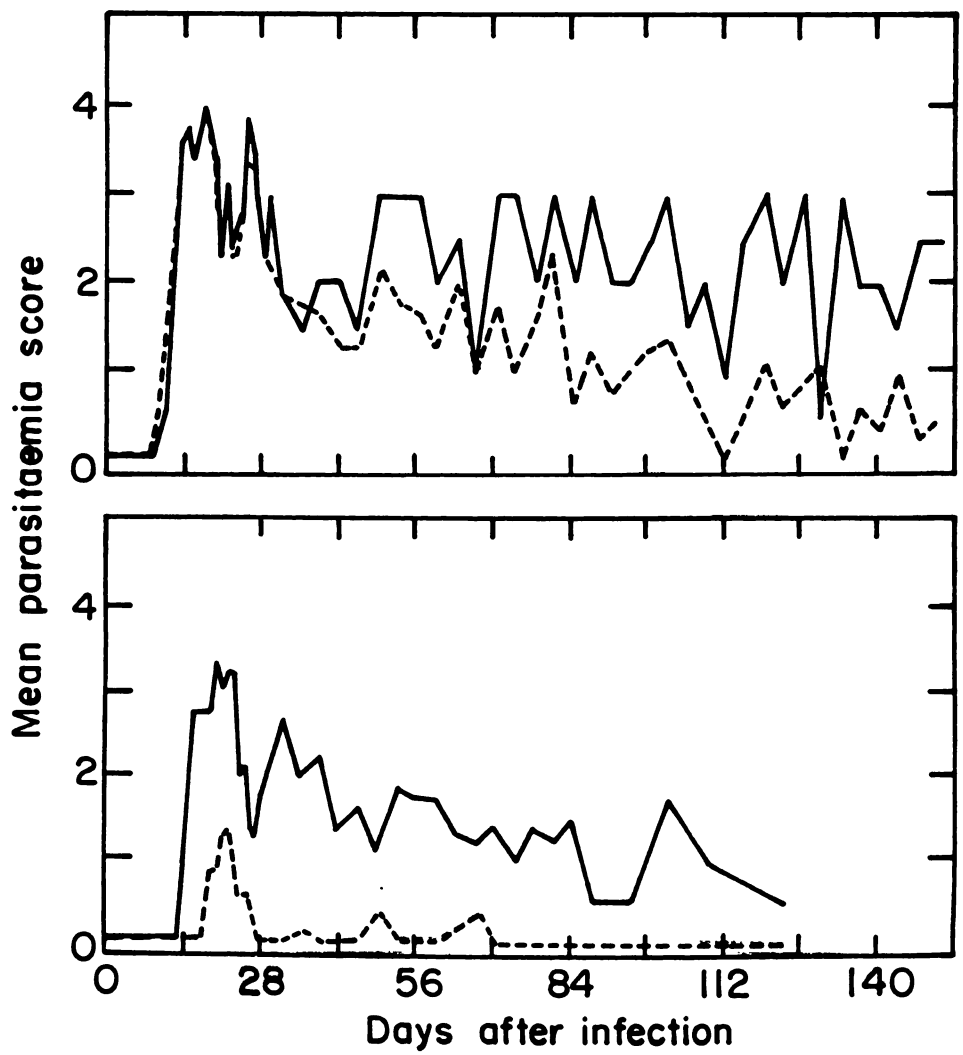


Figure 1. Changes in parasitaemia during a primary infection (a) and a rechallenge infection (b) with *Trypanosoma congolense* ILNat 3.1 in a group of N'Dama (- - -) and a group of Boran cattle (—). Reproduced from Paling *et al.*, 1991.

parasites persisted in the Boran whereas parasitaemia in the N'Dama decreased with time (Figure 1). These results clearly show that the trypanotolerant N'Dama can control parasitaemia, but the mechanism responsible for this control remains obscure (Paling *et al.*, 1991).

The difficulty in understanding trypanotolerance is due to the intricate host-pathogen dynamics in African trypanosomiasis. These dynamics involve many non-linear processes at the molecular, cellular and cell population levels in the parasite and in the host. We studied this problem using mathematical modelling techniques, analysing the major processes at the different organizational levels and their interactions. Subsequently, we used the model to examine the effect of variation in different parameters on the overall infection dynamics. We employed a model that retrieves the characteristics of parasitaemia quite accurately and, to date, is the only model that accounts for African trypanosomiasis in the individual host (Agur *et al.*, 1989).

Modelling Antigenic Variation in African Trypanosomes

Trypanosomes can proliferate in blood and can also invade other systems. Due to an efficient antibody-mediated immune response, the sharp increase in parasite numbers is followed by an abrupt decline. However, blood trypanosomes can escape the host's immune responses by undergoing antigenic variation of their unique cell surface coat protein, the variant cell surface glycoprotein (VSG). Since every coat usually consists of a single type of VSG, trypanosomes can change their antigenic identity by switching to the expression of a new VSG gene, thereby expressing a new coat. Each parasitaemia wave consists of a population of parasites, most of which display one kind of VSG on their surface. As the repertoire of potential VSG coats is very large (about 1,000 in *T. brucei),* blood-based infections are characterized by relapsing parasitaemia waves, which can progress for long periods of time (see Barry and Turner, 1991, for a review).

To explain the course of parasitaemia, a mathematical model was developed to study the interaction between the antigenically varying parasite and the host's immune system. The model focuses on the genetic events that underlie antigenic variation, and assumes that the transition from the expression of one VSG gene to the next is a random event, which can either be instantaneous or gradual. In the latter case, intermediates are presumed to exist, expressing two serologically distinct VSGs on their surface; these parasites are denoted double expressers (DEs). In this model the DE state may be a very brief episode in the parasite's life cycle, so that even if it is obligatory, the proportion of DEs in the population at any given moment may be very low.

The model was studied by numerical simulations for a large range of parameter values, and for different assumptions about the underlying processes. It succeeded in obtaining roughly ordered parasitaemia waves only if it assumed that i) the majority of parasites undergoes the DE transition episode, and that ii) different DE combinations vary in their susceptibility to the immune response against the precursor single expressers (SEs). Under these assumptions parasitaemia can be ordered even if individual parasites switch completely at random. Note that the precision in the order of parasitaemia and the regularity of waves depends on the proportion of parasites undergoing the

DE stage and on the variability in the intrinsic growth of different SEs or DEs (Agur *et al.*, 1989).

Modelling Trypanotolerance

The aim of this preliminary work was to identify host mechanisms that are responsible for the observed differences in parasitaemia profiles between trypanosusceptible and resistant cattle. The model will be used for checking which host factors may control the length of parasitaemia and the structure of waves. In addition, we will attempt to retrieve the reduction in parasite levels, observed in the trypanotolerant N'Dama cattle in late stages of the primary infection and throughout the rechallenge infection (see Figure 1).

It will be shown that parasitaemia profiles are relatively robust to changes in some ecological parameters, e.g., the parasite intrinsic growth rate, which traditionally is assumed to control population growth. In contrast, temporal parameters, such as the delay period prior to the production of high affinity antibodies, appear to have a significant effect on parasitaemia profiles.

General differences between hosts can be realized in the model in the parasite intrinsic growth rate, r, and in the carrying capacity of the host, K. In addition, hosts may vary in non-specific immune responses, e.g. immune cell general proliferation rate and mortality rate, as well as in antibody secretion rate, due to differences in cytokine secretion levels (Williams and Logan-Henfrey, this volume). The potential effect of these factors is examined below. Note that since our focus in this work is on parasite dynamics, we ignore the possibility of host mortality, as it may be only indirectly related to the parasite load.

Effect of Host-Difference in Carrying Capacity, K

The carrying capacity, K, measures the maximal density of parasites in the blood. A large K means that the parasite population can grow to large numbers before density begins to suppress population growth. Displayed below are simulation results of parasitaemia in two hosts, one in which maximal parasite density is $K = 10^4$ per ml (Figure 2a), and one in which maximal parasite density is $K = 10^7$ per ml (Figure 2b). One can note in these figures that carrying capacity has a striking effect on parasitaemia profiles. An upper limit of 10^4 on parasite density generates, for a host with 20 litres of blood (e.g, a cow), an ordered parasitaemia which progresses for an extended period. In contrast, the higher upper limit on parasite's density, $K = 10^7$, leads to a very acute early parasitaemia, with very dense high peaks, containing most of the antigenic repertoire. The reason is that a large K enables a fast increase in total parasite numbers to levels that permit an almost synchronous emergence of many variants. The sharp decline in parasite load after about one month of infection is due to the elimination of all the faster growing variants by the immune system. The latter effect is due to our assumption of a perfect immune memory: no mortality of specific B cells is allowed for, so that re-emergence of variants cannot occur. This assumption is relaxed in a further study (see below).

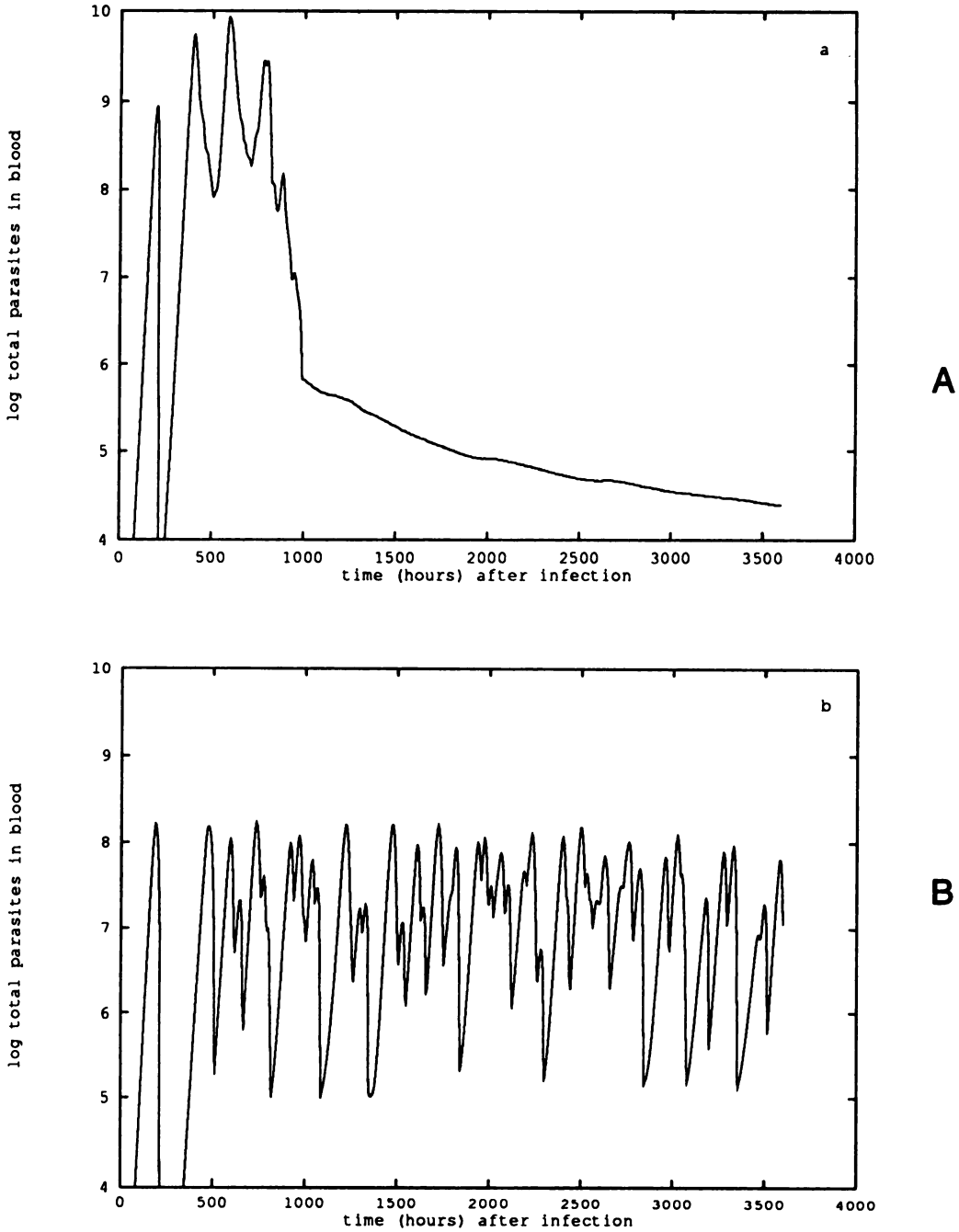


Figure 2. Effect of parasite density on parasitaemia profile. Parasitaemia obtained in simulations using the following parameters. Blood volume is 20 litres. Two parasites of a single VSG are initially introduced. The growth coefficient for single expresser variants is 0.85 per time unit, and for double expresser variants 0.2 per time unit; each simulation time unit represents six hours. B cell growth coefficient is 0.52 per time unit. Maximum antibody secretion rate is 170 per time unit. τ is three days. (a) $K = 10^7$; (b) $K = 10^4$. For other parameters, see Agur *et al.*, 1989.

Effect of Host-Differences in Parasite's Intrinsic Growth Rate, r

Reduction in the growth rate of all the parasites in the system has a relatively small effect on parasitaemia (not shown). Results suggest that for $K = 10^4$, a 20% reduction in the parasites' intrinsic growth rate has a negligible effect on the height of peaks, but parasitaemia is slightly less dense, as some of the very slow growing variants are now below detection level. When $K = 10^7$, a similar reduction in r reduces the peaks by about one order of magnitude, and increases the duration of parasitaemia from about one month to about three months.

Increasing the differences in variant-specific intrinsic growth rate has the effect of upsetting the order of parasitaemia and the characteristic structure of peaks, but it does not significantly alter the height of parasitaemia peaks (results not shown).

Effect of Host-Differences in Immune Cell Birthrate

Increasing B-cell replication rate by 20% does not have a significant effect, except for some dilution of parasitaemia (results not shown). This effect is similar to the above-mentioned effect of decrease in the intrinsic growth rate of the parasites.

Effect of Host-Differences in Antibody Secretion Rate

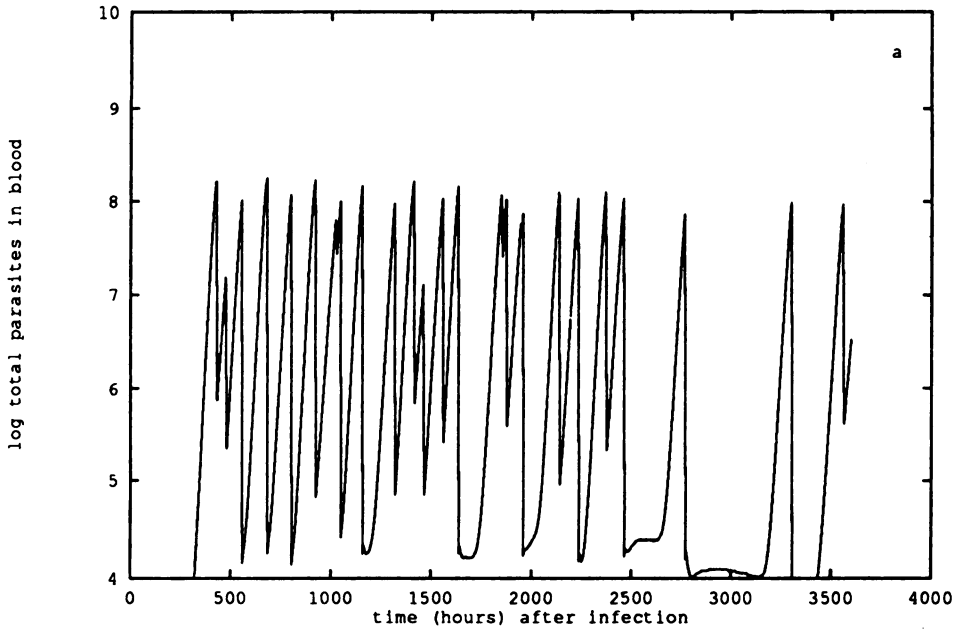
A hundred-fold increase in antibody secretion rate narrows the peaks but has no effect on their height or on the course of parasitaemia, apart from a slight dilution of the slowly growing variant peaks. This is so since, even now, antibody secretion rate is not sufficiently large enough to prevente the rapid rise of the fastest growing parasites (Figure 3a). In contrast, a two hundred-fold increase in antibody secretion rate has the effect of shortening the parasitaemia course: now the decline of the parasitaemia waves is so rapid that the probability of a successful antigenic switch is much reduced (Figure 3b).

Effect of Host-Differences in Immune Cell Death Rate

Significant B-cell mortality appears to lengthen parasitaemia, due to the reappearance of early variants. Variation in B-cell mortality *per se* cannot account for the N'Dama-Boran observed differences.

Effect of Host-Differences in the Time Lag Between Antigen Stimulation and the Onset of Specific Antibody Secretion

A theory of population dynamics in perturbed environments asserts that population persistence depends on the relation between the characteristic periodicity of the population and that of the environment (Agur, 1985; Agur and Deneubourg, 1985). Based on this theory we hypothesized that long-term persistence of the parasite population depends on



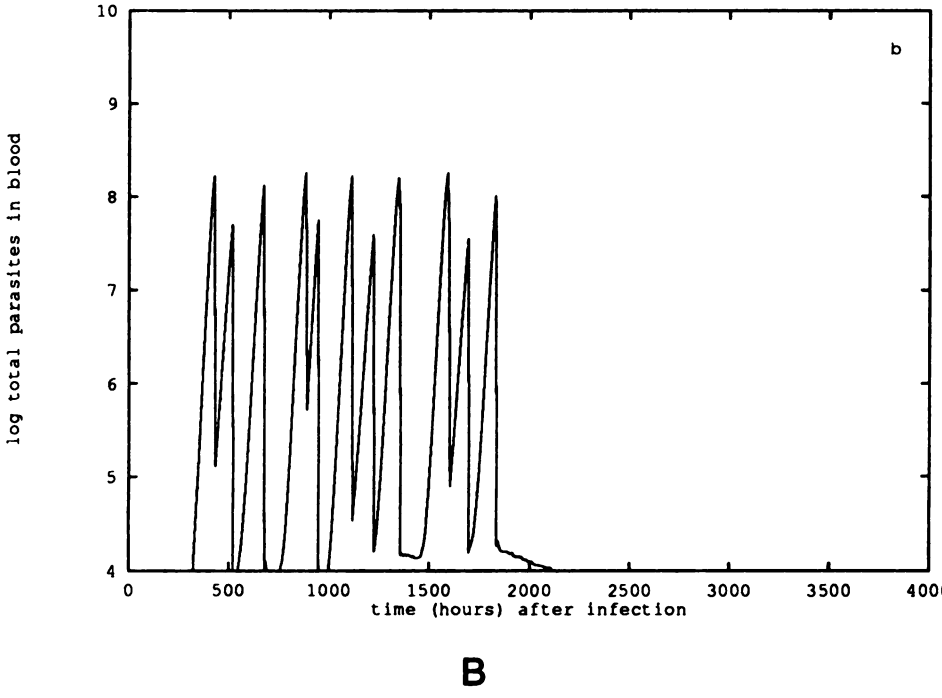


Figure 3. Effect of antibody secretion rate. All parameters as in Figure 2b, except that antibody secretion rate is (a) 17×10^3 per time unit, (b) 34×10^3 per time unit.

the characteristic time scale of the immune response, that is, on the lag between antigen stimulation and specific antibody secretion (see also Barry and Turner, 1991; Agur 1991). Such host differences may reside in the pre-immune repertoire or in the properties of affinity maturation.

To check the above hypothesis, parasitaemia was simulated using different values for the mean and the variance in the time-delay, τ, between antigen stimulation of specific B-cell proliferation and the onset of antibody secretion. Results suggest that this time-delay may indeed have a significant effect on parasitaemia profiles. However, the effect is remarkably different in hosts with different K's.

When $K = 10^7$ the general pattern of parasitaemia appearing in Figure 2a is maintained. This is so as long as for some variants, at least, the time-delay before antibody secretion is $\tau > 2$ days. Such a delay ensures that in a host with 20 litres of blood, the number of parasites becomes so large as to enable the quasi-synchronous emergence of most of the available variants. A significantly different parasitaemia occurs if $\tau \leq$ days (Figure 4a) for all the variants. Now the acute parasitaemia, in which all parasites appeared early in the infection, is replaced by less acute, but long and ordered parasitaemia, due to the suppression of parasite numbers early in the infection.

The picture is quite different when $K = 10^4$. We saw in Figure 2b that $\tau = 3$ days yields ordered parasitaemia. The same profile was obtained when the efficiency of the immune response was further decreased, so that $\tau = 4, 5$ days. We note, then, that a marked decrease in efficiency of the immune response does not alter parasitaemia profile when maximum parasite density is relatively low. The reason is that the depressed K prevents the increase in parasite numbers to the levels that allow for the co-emergence of many antigenic types. If variance in τ is increased, so that now $\tau = 3 \pm 1$ days, parasitaemia is somewhat diluted but the effect is not very significant. A completely different profile is obtained for $\tau = 2$ days. Now parasitaemia is significantly shorter, due to the increased efficacy of the immune response. Figure 4b is similar to Figure 2b in displaying simulation results of parasitaemia in a host having $K = 10^4$, except that now the time-delay preceding the onset of antibody secretion is not constant, but rather a random variable $\tau = 2 \pm 1$. One may note here a brief ordered parasitaemia, during which the peaks are reduced by about one order of magnitude. A further decline in parasitaemia peaks is obtained when $\tau = 2 \pm 2$ days, so that for some variants there is no delay in the onset of antibody secretion (they may be similar to previously encountered antigens). For other variants the delay may be as long as four days or more. Note that if specific antibodies are already present in the blood when the new VSG is detected (Agur, 1991) then the situation is equivalent to negative.

CONCLUSIONS

The main conclusion from the present study is that a model that can retrieve the roughly ordered, persistent parasitaemia (characterizing African trypanosomiasis) cannot be very resilient. In such a model a reasonable variation in most parameter values will either have an insignificant effect, or it will completely upset the structure of parasitaemia. Our study points to the time-lag between antigenic stimulation and the onset of antibody secretion as a

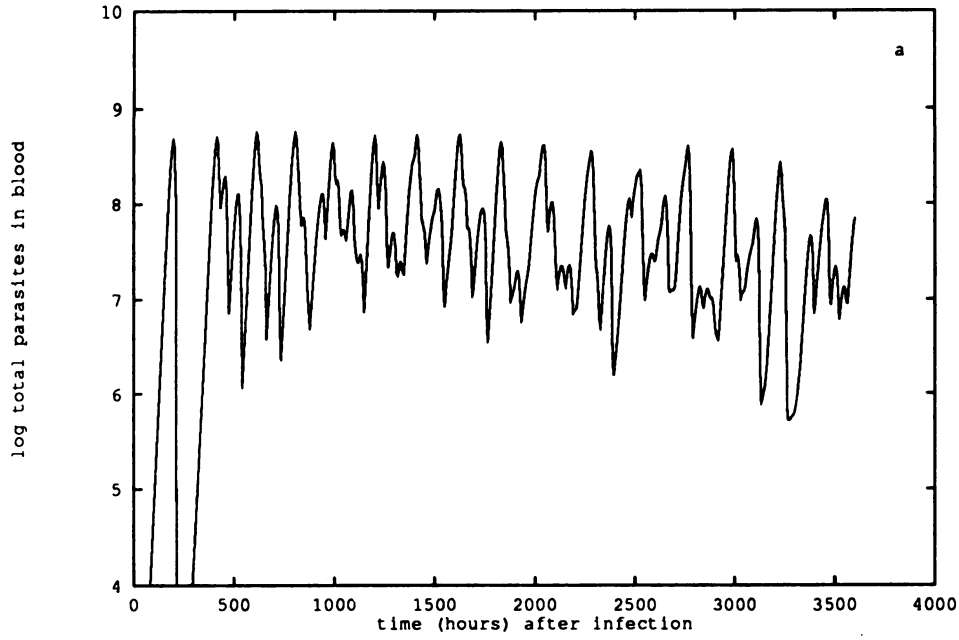


Figure 4. Effect of the time delay between antigenic stimulation and the onset of antibody secretion. All parameters as in Figure 2, except τ (a) $K = 10^7$, $\tau = 2 \pm 0$ days; $K = 10^4$, $\tau = 2 \pm 1$ days.

parameter which can modulate parasitaemia. In the present work we assumed that this lag is either constant, i.e., the same in all specific responses, or that it is a normally distributed random variable. The possibility that the time lag may progressively decrease during primary and rechallenge infection, by some kind of a "learning" mechanism, is implied by the parasitaemia profiles of *T. congolense* in N'Dama cattle (Paling *et al.*, 1991). This possibility will be further explored (Z. Agur and R. Mehr, in preparation). Support for our theoretical conclusions is provided by the observation that in mice, virulence of *T. congolense* is correlated with a late and transient protective antibody response; negligible virulence is correlated with an early protective antibody response (Roelants and Pinder, 1987).

At the present stage it is essential to obtain further information about real life parasitaemia in resistant and susceptible cattle. Thus we would like to know the structure of waves, i.e., the number of variants in each wave and their identity. In addition, it is important to evaluate the total number of parasites in individual hosts, rather than group averages. More information about affinity maturation in trypanosomiasis is also essential. Such information will hopefully validate our assertion that trypanotolerance resides in the immune response. Note, however, that the possibility of host differences in affinity maturation implies that cell-cycle genes may be involved. Theoretical results suggest that the onset of hypermutation depends on the number of B cells in the proliferating clone, and it has been suggested that the mechanism of monitoring this number may be related to the mitotic clock (Agur *et al.*, 1991). Another work suggests that the mitotic clock, i.e. cell-cycle duration and the number of cell divisions in a cell-lineage, may be modulated through small changes in the activity of some cell-cycle genes, such as *cdc25* or *wee1* (Norel and Agur, 1991). The implication of this is that even small host differences in the activity of genes that are not directly connected with the response to parasites can be responsible for differences in susceptibility to African trypanosomes.

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Session discussion

MODELLING OF THE IMMUNE SYSTEM

Following the introductory presentations of ILRAD's needs, it was agreed that modelling of the immune system *per se* is complex, and if interactions with parasites are superimposed, the complexity increases enormously. This complexity can be reduced considerably by focusing on components of the immune system that are relevant to the parasite in question. The discussion addressed the different contributions and approaches of modellers and experimentalists. On the one hand, it was stressed that experimentalists need to be tolerant of first generation abstract models; these invariably evolve as fresh information is incorporated. On the other hand, it was suggested for example that it would be useful if trypanosomologists could manipulate infection challenges to mimic antigenic waves and observe the immune responses that ensue.

A more specific discussion developed following Dr. Agur's paper on some aspects of host differences in trypanotolerance. It was emphasized that it is not known whether waves of antigenic variation occur in cultured trypanosomes. The model does not have affinity maturation of antibody responses incorporated in it. The view was expressed that there may be more than two VSG expression sites within a given trypanosome and that the basis of ordered expression of VSG variants is likely to be the siting of their genes within the genome.

The presentation by Dr. Kemp of the approach being taken at ILRAD to map bovine trypanotolerance genes included two questions to the assembly of modellers. These were:

- Can bulk segregant analysis be applied productively to outbred cattle populations?
- Can the segregation of multiple genes, each with defined contributions to a given trait, be modelled within outbred populations?

Neither question was satisfactorily answered in the ensuing brief discussion.

1

PARASITE VARIATIONS AND POLYMORPHISM

Parasite polymorphisms: modelling variations in African trypanosomes

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Parasitic protozoa are organisms with many interesting and variable phenotypes. The majority are transmitted to their vertebrate hosts by vectors in which they undergo complex cyclical development before acquiring the capacity to re-infect the hosts.

Many studies have been conducted on inherent characteristics of these parasites that enable them to display such variation; in this respect, the salivarian trypanosomes have been one of the most extensively studied. Trypanosomes change their antigenic profiles in the process of antigenic variation, which apparently occurs independent of the host but is qualitatively, and possibly quantitatively, modulated by the host immune responses. Depending on the antigenic repertoire of the parasite (as determined by its genotype), a trypanosome in the host blood stream will display a different number of distinct antigenic types in a semi-defined order. Attempts have been made to estimate empirically and by molecular hybridization using cloned VSG genes the number of different variants which can descend from a single trypanosome. Such analyses can be performed on a carefully selected sample of trypanosome populations. It would be informative to understand by simulation model the extent to which different hosts and host factors influence the dynamics of antigenic variation in a trypanosome of a particular genotype.

Trypanosomes display variability in the severities of the disease they cause in their respective vertebrate hosts; this is particularly true of trypanosomes collectively designated *Trypanosoma congolense*. The reservoir hosts and some domestic livestock appear not to suffer deleterious consequences upon infection by trypanosomes; on the other hand, exotic breeds of domestic livestock suffer more serious illness often resulting in death unless treated upon infection by the parasites. Evidence to date indicates that both the parasite and host genetic background as well as immune status contribute significantly to the clinical course and outcome of the disease. The extent of genetic polymorphism and proximity among trypanosomes can be estimated by mathematical analysis of randomly amplified polymorphic DNA (RAPD) markers and restriction enzyme fragment length polymorphisms (RFLPs). Similar analyses can be performed on the vertebrate hosts as well. With sufficient experimental data on both the parasite and the hosts, it should be possible to model the course of the disease in a given host infected with a single or multiple parasites of particular genotypes.

It has been established that different species of the African trypanosomes can infect a single tsetse vector and thus a single host. In such a situation, it is envisaged that genetic recombination could occur leading to new or novel genotypes which may display entirely

different clinical effects in different hosts. Given that different parasite genotypes can be identified accurately using DNA-based markers, it should be possible to have models which can predict recombination frequencies within parasite species, and the consequences of such events on parasite genetic repertoires (serodemes) and population types. Such a model could also provide information on how different parasite species interact with each other and with the different species of the vector and host in the presence of host immune responses, treatment of the host with different anti-trypanosomal drugs, different vector control strategies and a generally changing environment. It may also be possible to simulate responses of different parasite types to drugs in common use for treatment or management of the diseases they cause. Indeed, some of the most useful contributions of such models could include predictions of dynamics of parasite phenotypes such as drug resistance, vector transmissibility, virulence to host and other aspects of genotypic variation in parasite populations.

Polymorphisms in *Theileria parva*

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Theileria parva, an apicomplexan parasite of cattle and buffalo, causes a severe disease syndrome in cattle (variously known as East Coast fever, January disease and Corridor disease) and is distributed in large parts of eastern, central and southern Africa. ILRAD's major goal is to develop improved methods of controlling theileriosis, employing novel subunit vaccines. Better understanding of the epidemiology and biology of the parasite will contribute to this goal.

Parasite stocks isolated from the field are heterogeneous and exhibit extensive genotypic and phenotypic diversity. This genotypic diversity has been demonstrated by analysis of genomic DNAs from different stocks of parasites, using a major parasite-specific repetitive sequence. Virtually all isolates so far characterized show restriction fragment length polymorphism. There is also size polymorphism of *Sfi*I fragments in different stocks. Further analysis has revealed that this polymorphism is mainly confined to the telomere-bearing *Sfi*I fragments, suggesting that telomeric or subtelomeric regions may be active sites for the generation of sequence polymorphism within the parasite genome.

Phenotypic differences exist between parasites isolated from buffalo and cattle. The buffalo-derived *T. parva* parasites are usually more virulent in cattle and undergo limited merogony compared to cattle-derived parasites. A stock of *T. parva* from Zimbabwe has been isolated that causes mild disease in cattle and yet provides a broad protection against different stocks of parasites.

Antigenic diversity has also been demonstrated using a panel of monoclonal antibodies recognizing epitopes on the surface of *T. parva* schizonts. The gene encoding the polymorphic schizont antigen exhibits a series of complex polymorphic repeats in its central region. Phenotypic manifestation of the antigenic diversity is demonstrated in *in vivo* cross-immunity studies. Cattle immunized with one strain of parasite may not be protected if challenged with a different immunological strain. However, the antigens involved in inducing strain-specific immunity have not been identified.

In contrast, characterization of the gene encoding a surface sporozoite antigen p67 of *T. parva,* which induces protective immunity in cattle, has shown that it is highly conserved among all cattle-derived *T. parva* and is different from the gene in parasites isolated from buffalo. Thus there is a potential of development of a diagnostic marker for the identification of buffalo-derived *T. parva.*

Molecular characterization of the *T. parva* genome reveals four chromosomes. Sexual reproduction has been demonstrated to occur in laboratory experiments indicating a potential for generating novel genotypes during meiosis by independent assortment of chromosomes. As in *Plasmodium,* a potential for mutation during asexual division in the

bovine host may also exist although this has not yet been observed. A complete restriction map of the genome has been constructed using a 'linking clone strategy'. This has generated numerous chromosome specific *Sfi*I linking clones as markers. Additionally, several antigen and house-keeping genes and random cDNAs have been localized in the genome. Thus a large body of data exists on the genome of *T. parva* and numerous DNA and serological reagents are available for typing field populations of the parasite.

Knowledge of the characteristics of parasite populations in the field is a pre-requisite for developing theileriosis control strategies using novel vaccines. However before field studies are conducted it is necessary to consider the parasite traits which need to be identified. These include strain-specific immunity, virulence and infectivity. Markers for these traits are yet to be developed. If appropriate markers become available then, some of the important questions concerning field populations of parasites are:

- what is the prevalence of different parasite genotypes in nature (especially with regard to different immunological strains, virulence and infectivity to the vertebrate and invertebrate hosts)?
- what is the effect of an obligatory sexual cycle in *T. parva* on the genetic structure of parasite populations in the field?
- what is the effect of introducing new strains on the creation of novel genotypes bearing in mind that the sexual cycle is obligatory in the life-cycle of the parasite?
- what are the genotypic differences between parasites present in carrier animals and those in animals undergoing acute infections?

In the context of this workshop it is important to consider whether polymorphisms in genes of important biological traits, allelic frequencies of these genes, sexual recombination and population dynamics of these genotypes can be modelled. If so, what relevant data are required to construct these models and, finally, can these models be exploited to predict the effects of various control pressures such as vaccination, chemotherapy and tick control on the evolution of parasite populations in the field?

Application of modelling to trypanosomiasis chemotherapy

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Maintenance of domestic livestock in trypanosomiasis endemic areas is currently carried out in three different manners: controlling the vector tsetse fly, rearing trypanotolerant livestock and administering trypanocidal compounds to domestic livestock.

Chemotherapy and chemoprophylaxis of trypanosomiasis in cattle, sheep and goats is dependent upon the salts of three chemical compounds; diminazene (an aromatic diamidine), homidium (a phenanthridine) and isometamidium (a phenanthridine aromatic amidine). While isometamidium is primarily used as a prophylactic agent and diminazene is used only as a therapeutic agent, homidium is used both as a therapeutic and a prophylactic agent. All three compounds have been used in the field for over 30 years and the occurrence of resistance to each of the compounds (especially isometamidium and homidium) has been associated with their usage at sites across Africa. However, the mechanism(s) by which resistance arise(s) in the field are not clearly understood. Laboratory studies indicate that subcurative treatment dosages could be a precursor to the development of resistance to isometamidium and homidium. Furthermore, reciprocal cross-resistance is associated with the two compounds. However, the same does not appear to be true for diminazene since resistance to this compound is extremely difficult to induce when one treats infected animals with subcurative dosages. Furthermore, development of diminazene-resistance is not associated with cross-resistance to either isometamidium or homidium. Thus, diminazene is often used as part of a 'sanative pair', in conjunction with either isometamidium or homidium, to prevent the development of drug resistance.

Since the cost of developing new trypanocides is now prohibitively expensive, it is unlikely that new trypanocides will be forthcoming during the next decade. It is therefore important to maintain the efficacy of the existent trypanocides. To this end, the development of field-usable assays that will rapidly quantify the drug-resistance phenotypes of trypanosome populations in large numbers of cattle is required. Such quantitative information, when used in conjunction with data concerning the pharmacokinetics of the individual trypanocides in domestic livestock, should enable field workers to decide whether recommended dosage regimens for any of the three trypanocides will control the disease, whether *de novo* therapeutic regimens with any of the three trypanocides would be efficacious, whether alternative measures such as tsetse fly control are indicated, or whether a multifactorial integrated control strategy is required. It seems feasible that models may be valuable in integrating these variables and presenting them in a decision-making format. Ideally, such models should consider the long-term sustainability of the

chosen control strategy. However, the decision-making process is partly dependent on assays that will rapidly quantify the drug-resistance phenotype of large numbers of trypanosome field isolates. Since such assays do not currently exist, their development is one of the goals of ILRAD's trypanosomiasis chemotherapy project. Finally, the decision process is also dependent on a comprehensive understanding of the epidemiology of drug-resistant trypanosomes in the field. Because there is very little information on this subject, it is important that experimental protocols are designed to determine the factors responsible for emergence, maintenance and disappearance of drug resistance in the field.

Models for investigating genetic exchange in protozoan populations

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ABSTRACT

This first part this paper deals with the mode of reproduction of *Leishmania*, and its epidemiological consequences. The second part is about the evolution and measurement of virulence or pathogenicity.

The recent debate about whether parasitic protozoa are generally clonal is discussed. The arguments and the evidence are summarized as follows.

- A critique of population genetic methods for assessing the mode of reproduction of parasitic protozoa, mainly those proposed by M. Tibayrenc. The key question for protozoa has been framed in terms of the relative frequency of automixis and amphimixis. There are two main problems: (i) arguments have often been based on weak tests, particularly those which amount to the search for linkage disequilibrium, (ii) few data are available with which to carry out any test properly; sample sizes are very limited and samples from different countries and continents have been lumped together when it is inappropriate to do so.
- One practical consequence of clonality (high coefficient of inbreeding) in *Plasmodium* populations: the evolution of resistance to more than one drug. I use a stochastic population model for *Plasmodium falciparum* to confirm and extend the earlier findings that less inbreeding tends to slow the rate of evolution of resistance to a drug mixture.
- The available, equivocal evidence for *Leishmania*, which points towards occasional genetic exchange.

A second reason as to why we need to know about the mode of reproduction of *Leishmania* is identified and discussed: it is that pathogenicity may be associated with certain genotypes, as has been suggested for both American and African trypanosomes. Among samples of *L. infantum*, the analysis of isoenzymes and of kDNA endonuclease fragment patterns separates strains responsible for cutaneous and visceral disease. In the southern republics of the former USSR, human cutaneous lesions apparently occur following infection with one member of the *L. major* group, but not another. In the Peruvian Andes, clones and strains of *L. peruviana* have shown reproducible difference in virulence *in vivo* and *in vitro*. I describe a model of the *L. major* system which highlights the question of whether we are seeing a balanced polymorphism, or simply different but sympatric transmission systems.

The final problem is concerned with measurement of the preponderance of virulent parasites in a *Leishmania* population. A compartmental model of cutaneous leishmaniasis demonstrates the difficulty of using a simple index such as the ratio of person scar positive:skin test positive.

INTRODUCTION

Plasmodia reproduce sexually, whilst trypanosomatids reproduce asexually. For *Plasmodium*, this long-established view has not been seriously challenged. For *Trypanosoma*,

however, at least *T. brucei,* recent laboratory crossing experiments have shown repeatedly that genetic exchange between parasites can occur in tsetse flies, although it is not obligatory. Tait and Turner (1990) summarized the results of six crosses in which recombinants were produced on 14–45% of occasions.

These experiments have not yet been successfully repeated with any *Leishmania* species, or with South American *T. cruzi.* The best laboratory evidence that genetic exchange might occur in *Leishmania* is only partial evidence: G. Lanotte and J.-A. Rioux (personal communication) have observed and recorded, by videomicroscopy, promastigote fusion leading to the production of a synkaryon. It has yet to be demonstrated that fusion leads to the production of viable recombinant progeny.

For *Leishmania,* there is indirect evidence for hybridization between parasite species in field samples, though putative hybrids could be mutants or common ancestors. Isoenzyme analysis and molecular karyotyping have shown that an apparent hybrid of *L. major* and *L. arabica,* isolated in an area where both parasites have the same vector and reservoir host, does indeed have characteristics of both species (Kelly *et al.,* 1991).

All this is qualitative analysis. However convincingly it demonstrates that genetic exchange can occur, we should like to assess its frequency of occurrence in natural populations. The first part of this paper explores some of the quantitative methods which have been used to investigate this question for *Trypanosoma* and *Leishmania.* The answer has implications for the rate of evolution of drug resistance, the distribution of virulent or pathogenic genotypes in the population and antigenic variation. The second part of the paper illustrates the first in this list by making use of a population genetic model of the malaria parasite *P. falciparum.* The choice of an obligately sexual parasite in this context underlines the point that discussions about genetic exchange are as much about inbreeding (or, conversely, outcrossing) as they are about sexuality.

QUANTITATIVE ANALYSIS OF FIELD POPULATIONS

Single-locus analyses for *Trypanosoma* and *Leishmania*

Genetic exchange between parasites will tend to bring alleles within and between loci into association equilibrium. A lack of genetic exchange may be due to asexual reproduction, or, in a sexual population, to inbreeding. For segregation of alleles at any one locus, we look for Hardy-Weinberg equilibrium, reached in a panmictic population after just one generation of random mating. The three possible genotypes at a diallelic locus are expected to be seen in the proportions $p^2:2pq:q^2$, where p and q are the respective frequencies of two alleles, say A and a. Departures from Hardy-Weinberg equilibrium due to non-random segregation lead to a deficit of heterozygotes, and this deficit can be used to estimate the coefficient of inbreeding, $F = 1 - P_{Aa}/2pq$, where P_{Aa} is the observed frequency of heterozygotes.

Tests for departures from the Hardy-Weinberg ratio have their difficulties. One problem of working with parasites in vectors is small sample size. Infection rates in mosquito-like vectors, including tsetse flies and phlebotomine sandflies, are often very low—under 5% even in an area classed as highly endemic on the basis of infection in the vertebrate host

population. Smaller samples are more likely to show genotypes at frequencies which are statistically indistinguishable from the Hardy-Weinberg ratio. In other words, there is a greater probability, β, of making a Type-II error, which accepts the Hardy-Weinberg null hypothesis when it should be rejected. Really, $\beta \leq 0.05$ is needed before conformation with Hardy-Weinberg becomes convincing.

How many samples are required to avoid making a Type-II error? In the case of *T. brucei* some answers have been provided in a careful appraisal by Cibulskis (1988). Commenting on Tait's (1980) analysis of genotype frequencies for a diallelic locus and a sample of 17, Cibulskis calculated as shown in Figure 1. With this sample size and three genotypes, 120 genotype frequency distributions are possible. Every distribution is equally likely so is just the proportion of distributions that yield non-significant χ^2 values. In this case it is big at 72/120 = 0.6.

A much larger sample of 220 *T. brucei* stocks was collected by Gibson and Wellde (1985) from the Lambwe Valley in Western Kenya. The isolates from flies were particularly

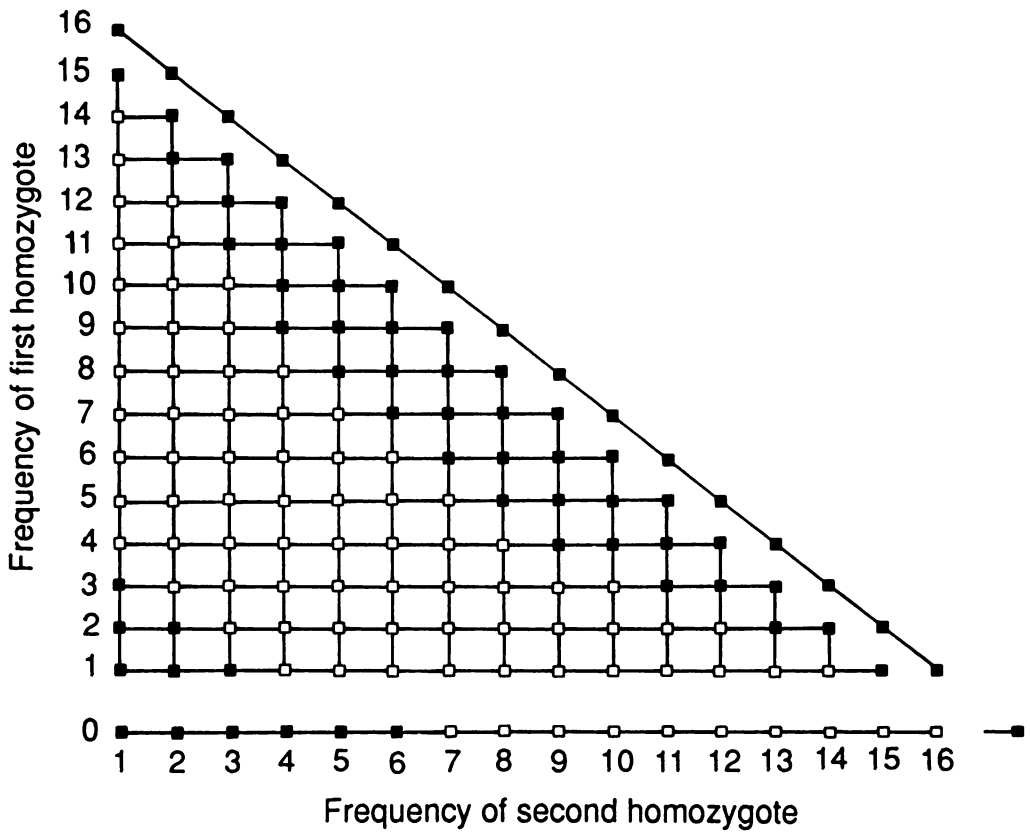

Figure 1. The distributions of genotype frequencies for a locus with 2 alleles and a sample of 17 isolates. Solid squares indicate those genotype frequencies which are significantly different from the Hardy-Weinberg ratio by χ^2 test ($p < 0.05$). Open squares indicate genotype frequencies which are not significantly different. From Cibulskis (1988).

striking with β in the range 0.07–0.205, depending on the precise method of analysis, and this range was lower than found in human isolates. These β's associated with the tsetse fly isolates point to conformation with Hardy-Weinberg, but are not low enough to draw firm conclusions.

However, they are interesting in the context of a second general problem associated with testing for departures from Hardy-Weinberg equilibrium. It is that disequilibrium can arise from processes other than asexual reproduction and non-random mating. In particular, selection may have occurred between the time of 'zygote' formation and the time of sampling. So the ideal analysis will look at the genotypes of the zygotes themselves. For *Plasmodium,* these are found in *Anopheles* mosquitoes and it is now possible actually to genotype the zygotes by making use of the polymerase chain reaction, PCR (Ranford-Cartwright *et al.,* 1991). For *Trypanosoma* too, the fusion products of gametes are found in the vectors, so samples taken from tsetse flies should be less biased by postzygotic selection.

Do samples of *Leishmania* parasites conform with the Hardy-Weinberg ratio? *Leishmania* are probably diploid (Bastien *et al.,* 1992) and, although no formal segregation analysis has yet been carried out on a large sample from a single population, Tibayrenc *et al.* (1990) have persuasively argued that some segregation genotypes which ought to occur have simply never been found in field samples. Among some Old World *Leishmania,* no heterozygotes have been found at all.

Joint-locus analyses for *Trypanosoma* and *Leishmania*

Recombination between loci leads to linkage equilibrium (somewhat misleadingly named since loci may be on different chromosomes in the same genome, i.e. unlinked). Given the pairs of alleles at two loci, A/a and B/b, the overall departure from the expected joint-locus frequencies, linkage disequilibrium, can be calculated from $D = P_{ab}P_{AB} - P_{aB}P_{Ab}$, where the P's denote the observed frequencies of the four possible haplotypes. In making calculations (as for *Plasmodium* below), dependence of D on allele frequency is conveniently removed by expressing it as a fraction of the maximum disequilibrium possible, D'. Furthermore, since D' can be either positive or negative, we use the modulus of its value, D' (in other words, always make the sign positive), in measuring the average departure from equilibrium. Otherwise the average of all the positives and negatives is zero. Extreme linkage disequilibrium is manifested in the widespread occurrence of identical genotypes and, conversely, the absence of certain recombinant genotypes (Tibayrenc *et al.,* 1990).

When there are numerous genotypes in relatively few samples, the expected genotype frequencies are too low to test against a χ^2 distribution. We can ask instead how many joint-locus combinations are expected in a sample of given size. In *T. brucei* collected from tsetse flies, Tait (1980) found 51 out of the 90 genotypes possible with five diallelic loci. The probability of obtaining different numbers of joint-locus combinations under the hypothesis of random assortment of genotypes is shown in Figure 2 (Cibulskis 1988). The probability of obtaining as few as 51 is very small, about 1 in 5000. Essentially the same results were obtained with a second set of data for fly infections (Gibson and

Wellde 1985). They were also obtained for human infections in the same area (Tait *et al.*, 1985) and in analyses by Cibulskis (1988). Tibayrenc and colleagues (1986) have also applied the same sort of argument to populations of *T. cruzi*, in which linkage disequilibrium is extreme.

By contrast, there is little sign of linkage disequilibrium in the population of *Leishmania infantum* studied by Blaineau *et al.* (1992). They looked at the distribution of eight, four and three variants of chromosomes I, II and V in 22 *L. infantum* isolates taken from a small area on the Franco-Spanish border. Again the sample size is small, and refers to isolates rather than clones, but the chromosome size variants are roughly in linkage equilibrium. For example, using the results shown in Figure 3, we can calculate the expected number of triplets which should be found one, two and three times. These expected numbers are 13.51, 2.96 and 0.65, which compare with the observed 16, 3 and 0. But the similarity could easily be due to chance. And there are other explanations: for example, the diversity of genotypes could be explained by a high rate of mutation (Blaineau *et al.*, 1992). As for trypanosomes, we need both laboratory experiments and further careful field studies with large sample sizes to resolve the issue.

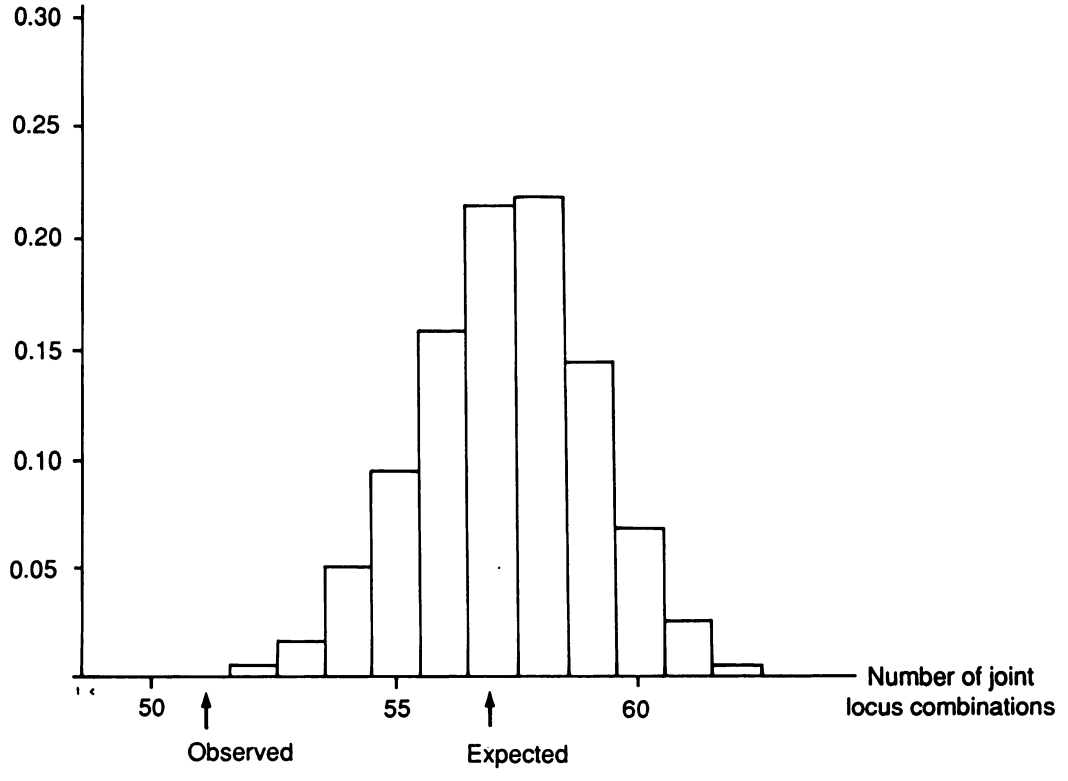

Figure 2. The expected number of joint-locus combinations in a sample of *T. brucei* from tsetse flies, compared with the observed number of combinations (51). The distribution of numbers expected was calculated assuming random reassortment of genotypes. From Cibulskis (1988).

Cladistic Analysis of Genotype Diversity

Cibulskis (1988) also used cladistic analysis to determine whether genetic exchange is likely to be important in *T. brucei* populations. In a population of asexual organisms, all new genotypes arise by mutation, and it is possible to calculate the minimum number of mutational steps, M, required to generate all observed genotypes in a sample. This shortest mutational pathway is called a Wagner network. For sexual organisms, mutation is only required to generate new alleles. With all the necessary alleles, all genotypes can arise by recombination. The shortest mutational pathway for sexual organisms will have length S (< M).

The difference R = M – S can be summarized as 'recurrent mutations'. Recurrent mutations do not give rise to new alleles, but to new combinations of alleles, and therefore serve the same function as recombination. In fact, since a recurrence of any mutation is thought to be unlikely, most of R could be ascribed to recombination. Although there are caveats (Cibulskis, 1988), large R suggests that some of the diversity of genotypes in a field sample has arisen by genetic exchange.

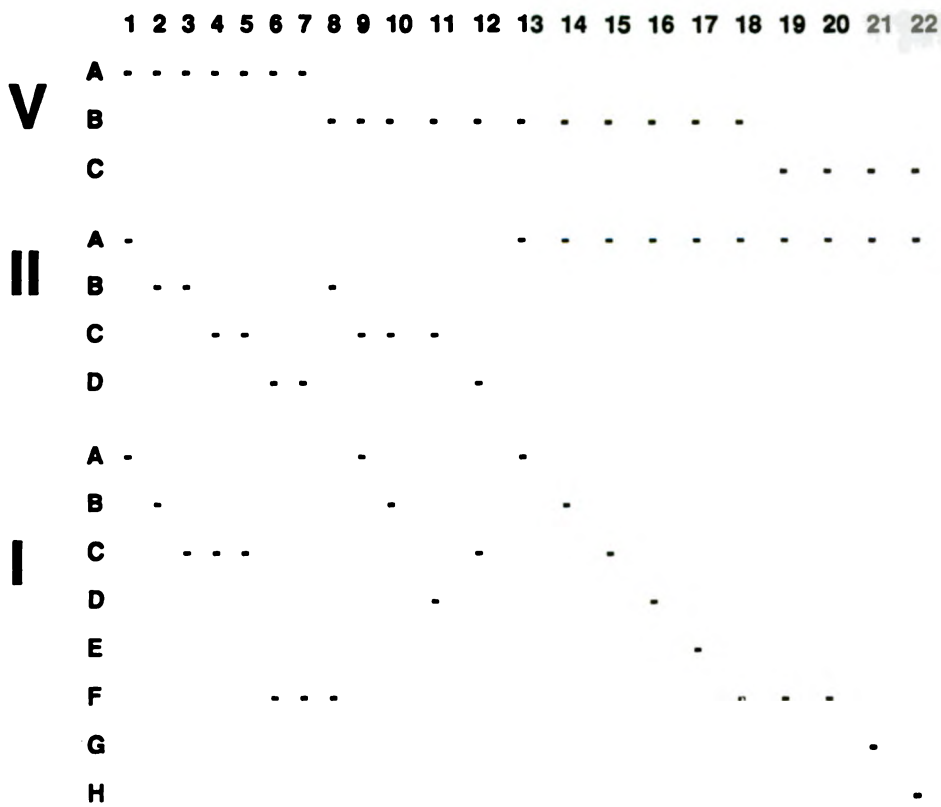

Figure 3. The distribution of chromosome size variants I, II and V in a sample of 22 strains of *L. infantum*. Modified from Blaineau *et al.* (1992).

In one sample of *T. brucei* from the Lambwe Valley, isoenzyme analysis identified 28 genotypes using five loci, giving $R \geq 22$. Cibulskis (1988) points out that this is almost three times greater than observed for the parthenogenetic weevil *Polyhydrosus mollis,* for which all variation is attributed to mutation. It is also comparable to R for one parthenogenetic population of the cladoceran *Daphnia pulex,* where sexual reproduction in recent history is thought to be responsible for some of the genotypic diversity. In sum, observed variation in the Lambwe Valley population of *T. brucei* cannot easily be explained by mutation alone.

RATE OF GENETIC EXCHANGE AND THE EVOLUTION OF DRUG RESISTANCE: THE EXAMPLE OF *PLASMODIUM.*

Given two novel antimalarial drugs, are they best used as a mixture or in sequence? The problem was first investigated quantitatively by Curtis and Otoo (1986), and the answer depends on the frequency of genetic exchange in the population in question.

Curtis and Otoo used a simple deterministic model employing the usual beanbag genetics (Haldane, 1964). In every generation of sexual reproduction, gametes were allowed to meet at random. They assumed either that recombination never occurred, or that recombination always occurred. With no recombination, there was no difference between the two strategies. With recombination, mixtures effectively delayed resistance, particularly when genes for resistance to both drugs were initially rare, and when drugs were available to a small fraction of people.

In fact, parasites probably do not live in randomly mating populations, and it is worth asking whether the Curtis and Otoo result holds when they are assumed not to do so. A significant feature of vector-borne parasites is that they live as semi-isolated sub-populations, confined to their vertebrate and invertebrate hosts. How great the isolation is will depend on the frequency with which a mosquito taking a bloodmeal acquires parasites of different genotypes, which depends in turn on the frequency with which vertebrates are superinfected, and the duration of the infection arising from each inoculation. It also depends on how many zygotes (oocysts) a mosquito can support. As isolation becomes greater, linkage disequilibrium is generated by random genetic drift between the subpopulations, and departures from Hardy-Weinberg equilibrium arise because inbreeding leads to a deficiency of heterozygotes.

To represent this patchiness, we need a model which keeps track of the *Plasmodium* population in each individual human and mosquito host. To capture the effect of genetic drift, the model needs to be stochastic. Figure 4 is a summary flow diagram of such a model; more details are given in Dye (1991).

We first compare the sensitivity of the two principal measures of the frequency of genetic exchange. In Figure 5, from left to right, linkage disequilibrium and the coefficient of inbreeding change as parasite subpopulations become increasingly isolated. In case A, mosquitoes are unrealistically permitted to acquire parasites more or less at random from the entire parasite population. Each infected mosquito is assumed to support just one oocyst, and each of the two necessary gametes (called gametocytes in the human host) is selected first by choosing an infectious person at random, and then by randomly selecting

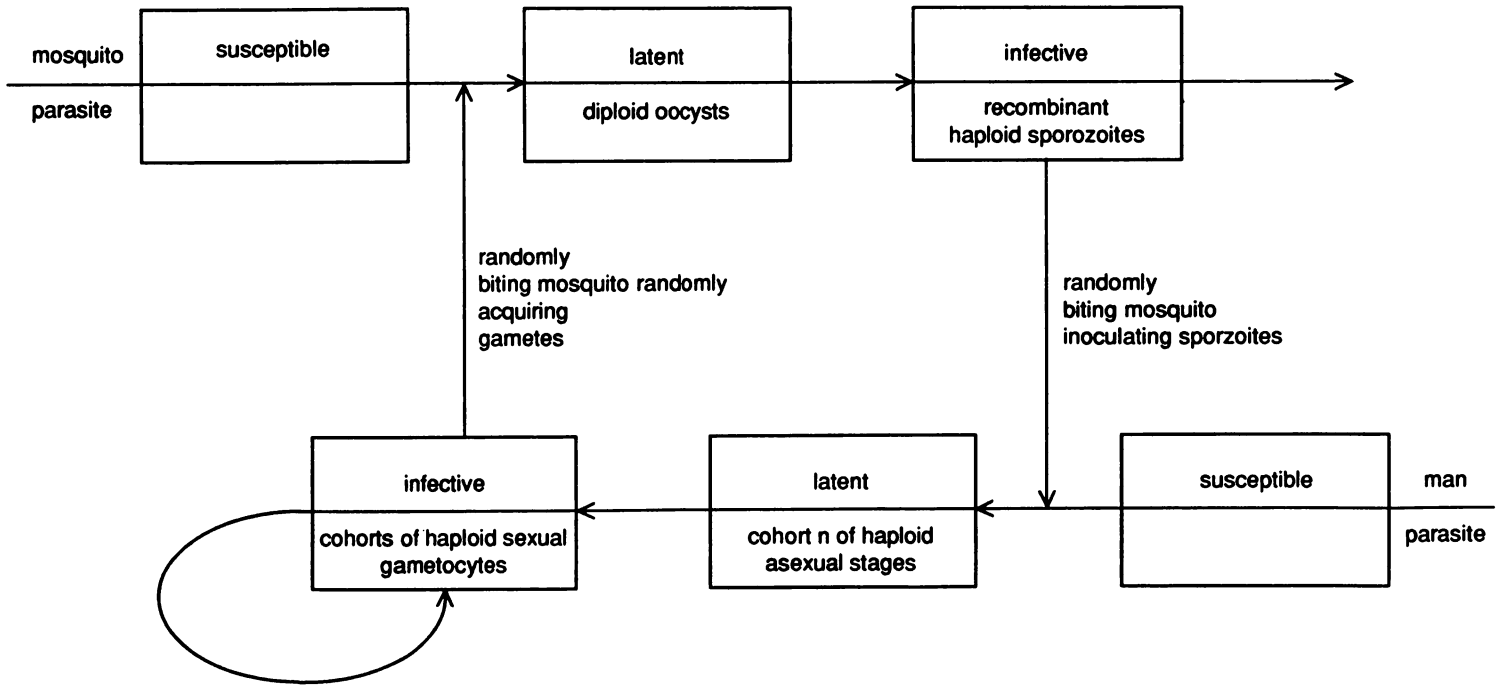

Figure 4. Flow chart summarizing a simple, stochastic model of *P. falciparum*.

one genotype from that person's subpopulation. In case B, pairs of mating gametes come from the same randomly chosen infectious host, and the frequency distribution of oocysts in mosquitoes is overdispersed with mode 1, precisely as found by Collins *et al.* (1984) in The Gambia. Case C is a hybrid of A and B: gametes come from the same infectious person, and each mosquito supports just one oocyst.

The results in Figure 5 need to be interpreted comparatively. A model of this kind cannot say how much linkage disequilibrium and inbreeding we expect to see in natural populations. A model to do this would have to take account of both the immune response to different genotypes, and of the mutation rate. The present model deals with neither, so conclusions about the relative magnitude of F and D will be much more robust.

Recall that when mating is random, Hardy-Weinberg equilibrium is reached in just one generation. By contrast, linkage disequilibrium is only halved after each generation of random mating (Maynard Smith, 1989). So, under the simplest assumptions, we may expect a joint-locus analysis to be more revealing than a single-locus analysis. Figure 5 actually suggests that, in this structured population, F is a more sensitive measure of non-random mating than D. The medians are higher and variation around them smaller.

Now imagine resistance to two drugs D_A and D_B to be conferred by two genes a and b, which are initially rare and at unlinked loci. Individuals taking drug D_A are susceptible to parasites of genotype a, but parasites of genotype a are killed before they can be transmitted. Likewise, only parasites of genotype b can survive treatment with D_B. Those taking the mixture $D_A + D_B$ are susceptible only to parasites of genotype ab. Alongside F and D in Figure 5, is plotted t_{50}, the median time for genotype a (and hence b, approximately) to rise to a frequency of 0.5 from an initially low value. More outcrossing effectively breaks up linkage disequilibrium and, in consequence, significantly delays the build-up of resistance to a mixture. Qualitatively, this is the same result as obtained by Curtis and Otoo (1986). It is just one example of the importance of knowing how much genetic exchange (inbreeding or outcrossing) effectively occurs in parasite populations.

CONCLUSIONS

Three methods have been used to investigate genetic exchange using samples collected from the field: (1) single-locus analysis (looking for Hardy-Weinberg equilibrium); (2) joint-locus analysis (looking for linkage equilibrium; and (3) cladistic analysis of genotype diversity.

For *T. brucei,* (3) suggests that the diversity of genotypes in field samples cannot easily be explained without postulating that genetic exchange occurs at least some of the time, but (2) indicates that recombination is nowhere near frequent enough to break down all linkage disequilibrium. These results are consistent with those from laboratory experiments, which have demonstrated directly that genetic exchange does occur, but not obligately. The results of (1) are so far inconclusive because of small sample sizes. By contrast, natural populations of *T. cruzi* show extreme linkage disequilibrium, indicating that genetic exchange occurs very infrequently, if at all.

Method (3) has not been applied to *Leishmania.* Applying (2) to a single population of *L. infantum* shows conformity with linkage equilibrium, but again this is suspect with small

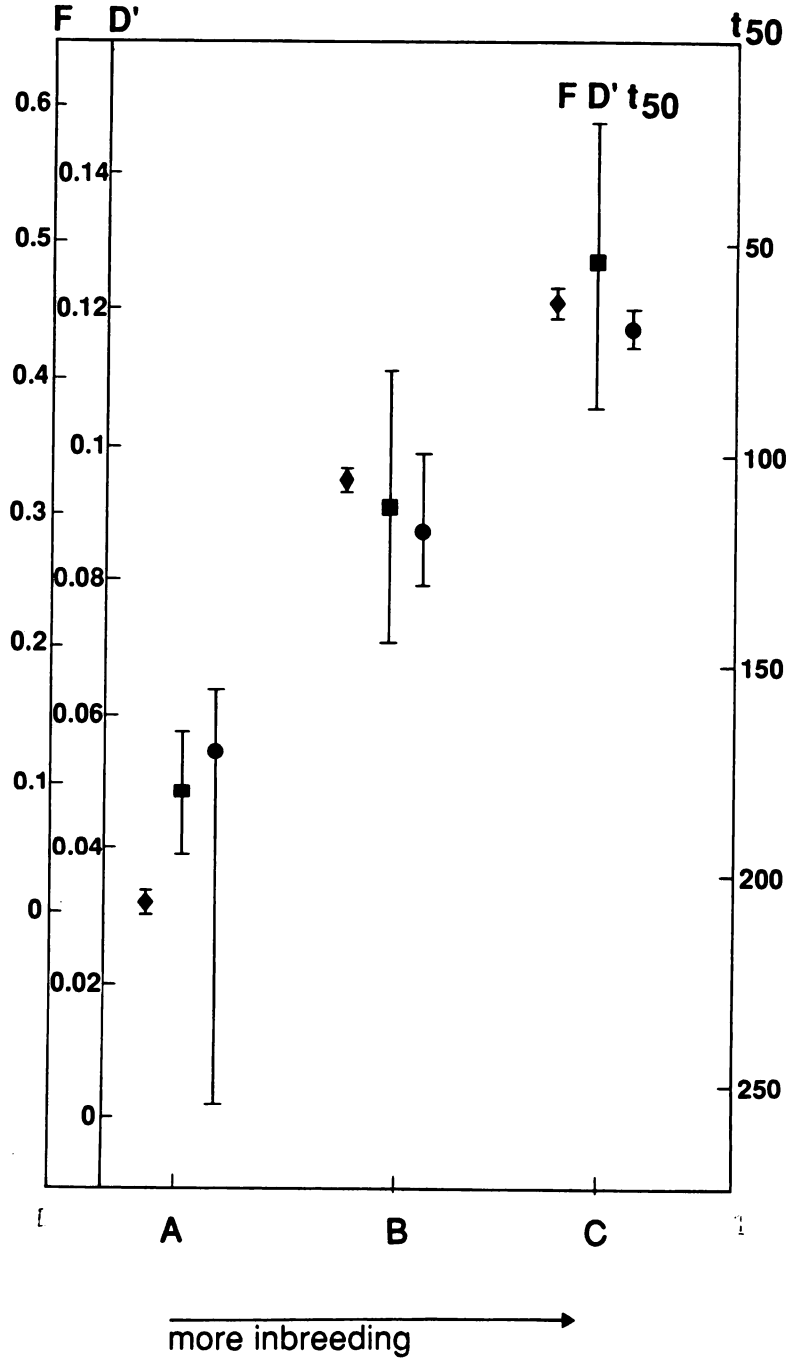

Figure 5. Linkage disequilibrium (D', squares), coefficient of inbreeding (F, diamonds), and the time taken for the frequency of resistance genes to reach 0.5 (t_{50}, circles), under different regimes of mating (see text). All points are medians, with 95% c.i.

samples. Careful segregation analyses (1) have not been carried out on large samples, but genotypes (particularly heterozygotes) missing from some samples suggest large departures from Hardy-Weinberg equilibrium. In sum, genetic exchange may well be more frequent among *T. brucei* than among *T. cruzi* or *Leishmania,* but it is too early to say so definitively.

The frequency of genetic exchange affects, among other things, the rate of evolution of resistance to drug mixtures. In general, resistance to a mixture is expected to arise more quickly when effective recombination occurs less frequently, that is, when there is more inbreeding or infrequent sexual reproduction.

All the quantitative methods of analysis described in this paper suggest that future field work should concentrate on collecting large samples from single populations. Only with more data of this kind will we be able to accurately assess the frequency and consequences of genetic exchange in natural populations of parasitic protozoa.

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Modelling anthelmintic resistance

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ABSTRACT

Anthelmintic resistance in nematode parasites of sheep and goats is now a firmly established phenomenon, particularly in warm temperate or tropical regions of the world. The evolution of resistance by nematodes to broad-spectrum anthelmintics is of particular concern, as there are currently only three different chemical families of such drugs. Resistance to two of these is already ubiquitous, with several reports of resistance to the third. With no new broad-spectrum anthelmintics on the horizon, it is vital that we learn to manage resistance and conserve susceptibility to these valuable drugs for longer than we have in the past.

A crucial factor in the evolution of anthelmintic resistance in a worm population is the extent to which survivors of drug treatment contribute their genes to future generations of worms. This contribution is influenced by frequency and timing of anthelmintic treatment, drug efficacy, life-expectancy and fecundity of adult worms, and current and future rates of larval intake. Larval intake, in turn, is determined by previous egg deposition, grazing management and weather. The acquired immune response of the host is of central importance through its effects on worm establishment, fecundity and death rate, and provides density-dependent regulation of worm populations.

Physical experimentation with such a complex system is difficult, expensive and above all time-consuming. Further, results are usually specific to the site and type of animal management used in the experiment. Because of the large number of climatic, biological and management variables that interact to determine the size and genetic constitution of a worm population, we believe that the only practical way to explore the system is with the aid of a model. Examples of the types of models used to investigate anthelmintic resistance are presented. The CSIRO model UNIVERSE is used to examine the consequences of some common management practices for evolution of anthelmintic resistance in the ruminant parasite *Trichostrongylus colubriformis*.

THE PROBLEM

Anthelmintic resistance in nematode parasites of sheep, goats and horses is now a firmly established phenomenon, particularly in warm temperate or tropical regions of the world (Waller and Prichard, 1986). The evolution of resistance by nematodes to broad-spectrum anthelmintics is of particular concern, as there are currently only three different chemical families of such drugs. Resistance to two of these, the benzimidazoles and levamisole/morantel is already common in sheep and goat nematodes, with several reports of resistance to the third, the avermectins (Prichard, 1990). With no new broad-spectrum anthelmintic families readily apparent, and only these three developed in the last 30 years, it is vital

that we manage resistance and conserve susceptibility to these drugs for longer than we have in the past.

A critical factor in the evolution of anthelmintic resistance in a worm population is the extent to which survivors of drug treatment contribute their genes to future generations of worms. Given that their initial domination of the post-treatment worm burden is progressively diminished by establishment of less-selected larvae from pasture (Martin, 1990), this contribution is influenced by frequency and timing of anthelmintic treatment, drug efficacy, life-expectancy and fecundity of adult worms, and current and future rates of larval intake. Larval intake, in turn, is determined by previous egg deposition, grazing management and weather. The acquired immune response of the host (Wakelin, 1987) is of central importance through its effects on worm establishment, fecundity and death, and provides density-dependent regulation of worm populations.

Physical experimentation with, or even monitoring of, such a complex system is technically difficult, expensive and, above all, time-consuming. Current technology is unable to detect anthelmintic resistance by any means short of full "treat-and-slaughter" trials until resistant worms comprise 25–50% of the worm population (Martin *et al.*, 1989; E. Lacey, unpublished data). Further, results are usually specific to the particular site and type of animal management observed. This is borne out by the common observation, in Australia at least, that the extent and type of broad-spectrum anthelmintic resistance varies widely among sheep farms within the same climatic region, sometimes reflecting varying patterns of previous anthelmintic use and flock management (Edwards *et al.*, 1986), and sometimes not (Waller *et al.*, 1988). Because of the large number of climatic, biological and management variables that interact to determine the size and genetic constitution of a worm population, we believe that the only practical way to explore the system of grazing hosts, helminth parasites and anthelmintics is with the aid of a mathematical model.

MODELS OF ANTHELMINTIC RESISTANCE

Although the use of biocides for control of both arthropods and helminths has led to similar problems of biocide resistance, Smith (1990) has suggested that the theoretical and modelling literature on the evolution of pesticide resistance in arthropods may not be directly applicable to superficially similar questions about anthelmintic resistance. There are three differences between arthropod and helminth populations that account for this difficulty of extrapolation. First, helminth generations are overlapping rather than discrete and contemporary generations can vary widely with respect to frequencies of resistance genes. Secondly, treatment of hosts with anthelmintics exposes only the parasitic stages of the helminth population to the selective effects of treatment; the numerous free-living stages on pasture escape selection at that time (Martin, 1985). Finally, nematodes are much more immobile than arthropods and rely overwhelmingly on their hosts for transport. Nevertheless, an examination of resistance management tactics used by entomologists reveals little that is conceptually new to helminthologists; the most effective tactic so far has been the reduction of pesticide use (Roush, 1990).

There have been few attempts to model the evolution of anthelmintic resistance. Models range in complexity from simple spreadsheet models used to examine components of the

entire system, such as the combined effects of drug efficacy and the size of the free-living fraction of the worm population examined by Martin (1990), to the complex simulation models described by Gettinby *et al.* (1989) and Barnes and Dobson (1990). Models of the genetics of anthelmintic resistance have been described by Anderson (1983) and Dobson *et al.* (1987). These sub-system models are valuable in exploring and understanding their restricted domains, but recommendations to manage resistance need to be tested either within the wider context of more comprehensive whole-system models, or in the field.

To capture the essential features of the interactions between parasitic and free-living populations, and the selective effects of anthelmintic treatment, an anthelmintic resistance model must at least include components that model the dynamics of both populations and the genetics of resistance. Details of model structure and examples of predictions have been published for three models of the evolution of anthelmintic resistance in nematode parasites of grazing animals. Gettinby *et al.* (1989) and Gettinby (1989; 1990) described a site-specific simulation model for *Ostertagia circumcincta* in sheep, which allowed examination of the parasite population dynamics and evolution of anthelmintic resistance in ewe-lamb management systems under various combinations of anthelmintic treatment and grazing management. While climatic factors influenced development and survival of free-living stages, and thus permitted an assessment of the effect of climate (Gettinby, 1990), the model in its current form recycles one year's meteorological data from its site annually for the duration of its simulation. The best strategies for minimizing selection of the worm population were associated with reduced frequencies of treatment and moving lambs to clean pastures at weaning (Gettinby *et al.*, 1989; Gettinby, 1990).

The model of Barnes and Dobson (1990) allows any sheep management system involving up to five flocks grazing up to five paddocks to be simulated. Based on extensive data on the population dynamics of the parasitic stages of *Trichostrongylus colubriformis*, the parasitic stage sub-model (Dobson *et al.*, 1990) is combined with a pasture sub-model which uses daily temperature, rainfall and evaporation to predict the population dynamics of free-living stages (Barnes *et al.*, 1988). Although site-specific, in the sense that it may be used to simulate results for a specific flock or farm, the model can be used to simulate results at any site for which daily climatic data are available. It has been used successfully for this purpose for several sites in Australia and Fiji.

Smith (1990) has presented the most general model of the evolution of anthelmintic resistance. It is neither site nor species-specific, and was used to examine the consequences of several drug management strategies for the evolution of single-gene resistance to one or two drugs. Population dynamics of the free-living and parasitic stages were modelled as a pair of linked differential equations for each worm genotype. These equations were solved numerically so that integration could be stopped when required for the application of anthelmintic treatment. Acquired immunity was not modelled explicitly, but worm populations were regulated by density-dependent mortality of parasitic stages. There was no provision for climate to influence development or survival of the free-living stages, nor for variations in grazing management involving pasture rotations. Effects of stocking rate could be examined indirectly by altering the parameter describing net infection rate.

While these restrictions may be limitations in any attempt to use Smith's model in a site- or species-specific manner (a purpose for which it was not intended), the strength of this approach lies in its generality and mathematical economy. The biologically complex

models of Gettinby *et al.* (1989) and Barnes and Dobson (1990) necessarily contain a profusion of equations and parameters, many of which have been questioned by the authors themselves, let alone by critics. In contrast, Smith's formulation of the population dynamics of the parasitic and free-living stages reduces the system to its bare but probably sufficient essentials; the only disputation that seems possible might be over the values chosen for the seven parameters. The model's major use will be in exploration of the interplay between nematode population dynamics, genetics and anthelmintic management: It will also be valuable as an aid in ranking of anthelmintic management options for conserving drug susceptibility. Comparison of predictions from Smith's model and those of the two simulation models could also be fruitful. Similar outcomes would indicate consequences arising mainly from population dynamics and the genetics of anthelmintic resistance. Different outcomes may point to grazing management or climatic factors being primarily responsible.

IMPLICATIONS OF MODELS FOR RESISTANCE MANAGEMENT

Management recommendations aimed at slowing the rate of selection of nematode parasites for anthelmintic resistance were urgently required before any of the three models described here were available to assist in their formulation. Of necessity, these recommendations (Prichard *et al.*, 1980; Anon., 1989; Coles and Roush, 1992) were made largely by analogy with measures adopted to manage pesticide resistance in arthropods or on the basis of limited experimental evidence with nematode parasites. Recommendations made in one or more of these papers that are particularly amenable to investigation with models are (i) reduce frequency of treatment, (ii) avoid under-dosing, (iii) slow (annual) rotation of anthelmintic groups and (iv) integration of anthelmintic treatment and grazing management.

Of these recommendations, only (i) has been universally accepted as being almost self-evident, and has been confirmed by several experimental studies (e.g. Barton, 1983; Martin *et al.*, 1984; Waller *et al.*, 1989) and by models (Gettinby *et al.*, 1989; Smith, 1990). Concern has been expressed about the implications of "dose-and-move" strategies for worm control on the grounds that they may select more powerfully for resistance (Le Jambre, 1978; Martin, 1985; Coles and Roush, 1992). This concern arises from consideration of a conceptual model—resistant worms surviving anthelmintic treatment and contaminating a clean pasture with eggs. When the conceptual model is broadened to allow for the reduction in treatment frequency permitted by such strategies, the concentrations of larvae on clean, or safe, pastures being small but not zero, and an anthelmintic efficacy of less than 100% against susceptible worms, the outcome seems less clear-cut. Moving sheep to lightly contaminated pastures after treatment did not select more rapidly for resistance than the same number of treatments given to set-stocked sheep in an experiment over five years reported by Waller *et al.* (1989). Simulations with computer models by Gettinby (1990) and Barnes and Dobson (1990) also indicated that dose and move strategies can provide more effective control with a lesser risk of anthelmintic resistance than set-stocking of ewes and lambs. We should point out, however, that results of such simulations are sensitive to assumptions made about the initial contamination of the safe pasture and the efficacy of the anthelmintic against susceptible and heterozygous resistant

worm genotypes. The latter point was discussed extensively by Smith (1990) in relation to his model and is considered below in relation to treatment efficacy.

There has been less general agreement among parasitologists about the effectiveness of recommendations concerning the avoidance of under-dosing (administration of less than the manufacturer's recommended dose) and slow (annual) rotation between unrelated anthelmintic groups. Reservations about these recommendations have been largely confined to verbal arguments after conference dinners, probably because of the paucity of evidence on either side. Waller *et al.* (1989) reported results with *Haemonchus contortus*, but not *T. colubriformis*, that slightly favoured slow rotation over rapid (every treatment) alternation between thiabendazole and ivermectin when treatments were given eight times per year. No such difference was evident when sheep were treated three times per year.

Sequential, Rotational and Mixture Strategies

Smith (1990) examined resistance management strategies assuming resistance to any drug was determined by a single major gene with two alleles conferring resistance or susceptibility. He found little difference between sequential and rotational strategies using two drugs in their effects on evolution of resistance to both drugs. Simultaneous administration of both drugs was much more effective in delaying resistance, but only if the frequency of resistance genes to either drug was initially low.

In the following simulations with the Barnes and Dobson (1990) model, we examine the consequences of these strategies for preserving susceptibility to two unrelated anthelmintics. The sheep production system used as the basis of all simulations was one in which 100 12-week-old lambs were purchased each year on 1 January and grazed the same 10 ha paddock for 11 months. They were then notionally sold and replaced with a new flock of lambs one month later. All lambs were given anthelmintic treatment on 1 January, 1 March and 1 May, in accordance with current strategic control recommendations for the Armidale District. Daily climatic data from the CSIRO Pastoral Research Laboratory at Armidale for the years 1959 to 1968 were used in all simulations, which were run for a 10-year period. It was assumed that the sheep entered the simulation on 1 January each year with a mean burden of 5,000 *T. colubriformis*, and that on their farm of origin no anthelmintic resistance had developed. Resistance to each drug was assumed to be controlled by a single locus on different chromosomes. For both loci there were two alleles, S denoting susceptibility and R denoting resistance. All worm genotypes were regarded as equally fit in the absence of anthelmintic treatment. Initial frequency of R alleles for both drugs was set at 0.001 on the simulated paddock, unless otherwise stated, and on the farm of origin. Efficacies of both drugs against their SS, RS and RR worm genotypes were set at 0.99, 0.5 and 0.1 respectively, i.e. resistance was assumed to be incompletely dominant. Individual lambs were regarded as dead when their adult worm burdens exceeded 50,000.

Figure 1 shows simulated mean adult worm burdens, faecal egg counts, infective larvae on pasture and R allele frequency in infective larvae on pasture over the 10-year period. Two treatment regimes are compared; no treatment, or treatment three times per year with the same drug on all occasions as outlined above. Over the ten years involving 1,000

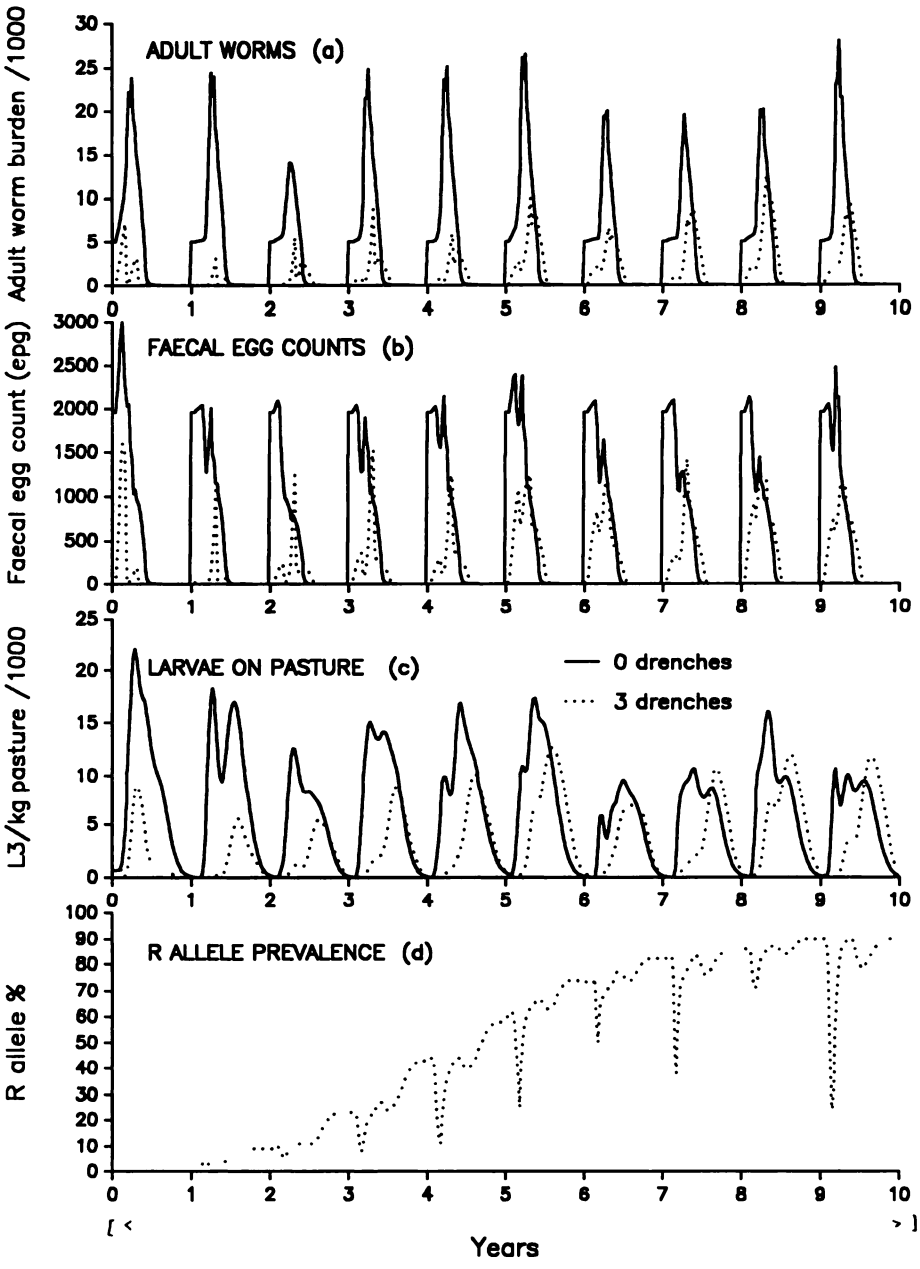

Figure 1. Results of simulation over ten years of the effect of no treatment, or three treatments per year on (a) adult worm burdens, (b) faecal egg counts, (c) concentration of infective larvae on pasture and (d) prevalence of alleles for resistance in the population of larvae on pasture. Initial frequency of R alleles was 0.1%, efficacy of the anthelmintic was 0.99, 0.5 and 0.1 against SS, RS and RR worm genotypes respectively. Sheep management is described in the text.

simulated lambs under the nil treatment regime, the model predicted 208 deaths from trichostrongylosis, compared with one death in the 3-drench program. Under this program, with the same drug used every year, R allele frequency in larvae on pasture approached 90% by the end of year 10 (Figure 1 (d)). The sharp decline and recovery in R allele prevalence near the beginning of each year was caused by the influx of SS genotypes in the 1% of susceptible worms surviving the 1 January treatment.

Figure 2 shows the effect on R allele prevalence of three different ways of managing two unrelated drugs in the same 3-drench program shown in Figure 1. In Figure 2 (a), drug 1 was used for the three treatments for the first five years, then drug 2 was used solely for the second five years. Resistance to drug 1 increased exactly as for the drug in Figure 1 (d) for five years, then declined when use of this drug was suspended, under the influence of the annual influx of S alleles carried in by the replacement lambs. In the second five-year period, resistance to drug 2 appeared, and by the end of the ten-year simulation the prevalence of R alleles to both drugs was in the 30% to 60% range.

When the two drugs were rotated annually (i.e. drug 1 used in year 1, drug 2 in year 2 and so on), R allele prevalence to both drugs after ten years was in the range of 40% to 60% as shown in Figure 2 (b). Differences between drugs 1 and 2 in trajectories of R allele prevalence were due to effects of different weather in the years the two drugs were used. The predictions of this model are therefore consistent with the predictions of Smith's (1990) model, in that there is no clear advantage of rotational over sequential use of two drugs. In Figure 2 (c), drug 1 was used for the first two treatments each year, while drug 2 was used only for the third treatment each year. Under this fast rotation regime, resistant survivors of drug 1 treatment on days 1 and 60 each year are largely removed by treatment with drug 2 on day 120. Worms surviving drug 1 therefore have, at most, 120 days each year to contaminate pastures, while worms surviving drug 2 have up to 245 days. These differences in relative opportunities to contaminate pasture are reflected in R allele prevalence to the two drugs over the ten years. There was little resistance to either drug for the first seven years and resistance to drug 1 remained low over the whole period. Resistance to drug 2 increased rapidly in the last three years to reach levels similar to those resulting from sequential or slow rotation strategies.

When the three treatments per year consisted of simultaneous administration of drugs 1 and 2, appearance of resistance to either drug was dramatically delayed. In order to show any significant appearance of resistance on the same set of axes used in Figure 2 we had to re-run the simulation with the initial frequency of R alleles set at 0.05, rather than 0.001 as in Figures 1 and 2. Results of a comparison between annual rotation between drugs 1 and 2, and a mixture of the two drugs are shown in Figure 3. Again, the predictions are consistent with those of Smith (1990).

Effect of Anthelmintic Efficacy

Four simulations were run using the same drug over ten years for the 3-drench program described previously. Initial frequency of R alleles was 0.001. Four dose rates of the drug were simulated, with results shown in Figure 4. Dose A gave the same efficacies against the SS, RS and RR genotypes as used in all previous simulations, namely 0.99, 0.5 and

0.1. Dose B simulated a minor reduction in dose rate, which, given the sigmoidal shape of the usual dose-response curve, was assumed to result in efficacies against the SS, RS and RR genotypes of 0.99, 0.1 and 0.1. Efficacies against SS and RR genotypes were thus unchanged, with the only effect of the reduced dose rate being reduced efficacy against heterozygous resistant worms. Dose C simulated an increased dose rate, with efficacies of 0.99, 0.9 and 0.1 against SS, RS and RR worms. Finally, dose D simulated more extreme under-dosing, with an efficacy set of (0.90, 0.1, 0.1), i.e. reduced efficacy against SS genotypes.

Figure 4 shows that in comparison with the default efficacy set (0.99, 0.5, 0.1), mild under-dosing with reduced efficacy against RS worms (dose B) hastened selection for resistance for the first six years of the simulation. The sudden decline in R allele frequencies

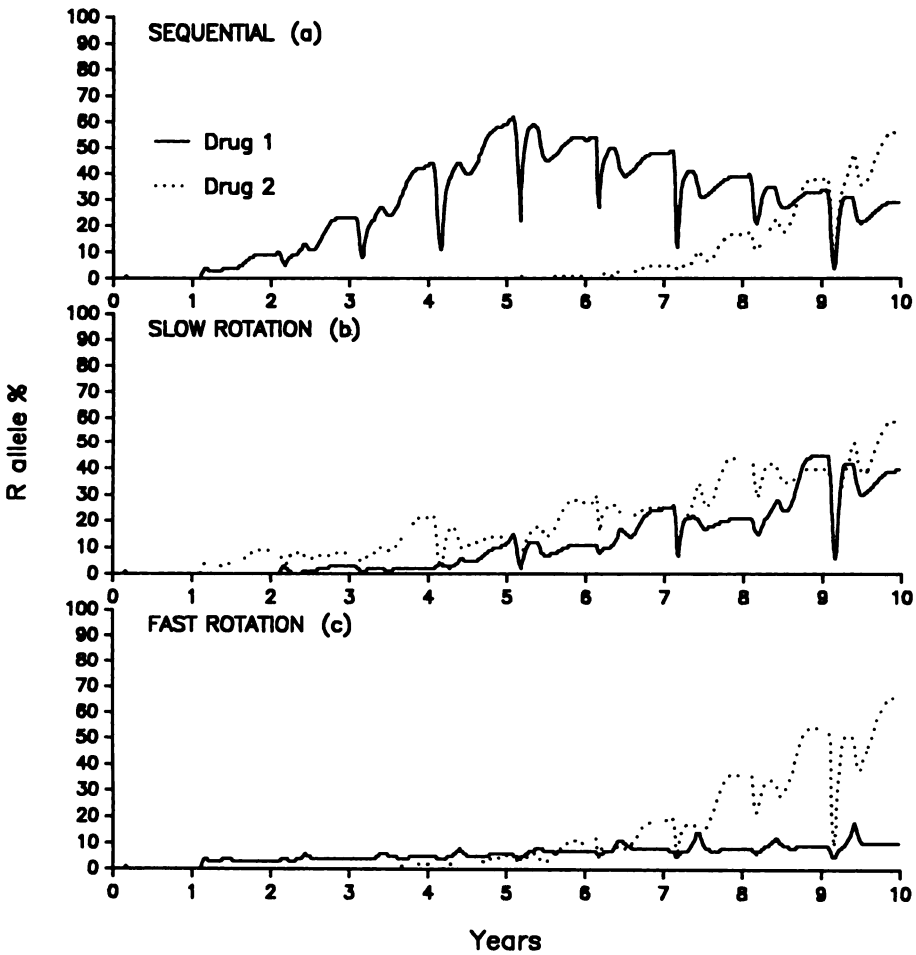

Figure 2. Simulated effects on prevalence of R alleles in infective larvae on pasture of three strategies for managing two unrelated anthelmintics. (a) Drug 1 used exclusively for the first five years, followed by exclusive use of drug 2. (b) Drugs 1 and 2 used in alternate years. (c) Drug 1 used for the first two treatments in each year and drug 2 used for the third treatment in each year. Initial R allele frequency, drug efficacies and sheep management as for Figure 1.

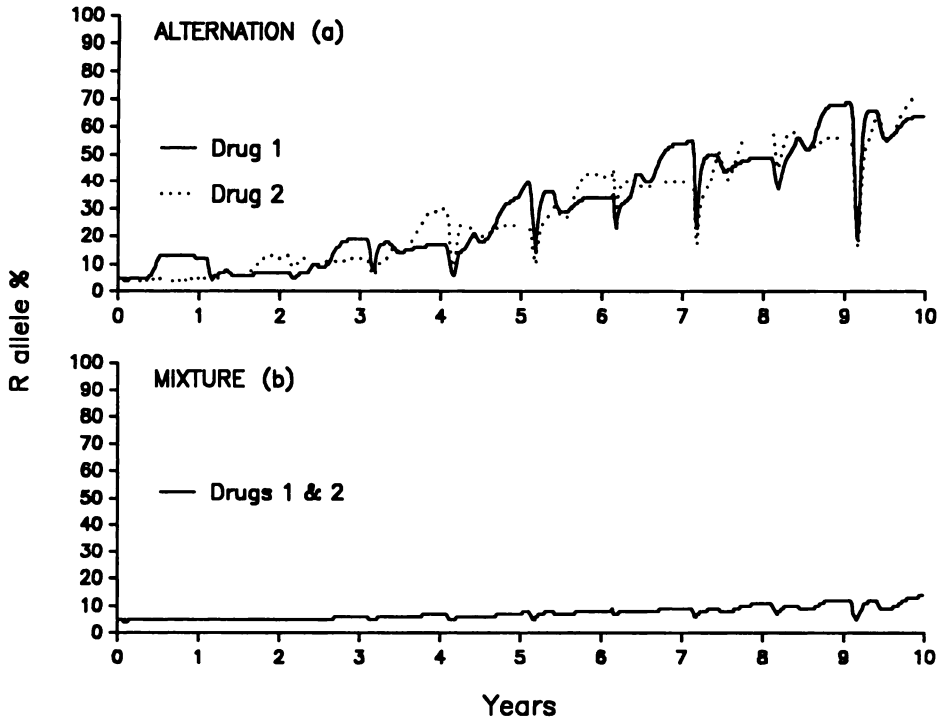

Figure 3. Comparison between effects of (a) annual alternation and (b) simultaneous administration of two unrelated anthelmintics on evolution of resistance. Initial frequency of R alleles 5%, drug efficacies and sheep management as for Figure 1.

in year 6 was produced by unusually small concentrations of larvae on pasture at the beginning of that year. Dose C, representing an increased dose with greater efficacy against RS worms, and dose D, representing gross under-dosing with reduced efficacy against SS worms both resulted in weak selection for resistance compared with dose A. These results, which seem surprising at first, can be explained in terms of gene frequencies among survivors of the four dose rates. Doses A, B and C differed only in their efficacies against RS genotypes, and their apparent effectiveness in selecting for resistance increased from C to A to B, which was inversely related to their efficacies against RS worms. Survivors of dose B included a greater proportion of RS worms (0.9) than did survivors of dose A (0.5), which in turn represented a greater proportion of RS worms than did survivors of dose C (0.1). For dose D, which simulated extreme under-dosing with a reduction in efficacy against SS worms from 0.99 to 0.90, there were now ten times as many SS worms among the survivors, but only five times as many RS worms, when compared with the default dose A. The net effect has therefore been a reduced intensity of selection for resistance.

This biphasic response, with increasing evolution of resistance associated with increasing anthelmintic efficacy against SS genotypes, followed by decreasing resistance with increasing efficacy against RS genotypes was also noted by Smith (1990), and was attributed to dilution of the very small number of RS survivors by incoming larvae from

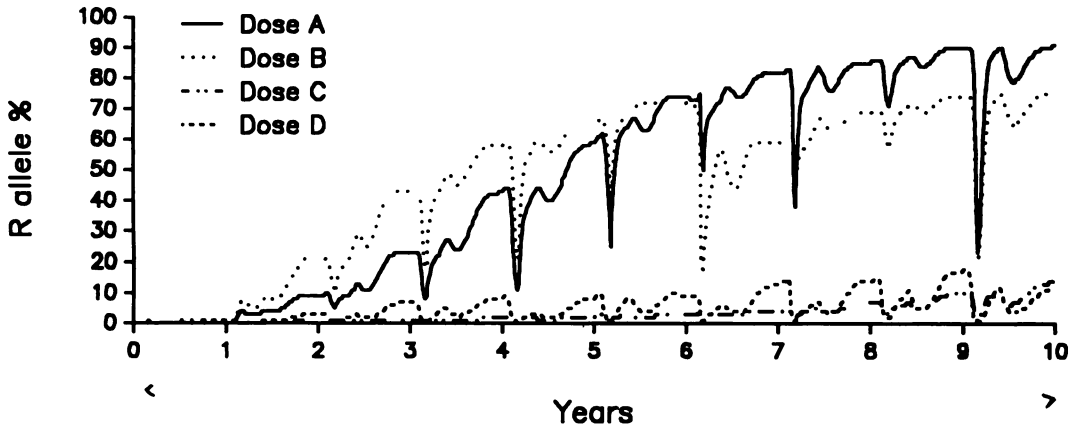

Figure 4. Effects of four dose rates of anthelmintic on evolution of resistance. Initial R allele frequency and sheep management as for Figure 1. Dose A killed 0.99, 0.5 and 0.1 of SS, RS and RR worm genotypes respectively. Dose B killed 0.99, 0.1 and 0.1, dose C killed 0.99, 0.9 and 0.1 and dose D killed 0.9, 0.1 and 0.1 of SS, RS and RR genotypes.

pasture once efficacy against SS worms reached 100%. While dilution effects are important, we believe that the phenomenon is more directly attributable to the effects of differential anthelmintic efficacy against the worm genotypes.

Considering the simplest case, of resistance attributable to variation at a single locus, where R allele frequency is p and S allele frequency is q, $p + q = 1$, and the population in Hardy-Weinberg equilibrium, if:

α is proportion of SS genotype surviving treatment

β is proportion of RS genotype surviving treatment

τ is proportion of RR genotype surviving treatment

then p after treatment as a multiple of p before treatment can be shown to be:

$$\frac{\beta q + \tau p}{\alpha q^2 + 2\beta pq + \tau p^2}$$

This ratio is a measure of the selective effect of the treatment and is tabulated in Table 1 for a range of efficacies against SS and RS worm genotypes. As efficacy against SS increases down the columns of Table 1, so R allele frequency in surviving worms after treatment also increases. As efficacy against RS increases across the rows, R allele frequency after treatment declines, although for the low value of $p = 0.001$ chosen for this example the values in the table are more sensitive to SS efficacy than to RS efficacy.

Spatial Rotations

One of the major differences between arthropods and nematodes that has not been exploited in resistance management strategies is the relative immobility of nematode

Table 1. Ratio of R allele frequency after treatment to R allele frequency before treatment, for a range of treatment efficacies against SS and RS worm genotypes. R allele frequency before treatment was 0.001, efficacy against RR worms was 0.1.

Efficacy against SS (1-α)	Efficacy against RS (1-β)					
	0.000	**0.100**	**0.200**	**0.500**	**0.900**	**0.990**
0.900	9.8	8.9	7.9	5.0	1.0	
0.950	19.3	17.4	15.5	9.8	2.0	
0.980	45.5	41.4	37.1	23.9	5.0	
0.985	58.9	53.7	48.3	31.3	6.6	
0.990	83.5	76.4	69.1	45.6	9.9	1.1
0.995	143.1	132.6	121.4	83.5	19.4	2.2
0.998	250.3	237.2	222.5	167.0	45.9	5.4
0.999	333.6	321.8	308.1	250.5	84.1	10.7

parasites. Barnes and Dobson (1990) noted the possibility of maintaining susceptibility to different anthelmintics in different paddocks of a farm. A simple example is presented in Figure 5, where a farm, or part of a farm, is divided into three paddocks of similar carrying capacity. Using the same notional production system used in previous simulations, purchased weaners were treated with drug 1 on day 1 as they entered paddock 1, drug 2 on day 120 when they were moved to paddock 2, and drug 3 on day 240 when they were moved to paddock 3. To make the management system more commercially realistic, a flock of mature wethers was grazed behind the weaners, in the paddock they had last vacated, so that at any time two-thirds of the area was being grazed and one-third spelled. These wethers were relatively resistant to nematode infection and received no anthelmintic treatment. Simulations over 20 years with Armidale climatic data, an initial frequency of R alleles to each drug of 0.001 and the default anthelmintic efficacy set (0.99, 0.5, 0.1) showed that mild resistance to drug 1 evolved on paddock 1, to drugs 1 and 2 on paddock 2, and to all three drugs on paddock 3. This did not lead to problems with nematode control, as the specific drug used on lambs before entering a specific paddock retained its initial efficacy for the full 20 years of the simulation against worms picked up from the previous paddock. When the same grazing management system was simulated with the three drugs used in annual, rather than spatial rotation, intense resistance to all drugs evolved on all paddocks, with adverse consequences for worm control.

WILL MODELS HELP SOLVE THE PROBLEM?

Given the extremely slow observed rates of reversion to anthelmintic susceptibility once use of an anthelmintic is discontinued (Martin *et al.*, 1988), it is difficult to see how modelling, or indeed any other approach, can help to restore susceptibility in parasites that

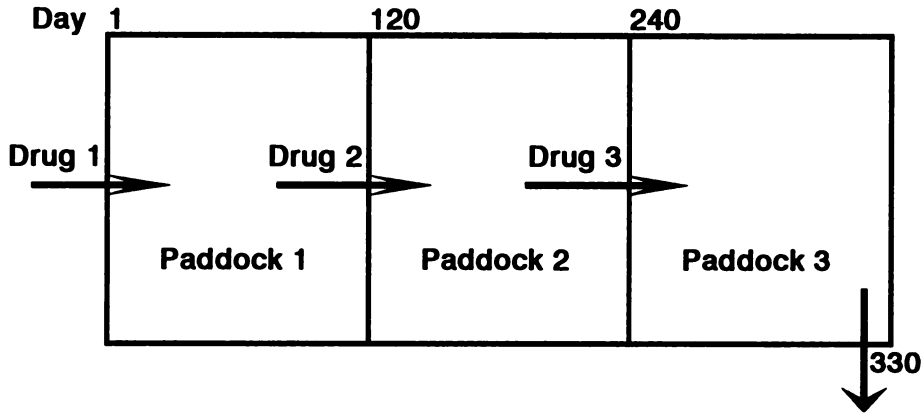

Figure 5. Diagrammatic representation of a simple spatial rotation of three anthelmintics. The three paddocks constitute a whole farm, or part of a farm where susceptible animals are grazed. Drug treatment is only given at times of movement of hosts to new paddocks in the direction shown by the arrows. Larvae on paddock 1 remain susceptible to drugs 2 and 3, and larvae on paddock 2 remain susceptible to drug 3, thus a drug with high efficacy was always available, despite the development of resistance.

have already evolved substantial levels of resistance. Van Wyk and van Schalkwyk (1990) have experimentally overwhelmed resistant *H. contortus* in the field with a laboratory-bred susceptible strain, but the logistics of doing this on thousands of farms for even one nematode species are daunting.

Modelling of anthelmintic resistance enables evaluation of strategies for conserving susceptibility to new or existing drugs. Currently available models indicate that reductions in treatment frequency, particularly when allied with grazing management, judicious choice of dose rates and combinations of unrelated anthelmintics can materially extend the useful life of effective anthelmintics. Spatial rotation of anthelmintic groups among the various paddocks of a farm also shows promise of delivering sustainable anthelmintic control programs. The biological and management flexibility of the Barnes and Dobson (1990) model has also led to its use in preliminary evaluation of non-chemical control technologies such as genetically resistant sheep (Barger, 1989; Windon, 1990), biological control and vaccination. Although models may not solve our current problems of anthelmintic resistance they will certainly help us to avoid exacerbating them, and to avoid repeating our past mistakes with future anthelmintics.

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Session discussion

The issue of drug resistance in several different parasites was discussed and the view was expressed that before modelling the phenotype of drug resistance in trypanosomes, data on the biological basis of the resistance should be obtained. It was suggested that once the mechanism of drug resistance was identified, models could be developed considering whether the resistance was due to point mutation, gene amplification or deletion. If resistance was due to epigenetic events, the approach to modelling would be different.

It was pointed out, however, that the model presented on anthelmintic resistance was based on the assumption that there is a genetic basis for resistance, since there are no biological data available on the mechanisms of resistance to anthelmintics.

The question was raised as to whether anthelmintic resistance models could be applied to study acaricide resistance in ticks. It was the opinion of several of the modellers that they may not be directly applicable as the current anthelmintic models are based on the assumption that there is a single locus for anthelmintic resistance in nematodes and that this may not be true for acaricide resistance in ticks. It was pointed out that although there had not been many studies of the genetic mechanisms of anthelmintic resistance, it had been found that there are generally one or a small number of genes involved, hence the provision for up to three genes controlling resistance in the model presented.

The issue of whether the model presented allowed for reversion of anthelmintic resistance was brought up. In replying, the modeller stressed that there was little information on this subject and the opinion was expressed that reversal of resistance appears to be very slow.

The anthelmintic resistance model will be mainly used by field veterinarians and extension workers, not by farmers, because a knowledge of parasitology is required to operate it.

Subsequent to a discussion on the role of models in analysing drug kinetics in trypanosomes, it was pointed out that a modelling approach can be useful, even if the model is wrong, in order to dissect and understand the processes involved.

As a result of a question regarding necessary vaccine coverage levels to achieve population immunity, a general discussion developed about the level of immunological protection or chemotherapeutic cover required for different diseases and epidemiological situations. It was emphasized that one must consider the levels of benefits considered to be essential or acceptable and pointed out that control strategies that did not provide 100% protection were by no means useless.

EFFECT OF DISEASE CONTROL PROGRAMS

Modelling vector-borne disease epidemiology and the impact of control programs

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It is anticipated that improved control of tick-borne diseases and trypanosomiasis will be made possible through the development of recombinant antigen vaccines, enhanced genetic resistance and other technologies, the application of which will need to be responsive to the varying demands for disease control in different regions and production systems of Africa. The demand for control of tick-borne diseases and trypanosomiasis varies considerably in the continent depending on their distribution, the level of losses caused by them and on the economic outputs of the livestock production systems in which they occur. Given these variations, and the impracticality of gathering data representative of all possible conditions, the use of models offers a strategic method of quantifying the productivity effects of disease, permitting socioeconomic impact evaluations of disease control measures to be performed.

The level of losses caused by tick-borne diseases is affected by numerous factors, particularly host susceptibility, the dose of infection (dependent partly on tick infestation levels) and the age at which infection occurs. Thus in cattle production systems with indigenous East Africa zebu in the Lake Victoria Basin, where at least two generations of the vector *Rhipicephalus appendiculatus* occur each year, where all instars may occur on livestock at the same time, where the majority of animals are carriers of *Theileria parva* at low levels of parasitaemia, and where virtually all animals are infected as calves and become immune before reaching three months of age, little or no clinical East Coast fever (ECF) occurs as a result of *T. parva* infection. In contrast, in areas where *R. appendiculatus* infestations are strictly seasonal and only one generation occurs each year, where clinical cases (with higher piroplasm parasitaemias) occur, and where all animals are not infected as calves, even indigenous cattle may experience outbreaks of clinical theileriosis. In both areas, the introduction of Taurine cattle and their crosses increases the incidence of clinical disease.

The situation in which little or no losses occur due to clinical disease, termed endemic stability, only exists for *T. parva* infections in a few areas of eastern Africa, but for babesiosis and anaplasmosis it is much more widespread in the continent. The situation for heartwater is not well documented, but widespread endemic stability is suspected in many areas. The artificial induction of endemic stability through the use of vaccines will provide the most effective and sustainable option for tick-borne disease control in the future. The determination and quantification of the variables contributing to endemic stability and instability are therefore crucial in identifying target populations for tick-borne disease control programs, and assessing their impact.

The most important quantitative indicators of the presence of endemic stability and instability to tick-borne diseases are incidence of infection, incidence of disease, case-morbidity and case-fatality rates in young cattle. Stability is characterized by a high incidence of infection in this age group, but low levels of disease. Instability is generally characterized by a low and variable incidence of infection, and high incidence of disease. Regrettably, disease incidence, case-morbidity and case-fatality rates are rarely measured accurately under field conditions, and estimates of disease occurrence generally rely on antibody prevalence rates as a surrogate for incidence of infection (and for prevalence of immunity). Thus, it is important to determine whether it is possible to quantify the relationship between antibody prevalence and these indicators under different conditions and with different tick-borne disease combinations, and to determine the relationship between these indicators and productivity effects (in terms of milk, meat, traction and manure). An important component of this process is to determine the relationship between antibody prevalence, as measured by current and developing serological tests, and population immunity in the sampled cohort to the spectrum of tick-borne disease antigens they are likely to encounter.

A first step in modelling this dynamic process has been made for *T. parva* by Medley, Perry and Young (described earlier in the workshop), who simulated endemic stability and tested the effect of tick abundance and carrier state prevalence on its maintenance. However, in order to assess the validity of such models on a broader scale, they require testing in other endemically stable and unstable states. Regrettably, due to the intensive nature and high cost of prospective studies needed to validate such models, few data sets exist.

Eventually, it is hoped that such studies will lead to the development of user-friendly models that assess the efficacy of tick-borne disease control options for given herds, districts or regions, determine their effects on livestock productivity and assess their economic impact. With tsetse-transmitted trypanosomiasis, similar models are required, but due to differences in the immune mechanisms involved, it may not be possible to base them on the concepts of stability and instability. Furthermore, it is anticipated that the mechanisms involved are more complex and less predictable.

Needs for modelling socioeconomic and environmental impacts of livestock disease control

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One of the research areas of ILRAD requiring modelling is the assessment and prediction of the probable economic, socio-cultural and environmental impacts of alternative control technologies for trypanosomiasis and tick-borne diseases in different production systems and agro-ecological zones in Africa and elsewhere. The application of new technologies to control these and other diseases may cause unforeseen economic, social and environmental consequences for segments of the human population. These effects, which may be better understood and projected through modelling, can include changes in livestock and human population densities, changes in patterns of land use accompanied by environmental changes, increased conflict over resources, disruptions of local social patterns, and increases in income and wealth disparities within the population. Moreover, other constraints within the overall livestock management system may serve to suppress potential benefits resulting from improved livestock disease control. These can include the existence of other diseases, poor animal nutrition, labour scarcity and lack of access to supporting services such as animal health delivery system, artificial insemination or credit for improvement of livestock. Modelling can help in identifying such constraints, or in evaluating their effects on potential impacts of alternative control strategies. *Ex-ante* assessment and prediction of the impacts of disease control through modelling can also help in avoiding possible deleterious effects in the application of new control technologies. It also provides useful information to farmers, governments and donors in order to assist them in planning better (strategic and systematic) disease control programs. In addition, such information can help in prioritizing the allocation of resources to disease research.

There are not always sufficient data, in content or quality, for assessing and predicting socioeconomic and environmental impacts of disease control. In many instances, the gathering of such data by field studies is unrealistic and costly, particularly given the large and varying geographic areas involved. A more cost-effective approach is to develop models using available field and secondary data that are supplemented by expert opinion, and then use such models for desk-top experimentation and extrapolation in *ex-ante* analyses. An additional advantage of models is that once developed and verified they provide a standardized method of data analysis which can be extended to users in different areas and countries, particularly if the models are developed and packaged in user-friendly computer software.

ILRAD has developed and applied spreadsheet models for assessing annual economic losses due to East Coast fever and the financial and economic impacts of its control by immunization at farm and above farm level. These models are being adapted and improved, in collaboration with the AP Consultants of the UK, for the analysis of trypanosomiasis control. In collaboration with Texas A & M University, a whole farm simulation model has been developed and applied for assessing and projecting farm level financial and nutritional impacts of ECF immunization under small-holder dairy production systems; a similar simulation analysis approach can be extended to trypanosomiasis control in sedentary livestock production systems. ILRAD's current modelling efforts, however, tend to emphasize micro-financial/economic aspects of livestock disease control effects. Macro-economic sectoral, trade and policy issues are not fully incorporated. In addition, linkages of financial/economic relationships to physical (ecological), biological (epidemiological) and socio-cultural (welfare) factors of livestock production systems are weak. Future modelling needs will require integration of micro- and macro-economic factors involved in livestock disease control with ecological, epidemiological and socio-cultural factors for more comprehensive assessments of the impacts of alternative control strategies. Such integrated model(s) will, however, be complex, and technical, data procurement problems and modelling mechanisms required are issues that must be addressed. The model(s) developed would ideally be suitable for application to different livestock production systems in different environments.

The relationship between infections, diseases and their economic effects

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ABSTRACT

For very few disease agents does infection automatically mean that clinical disease will be expressed. In epidemiological terms, for most diseases there are various risk factors which influence whether an animal which is exposed to an agent becomes infected and generates a host response, and a second (frequently overlapping) set of risk factors which determine whether the infection proceeds sooner or later to clinical disease. Risk factors vary widely in their nature, ranging from the genotype of both host and agent, through the nutritional state of the host at the time, to short-term weather conditions at the location where the animals are kept. Traditionally these have been classified into host, agent and environment factors, but I would argue that this is in some respects too static a view of the initiation of disease, and that we should look for a more dynamic way of viewing the interactions. Computer modelling is one way of representing epidemiological interaction realistically and dynamically. While some risk factors are common to many different infectious diseases, others are very specific to a single disease, and it is unwise to extrapolate from knowledge of relevant risk factors for one disease to conclude that the same factors are necessarily important in other superficially similar diseases.

Many diseases exert their effect on productivity most strongly in the early subclinical stages of infection, when there may not necessarily be any evidence of disease, while in others the effects grow as the clinical severity rises. Overall, the scale of effects of disease on productive capacity of animals is surprisingly large, much greater than would occur by depriving the animal of an apparently similar quantity of nutrients. While it is not completely clear why particular diseases have the effect they do on animal productivity, a reasonable overview of why disease so adversely affects productivity has emerged in recent years, and this is presented in this paper. The main effect of disease appears to be on protein metabolism. In addition, some diseases reduce efficiency of utilization of various micronutrients, such as Cu or P. The primary metabolic effects of disease then produce a cascade of secondary effects which can be measured in economic terms. In developing a model of a disease process as a basis for decision-making, consideration must be given to accurately representing these various effects for the particular disease.

THE RELATIONSHIP BETWEEN INFECTION AND DISEASE

For very few disease agents does infection automatically mean that clinical disease will be expressed. In epidemiological terms, for most diseases there are various risk factors which influence whether an animal which is exposed to an agent becomes infected and generates a host response, and a second (frequently overlapping) set of risk factors which determine whether the infection proceeds sooner or later to clinical disease. Risk factors vary widely

in their nature, ranging from the genotype of both host and agent, through the nutritional state of the host at the time, to short-term weather conditions at the location where the animals are kept.

While some risk factors are common to many different infectious diseases, others are very specific to a single disease, and it is unwise to extrapolate from knowledge of relevant risk factors for one disease to conclude that the same factors are necessarily important in other superficially similar diseases. Risk factors can be identified and the scale of their impact (measured variously as relative risk and attributable risk) assessed through appropriate epidemiological study designs using observational data.

Such studies do not always discriminate between infection and disease, including animals as 'cases of disease' only if they show recognizable clinical signs. However for the types of diseases we are currently seeking to control, it is increasingly necessary to look separately at the process of initial infection, at the process of conversion from infection to disease, and at the ways in which animal productivity is affected at each stage. Similarly for non-infectious diseases, there will tend to be a process of lesion production and a subsequent process of development of clinical disease.

A SYSTEMS VIEW OF INTERACTIONS AMONG FACTORS TO PRODUCE DISEASE

Traditionally the influences on disease occurrence have been classified into host, agent and environment factors, but we would argue that this is in some respects too static a view of the initiation of disease, and that we should look for a more dynamic way of viewing the interactions. System diagrams aim to represent through boxes and arrows the pathways by which components of a total biological system interact to create the various processes which drive the system through time, and generate whatever 'outcome' variables are decided by the observer to be of interest. In the case of diseases, the outcome variable may be the prevalence or incidence of the disease as determined by the underlying transmission processes, or it may be the (altered) productivity of the animals when affected by the disease. Through the system diagram approach, not only can host, agent and environment be treated as multifactorial influences in themselves (for example breaking environment into multiple climate variables, shelter, nutrient availability etc.), but the nature of the interactions within and among the various factors can be represented precisely, using arrows only between those factors for which an interaction is thought to occur.

Figure 1 shows one such example of a system diagram developed in order to represent the causal processes and the way in which they are believed to interact to produce a particular disease. The example chosen is one form of lameness in dairy cattle, known as white line disease. This can cause lameness directly but can also lead on to sole abscess which causes even more severe lameness. The figure is based upon research at both herd and individual animal level, and draws together factors which can operate at each of these levels to influence whether or not an individual animal develops a subclinical lesion or becomes clinically lame, and whether the herd has a high or low incidence of clinical lameness. This particular disease is non-infectious, but such representations are even easier to formulate for infectious diseases where the interactions tend to follow more standard patterns.

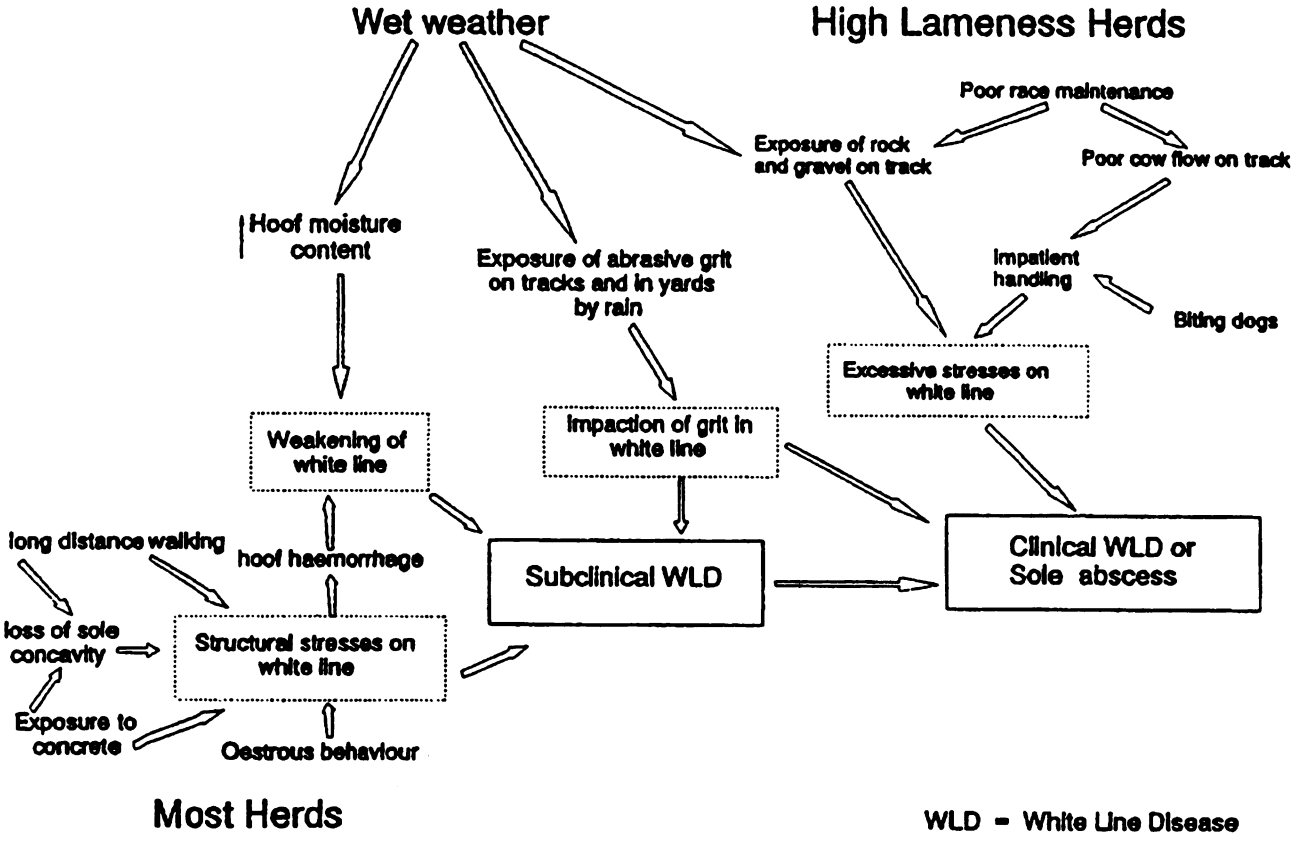

Figure 1. A path diagram for white line lesions that shows likely causal links between risk factors that predispose to both subclinical and clinical disease.

Such a system diagram is helpful in presenting an understanding of how factors influence disease processes, but it is still static, in that it does not provide any way of analysing and understanding the dynamics of the disease process over time or its spatial spread for diseases which show spatial patterns of occurrence. Computer modelling takes the process a major step further forward and is the most effective way of representing epidemiological interactions realistically and dynamically. Typically nowadays a computer model is designed by first formulating a system diagram, plus sub-diagrams exploring in more detail each specific facet of the disease processes and then programing a computer to mimic the processes and progress the total system forward through time.

In other papers presented at this workshop, techniques of modelling are considered for different types of disease. However if modelling of parasitic diseases is to include representing their economic effects, then it is necessary to formulate an adequate representation of this part of the disease process to complement the epidemiological part of the total model. This paper therefore concentrates on how disease agents affect productivity of animals and how this should be included in a computer model.

MECHANISMS BY WHICH DISEASE MAY ALTER ANIMAL PRODUCTIVITY

Figure 2 summarizes the various pathways through which disease can adversely affect the productivity of a livestock herd. In the case of infectious and parasitic diseases the underlying principle is that a disease agent is in constant competition with its host for access to nutrient supplies. The agent is successful if it can divert for its own use and reproduction, nutrients which the animal would otherwise have used for growth and production. The agent must therefore have some adverse effects on the host if it is to survive and multiply. Non-infectious diseases cannot be understood in the same simple way, but do frequently represent a change in ecological balance, in which the flow of nutrients and toxins (copper deficiency, facial eczema, etc.) or of controlling signals (hypocalcaemia, ketosis, etc.) through the agricultural ecosystem is distorted by human or environmental interventions of some type. Some of the same principles therefore apply.

The purpose of Figure 2 is to summarize all the possible direct and indirect mechanisms through which a disease can influence the productive efficiency of livestock. Not all diseases will have all of the effects, but in representing economic effects in a model it is necessary to consider all possibilities and select for inclusion those which appear to be relevant. Each of the mechanisms will be discussed individually and then consideration will be given to how they should be combined to evaluate the effect of disease on profitability.

EFFECTS ON INGESTION

Many diseases alter feed intake in affected animals. In almost all cases intake is reduced (Hawkins and Morris, 1978), but rarely it may be increased (Dargie, 1973). Diseases which cause pain during prehension (contagious ecthyma of sheep) or mechanical difficulty (actinobacillosis of the tongue in cattle) will reduce intake temporarily. Diseases which affect locomotor ability or reduce appetite due to a fever or similar discomfort will also

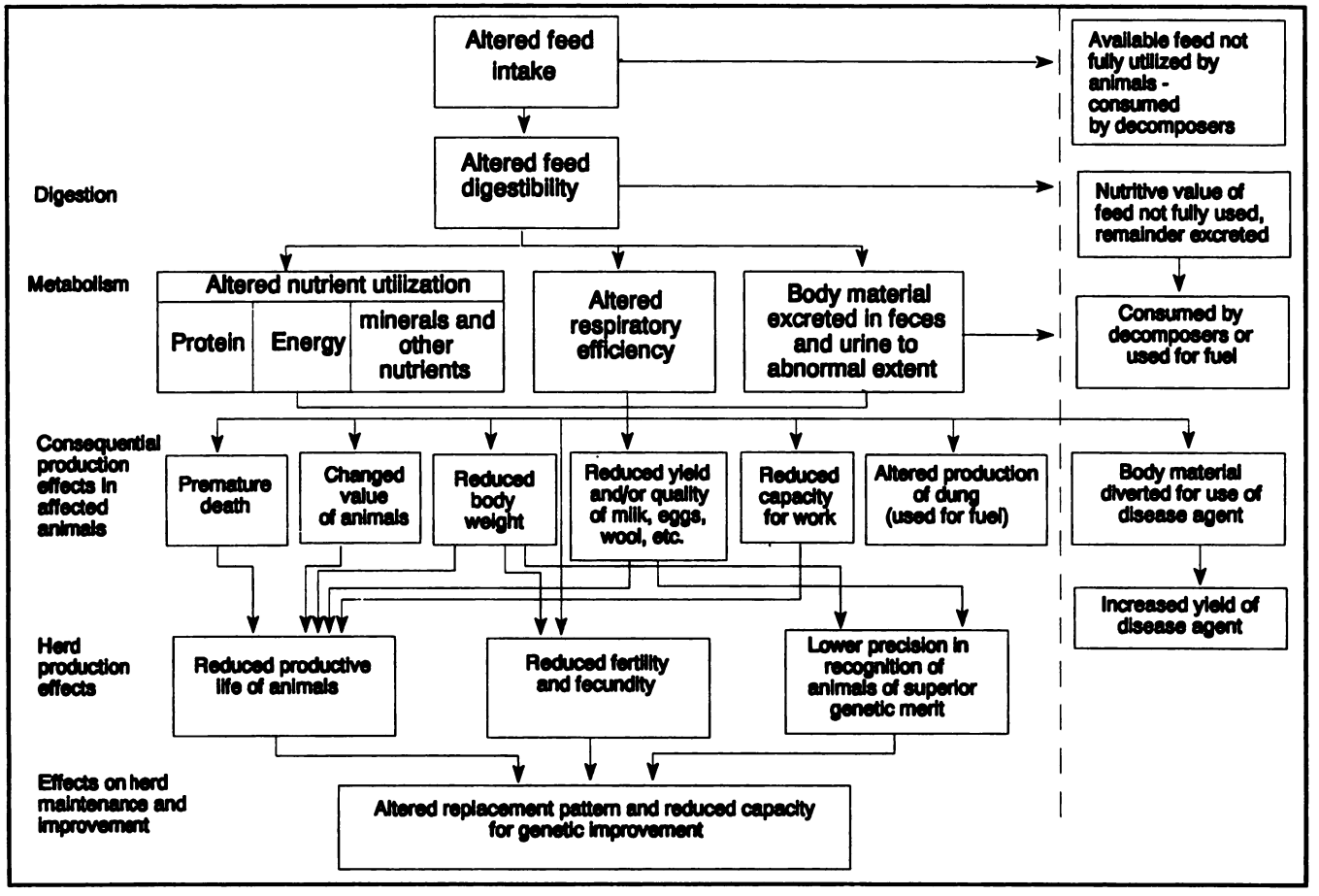

Figure 2. The various ways in which disease may affect the productive value of animals in a herd or flock.

lower intake. However many diseases appear to reduce intake in subtle ways which may not be recognized unless careful measurements are made. These effects have been documented most carefully for parasitic diseases (Larbier *et al.*, 1974), although in some cases intake has been reduced only in more severe forms of the disease (Hawkins and Morris, 1978). Depression of feed intake can also occur in non-infectious diseases such as nutritional deficiencies (Scott *et al.*, 1980).

It is intriguing that feed intake should be commonly depressed by disease when other evidence shows clearly that feed requirements are increased by many of the same diseases, since productivity falls under the influence of the disease. From the limited studies which have been conducted to resolve this apparent paradox, it would appear that it results from disturbances in body homeostatic mechanisms of the host. Symons and Hennessy (1981) have found that choleocytokinin levels rise as appetite falls in *Trichostrongylus colubriformis* infestations, and return to normal in line with appetite when the infestation is terminated. In the same disease, corticosteroid levels rise and thyroxine levels fall in response to the parasite, while insulin levels fall apparently in response to reduced intake rather than directly due to the parasite (Prichard *et al.*, 1974; Hennessy and Prichard, 1981). The disease agent may also in some cases produce a toxic substance which depresses intake directly (Seebeck *et al.*, 1971). It is important to differentiate between diseases which merely depress feed intake and those which lower the efficiency of feed conversion—with or without any effect on feed intake. Seebeck *et al.* (1971) called the effect on intake the *anorectic effect* and that on feed conversion efficiency the *specific effect.* The specific effect is the more serious of the two, since lower production is achieved from the same feed intake and efficiency of the production process is adversely affected, whereas the anorectic effect reduces both intake and output without altering the efficiency of production. This differentiation is an important consideration in studies of animals which consume purchased feed, such as pigs. It is less important in grazing ruminants, for which feed production is closer to being a fixed cost.

EFFECTS OF DISEASE ON FEED DIGESTIBILITY

Disease agents do not normally seem to affect feed digestibility, even in the case of diseases which undoubtedly alter the morphology and physiological function of the gastrointestinal tract (Parkins *et al.*, 1973; Reveron *et al.*, 1974). Barker (1974) found that abnormal mucosa was not necessarily linked to poor growth, and it seems that changes in the mucosal surface itself are not responsible for the change in feed conversion efficiency which results from parasitism and other diseases, but rather the physiological processes that occur after absorption. Similar findings have been obtained with parasites such as *Fasciola hepatica* which do not cause mucosal changes (Hawkins and Morris, 1978). One of the few reports of a reduction in feed digestibility for ruminants was for magnesium deficiency in dairy cows (Wilson, 1980). However the situation may be different in monogastric animals, since two studies of the effects of internal parasites in pigs both showed reductions in feed digestibility (Hale and Stewart, 1979; Hale *et al.*, 1981).

It nevertheless seems likely that, at least in ruminants, adverse effects of disease on productivity which cannot be explained by reduction in feed intake can reasonably be

attributed to lower feed conversion efficiency; although as Symons (1969) points out, digestibility trials are a crude method of assessing changes in digestive function. It is also clear that the nature and extent of pathological changes in the body cannot be used as any direct guide to the severity of effects of a disease on productivity.

EFFECTS OF DISEASE ON PHYSIOLOGICAL PROCESSES

Diseases can modify many different physiological processes, such as nutrient metabolism, respiration and excretion. Most of the available data relate to parasitic diseases and the evidence from these studies suggests that the fundamental effect is on protein metabolism.

Steel (1974) and Symons and Steel (1978) have reviewed the metabolic consequences of gastrointestinal parasitism, with particular reference to sheep. They conclude that helminth disease causes a series of metabolic changes to occur in the animal, the primary impact of which is on protein metabolism. The effects, however, carry through to the metabolism of other nutrients. The result is to produce a syndrome analogous to undernutrition.

In gastrointestinal nematode infestations, plasma is lost into the digestive tract at the attachment sites of the parasites, and haemoglobin is also removed by blood-sucking parasites. Much of this protein is digested and reabsorbed lower in the tract, but the host uses energy and protein to replenish the mucosa and plasma proteins which have been depleted. This places demands on the liver and increases its nutrient utilization. There is increased excretion of nitrogen as urea in urine, demonstrating that recycling of the nutrients is not completely efficient in maintaining nitrogen balance, even though considerable energy costs are incurred by the host for increased protein synthesis.

Animals tend under these circumstances to run down their pool of plasma proteins because production in the liver cannot keep pace with the loss, even though the synthesis rate is unusually high. Adjustments are made to other nitrogen-using processes of lower priority, notably synthesis of wool protein and muscle protein. In sheep, sulphur-containing proteins are put in especially short supply by *Trichostrongylus colubriformis* infestation, demand cannot be met, and wool production shows an exceptionally large fall.

If feed intake is reduced either due to the parasite or to a low plane of nutrition, protein intake may fall below the level required to maintain an adequate serum protein pool. Bown *et al.* (1986) have shown that direct post-ruminal infusion of casein in sheep receiving daily doses of larvae of *Trichostrongylus colubriformis* increased nitrogen retention five-fold, and supported the argument as outlined above that the primary defect is one of protein loss and an anabolic cost of tissue regeneration. Infusion of glucose in amounts isocaloric with the casein only doubled nitrogen retention, showing that energy supplementation was not as beneficial as protein replacement.

A contrasting example to *Trichostrongylus colubriformis* is the cattle tick *Boophilus microplus,* which sucks blood much like some internal parasites, but differs in that the animal cannot recover any of the nutrient content of the blood in this case. The effects of ticks on host metabolism have been studied by Seebeck *et al.* (1971), O'Kelly *et al.* (1971) and Springell *et al.* (1971). Haemoglobin and plasma albumin fell, whereas globulin rose. Thus the animal was able to synthesize increased supplies of globulins, but could not

maintain levels of the other two blood constituents. This was attributed in part to a disturbance of protein metabolism, but the injection of a toxin by the tick was also hypothesized. To further emphasize the tenuous link between the pathology of a disease and its effects on productive processes, O'Kelly and Kennedy (1981) found that ticks adversely affected function in the gastrointestinal tract and reduced organic matter digestibility. It is difficult to explain why this should be so when such effects are not common for parasites directly affecting the tract.

Although these are the two most fully studied diseases, evidence for other diseases in a variety of species confirms the central importance of the derangement of protein metabolism in the disease process. There is also impairment of energy metabolism, but this appears to be largely secondary to the alterations in protein metabolism, and is a result primarily of the energy costs of tissue regeneration.

Mineral and micronutrient metabolic flows are also altered by parasitic diseases, which are the only ones to have been studied. There is reduced retention of ingested calcium and phosphorus in growing sheep infested with *Trichostrongylus colubriformis* or *Ostertagia circumcincta* (Symons and Steel, 1978). Consequently, bone growth and skeletal development are impaired, and this can reduce mature body size and capacity to accumulate muscle (Sykes *et al.*, 1977). Cobalt, copper and vitamin status of animals have all been reported to be affected by parasitism (Downey, 1965, 1966a, 1966b) as well.

Since lung disease can adversely affect productivity, another mechanism by which disease might impair physiological function is a reduction in respiratory function. It seems more likely, however, that it is the regenerative process following lung disease which cause the production deficit.

MEASURABLE EFFECTS OF DISEASES ON LIVESTOCK PRODUCTIVITY

The functional derangements described above translate into measurable economic effects in a number of ways, summarized in Figure 2.

Premature Death

This effect is the easiest of all the consequences of disease to measure, and therefore tends to be considerable over-emphasized in comparison with other effects. In economic studies, death losses should be measured as the difference between the potential market value of the animal and its value when dead (which may not be zero), less the costs which would have been incurred in obtaining the market value (such as extra feed and care to market age, marketing costs, etc.).

Changed Value of Animals and Products From Slaughtered Animals

Diseased animals may have lower market value either due to visible lesions or due to indirect changes in appearance or body conformation which make them less attractive to buyers. True market value of final products may be altered due to changes in the ratio of

meat to fat or to bone (Springell *et al.*, 1971; Sykes *et al.*, 1980), or reduced protein content. The value of offals may also be reduced due to pathological changes caused by agents such as *Fasciola hepatica* or *Echinococcus granulosus*. Presence of lesions of a zoonotic disease may render the animal totally unfit for consumption.

Some diseases (such as caseous lymphadenitis in sheep) may render products less attractive to the consumer for aesthetic reasons, and hence may reduce meat consumption. Diseases which affect the skin, such as warble fly infestation or even sheep lice (Britt *et al.*, 1986), may reduce the market value of hides or their value to the user.

Reduced Liveweight Gain

There have been well in excess of 50 published studies on the effect of diseases on weight gain in animals and in general they find that diseased animals gain weight more slowly than equivalent disease-free animals. Notable as an exception is lice infestation in cattle. It has been among the most intensively studied but the evidence shows that differences in weight gain between infested and free animals are modest or negligible, and certainly not enough to yield an economic benefit from treatment. Therefore caution is required in assuming an effect on weight gain of a disease without experimental data to support it.

Reduced Yield and Quality of Products From Live Animals

Yield of products such as milk, wool and eggs may also be reduced by disease, and there have been numerous papers showing the effect of various diseases on wool growth or milk-yield. Quality of the products may also be reduced, as in the case of the changes in milk composition which result from bovine mastitis, and these may or may not be detectable by the consumer. In the first case price will fall and the livestock producer will suffer; in the second case, the consumer will suffer the loss. For example, parasitic disease can reduce the market value of wool per kg, as well as the quantity produced (Morris *et al.*, 1977); but the structural characteristics of the wool may also be altered in ways which reduce its value to the manufacturer but cannot be detected in the normal marketing process (Johnstone *et al.*, 1976). It has also been shown that parasitic disease can affect the taste of meat (Garriz *et al.*, 1987).

Reduced Capacity for Work

Worldwide, the single most important use of animals is as a source of traction. The second largest (after dung) productive energy output of animals in developing countries is for work, and products considered as of central importance in developed countries are seen as bi-products under those conditions (Odend'hal, 1972). There have been no published reports directly measuring the effects of diseases on capacity for work, but field evidence is that diseases can severely curtail rice paddy preparation and other tasks for which

animals are essential, so this effect can be very important and should be considered in developing countries.

Altered Production of Dung for Fuel and Fertilizer

In Asia and Africa cattle dung is a vital source of cooking fuel and in much of the developing world it is an important fertilizer. Diseases which cause high death rates in cattle will also indirectly influence human nutrition by reducing dung supplies.

Altered Feed Conversion Efficiency

As discussed earlier, it appears that disease primarily affects animal productivity by altering the metabolic processes for protein and other nutrients, thereby reducing the feed conversion efficiency of affected animals and producing a number of ramifications which reduce herd productivity. Feed intake may also be reduced, but this is not usually the primary effect.

Feed conversion efficiency is the ultimate measure of the influence of disease on the production process, but its measurement requires accurate measurement of feed intake, and that is only possible under controlled feeding conditions. In grazing systems it is usually reasonable to take changes in productivity as an adequate indication of changes in feed conversion efficiency when comparing diseased and disease-free animals kept under identical conditions.

Intuitively, it seems likely that the rate of decline in productivity would increase as the disease becomes more severe and body functions become more deranged. However, the limited evidence available favours the alternative view that the most dramatic changes occur at low or subclinical levels of disease, and that each additional parasite, for example, has less effect than the one before it (Hawkins and Morris, 1978). This emphasizes the importance of the health management approach in which the focus is on optimizing productive efficiency rather than the clinical approach in which a disease must be detectable to be considered important.

EFFECTS OF DISEASE ON HERD PRODUCTIVITY

The effects of disease flow through from consequences for individual animals to broader ramifications for herd replacement and improvement.

Reduced Productive Life of Animals

Apart from animals which die, all remaining herd members are culled when the manager considers them less potentially productive than the animal which would replace them. This issue has been investigated in detail by Renkema and his co-workers (Renkema and Stelwagen, 1979; Korver and Renkema, 1979; Dijkhuizen *et al.*, 1985a, 1985b). They

showed that in general a substantial economic benefit could be achieved by taking action to extend the herd life of the average dairy cow, principally by reducing the amount of involuntary culling due to health-related causes. This is not limited to disposal specifically because of disease, but also includes culling for low yield or other causes, where the underlying cause is lowered productivity due to disease, but the manager is unaware of this fact.

Less Accurate Genetic Selection

If a disease alters any of the components of productivity which are the subject of genetic selection pressure in the herd (such as milk or wool yield), it will affect the efficiency with which animals of superior genetic merit are identified, especially if the probability of an animal being affected by the disease is unrelated to yield level. Provided susceptibility to the disease and yield level are not correlated, the presence of the disease will confound the genetic selection effort. For example, Johnstone *et al.* (1976) showed that internal parasitism can affect wool production by sheep in ways which distort selection by objective measurement of wool characteristics. Since resistance to internal parasitism cannot be regarded as a heritable trait for practical purposes, genetic selection will be more efficient if effective parasite control is being carried out in the herd.

EFFECTS ON CAPACITY TO MAINTAIN AND IMPROVE HERD

If fewer progeny are born, less animals are available as herd replacements or for sale as market products. Thus not only will livestock sale income be reduced, but management flexibility for herd improvement will be curtailed. It is self-evident that diseases of the reproductive tract in both males and females can substantially reduce the level of reproductive performance, and hence the number of progeny born in the herd.

Less obviously, diseases which adversely affect body metabolism (but do not directly affect the reproductive tract) can also affect the number of progeny born. The mechanisms have not been fully explored, but may well operate through an effect on liveweight and condition, or through indirect means such as the induction of pyrexia at critical stages in the reproductive process. For example, both gastrointestinal parasites (Murray *et al.*, 1971) and liver fluke (Hope Cawdery, 1976) have been shown to affect reproductive performance in ewes. In cattle, bovine leucosis (Schmied *et al.*, 1979; Parchinski, 1979) and ephemeral fever (Theodoris *et al.*, 1973) have been reported to affect reproduction. If reproductive performance is too poor, it may even become impossible to maintain herd size through home-bred replacements, necessitating the purchase of breeding animals with all the additional risks which that entails.

EFFECT OF DISEASE CONTROL MEASURES IN PRODUCTIVITY OF ANIMALS

In evaluating the economic benefit of disease control, it is necessary to consider not only the difference in productivity between diseased and disease-free animals, but also

the changes in productivity which follow elimination of a disease from an affected animal.

This has not been studied for very many diseases, but some examples exist. For instance, bovine mastitis appears to be a disease for which complete regeneration occurs in most animals over the dry period following elimination of an infection (Morris, 1973), although yield remains depressed for the rest of the lactation in which a cure is achieved. Conversely, when infestations with *Fasciola hepatica* are eliminated in growing animals, sheep do not regain their former productivity or feed conversion efficiency, even when the infestation had existed for as little as eight weeks (Hawkins and Morris, 1978). In a study of a nematode parasite, wool growth and liveweight gain responded quite differently to anthelmintic treatment (Coop *et al.*, 1984).

Therefore each disease type must at least in the first instance be considered separately, since the nature and extent of recovery following elimination of a disease is not predictable from general principles. The selection of an economically optimal control strategy will be strongly influenced by this consideration.

EFFECTS OF ANIMAL DISEASE ON HUMAN WELFARE

Effects on Human Nutrition

The major direct effect of animal disease on human well-being is through reducing the supply of high quality protein, such as diseases which reduce the supply of milk for young children. Animal products are also important sources of other nutrients, notably minerals and vitamins, and diseases can both reduce the total supply of animal products and modify the composition of animal products in ways which reduce their nutritional value (Huss-Ashmore and Curry, 1992).

Effects on Community Development

As well as the effects on human nutrition, animal diseases can affect other aspects of community welfare, especially in developing countries. As discussed earlier, the two most important services provided by animals in such circumstances are traction and dung production, and disease may reduce the supply of both of these. Animals are also important sources of products (wool, hair, hides, feathers, fur, etc.) used for clothing, decoration and for manufacture of utensils and other products. A further effect of those animal diseases which are zoonotic is to cause disease in the human as well as the animal population, thus amplifying their impact.

Cultural Significance of Animals

In most communities animals serve functions far beyond the utilitarian roles which are the focus of this paper. While these are not strictly economic in nature, they are vital functions which should be included in any consideration of the significance of animal disease.

EFFECTS OF DISEASE ON ANIMAL WELFARE

In considerations of animal welfare issues, little is said about the importance of ensuring through disease control that animals are in a healthy state—yet this is a vitally important issue in protecting the welfare of managed animals. It deserves more prominent attention in discussions of animal welfare matters.

INCLUSION OF ECONOMIC EFFECTS IN A DISEASE MODEL

The formulation of an economic analysis for parasitic diseases is described by Morris and Meek (1980). Meek and Morris (1981) showed how economic components could be built into a computer model, which could then be used to conduct comprehensive evaluations of alternative parasite control programs.

Provided that the relevant items from Figure 2 are included into the total simulation model by linking them to the appropriate ecological and epidemiological indices within the overall system model, then estimation of the benefits of disease control strategies within the simulation model becomes straightforward, and depends only on the availability of suitable field data on the effects of the disease on various yield measures. If such data are unavailable when the model is formulated, guesstimates can be used initially and sensitivity analysis applied to determine which of the productivity indicators most urgently need field refinement.

Estimation of costs at farm level can usually be done quite simply from information on the unit costs of control measures, since a partial budgeting approach to such economic analyses is almost always adopted at this level.

In regional evaluations it may be necessary to build a complete model of a regional disease control program. However in many cases it is sufficient to run the model for various types of farms and sets of conditions and then to combine these through an electronic spreadsheet in which the regional total effects are calculated, taking into account costs above the farm level and possible supply/demand consequences of disease control programs.

CONCLUSION

In building a computer model of a parasite control issue, economic components can readily be included in the total model formulation, provided that their inclusion is thought through from the start and conforms to current understanding of the ways in which disease influences productivity. In this way a computer model can examine not only the epidemiological consequences of a disease, but also the economic effects at farm and regional or national level which might flow from possible control programs.

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Modelling livestock productivity

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ABSTRACT

What are the main economic issues in modelling cattle disease control? Many diseases reduce the productivity of African livestock production. Among those diseases are several borne by such vectors as ticks and biting flies. While much is known about the biology and control of such diseases, and about the vectors that transmit them, little is known about related economic problems. Economic issues include the expected returns to disease control, production risks and their relations to the returns to disease control, and the incentive problems involved in disease control programs.

This paper examines those economic issues in the following manner. First, an economic model of livestock production is presented which allows analysis of the effects of stock diseases. Second, results from the model are presented under different market structures and levels of disease. Third, attention is given to risk and incentive problems faced by producers which might make them unwilling to adopt apparently promising disease control methods. The fourth and final section is a summary and conclusion.

MODELLING CATTLE PRODUCTION

This section sketches a model of cattle production under conditions representative of the semiarid rangelands of Africa, extending that developed by von Kaufmann *et al.* (1990).

The notation is:

Variables

q = number of animals in the herd
Z = quantity of non-veterinary variable inputs
V = quantity of veterinary inputs
X = long-term average quantity of pasture production
M = long-term average consumption of pasture by cattle
S = a stock of L, Z, V, or X
m = annual consumption of pasture by livestock
x = annual quantity of pasture production
b = number of animals sold annually (physical offtake)
θ = percentage of herd sold annually (offtake rate)
d = economic losses to animal disease
π = profit or net revenue

Parameters

ϕ = rate of natural herd growth
p = price of liveweight
c = market cost of non-veterinary inputs
c_1 = market cost of fixed veterinary inputs
c_2 = market cost of variable veterinary inputs
u = transport costs from domestic to international market
n = an elasticity
Φ = average annual intake of pasture per tropical livestock unit*
α = probability that vector will transmit pathogen to herd
β = probability that an animal will become infected
Γ = morbidity factor (response of animal productivity to disease)
r = real rate of discount

Indices

t = year
i = animal class (e.g., four-year-old males)

Suppressing the subscript 'i' for animal class, the general form of the herd's growth is:

$$(1)\ q_{t+1} = q_t^* (1 + \phi_t - \theta_t)$$

By assumption producers can purchase no stock,† so $\theta \geq 0$, and, by definition, they cannot sell more than they own, so $\theta \leq 1$. The parameter ϕ is obviously ≥ 0, meaning that herd growth has to be non-negative. The profit (or net revenue) function‡ corresponding to equation (1) is:

$$(2)\ \pi_t = P_t\theta_t q_t - cZ_t.$$

Because animals can be sold now or in the future, the income from their sale depends not only on the offtake in the current year, but in all future years as well. This necessitates modifications in equation (2) to maximize the present value of net revenue (NPV) over all years, as follows

$$(3)\ NPV_\pi = \Sigma_t (P_t\theta_t q_t - cZ_t)^* e^{-rt},$$

where 'r' is the real rate of discount.

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* A tropical livestock unit (TLU) is the equivalent of 250 kg animal.

† The justification for this assumption is that uninsurable risks (sometimes called moral hazard) in the market for breeding stock make it too risky to buy animals for anything other than immediate consumption (Binswanger and McIntire, 1987).

‡ Milk production is excluded.

PASTURE PRODUCTION

Pasture and other roughages, such as crop residues and browse, are the principal feed of most African livestock. The model treats pasture as a random variable because feed supply is typically not under the control of the producer. The annual quantity of pasture, where the latter refers to the total of all available roughages, is given by

(4a) $x_t = X + \mu_t$,

where μ_t is the random deviation (mean of 0) from long-term average pasture (X) availability.

The annual consumption of pasture by livestock is

(4b) $m_t = q_t * \Phi$.

In long-run equilibrium, all pasture is consumed by stock (i.e., M = X). Each year producers have to apply rules of offtake from their herds so as to arrive at a herd size feasible with available pasture.* Two offtake rules are discussed in a later section.

MODEL PRICES

Prices of liveweight can be determined in two different market structures. One structure is to allow domestic prices to be determined by world prices and transport costs, as in

(5a) $p_t = P + u$,

where the price in year 't' is always equal to the long-term average world market price (P) plus transport costs (u) from world to domestic markets. This is called the world market structure.†

An alternative structure is to allow domestic prices to be determined generally by herd offtake within certain limits, as in

(5b) $p_t = f(b)$,

where $dp/db < 0$.

The values of p_t are bounded within limits set by producers' behaviour and transport costs. Initially,

(5c) $p_t = (b_{t-1})e^{-n}$,

where $b_{t-1} = q_{t-1} * \theta_{t-1}$, q_{t-1} is the average quantity produced in the previous year, θ_{t-1} is the offtake rate in the previous year, ^{n} (> 0) is the price elasticity of demand for beef, and p_t is the market price in year 't'. The values of p_t from equation (5c) are constrained by:

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* A recent paper allows for feedback between q_t and x_t in which $q_t > Q$ causes $x_{t+1} < x_t$. This is not done in the present model.

† This specification assumes that the country is a net importer of beef; if it were a net exporter, then the equation would be $p_t = P - u$.

(5d) minimum of $p_t = P - u$, and

(5e) maximum of $p_t = P + u$.

Equations (5c) through (5e) say that the domestic market price is determined solely by offtake in the previous year. It is independent of world prices, unless the domestic price falls below $P - u$, or if it rises above $P + u$.

Market prices of inputs (the parameters p, w, c, and r) are assumed to be unaffected by herders' actions and to be constant in real terms over all years.

THE ECONOMIC EFFECTS OF DISEASES

The economic effects of animal disease on livestock productivity depend, in general, on the probability of disease transmission and subsequent infection, the effects of infection on the productivity of individual animals, and the costs and benefits of control measures available to producers. The notation for the disease process is:

τ = the economic loss associated with vector borne disease;
α = the probability of disease transmission to any individual in herd by a vector;
β = the probability of infection of an individual animal in a herd;
Γ = the morbidity of infected animals.

A general representation of the economic loss is:

(6) $\tau = f(\Gamma, V, p, c_1, c_2)$.

In equation (6) the economic loss depends on the physical costs of morbidity in infected animals (parameter Γ), the quantity of veterinary inputs (V), the price of livestock output (p), and the costs of veterinary inputs (fixed, c_1, and variable, c_2). The specification is

(7) $\tau = p((\Gamma(V) - c_1 - c_2 V$.

The loss to the producer caused by disease is the value of productivity losses ($P((\Gamma(V))$ minus the fixed and variable costs of veterinary inputs. Morbidity, Γ, is a function of the probabilities of transmission and of infection, the maximum morbidity (K) relative to the value of the animal, the quantity of variable disease control inputs (V), and the effect of such inputs on morbidity (the parameter 'n') as follows

(7a) $\Gamma = \alpha\beta K(1 - V^{-n})$

Substituting into (7) with (7a) gives

(7b) $\tau = p\alpha\beta K(1 - V^{-n}) - c_1 - c_2 V$.

Given that $K \equiv 1$, that α and β are bounded by 0 and 1, and $V \geq 0$ implies that Γ is also bounded by 0 and 1. Dividing (7b) by p converts τ into the relative loss of output caused by livestock disease, as in

(8) $\tau' = \alpha\beta K(I - V^{-n}) - c_1/p - (c_2/p)V$.

If there are no fixed or variable costs (i.e. $V = c_1 = 0$), then $\tau' = \alpha\beta K$.

Accordingly, if it were certain that the disease would be transmitted and cause infection (i.e. $\alpha = \beta = 1$), then τ' would also be equal to 1.

Substituting τ' into (3) gives

$$(9)\ NPV\pi = \Sigma_t\ [pq_t\ (\theta_t - \tau'_t) - cZ_t]^* e^{-rt}.$$

The probability of transmission, α, varies among herds as some are exposed to areas infested with vectors (for example tick-infested pastures) while others are not exposed. It is expected to be positively correlated with the numbers of animals per unit of land, being low on land with few animals and high on lands with many animals.

The probability of infection, β, does not vary among the individuals in a herd because the animals are assumed to have similar genetic makeups. The random variations between individuals in the herd are further assumed to be unrelated to producers' decisions. The probability that an animal will become infected is then simply the product of the probability that the vector will transmit the disease to an individual times the probability that the affected individual will become infected.

The calculation of equation (9) is presented in Table 2. First, values of α and β are postulated. The parameter 'K' is set to 1 to indicate the maximum loss from morbidity. The marginal effect of variable inputs on morbidity from disease ('n') is specified at both high and low values. The optimal level of veterinary inputs is then calculated from the morbidity function, and profit at that optimal level is calculated from equation (9).

THE EFFECTS OF RISK

African livestock producers obviously face important risks to their herds from many factors. Risks considered here are price, pasture production and disease.

Most producers will have some degree of aversion to risk. The cost of such risk aversion can be understood as the loss of utility caused by the natural variation in revenue from a productive activity; although some producers may prefer such variation, they are not considered here. The calculation of this utility loss is done by modifying the profit function for the herd (equation 3) to express it in terms of utility. The relation between utility and profit (or some measure of income or consumption) is known as a utility function. One common functional form is the logarithmic (Anderson *et al.*, 1977),* as in

$$(10)\ U = \log_e\ (W_0 + \pi) - 0.5\pi^2/(W_0 + \pi)^2 + 0.33\pi^3/(W_0 + \pi)^3$$

where π is the mean, π^2 the variance, and π^3 the skewness of the net present value of profits derived from equation 9. The variable W_0 is the initial wealth of the herd owner, defined as the total value of livestock at the beginning of the model period. Utility (U) in this formulation is always affected positively by mean profit and initial wealth, and always negatively by increasing variance of profits (because $\pi^2 \geq 0$ by definition).

* There are many others. The logarithmic utility function of wealth has the desirable property of lower risk aversion with higher wealth.

Table 1. Initial parameter values used in the model.

Class	Numbers	Weight (kg)
Inputs		
Labour input (L), years/animal	.10	
Non-veterinary inputs (Z), units	1	
Veterinary inputs (V), units	1	
Number of animals	25	
Costs		
Wage (w), $/year	20	
Variable cost of veterinary inputs (c2) , $	.50	
Prices		
Price of livestock output (p) , $/mt	$850	
Discount rate (r)	10%	
Other parameters		
Herd growth rate (ϕ)	20%	
Elasticity of livestock product demand (π)	−.70	
Herd structure and stock weights		
Cows	9	186
Calves, 0–1 years	3	62
Calves, 1–2 years	3	125
3 year females	2	150
4 year females	2	186
3 year males	2	175
4 year males	2	190
5 year males	1	190
6 year males	1	190
7 year males	0	190
8 year males	0	190
9 year males	0	190
10 year males	0	190

The effect of skewness in profits on utility is ambiguous. The effect is positive (negative) if the skewness is itself positive (negative). For example, the distribution of profits is positively skewed if the herd owner experiences a few very good years and many years a little below the average. It is even conceivable that a producer in a highly skewed environment would accept negative mean profits if the skew of profits were great enough.

Table 2. Calculation of loss to morbidity.

	Disease Pressure		
	High	Low	Risky
Probability of transmission	.90	.30	.67
Probability of infection	.90	.30	.67
Maximum (K)	1.00	1.00	1.00
Fixed cost (c1)	.00	.50	.00
Variable cost (c2)	.50	.10	.50
Marginal physical product of variable input (n)	−1.00	−2.00	−1.00
Price (P)	.70	.80	.90
Profit @ 0 input use			
absolute	−.57	−.57	−.41
relative to price	−.81	−.72	−.45
Optimal input use	1.06	1.13	.90
Morbidity @ optimal input	.76	.07	.50
1—morbidity @ optimal input	.24	.93	.50
Profit @ optimal input use			
absolute	−.40	−.55	−.25
relative to price	−.57	−.68	−.28

RESPONSES TO RISK

African herders have few responses to the risks of pasture production. Because it is generally uneconomic to produce forage crops or other substitutes for risky pasture production (McIntire *et al.*, 1992), risk avoidance most often includes diversification of species or breeds, stock mobility, and varying offtake as a function of available pasture. The only such strategy analysed here is varying offtake, as noted in the following discussion of offtake rules.

Herders have even fewer alternatives for avoiding the risks caused by livestock disease. Herd diversification might not be effective, as different breeds might often be susceptible in similar degree to the same disease. Mobility may only be a seasonal alternative for avoiding disease and can be limited by availability of pasture. The sole strategy for reducing the effects of disease and thereby cutting risks of livestock morbidity and death is to increase the use of veterinary inputs.

OFFTAKE RULES

Herd offtake changes as a function of price and climatic variations that affect pasture productivity and subsequently herd growth. One way to model offtake changes is to solve

equation (3) by setting constraints to the parameter θ. Those constraints are known as offtake rules (McIntire, 1991), of which two are analysed here.

Partial Feed Equilibrium Rule

With this rule, the manager adapts offtake to the average availability of pasture. Owners sell no animals if pasture production is above the long-term average; but sell some when pasture production is below the long-term average. This means either

(11a) if $x_t > X$, $b_t = 0$; or

(11b) if $x_t \leq X$, $b_t = -(x_t - X)/\Phi$,

where b_t is the number of animals sold in year 't'. The rationale for this rule is the observation that producers build up their herds during good years when pasture production is above average, and that they sell animals when pasture production is below average because they expect that the animals will lose weight or die for lack of pasture. Admittedly, the pasture produced above the long-term average ($[x_t > X]$) is wasted in this specification.

Target Breeding Herd Rule

With this offtake rule, the herd manager sells a number of breeding females sufficient to maintain an initial number at the optimal expected sale age. This is a formulation of the argument of Dahl and Hjort (1976) that producers seek to minimize the risk of falling below a minimum herd size. The target breeding herd rule means

(11c) $b_{jt} = q_{jt} - q_{jo}$

where the subscript 'j' refers to breeding females and the term q_{j0} is the number of breeding females in the herd at the beginning of the model period. The term q_{j0} is set proportionately equal to values observed in African field studies (Itty, 1992). The offtake rules in equations (11a) and (11b) apply to all other herd classes.

INITIAL MODEL VALUES

In summary, the model has three state variables—price, pasture production and morbidity—and two control or decision variables—offtake and the quantity of veterinary inputs used. The model can be run with deterministic or stochastic values of the state variables. The means of price and pasture production are used for their deterministic values. Somewhat hypothetical values of the morbidity variables were used in the deterministic version. For the stochastic value of pasture output, a random number generator is used to simulate a positively skewed distribution. The resulting values of x_t subsequently determine p_t the other state variable, through equations (5c), (5d) and (5e). A sample size of 50 is used in the stochastic simulations.

Representative initial values are shown in Table 1. The livestock breed is assumed to be zebu cattle. Cattle are herded on ranges and receive little supplementary feed, veterinary care, or non-feed inputs except labour. The initial herd size is 25 adult animals.

The cost of non-veterinary inputs is US$ 0.50/unit, based on research in the ATLN (Itty, 1992). The world price of one metric tonne of liveweight is US$ 850, or US$ 213 for an animal of 250 kg liveweight (Itty, 1992).

RESULTS

The model was used in several experiments to test the effects of the parameters, μ, β, n, P. and c_1 on producers' demands for veterinary inputs under different scenarios about offtake rules. The calculation of the morbidity function and the related profit function for disease control is given in Table 2. Scenarios and some initial results are in Table 3.

PRICES DETERMINED BY WORLD MARKET

In the unlikely case of no animal disease, fixed pasture production, and fixed output prices, the only decision variables are the offtake rules because disease control is unneeded by definition. Income in scenario 1 would be US$ 4,300 with the target offtake rule and US$ 4,700 with the feed equilibrium rule.

If pasture production is variable, then incomes are lower still, under both offtake rules. The relative variability of income is much higher under the feed equilibrium rule, both in relation to the offtake rule in this scenario and with respect to the feed equilibrium rules in the preceding scenario.

In scenario 2, pasture production is variable, but world prices still hold, and there is no animal disease. Incomes are much lower than in scenario 1 because the necessity of adjusting offtake (with either rule) to feed availability means that animals cannot always be sold at the optimum age, as they could be if pasture production were constant, or if there were sources of supplementary feed. Income is slightly lower and slightly more variable with the feed equilibrium rule than with the target rule, and the latter rule has a higher probability of negative income.

Despite a low level of stock disease in scenario 3, mean income, relative income variability and utility do not change from scenario 2 except for some minor variation due to sampling error in the simulations. In scenario 4 (high disease), mean income and utility fall, while the relative variability of income rises. Minimum income, a measure of the worst risk to the producer, falls in scenario 4.

PRICES DETERMINED BY DOMESTIC MARKET

A more realistic group of scenarios is one in which domestic prices diverge from world prices. Even in the absence of animal disease, income will fall. The results (scenario 5 in

Table 3. Offtake rules (NPV of income or utility).

Scenario	Target	Feed Equilibrium
1. Assured pasture production, world prices no disease		
Mean	4.30	4.70
Utility	4.77	5.20
2. Variable pasture production, world prices, no disease		
Mean	2.88	2.63
Minimum	−.33	−.39
Cv	30.4%	35.7%
Utility	3.67	3.52
3. Variable pasture production, world prices, low disease		
Mean	2.91	2.67
Minimum	−.32	−.38
Cv	30.3%	35.5%
Utility	3.71	3.56
4. Variable pasture production, world prices, high disease		
Mean	2.07	1.74
Minimum	−.47	−.60
Cv	33.6%	45.8%
Utility	2.77	2.58
5. Variable pasture production, endogenous prices, no disease		
Mean	2.13	1.79
Minimum	−.31	−.55
Cv	31.2%	43.4%
Utility	2.81	2.61
6. Variable pasture production, endogenous prices, low disease		
Mean	1.94	1.59
Minimum	−.30	−.58
Cv	31.5%	46.6%
Utility	2.60	2.40
7. Variable pasture production,endogenous prices, high disease		
mean	1.36	.96
Minimum	−.45	−.73
Cv	36.7%	67.9%
Utility	2.05	1.87
8. Variable pasture production, endogenous prices, variable disease		
Mean	1.94	1.58
Minimum	−.27	−.55
Cv	31.5%	46.9%
Utility	2.60	2.40

Table 3) show that income would be much lower than in scenario 2 and, in particular for the feed equilibrium offtake rule, that the relative variation of income is greater.

Income is lowest and most variable under high disease pressure (scenario 5). Income is lowest and most variable with the interaction of variable pasture production, endogenous prices, and high disease pressure (scenario 7). Partitioning the 68% fall in income from the best scenario (1) to the worst (7), shows that 33% is due to moving from assured pasture

production to variable (scenario 1 to 2), another 17% is due to moving from world to endogenous prices (scenario 2 to 5), and another 18% is due to moving from no disease to high disease (Scenario 5 to 8).

A likely scenario is one in which disease is random, unknown to the producer in advance. Herd managers will have expectations about the likelihood of disease, but cannot know its exact level. Therefore, they must make decisions about veterinary inputs without full knowledge about the likelihood of disease. They may also lack complete knowledge of the effects of veterinary inputs on stock productivity.

The scenario in which disease is random is as follows. To simplify the exercise, the probability of infection is assumed to represent both the probability of disease transmission to a member of a herd and the subsequent infection of the animal. Equations (8a) and (9) can then be used to derive the expected value of V, the level of variable inputs, given that β is random.

(12) $E(V) = [c_2/(-np\beta K)]^{-1/(-1-n)}$.

If β varies with a positively skewed distribution around the central value of 0.3, and all other parameters are as in scenario 6, then the results are as shown for scenario 8 in Table 3. Mean income, utility and relative variation of income do not change from scenario 6 to 8. There is some increase in the relative loss to disease in scenario 8 with either offtake rule.

DISCUSSION

The costliest risk, in terms of foregone average income, is lack of feed caused by variable pasture production (Table 3). The variability of feed supply cannot be economically compensated by such measures as forage reserves and supplemental feed.

The loss caused by the variability of domestic livestock prices and high animal disease was about 54% of the absolute loss caused by variable pasture production.

Incorporating the variance and skewness of income into the analysis did not change the results dramatically. The utility measure based on wealth and the mean, variance and skewness of income, as compared to utility based only on mean income and wealth, was about 10% less with the target offtake rule and 4% with the feed equilibrium rule (Table 3).

EFFICIENCY OF OFFTAKE RULES

The efficiency of the two offtake rules was very similar. The target offtake rule gave slightly higher income, less income variability, and higher utility than did the feed equilibrium rule. These offtake rules—if they were not already evident to experienced herders anyway—could not form the basis of new management practices to be recommended to producers by the extension service.

One interesting finding is that the conservative target offtake strategy did not make income substantially less variable than the feed equilibrium strategy. Another is that risk-aversion made less difference to the feed equilibrium strategy than to the target offtake

strategy, apparently because the distributions of profits with the latter offtake rule were less negatively skewed.

INCENTIVE PROBLEMS

Incentive problems resulting from producers' biased subjective estimates of the likelihood of stock disease can lead to inadequate preventive treatment of those animals. Inadequate prevention of some stock could, in turn, cause more widespread and severe outbreaks of disease than would occur if all stock were treated correctly.

The results presented here indicating a sharp difference in economic results between low and high vector pressure situations suggest that there is potential for an incentive problem of this type to occur. In particular, if a sudden outbreak were to occur—for example, if vector pressure rose suddenly—then it is unlikely that all producers would react with the same celerity. Therefore , to prevent damage to livestock productivity, preventive treatment would have to be mandatory or sustained extension campaigns would be needed to raise producers' awareness of disease costs. Preventive treatment or extension would probably require substantial costs which would have to be subsidized because producers would fail to buy the economically optimal amount.

FUTURE RESEARCH

The paper has probed the probable consequences of variations in pasture production, output price, and livestock morbidity caused by disease on returns to livestock production and on the demand for veterinary inputs. Because the African data on livestock productivity are so sparse,* we lack good statistical estimates of production or cost functions for cattle and other stock, including the effects of such factors as disease, feed and management. A further problem is that producers lack complete knowledge of the effects of veterinary inputs not only on average output but also on its variance and skewness illustrate this problem in a study of California dairying).

Difficult incentive problems arise from the distributions of vector attack and disease transmission. In this paper, for lack of information about a more appropriate specification, it was assumed that those probabilities were not affected by the producers' actions. This assumption may be weak if either of those probabilities can be affected by the stocking rate. If the stock rate does affect the likelihood of attack or of subsequent infection, then not only must the decision of the individual herd owner about the intensity of production be taken into account, but that of all other herd managers likely to use the same common grazing areas must be considered too. Those decisions would greatly complicate economic analysis of the optimal level of disease control efforts to deploy because then the consequences of individual producers' decisions would not be independent.

* It was originally intended to use the data in Itty (1992) to estimate a production function for cattle with veterinary inputs and labour, among others, as explanatory variables. However, even that data, which are from the ATLN were not useful for that purpose.

With respect to disease, note that the low disease pressure scenarios could result from spraying to control vectors. This is likely to bias producers' subjective estimates of the severity of outbreaks, e.g. they would make producers initially misinterpret a high pressure situation as a low one. Second, the sudden outbreak of disease is not likely to self-correct via the mechanism of rising prices. This is because rising offtake leads to falling prices in the short run, making the return to veterinary inputs low. Third, the long term development of feed production, by reducing the cost of livestock production, can also reduce the unit price, thereby cutting the derived demand for veterinary inputs.

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Potential for modelling ecological responses to the control and prevention of disease in African livestock populations

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ABSTRACT

The environmental consequences of livestock disease are increasingly being taken into account by policymakers and livestock disease specialists. Ecological modelling can help assess how livestock disease suppression may indirectly affect the environment through increases in livestock and human populations and associated grazing pressures. It can also help in assessing ecological constraints on livestock production, which affect the economic benefits of disease control. Ecological modelling can be used to assess environmental responses as well as ecological constraints.

Ecological modelling has advanced over the last decade due to technological as well as scientific progress. Spatially explicit models are now used at landscape to global spatial scales. Models are now readily integrated with geographical information systems and remote sensing.

Land-use models must be used to predict land conversions to livestock-based agriculture. Ecological models must then be used to model vegetation and soil responses to human and livestock utilization. Agro-ecosystem models can be used similarly. Finally, the predicted alterations in vegetation and soils must be used in models of wildlife habitat suitability, movements, and spatially and non-spatially structured population dynamics.

INTRODUCTION

Sustainable development is the development that meets the needs of the present without compromising the ability of future generations to meet their own needs—World Commission on the Environment and Development

With increasing emphasis being placed on ecologically sustainable economic and agricultural development and the rapidly increasing human populations in Africa, the potential ecological consequences of livestock disease control are likely to be taken into much greater account than they have in the past. Humans are only now realizing that producing food, providing shelter and increasing their comfort can have important side effects.

There are many potential environmental consequences of livestock disease control. Livestock disease strongly limits livestock and thus human populations throughout Africa. The hoped for result of livestock disease control is that livestock populations will increase. Unfortunately, this may have undesirable side effects like overgrazing (Sinclair and Fryxell, 1985; Bosch, 1989), soil deterioration (Lal, 1988; Graetz, 1989), competition with wildlife species and alteration of wildlife habitat (e.g. Talbot, 1972; Myers, 1973; Coe,

1980; Williamson *et al.*, 1988). Many of Africa's national parks may owe their existence to the fact that tsetse makes them unsuitable for livestock (Coe, 1980). There are potential side effects of vector control programs that may arise from frequent herd movements to dips, bush clearing, burning and spraying. Along with increased livestock populations come elevated human populations. In Africa, this may imply increased levels of wood harvesting for fuel and construction. In productive areas, wildlife habitats will be converted to croplands. Finally, humans may elect to control or even eliminate wildlife populations in surrounding wildlands to eliminate disease vectors and prevent crop depredation. In the long run, negative ecological side effects have negative economic consequences as the ability of land to support grazing, cultivation, forestry and tourism declines.

In addition to improving our understanding of environmental consequences, ecological modelling may play useful roles in assessing the costs and benefits of disease control. Ecological modelling can be used to assess ecological constraints on livestock productivity. Calculations of the potential benefits of disease control depend upon correct assumptions of the maximum potential productivity that can be realized after the disease has been controlled, which in turn is affected by levels and dynamics of forage productivity. Also, livestock disease vector distributions and abundances are determined by vegetation as well as by climate.

The purpose of this paper is to explore the possibilities for using modelling to examine the likelihood of success of livestock disease control programs. If ecological costs and benefits can be incorporated into these considerations, implementation strategies of disease control programs could become more effective, more strategic, and more sustainable. Ecological modelling capabilities have advanced considerably over the last two decades. It is much more feasible now than it was a decade ago to use models to help assess the environmental consequences of livestock diseases and their control. I briefly discuss the needs for considering environmental consequences of disease control, then identify modelling procedures that can be used, drawing in part from experience gained modelling a pastoral ecosystem in Kenya.

WHEN TECHNOLOGICAL INTERVENTIONS OVERCOME ECOLOGICAL CONSTRAINTS

In ecosystems that have not been affected by technological development, native grazers and browsers tend toward the natural 'carrying capacities' of their environments set by vegetation, water availability, predation, disease or other limiting resources. Periodic droughts or even long dry seasons act as 'bottlenecks' that keep populations well below levels that fully exploit vegetation resources. Predators and disease add further constraints on population rates of increase. Undeveloped pastoralism is limited by many of the same constraints.

Technological intervention into livestock-based human ecosystems tends to relieve these constraints, pushing populations to become limited only by forage and subsidies from outside the system. Water limitations are overcome by the development of wells, boreholes and reservoirs. Simple technological interventions by pastoralists like the protection of

livestock from predators and shepherding to forage may cause livestock populations to be higher than their wildlife counterparts (however, wild ungulates in the Serengeti number over two million and seem to be food-limited rather than predator-controlled). Interactions with regional and national markets permit destocking during periods of low production, but they also permit more rapid and complete restocking. Energy subsidies to the system such as fertilizer and energy used to cultivate grain for livestock feed tend to boost population growth. It is easy to see that supplemental feeding of grain to a herd will relieve the natural forage limitation set by pasture or rangeland plant productivity.

Controlling livestock diseases where they currently have significant impacts on livestock mortality will likewise tend to force populations to levels where forage, and thus naturally regenerating resources, become limiting. Indeed, it is possible with technology to push livestock populations beyond their sustainable carrying capacities.

The risks of technological intervention are particularly acute on technological 'frontiers' like the American west at the turn of the century or the African Sahel from the 1950s onward (Sinclair and Fryxell, 1985; Le Houreou, 1989). At the frontier, natural resource levels are relatively high, thus promoting population expansion in the short-term at the expense of slow declines in natural resources over the long-term. In the Sahel there was widespread water development, which along with ample forage allowed the development of higher livestock densities. Eventually, however, the system was run down in many places. Indeed, much of Africa today is a technological frontier.

Ecological models that attempt to predict the potential consequences of livestock disease control must be able to describe the effects of these ecological constraints on current livestock populations. In much of Africa this implies that models must represent the effects of water availability and disease on herd density, as well as the effects of forage limitation. When diseases are controlled, it is likely also that other constraints will also be relieved through water development, improved marketing infrastructure, greater feed imports, and others. If these associated developments are ignored, the effects of disease control are likely to be underestimated.

Similarly, Geerling *et al.* (1986) suggested that integration of ecology in development requires 1) quantification of natural resources flows in terms of carrying capacity, 2) identification of natural ecological regulating factors in the natural and the developed system, 3) assess interventions to counter the natural regulating factors and potential side effects, and 4) define measures to integrate interventions with socioeconomic system to achieve balanced development.

MODELLING ECOLOGICAL EFFECTS IN RELATION TO CARRYING CAPACITY

Ascertaining ecological responses to livestock disease control can be compared to the problem of determining ecological carrying capacity for livestock and humans. If disease impacts on herd sizes can be predicted, then it is possible to at least assess whether there is any risk that carrying capacity will be exceeded.

In simple terms, livestock carrying capacity is the number of animals that can be supported over the long-term to achieve some dynamic equilibrium amongst soils, plants

and animals. The amount of forage that can be sustainably produced under grazing or browsing is therefore central to carrying capacity calculations. While carrying capacity calculations are often based upon a fixed or average quantity of resources which then determines the number of resource users that the area can sustain (e.g. Coe *et al.*, 1976; Kalff *et al.*, 1985), carrying capacity is dynamic (e.g. Geerling and de Bie, 1986). In arid and semi-arid regions, carrying capacity varies greatly within and among years due to plant responses to rainfall variation and time lags in plants responses. Dynamic simulation models can represent these variations, as well as subsequent population responses.

The concept of carrying capacity can take on varied meanings according to the objectives of land use (Geerling and de Bie, 1986; Coughenour and Singer, 1991). If the objective is to maximize wildlife diversity, the definition will be different than if the objective is to maximize energy and nutrient transfer to human populations. In production-oriented livestock systems, carrying capacity may be the number of animals that can be supported to attain maximal sustainable production over the long-term. Extinction of a minor plant species may be tolerated because its contribution to productivity is believed to be negligible, or is not understood. In pristine nature preserves, carrying capacity is defined by a naturally regulated animal population level. Plant species may persist because they evade herbivory or because herbivore populations do not increase to threatening levels. Thus, the potential for conflicts of interest between maximizing sustainable production and maximizing biodiversity become readily apparent.

Carrying capacity is actually a continuum along a gradient of what is demanded from an ecosystem. At the least, carrying capacity should be defined as the maximal stocking rate that ensures long-term agro-ecosystem sustainability. The most demanding definitions would arise where there is conservation of pristine wildlife ecosystems that harbour large reserves of biodiversity. In between, there is a wide range of acceptable livestock population levels. However, it is much more difficult to predict the consequences of a continuum of livestock densities than it is to simply predict a single valued carrying capacity that meets a single set of resource management objectives.

Thus, predictions of long-term agricultural and ecological sustainability in relationship to variations in livestock abundance are needed to assess the full range of ecological impacts of livestock disease control. These predictions require a synthesis of the long-term effects of livestock on forage plant production and survival, the effects of human wood use on woody plant populations, the direct and indirect effects of livestock on soil structure and fertility, and the secondary impacts on wildlife arising from competition for forage or alteration of habitat. The calculations must take into account temporal and spatial variations in carrying capacity due to climatic variability and landscape heterogeneity.

ECOSYSTEM MODELLING: NEEDS AND CAPABILITIES

Livestock effects on plants and soils, and human effects on plants, soils and wildlife involve indirect as well as direct effects (Figure 1). For example, direct effects on plants are ramified into soil responses. Livestock and human impacts on vegetation have consequences for wildlife habitats. These interactive responses involve processes of plant

growth, soil moisture dynamics and ecosystem nutrient cycles. Interactions and feedbacks among these processes occur at the ecosystem level of organization. Ecosystem studies take into consideration abiotic as well as biotic interactions, including the flows of water, carbon, inorganic nutrients and energy among soils, vegetation and animals. Indeed, an ecosystem is defined as an assemblage of abiotic and biotic components comprising an interdependent system (Tansley, 1935).

Models must be capable of simulating plant responses to various levels of grazing pressure. Plants generally respond positively or neutrally to light and moderate grazing and negatively to heavy grazing. Livestock and human impacts involve ecosystem level interactions among grazers, plants, soil and climate. There are several mechanisms involved in the response; alteration in photosynthetic leaf area, changes in photosynthesis rate, reductions in rates of soil water use by plants, increased rates of nutrient recycling by herbivores, meristems mortality arising from trampling and uprooting and other processes. Some responses are due to effects on plant numbers and sizes that arise from altered mortality and recruitment rates. Sustained overgrazing eventually results in soil deterioration. As plant productivity is diminished, carbon inputs to the soil decrease and

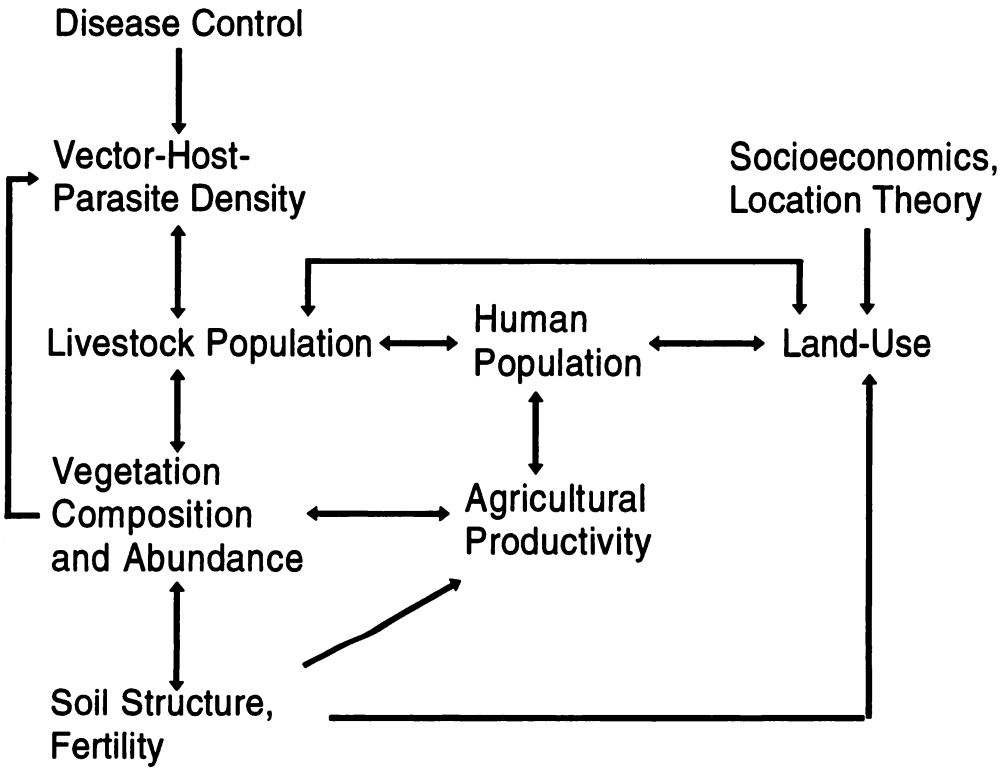

Figure 1. Direct and indirect interactions among livestock disease, livestock populations, ecological processes and humans. Note that livestock populations both affect and are affected by human land-use patterns.

soil organic matter declines along with soil fertility. Lack of vegetation cover may expose soils to direct raindrop impact, which can cause soil capping, increased runoff and finally erosion. These negative effects on soil fertility and water balance may induce a positive feedback cycle, as plant growth is further decreased, which then causes further soil degradation.

Ecological modelling can also be used to disentangle ecological constraints on livestock production. Natality, mortality and resultant livestock herd dynamics may be simulated in response to animal condition, which depends partially upon forage intake rate. Disease effects can be modelled independently through their effects on animal weight gains, forage intake rates or mortalities. In most rangeland ecosystem models, the rate of forage intake by livestock depends upon the standing stock and nutrient content. Forage quantity and quality are predicted using plant growth models, taking into account water and nutrient limitations. Livestock growth is often simulated based upon the balance between energy or nitrogen forage inputs and metabolic losses. Energetic losses incurred by travelling to water and lactation are added to costs of basal metabolism (e.g. Coppock *et al.*, 1986).

Mathematical models of ecological interactions predate the computer age by decades. Computer simulation models were first applied in ecology in the 1960s (e.g. Watt, 1968; Bledsoe and van Dyne, 1969; Odum, 1971). Computers revolutionized ecological modelling by enabling simulations of ecological interactions which were too complex to solve analytically. Modelling was increasingly employed by systems ecologists after that. Between 1970–1975, large ecosystem modelling programs were supported by the International Biological Program (IBP). Models were developed for sites in the grassland (e.g. Van Dyne, 1972; Innis, 1978) as well as other biomes. Ecosystem models continued to be developed after IBP.

The modeller's working environment is much more advanced now than it was ten years ago. Until about 1983, models were generally programmed using punch cards and run in batch mode on mainframe computers with relatively large memory capacities but slow processing speeds. The first microcomputers such as the 8086 and 80286 class machines available during the mid and late 1980s were still too slow and memory limited to be used for serious ecosystems modelling. Minicomputers were used extensively during that time while modellers moved from batch-oriented to interactive, terminal- or workstation-based environments. Now, however, serious ecosystem models can be developed and run on 80386 and 80486 class micros, as well as more sophisticated workstations. Software has also advanced dramatically over the last several years. Using 32-bit compilers, models having huge memory demands can be implemented. Skilled modellers can now develop or customize models in a small fraction of the time required a decade ago.

Increases in computer speed have made long-term and large-scale simulations feasible. Earlier ecosystems models were typically executed for one- to five-year time periods due to limitations in computer speed. Now, daily time step models can simulate decades of real time while weekly and monthly models routinely simulate centuries. Monthly and annual simulations of thousands of years are possible. Until recently, ecosystem simulations were limited to points or individual sites. Spatial heterogeneity plays a significant role in ecosystem function, and must be taken into account in ecological models, particularly for large spatial areas. Only several years ago did ecosystem modellers attempt to develop spatial simulation models. Spatial models are considerably more demanding of processor

speed because model calculations must be performed at each and every spatial location. While a few large spatial models can only be run on supercomputers, most spatial simulation models can now be executed on micros and workstations as well.

The development of spatial data analysis systems has paralleled the above chain of events, also due to advances in computer technology. Many of the early hopes of remote sensing science during the late 1960s and 1970s are now being realized because it is now possible to store and process large amounts of data quickly and effectively. User friendly geographical information systems (GIS) are revolutionizing natural resource sciences and applications.

Recent developments, now ongoing, are the linkages of systems modelling with GIS and remote sensing, and the development of user friendly interfaces for models. There are but a handful of successful ecosystem model-GIS linkages at this time, but that is rapidly changing. Only now are there being developed graphical 'point and click' user interfaces that command linked systems of ecosystem models and GISs.

There have been many important advances in the field of computer-based decision support systems (DSS) (Stuth and Lyons, 1993). DSS use heuristic approaches to solve complex problems involving integrations of ecological and economic factors. A wide range of tools and information sources, such as simulation models, expert systems, databases, GIS and remote sensing, are integrated. The design and construction of DSS are all oriented to the needs and ease of use of an end user (Stuth and Stafford-Smith, 1993).

MODELLING INTERACTIONS BETWEEN LIVESTOCK, HUMANS AND WILDLIFE

Interactions between livestock, humans and wildlife can be modelled by representing vegetation responses to livestock and human utilization (Figure 2) and subsequent wildlife responses to the associated alterations of their habitats (Figure 3). The spatial distributions of wildlife habitats and extensive livestock systems impact the sustainabilites of both (Coughenour, 1991c).

However, how do we model patterns of land-use change? Human land-use impacts are particularly problematic for ecological modellers as it is really beyond the traditional bounds of their discipline. While geographers have developed models of human population distributions (e.g. Thomas and Hugget, 1980), there has been little interaction between ecologists and geographers. Two fundamentally different approaches to predicting land use might be recognized. The first is purely geographic and would predict changes in land use from environmental and economic variables and location theories. The second approach would be to predict livestock population dynamics at large spatial scales based upon environmental constraints, and then base land-use changes upon changes in livestock abundance as well as other geographic considerations. In reality, livestock abundance and land use are interactive, with causality flowing in both directions (Figure 1).

Maps of potential land use in Africa such as those developed by the FAO can possibly be used as a basis for predictions. However, it is critical to obtain data for actual land use. Ecological, disease and other constraints on land use are likely to cause substantial

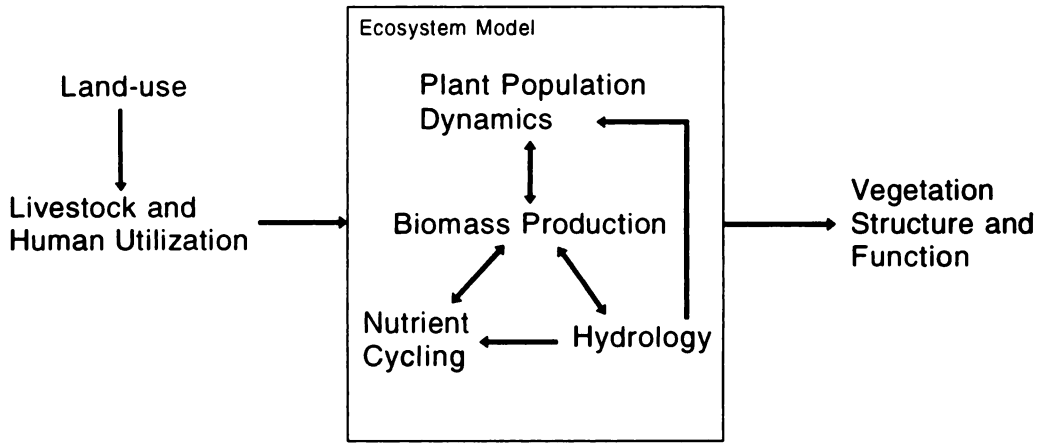

Figure 2. A major role of ecosystem models is to calculate the effects of livestock and human resource utilization upon vegetation structure and function. Ecosystem models represent interactions among plant populations, biomass production, hydrology and nutrient cycling.

differences between actual and observed land use. It would, however, be highly instructive to compare potential and actual land use in relation to prior livestock disease controls and other factors. This would provide useful information for the development of land use change models.

Possibly, a rule-based modelling approach could be taken to represent land use changes. Rule-based modelling, a branch of artificial intelligence, encodes knowledge into logical if-then relationships. Effects may be probabilistic related to causes. Probabilities of land-use change could be functions of environmental variables such as rainfall and soil fertility as well as economic and geographic factors. A wide range of outcomes may be possible, depending on which rules are stochastically invoked; however it may be desirable to track only the most probable outcome.

A further requirement is to predict the secondary ecological responses to either livestock increases or land-use change or both. Ecologists can readily predict potential vegetation responses to climate variables like rainfall, potential evapotranspiration, growing season length and temperature (e.g. Cramer and Leemans, 1993; Emmanuel *et al.*, 1985). However, this approach does not take into account human land-use impacts nor does it model transitional vegetation types, dynamics or new types of vegetation (i.e. new combinations of plant types). Again, a rule-based approach could be employed to account for human impacts. Rules would have to be developed from existing data bases that quantify relationships between rates of forest clearing, burning, cultivation, road building, etc. and increases in livestock-based human populations and land usage. The rates of land use and vegetation change may also be predicted to enable scenarios to be created at various points in time into the future. Rates of deforestation can be calculated based on human wood demands and rates of wood production by trees. The latter may be predicted from rainfall and other variables, however such predictions are limited because wood production rates also decline as tree population densities decrease.

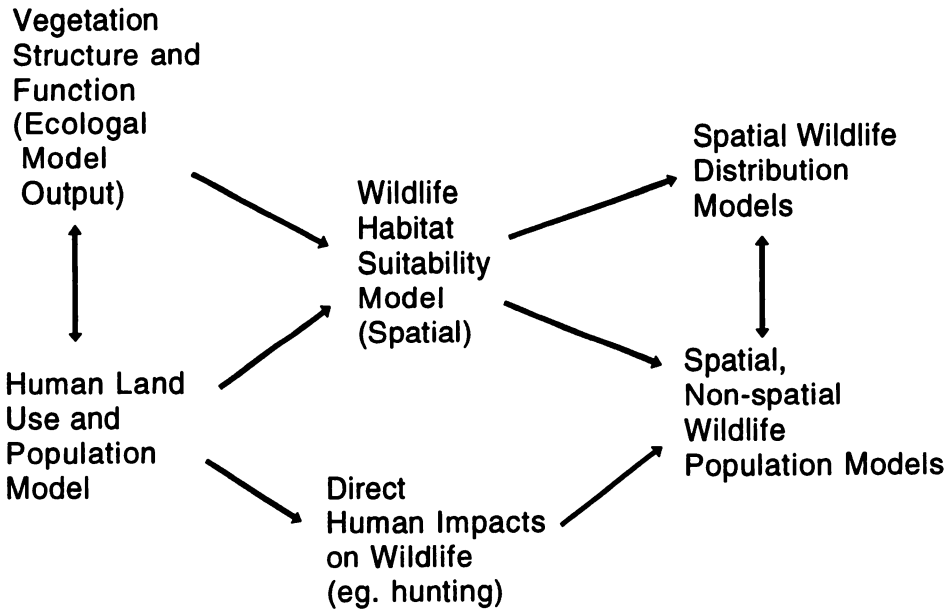

Figure 3. Predictions of vegetation responses from ecosystem models are used as inputs to models of wildlife habitats, distributions and populations. Wildlife includes plants as well as animals. Human land-use models provide inputs to wildlife habitat suitability as well as vegetation models. Humans may directly impact wildlife populations by hunting, culling etc.

Responses to human land-use practices can also be modelled more explicitly using process-oriented ecosystem models as discussed in the previous section. Plant growth rates and population dynamics and their responses to utilization (e.g. Coughenour, 1984, 1991a; Fulton, 1991) are simulated, along with their interactions with water budgets and nutrient (N,P) cycles (e.g. Parton *et al.*, 1987).

Modelled vegetation responses are used as inputs to models of wildlife habitat suitability. Habitat suitability models have been developed and used extensively during the last decade (Verner *et al.*, 1986). Habitat attributes such as vegetation type and abundance, topography and distance to water are used to assess the suitability of a habitat for various wildlife species. These models are usually based on observed correlations between habitat variables and the distributions and abundances of wildlife species.

An important habitat variable is the amount of forage biomass available to wild herbivores. Competition between livestock and wild herbivores may be explicitly modelled by simulating decreases in forage standing crops due to their respective forage offtakes. Foraging models then respond by predicting reduced rates of forage intake. In a more simplified approach, the surplus forage after livestock consumption could be calculated and then used as an input to a habitat suitability model.

The increasing emphasis that is being placed on conservation biology and biodiversity at regional, national and global spatial scales is beginning to yield new techniques for assessing wildlife distributions and critical wildlife areas. Geographic techniques are used to map biodiversity from species inventory data and range maps. Analyses are then

performed to optimally locate wildlife preserves to maximize biodiversity. Within the US Fish and Wildlife Service the GAP analysis program has emerged (Scott *et al.*, 1993). This is a geographic inventory and analysis of critical gaps in the distribution and abundance of wildlife species and their habitats. Other similar techniques were reviewed by Pressey *et al.* (1993). A limitation of these approaches is that they are static rather than dynamic. They characterize potential habitat value, but do not examine population dynamics or animal movements to arrive at the potential.

As human populations increase, it becomes increasingly difficult to set aside large, intact natural ecosystems for conservation. Instead, human land use must be managed to minimize negative impacts. In order to accomplish that, it is necessary to determine what population sizes or densities are needed to ensure long-term persistence or viability. Conservation biologists estimate minimum viable population sizes or densities (MVPs) in cases where the biology of a species is well understood. A number of approaches have been used to estimate MVPs (Soule, 1987; Boyce, 1992). Generally, simple population dynamics models are employed. Models are run repeatedly, with stochastic environmental variations in birth and death rates among runs that reflect the range of variation likely to be encountered due to climate variation, disease outbreaks and other catastrophes (as in Monte Carlo modelling [see Morris, this volume]). In some cases the effects of spatially structured metapopulations, with stabilizing dispersal and movements among subpopulations, are considered. These are risk analyses in that they attempt to determine risks of extinctions in probabilistic terms (e.g. a 95% probability of persistence over 100 years) (Burgman *et al.*, 1993).

These techniques can be usefully merged with assessments of current and projected livestock distributions and associated land conversions to cultivation and pasture. The linkage between those projections and potential impacts on biodiversity will be problematic, however. Qualitatively, it is often assumed that livestock development will have negative effects on wildlife, but quantitative assessments are lacking. Furthermore, impacts of livestock development fall along a continuum—impacts can be minimized through proper land-use planning, herd management and resource management tactics and their environmental consequences must be included in models of the environmental consequences of livestock disease and disease control.

PREVIOUS EXPERIENCES USING ECOSYSTEMS ANALYSIS IN AFRICAN LIVESTOCK AND WILDLIFE ECOSYSTEMS

Applications of an ecosystem approach have been rare in studies of African livestock or wildlife. Although ecosystem level analyses have been conducted for over two decades, many of these exercises have been academic or have not considered humans. Exceptions are modelling studies of pollution impacts (many), agricultural practices (e.g. Cole *et al.* 1989), the works of H.T. Odum (1971), global modelling studies (Meadows *et al.*, 1972) and human ecology studies (Little *et al.*, 1984, Moran, 1987; Weinstein *et al.*, 1983).

The South Turkana Ecosystem Project (STEP) in northwest Kenya employed an integrative, multidisciplinary ecosystems approach to understand the structure and

functioning of a nomadic pastoral ecosystem. STEP, funded by the US National Science Foundation, conducted research on pastoral ecology in the southern portion of Turkana District, Kenya, over a 13-year period, beginning in 1980 (Little *et al.*, 1984; Ellis and Swift, 1988; Coughenour *et al.*, 1985, McCabe and Ellis, 1987). STEP linked together studies of climate, soils, hydrology, vegetation, livestock and human biology and behavior. Systems modelling was used throughout the project.

STEP studies focused on a 10,000 km^2 area of the southern portion of Turkana District, Kenya, that is topographically, geomorphically and climatically diverse. South Turkana is mainly arid (300–550 mm/yr rainfall), but also includes very arid (150–300 mm/yr) and semi-arid (450–900 mm/yr) climatic zones. Vegetation is a diverse mixture of dwarf shrub grassland, dry thorn bushland, grassland and savanna. Pastoralists are nomadic, retaining a traditional subsistence lifestyle that depends on products of goats, sheep, cattle, camels and donkeys. Milk is by far the most important livestock product (Galvin, 1988). Pastoralists move several times per year in response to changing distributions of forage, water, security and another factors (McCabe, 1983; McCabe and Ellis, 1987).

It became apparent early in the research (ca. 1983) that a spatial data base was needed to organize information and conduct ecosystem analyses. Soils, landform, topography, hydrology, vegetation and climate maps were computerized using a GIS. Maps of seasonal and permanent wells and large rivers were used to develop maps of distance to water. A temporal sequence of monthly rainfall maps was generated for a seven-year period (1982–1988) from rainfall data gathered at irregularly spaced weather stations in the study area. Rainfall maps were then generated using spatial interpolation, accounting for effects of elevation.

Satellite remote sensing data were useful for verifying model predictions of green vegetation dynamics. Normalized difference vegetation index (NDVI) maps were derived from reflectance data from the AVHRR sensors on NOAA polar orbiting satellites (Tucker *et al.*, 1985). The first data that NASA (C.J. Tucker) provided to us in 1984 were monthly NDVI images of 7.5 × 7.5 km pixels. Later 4.2 × 4.2 km data were provided. Time series of monthly NDVI images from 1980–1988 were used to verify ecosystem model predictions of the distribution and dynamics of green plant biomass.

Diverse studies of vegetation, livestock and human ecology were synthesized in a static energy flow model of the ecosystem (Coughenour *et al.*, 1985). Spatial vegetation data were integrated into total ecosystem estimates of plant productivity. We were able to quantify the amount of energy fixed by plants, consumed by animals, and then transferred to humans. This modelling exercise forced us to identify interdependencies in the system in quantitative terms. We identified where the inefficiencies of energy transfer were located, how these transfers were ecologically constrained, and why these inefficiencies were ecologically significant. The analyses revealed significant differences between the structure and functioning of production-oriented systems such as the raising of livestock for meat and maintenance-oriented systems such as subsistence pastoralism.

A spatial, dynamic ecosystem simulation model (SAVANNA) was later constructed (Coughenour, 1991b, 1992). This model simulates soil water balance, plant growth, livestock foraging and livestock condition for 4.2 × 4.2 km grid cells. Simulated pastoral livestock are dynamically distributed over the landscape in relation to habitat suitability,

which is modelled from the combined distributions of forage, water, topography and woody canopy cover. Data stored in the GIS database are used for model initialization. GIS is used to analyse and plot model output. Monthly rainfall maps are used as model inputs. We used the model to demonstrate the significance of spatially heterogeneous landscapes for ecosystem level function and we assessed the importance of livestock movements for ecological stability. Simulations demonstrated the significance of livestock movements (e.g. Coughenour, 1991c) and the effects of restrictions on livestock movement arising from livestock raiding by a neighbouring tribe.

A more developed version of the SAVANNA landscape model simulates plant population dynamics as well as biomass production for multiple life forms or functional groups of plants. The effects of livestock grazing and browsing on plants are mechanistically, but parsimoniously, represented (Coughenour, 1991a). Multiple livestock species can be simulated. The energy balance of livestock is explicitly modelled as are weight dynamics. Livestock population dynamics of five sex/age classes are simulated. Mortality and natality rates are functions of livestock condition index, i.e. current body weight relative to minimum and maximum body weights.

SAVANNA is optionally implemented in a newly developed GIS-based graphical user environment (Oyasin Circle Solutions, Longmont, Colorado). Linkages between ARC/INFO data and the model are transparent. Point and click menu environments or 'shells' are customized to automatically perform complex procedures demanded by particular users.

We have coupled the ecosystem model to a model of pastoralist decision making based on an earlier model developed by D. Swift *et al.* (Ellis *et al.*, 1990). A similar model was developed by Weinstein *et al.* (1983). Subsistence pastoralism is represented in terms of energy supply and demand from livestock and from other sources of food energy. A rule-based approach to pastoral decision making is taken. In times of livestock food shortage, a set of prioritized actions are implemented for making up the shortfall, ranging from slaughtering to hunting to famine relief. The model includes options for interactions with a market economy in which livestock are bought and sold. Cash derived from livestock sales may be used for buying livestock, food or non-food items according to prevailing circumstances. Currently, the model is being used to examine effects of different plans and scenarios of water resource development, marketing improvements and livestock mortality rates (G. Njiru, Ph.D., in progress).

The ecosystem modelling approach used in STEP would be directly applicable to assess effects of the control of livestock diseases in the semi-arid climatic zone where spatially extensive and relatively low input livestock production systems are common (e.g. large individual or group ranches, communal grazing area and transhumance). Human populations in these semi-arid climatic zones are expected to increase substantially.

There are some important differences between the subsistence pastoralism of arid Turkana and more sedentary production-oriented systems characteristic of semiarid and subhumid climatic zones. However, ecological models are generally applicable to a wide range of ecoclimatic zones. For instance, vegetation production and plant responses to grazing in SAVANNA are modelled in exactly the same fashion for arid and subhumid systems, using different parameterizations. The SAVANNA plant growth submodel has been used to simulate subhumid Serengeti tallgrasses (Coughenour, 1991a), as well as tree, shrub and grass species from the cold temperate zone in Canada.

While livestock in high production zones do not move as extensively as they do in Turkana, the SAVANNA livestock distribution modelling approach might be adapted to simulate reallocation of animals among ranches or farms or even regional scale distributions of sedentary livestock enterprises in relation to changes in livestock habitat suitability or localized excesses or deficiencies in herd sizes. Livestock would not be freely redistributed on a monthly basis as they are now in the Turkana version of SAVANNA; however, limited redistributions may simulate market exchange (destocking, restocking) responses to landscape, regional and national climate patterns as well as gradual changes in constraints on land use such as those arising livestock disease control. More sophisticated marketing and geographic models may come into play later.

In intensive livestock production systems there may be high levels of investment in farm infrastructure and maintenance, and significant cash outlays may occur for the purchase of animal feed. Thus, a farm or ranch level livestock management model with appropriate accounting procedures and management options (e.g. Stafford-Smith and Foran, 1990; Morris, this volume; Wight and Skiles, 1987; Mukhebi *et al.*, 1989) should be used in place of the pastoralism submodel that was used in the Turkana modelling work.

CONCLUSIONS

We now have the capacity, using models, to make reasonably informed predictions about long-term ecological responses to African livestock development. We can use models to estimate changes in soil fertility, tree cover and herbaceous and woody biomass production in response to livestock production systems and climate over 10–100-year periods, accounting for the effects of spatial variations in climate, soils, topography and vegetation over landscapes, regions and the continent.

It would be useful to begin applying models to a few landscapes or subregions where there are sufficient data to parameterize and test the models. These data would include climate, soils, vegetation, topography, wildlife distributions and human population density and land use. Optimally, the study area(s) would encompass a sufficiently wide range of climate, soils, vegetation and land uses to develop an understanding of how these factors affect ecological responses. Longitudinal data on ecological and human responses over time are equally important. Thus, it will probably be necessary to capitalize upon prior research programs.

Maps of maximum sustainable livestock densities for landscape or regions may be developed or the models may be used to analyse the spectrum of responses and their sensitivities to specific variables. The use of ecosystem models to assess livestock production and disease responses to ecological constraints should not be overlooked. This information is useful in estimating potential sustainable livestock production at various levels of investment in disease control and where disease control will be most effective.

Spatially implemented ecosystem models like SAVANNA or CENTURY (Parton *et al.*, 1987) can therefore address many of the potential environmental consequences of livestock disease control. They can address the side effects of livestock population increases by simulating plant and soil responses to herbivory, burning, brush clearing, wood cutting and land-use change. Potential overuse of areas near dips can be represented by modelling

livestock density distributions. Simulated soil and vegetation responses can then be used in models of wildlife habitat suitability. The responses of wildlife populations to these changes could be estimated by using the outputs of the ecosystem models as inputs to wildlife habitat suitability models. In some cases population models would be employed to estimate wildlife population dynamics and minimum viable population sizes or densities.

Modelling in natural resource management, as in other fields, should be viewed as part of an ongoing process. In adaptive resource management (Holling, 1978; Walters, 1986), managers continually learn about ecological responses to their actions by employing a wide range of tactics and carefully observing the results. Simultaneously, models become increasingly robust as they are tested, fail and are then improved. Over the long-term (decades), iterations between modelling, research and management converge on optimal solutions. While models can and should be used as tools for decision support, many of the most important benefits of models are derived from participating in the modelling process.

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Session discussion

The poor quality of existing data on the effect of diseases on production, the economic effect of diseases under different circumstances and the lack of data in several key areas enabling us to understand the complex interactions of the mechanisms involved was recognized to be a problem, even in developed countries. The example of trypanosomiasis was raised, in which not only the pathogenic effect of acute or chronic anaemia plays a role, but also the high protein and energy cost of replacing lost haemoglobin.

However, it was emphasized that methodologies both for field assessment of economic impact and for the broader scale assessments were available, and have been applied for some diseases. Examples presented were studies to assess the relative importance of diseases of livestock in Thailand, and the economic importance of ECF in eastern and southern Africa.

An example of the ranking of direct losses caused by diseases to the sheep industry in Australia was presented, and a broad estimate that diseases were accounting for 20–30% losses in current production was proposed. As far as trypanosomiasis was concerned, the importance of indirect losses was emphasized.

The discussion then focused on the type of economic analysis required. Although there is a political and donor need for absolute figures on the possible losses incurred by livestock industries, more realistic estimates are those that measure the extent to which disease impact can be reduced by control measures; assessment should be done on the basis of benefits to be achieved as a result of particular control options, not total losses incurred as a result of the presence of the disease.

The possible source of funding for these activities was discussed. As an example the role of the pharmaceutical industry in the development of the helminth models was highlighted. However, concern was expressed about the possible distortion that may result in the development of integrated control programs where all interests might not be served. The public sector may need to play a significant role, particularly in the early stages.

MODELLING SYSTEMS

Modelling: a review of systems and approaches for vector-transmitted and other parasitic diseases in developing countries

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ABSTRACT

During the last 30 years, modelling has increasingly played an important role in improving the efficiency of agricultural production systems. In the case of vector-borne diseases, most of the approaches have focused around calculus methods to describe the dynamics of the interactions of host and parasite, or empirical simulation models to describe the parasite/vector behaviour in relation to environmental conditions. This review gives a brief tour of various modelling techniques and their attributes. The techniques include the 'spherical cow' approach, analytical methods, simulation and statistical modelling. Within the agricultural community there is an expectation that models will become available as 'products' for a wide range of decision-making and problem-solving tasks. If the expectation is to be realized, the context in which models will be used and delivered will be important. The opportunity for creating information models that combine modelling techniques with the heuristic knowledge of experts and relevant disease information will be examined.

INTRODUCTION

Extract from Assessment of Animal Agriculture in Sub-Saharan Africa, Executive Summary, Winrock International, 1992.

> *'Between 1990 and 2025, enormous demographic and social changes will sweep sub-Saharan Africa . . . . If livestock production grows no faster than it did between 1962 and 1987, the region will face massive deficits in supplies of meat and milk by 2025.*
>
> *'The highest priority for animal health research is to develop sustainable means to prevent and control the environmentally related diseases including trypanosomiasis, theileriosis, anaplasmosis, babesiosis, cowdriosis and dermatophilosis.'*

Measurement has played a key role in improving the efficiency of agricultural production systems in the developed countries. It has given birth to quantitative biology and stimulated the current interest in mathematical modelling as a basis for decision making and planning. Existing models of host-parasite behaviour raise the question as to how best they can serve the functions of sustaining and increasing food production in

developing countries where parasitic diseases are a major constraint. Currently, there is a need for a greater understanding of what models can offer and how they can serve research programs.

In the case of vector-borne diseases most of the modelling approaches have focused around calculus methods to describe the dynamics of the interactions of the parasite/vector behaviour. This review briefly discusses some modelling techniques and their attributes. The techniques range from the 'spherical cow' approach popularized by Harte (1988) as an approach for environmental modelling, to the information models that combine traditional modelling techniques and the heuristic knowledge of experts within a disease management framework.

ANALYTICAL MODELS

The 'spherical cow' modelling approach was used by Harte (1988) to illustrate that a great number of real problems could be solved using very simple approaches. In particular, the spherical cow refers to the case of a group of academics who when invited by a farmer to investigate milk production in cows presented their findings on the basis of each cow being a sphere. The key feature was the reduction of the problem to simple components. For example, a planner that replaces a national dairy herd of 1 million indigenous cattle with exotic cattle that produce 25% more milk will only require a national herd of size 0.8 million to produce the same amount of milk. However, if the prevalences of vector-borne disease in indigenous and exotic cattle are 10% and 15% respectively the number of cases will rise from 100,000 to 120,000. If the exotic cattle are capable of increasing milk production by 60% a national herd of size 0.625 million will be needed and the number of cases of disease will drop to 93,750. The evaluation of the increase in milk production needed from exotic cattle to produce the same amount of milk and not increase the number of cases of disease can be modelled by two equations:

$$N_{indig} L = N_{exo} L (1 + m)$$

and

$$P_{indig} N_{indig} = P_{exo} N_{exo}$$

which solve to give

$$m = P_{exo}/P_{indig} - 1$$

where N_{indig} and N_{exo} denote the number of cattle in indigenous and exotic herds, P_{indig} and P_{exo} the prevalence rates of disease in indigenous and exotic cattle, L the average amount of milk proposed by an indigenous cow and m the percentage increase in milk production by an exotic cow.

From this simple model more precise models can be built to take account of lactation, management practice, welfare and the cost of change. Often for vector-borne diseases such models lead to analytical methods and in particular the use of differential equations which model the instantaneous rate of change of a population or how population numbers change from one period to another. These often can be rearranged algebraically to give a solution or alternatively solved using computer methods. On the other hand they make very general

assumptions about the behaviour of the vector, parasite and host populations. Good examples of the differential equation approach exist for trypanosomiasis (Milligan and Baker, 1988; Rogers, 1988) and for theileriosis (Medley *et al.*, 1993), and the difference equation method was successfully used in the Garki Project to model the control of malaria in West Africa (Molineaux and Gramiccia, 1980). The recent work of Anderson and May (1991) provides a comprehensive treatment of the role of differential equations as models for infectious diseases of humans.

Other analytical methods do exist. Leslie (1945) (see Williamson, 1972 for applications) pioneered the use of matrix theory and Lewis (1977) the use of networks as methods for describing changes in populations divided into stadia. Both of these methods have been used to model the life cycles of parasites of domestic livestock (Gettinby and McClean, 1979; Paton and Gettinby, 1985; Gettinby *et al.*, 1988).

SIMULATION

Stimulation is a technique whereby a physical process can be mimicked using a model which preserves the essential features of the process. The model can be analogue, but more often it is abstract and expressed in mathematical terms. The purpose of simulation is to obtain results on the behaviour of complex processes. In addressing agricultural problems, simulation models have the obvious advantage that they enable large-scale processes which involve the relationship between man, plants, animals and the environment to be modelled. Such models are referred to as system simulations (France and Thornky, 1984). Results are normally obtained once data inputs have been given to the models and so the findings are specific and not intended to provide generalizations. In the past, this has been one reason why simulation models have not been widely adopted.

DETERMINISTIC SIMULATION MODELS

Simulation models appear in numerous forms. Like most modelling approaches, simple classification is into deterministic and stochastic models. Deterministic simulations deal with models which do not take direct account of uncertainty that may occur within the physical system. The resistance of a species to chemical treatment and the suitability of species to geographical sites have been the subject of deterministic simulation models.

CHEMICAL RESISTANCE

In an investigation into the evolution of resistance to insecticide, Georghiou and Taylor (1977a, 1977b) simulated the survival behaviour of an insect population from one generation to the next using the logistic equation:

$$N(t+1) = N(t) \exp[r(K-N(t))/K]$$

where N(t) is the number in the population in generation t and N(t+1) the number at time t+1. K is the parameter denoting the maximum size the insect population can attain and r

is the growth rate parameter. Assuming a single locus model with two alleles R (for resistant) and S (for susceptible), separate simulations can be undertaken for insects with genotypes RR, RS and SS. The total number of insects to reach adult stage in each generation is then

$$N = N_{RR}W_{RR} + N_{RS}W_{RS} + N_{SS}W_{SS}$$

where the Ws take account of the different survival rates of insects under insecticidal challenge.

For data inputs r, K and Ws, the model provides results for the population size and the R gene frequency in each generation, mimicking the real life development of a population of insects exposed to insecticidal treatment. By varying the basic model, the simulations provide information on the consequences of immigration, refugia and various insecticidal control regimes. In particular the work demonstrated that refugia, whereby insects avoid contact with the chemical due to sequestration within the plant etc., has a profound effect on slowing the rate of evolution of the R allele.

BIOLOGICAL INDICES

An index which reflects the state of a biological system is one of the basic types of simulation models. Climatic indices which provide measures of the likelihood of the presence of species which vector disease have been sought ever since the study of epidemiology began. MacLeod (1932) made one of the earliest references to this approach, when it was noted that tick activity appeared to be related to weekly mean maximum air temperature. However, an index based on temperature alone has never proved to be an adequate indicator of the incidence of tick-transmitted diseases.

More recently, there have been more successful attempts. The Ecoclimatic Index (EI), calculated by the Climex model (Sutherst and Maywald, 1985) has proved useful in the study of the distribution of African ticks (Lessard *et al.*, 1990; Perry *et al.*, 1990). The index can be calculated for different geographical locations and consequently is particularly well suited for computer mapping. The index is the product of a growth index and a survival probability and takes the form

$$EI = 100\ \Sigma GI_j / \{52(1\text{-}CS)\ (1\text{-}DS)\ (1\text{-}HS)\ (1\text{-}WS)\}$$

where GI_j is the growth index in week j, CS is the cold stress index, DS is the dry stress index, HS is the hot stress index and WS is the wet stress index. The growth index is calculated from temperature, moisture and day-length data, and the survival probability is calculated from the values of stress estimated for the species at a particular site. The index is a measure of the propensity of a particular species to exist at a particular site based on environmental factors.

Bioclim (Busby, 1986), is another example of an index which can be used to simulate the distribution of a species or vegetation type which is influenced by climate. Unlike the EI index, Bioclim works on an induction principle. Species prediction is based on matching climate with sites where the species is known to exist. The method requires detailed and reliable meteorological surfaces.

STOCHASTIC SIMULATION MODELS

Statements about expected performance usually consist of a single number or point estimate without any measure of confidence. Random variation is at the very centre of biological systems. Consequently, stochastic models can be important. These models allow for the complex interactions between systems such as the random movements of vectors that transmit disease to animals or the random occurrence of environmental mishaps.

EAST COAST FEVER MODELLING

ECFXPERT (Byrom and Gettinby, 1992) is a systems stochastic model which deals with the biological details relevant to the transmission of the disease East Coast fever (ECF) to cattle from ticks under different environmental conditions. It is stochastic and random numbers generated within the computer are used to simulate day-to-day variations in the transmission of the disease and also to mimic the changes in daily temperatures which control the development of the tick population. The computer model contains four simulation models: a tick model, an ECF model, a dipping model and a chemotherapy model. The tick model is for the investigation of tick populations alone. The ECF model investigates the incidence of disease in cattle by modelling tick, parasite and herd interactions. The dipping and chemotherapy models look at the effect of tick and parasite control on the incidence of disease. An important aspect of these simulation models is that they are based on empirical data and expert findings and opinions extracted from the ECF literature, covering 80 years of research. The model is designed to be used by people from different disciplines in helping to answer differently motivated questions concerning ticks and disease. The model can also be used as a planning tool to determine effective research programs by performing computer experiments to assess the impact of findings and to assist with the design of experiments.

ECFXPERT contains comprehensive data on ticks and ECF, providing a learning facility for users with limited knowledge of the disease. On request, help messages appear in windows on the screen, and dictionary key words on which more information is available are highlighted. In a similar way a bibliography containing references to relevant literature and scientific papers can be accessed.

The ECFXPERT model has been used to examine the effects of year-to-year variation in climate and the effect of changing trends in annual temperatures on the distribution of attached ticks and disease incidence over a 20-year period. Recent findings using ECFXPERT suggest that, in the absence of wild hosts and other reservoir hosts for ticks, the infection dies out within a herd of cattle after several years if infected cattle develop sterile immunity. In contrast, if infected cattle are carriers the infection can remain within the herd indefinitely.

WEATHER CHARACTERIZATION

The presence and severity of many diseases of animals is greatly influenced by climate, or more precisely weather. Diseases such as malaria, schistosomiasis, leishmaniasis,

filariasis and trypanosomiasis depend on vectors such as mosquitos, molluscs and flies for their transmission. These vectors have life cycles with periods of development and activity which are regulated by temperature and rainfall. Weather conditions are therefore one of the most important factors in determining short-time patterns of disease. Much work has been done on analysing historical meteorological records in an attempt to find parsimonious representations of the data (Thornthwaite, 1948). Using these representations, simulation methods can be employed to generate synthetic weather data representing the pattern typical for season and region (Richardson, 1985).

In the UK, meteorological parameters are normally summarized over a standard average period of 35 years by the meteorological office. This period is considered suitable to provide adequate estimates of short- and long-term trends. For many areas, averages and standard deviations of the daily maximum and minimum screen temperatures for each month are usually sufficient, as daily temperatures can be generated using random numbers from appropriate probability distributions. Changing trends in temperature can be predicted using time series methods. However, the most important natural resource in agricultural ecosystems is water. Compared with temperature, it is precipitation which is the most variable, particularly in the tropics. In a study of dry spells, Stern *et al.* (1982a, 1982b) identified the proportion of dry spells in the month of July as being very different at Sholapur and Hyderabad in India, yet both areas have the same average rainfall and a rainy season which occurs between June and October. Models of rainfall have generally focused on first determining a probability model for whether or not a day is wet or dry, and then determining a probability model for the amount of rain falling on each wet day. For the former, Markov models which predict wet days depending on whether the previous days were wet or dry have been widely adopted (Gabriel and Neumann, 1962), whereas probability distributions such as the gamma curve have been used as sampling distributions for the amount of rainfall.

TOOLS FOR SIMULATION

Historically, the development of simulation has been closely aligned with the development of computers. In the case of stochastic simulations of systems, Monte Carlo techniques were first proposed around the middle of this century. Much of the effort has been and still is concentrated on how computers can best produce pseudo-random numbers using random number generators. Genuine random numbers are difficult to produce and pseudo-random numbers must pass various tests before being accepted as suitable approximations. There are few comprehensive textbooks on the technical aspects of simulation. One of the earliest treatments of random number generation and systems simulation is given by Tocher (1963). More recently, there has been a renewed interest in the subject as reflected by undergraduate texts by Morgan (1984) and Ripley (1987).

Applications of simulation are still widely written in fundamental programing languages such as Fortran, Pascal and more recently C. A systems simulation developed using these languages can take time and is not flexible. There have been many attempts to produce computer languages specifically for the purpose of simulation. Most of these have focused on the simulation of events in discrete time but these are not particularly useful

for models of agricultural systems. Examples are GPSS, SIMSCRIPT and GASP, which simplify the tedious task of writing program code. There have been some attempts at constructing software for systems simulations. CSMP and DYNAMO are Fortran-based languages which can be used to solve equations used to describe the relationships between components of the system. In contrast, STELLA allows the user to specify the model in graphic form using different letters to denote interrelationships. These graphical relationships are converted into equations which are then simulated. The philosophy adopted in STELLA means that the process of specifying the model is simplified and no programing experience is needed to run simulations. Other recent developments in simulation have focused on object-oriented programing and the use of icons within models to depict the behaviour of a system, and to improve the graphical presentation of results.

BENEFITS OF SIMULATION

Simulations usually depend on the computer generation of random numbers to mimic environmental variation relevant to vector populations. By repeating the simulations using different patterns of random numbers, different results but with a similar pattern are obtained. This enables confidence intervals to be placed on findings. The use of simulation models as a means of undertaking computer experiments has become important. Computer experiments make use of existing information and they provide an alternative to expensive and prohibitive field studies.

Computer simulation models will often generate results that are intuitively obvious or, more realistically, generate facts that should have been obvious. However, counter-intuitive results are one of the important benefits of a simulation model. Obtaining results which appear puzzling or which are not consistent with expectation often leads to a thought model. The thought model is a simplification of the simulation model in order that the counter-intuitive results can be explained.

DATA MODELS

Until the 1900s, agricultural systems evolved very slowly. The selection of animals that could resist disease and increase food production was based on the subjective preferences of breeders. It was not until the scientific advances of this century did the benefits of detailed recording and analysis become apparent. Simple statistical analyses were to reveal that increased productivity could be achieved from cattle by selection on the basis of liveweight gain, which had a high heritability, and not calving intervals which had a low heritability. During the last 20 years, new technologies centred around the collection, analysis and use of data have continued to improve the efficiency of agricultural production systems. Spreadsheet models have become an effective tool for the management of production resources and databases can be used as models or to support analytical and simulation models. The ILCA Bio-Economic Herd Model for microcomputers (IBIEHM) is an example of a spreadsheet model which predicts costings associated with herd dynamics (von Kaufmann *et al.*, 1990). The program is designed to interface factors such as milk offtake and liveweight gain of animals with costings and so produce balance sheets. In particular, it compares the performance of a herd over a period of years with the

performance which might be expected after intervention. The *modus operandi* of the model requires any intervention to be expressed in terms of its potential effect on liveweight gain, milk production, etc. The model generates yearly predictions and requires a careful specification of all terms relevant to herd structure and details of all associated costs such as fodder production.

Databases represent an important source of knowledge and their use has become prominent due to inexpensive storage methods and ease of access. Geographical information systems of vector-borne diseases have been at the vanguard of database models. Traditionally, data have been considered the domain of researchers for the purpose of statistical analysis and the identification of 'significant' differences. However, statistical analysis is a form of model building which can and should provide a statistical model. The data reduction methods now widely available with General Linear Model procedures in statistical software packages make it possible to construct regression and logistic regression models that describe the relationship between states of disease and environmental factors. This approach has been the subject of analyses of the ILRAD Tick Unit database where there is evidence that linear models of animal and tick characteristics can help predict the pattern of disease within an animal once infection has taken place.

Alternatively, databases can simply be interrogated and inferences based on observed frequencies of events. This makes the assumption that historical findings are a good predictor of future behaviour which is often not unreasonable for short-term predictions of disease patterns.

INFORMATION MODELS

Vector-borne diseases are complex and their study occupies a large and diverse community of people. The development of models to serve the needs of planners and decision makers must recognize the cross-disciplinary nature of the issues involved. This means that results from any model must be interpreted in the context of the problem under consideration.

Trypanosomiasis is unique amongst vector-borne diseases because of its diversity and complexity. At least seven species of trypanosomes are known to be pathogenic to man, domestic animals and wildlife. These species can infect over 30 species and sub-species of flies and often a host or vector will have concurrent infections. The tsetse vector survives in habitats ranging form dry savanna to humid forest. Control of the disease in cattle can be attempted using trypanocidal drugs, trypanotolerant cattle or tsetse population reduction. Each method of control has environmental implications. A substantial body of research literature has been generated for trypanosomiasis and this desperately needs to be brought together in a fashion that can make it useful. A number of analytical mathematical models exist which attempt to provide insight into disease transmission and control (Milligan and Baker, 1988; Rogers, 1988).

As with most vector-borne diseases, people and text are the two traditional knowledge sources in trypanosomiasis. People are the original source and text is used to capture knowledge in a fixed reliable form which is widely available. The knowledge found in text and used by people to solve problems can be represented using the 'production rule' approach to expert systems whereby knowledge is expressed in a series of *if*... *then* rules.

In addition, the information within text can be organized to be read in non-linear fashion using hypertext. Data found within literature forms the basis for mathematical models. By combining expert systems, hypertext and modelling as illustrated in Figure 1, there is the potential to construct information models which are more effective than the use of each approach in isolation.

This philosophy has been undertaken in developing an experimental Trypanosomiasis Information System (Forsyth *et al.*, 1992) for use on personal computers. As illustrated in Figure 2 the Trypanosomiasis Information System primarily consists of browse, literature sources and expert systems. The literature sources represent key papers which have hypertext links so that the user may easily move from one piece of text to another. This provides the user with a quick learning environment. Two expert systems are illustrated, one solves problems on which traps and targets might be appropriate for controlling tsetse populations and the other advises on the diagnosis of trypanosomiasis in cattle and the recommendation of viable drug treatment. The latter expert system includes the use of a geographical database for the Berenil Index. Although such a database does not yet exist, it serves to illustrate the way in which results from analytical and data models could be used within the problem solving context. As illustrated in Figure 3, modelling could be delivered as an integral part of the information system software or alternatively external

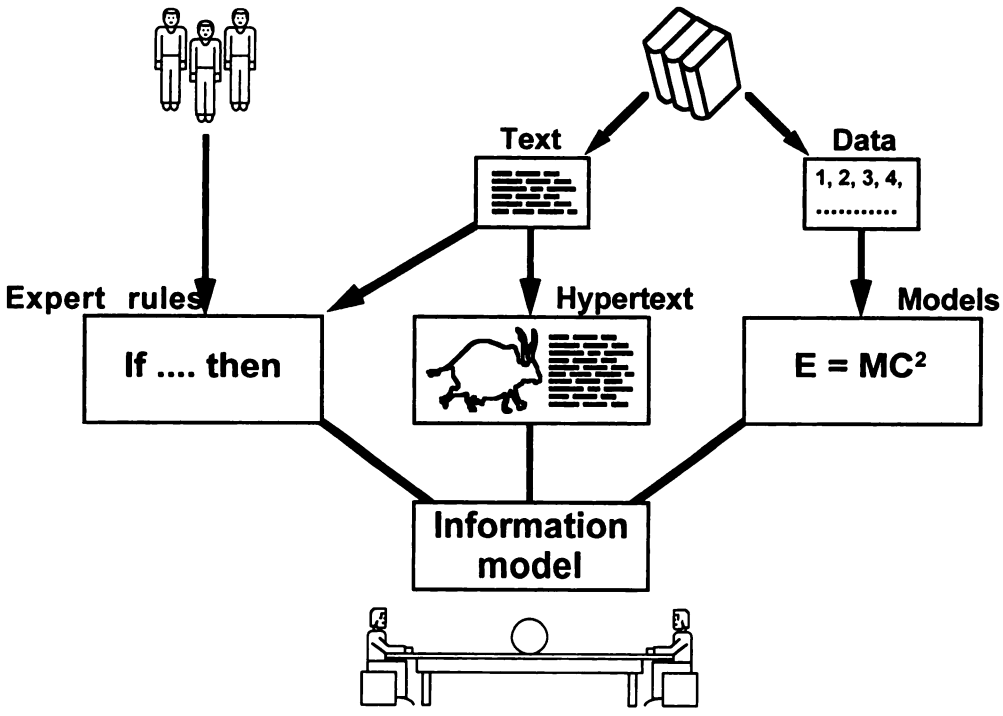

Figure 1. The use of traditional knowledge sources within information models.

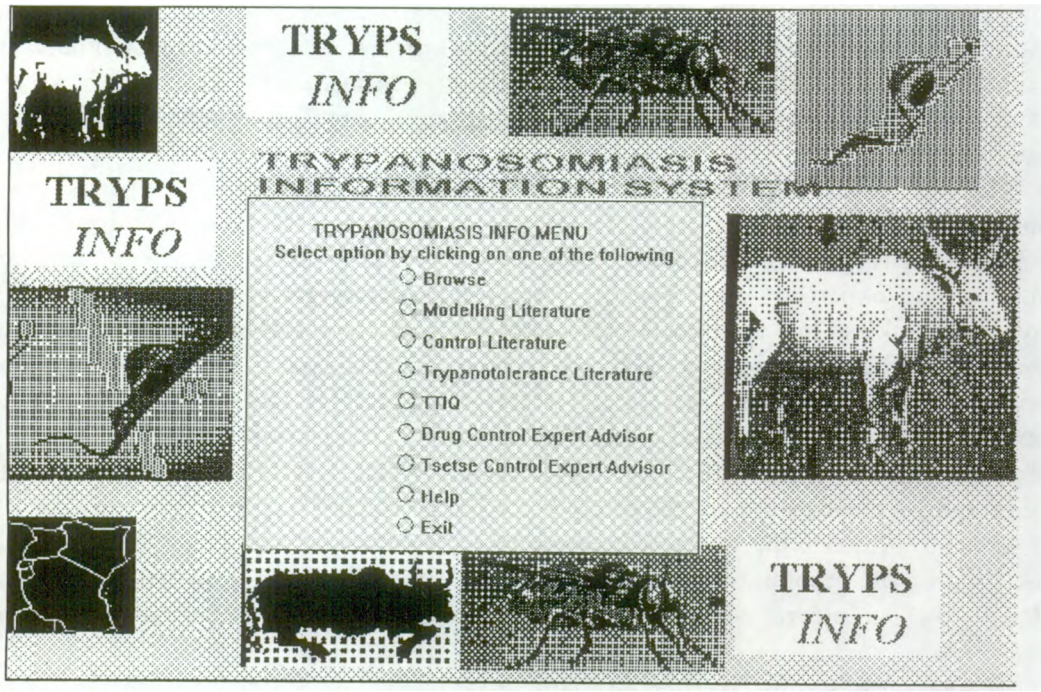

Figure 2. User options within an experimental trypanosomiasis information system.

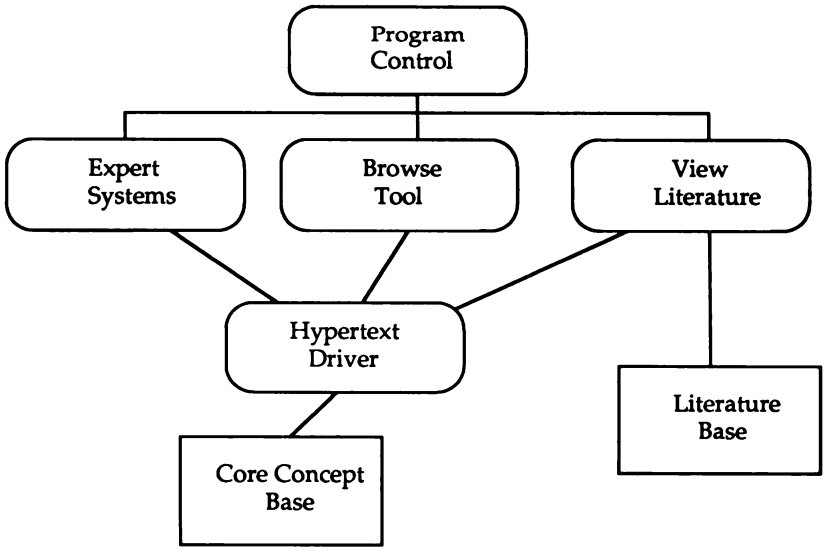

Figure 3. The potential role of mathematical models and databases within information models for vector-borne diseases. Source: After a model originally proposed in A.J. Forsyth, A Hybrid Information System for Animal Trypanosomiasis, MSc thesis, Department of Information Science, University of Strathclyde, 1991.

modelling routines could be called. Throughout the expert system's question-and-answer session, the hypertext links are fully accessible.

Models that serve a range of agricultural research areas are gradually becoming a reality. A UK register of agricultural models exists (Squire and Hammer, 1990) and the Australian Bureau of Rural Resources has recently devoted several issues of *Agricultural Systems and Information Technology* newsletters to special issues on livestock models (see *Agricultural Systems and Information Technology on Sheep Industry Software* 4 (No. 1), May 1992, and *Animal Health* 5, (No. 1), September 1993).

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Modelling disease on a geographical surface

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ABSTRACT

Until recently, models of animal diseases concentrated almost exclusively on trends over time and on differences in model predictions between various categories of animals within the modelling process. Despite the obvious importance of spatial aspects in many diseases, representation of these issues was either absent, or included in some simplified form. The reason for this was simple enough. There were no satisfactory ways of representing geography in a model without (for example) constructing a matrix which represented a grid of locations of interest and defining a vector of variables for each grid point that contained the values which would control the spatial variability of the model. While we have used this approach successfully, it is cumbersome and such models would run far too slowly unless various tricks were used to reduce processing time. Moreover it was difficult to avoid the models being somewhat artificial in the way they handled spatial issues.

It is now becoming quite practical to represent these spatial aspects much more effectively, as a result of two developments. Firstly, computer hardware development has of course been extremely rapid. Arising in part from the hardware developments, the second step has been the growth of software capable of representing spatial issues in ways which enable modelling to incorporate geographical aspects of disease realistically without imposing unworkable demands either on data inputs or on processing time. Within the spectrum of such software developments, the highest level programs are the true geographical information systems (GIS), which not only represent physical relationships among different locations accurately (i.e. contain topology), but more importantly represent different attributes of each location within separate coverages or layers of the GIS in such a way that information about each feature of the landscape can be kept separate, yet interrelated however may be required for modelling purposes. The two main methods of representation in a GIS, vector and raster (grid), have their merits for modelling purposes, and we choose whichever suits our needs best for a particular model. The distinction is in any case gradually disappearing as the more advances GIS programs take up characteristics of both systems. Examples of various forms of geographical modelling are provided in the paper.

INTRODUCTION

Until recently, models of animal diseases concentrated almost exclusively on trends over time and on differences in model predictions between various categories of animals within the modelling process. Despite the obvious importance of spatial aspects in many diseases, representation of these issues was either absent, or included in some simplified form. The reason for this was clear enough. There were no satisfactory ways of representing geography in a model without stylizing the spatial information in some way, such as considering all points to lie on a regular grid and relating variables to each of the fixed grid positions. While we have used this approach successfully, it is cumbersome and such

models would run far too slowly to be of practical value for large areas unless various tricks were used to reduce processing time. Moreover it was difficult to avoid the models being somewhat artificial in the way they handled spatial issues.

It is now becoming quite practical to represent these spatial aspects much more effectively, as a result of developments in computer hardware and software. Not only are processor speeds much faster and memory capacity far higher (so that data can be handled in RAM during a simulation rather than constantly writing to and from disk), but just as importantly the move to graphical screen management rather than text-based screen presentation has allowed far greater realism in handling spatial issues both within the model and in visual presentation of findings.

Arising in part from the hardware developments, the second step has been the growth of software capable of representing spatial issues in ways which enable modelling to incorporate geographical aspects of disease realistically without imposing unworkable demands either on data inputs or on processing time.

MECHANISMS OF REPRESENTING SPATIAL ASPECTS WITHIN A MODEL

Within the spectrum of software developments, the highest level programs and the most useful are the true geographical information systems (GIS), which not only represent physical relationships among different locations accurately (i.e. contain topology), but more importantly represent different attributes of each location within separate coverages or layers of the GIS in such a way that information about each feature of the landscape can be kept separate, yet interrelated to other information about the same location in whatever ways may be required for modelling purposes. This makes it very efficient to link a dynamic modelling process to geographical information, drawing on location information as a factor in the dynamics of the disease process, and writing results back to the GIS so that it can represent them visually.

The two main methods of representation in a GIS, vector and raster (grid), each have their merits for modelling purposes, and we choose whichever suits our needs best for a particular model. The distinction is in any case gradually disappearing as the more advanced GIS programs take up characteristics of both systems. Vector representation within a GIS means that location data is stored as points, lines and polygons, and that any point or area can be given characteristics which accurately represent its status with regard to a set of variables of interest. Thus if it is necessary in a model to represent true geographical boundaries (between farms, provinces or countries, for example) then a vector approach is necessary. In a raster system information is stored in relation to units within a grid structure, and a single unit within the grid must have a single value for any particular feature. Although in some raster systems the grid unit can vary in size across a particular map area, the ability to accurately represent boundaries is sacrificed for simpler representation which reduces data storage and processing requirements. Many models are well suited to a raster representation either directly or with some adjustment, and the output can be mapped if necessary to a vector base map. Models which use a true GIS can in principle be transferred from one geographical area to any other area for which the required input values to the model are available.

The choice of GIS software to use depends in part on the availability of a method of bridging between the geographical data and the modelling process, which is better developed in some systems than others. In certain cases it is even possible to model within the GIS, rather than by drawing upon data in the GIS to influence the operation of an external model.

Below the level of the full GIS, it is possible to buy or create programs which have sufficient of the attributes of a GIS to enable models to interact with them to create a geographic representation of a disease process without the high cost of buying a GIS. Such models do not however have inherent capacity to be 'moved' to different locations without the user personally capturing the necessary structural information for the new location.

EXAMPLE MODELS

The principles of geographical modelling can be best explained by describing three example models from our work, which contain the spectrum of these characteristics.

FarmORACLE

This is a model of a mixed livestock grazing farm in a temperate climate which can be used to evaluate management and disease control strategies. Feed intake, metabolism and productivity of each species and category of livestock are modelled on a pasture-based grazing system, with pasture supply and regrowth being calculated in a sub-model. In order to do all of this the model must 'understand' each paddock, and have information on such items as its soil type, available soil nutrient levels, aspect and slope. To achieve this, a scanned image of the farm map is used to create a quasi-geographical representation within the program of each of the paddocks on the farm, so that the model can interpret a paddock rotation system effectively for that farm (or any other farm) and can manage the farm in a sensible fashion using information supplied about the pasture growth capacity of each area.

When a farmer creates the image of his farm in the model, he can then provide information about each paddock which can be stored with a link to the map 'paddock'. This is not a true GIS but it appears to the user to have geographical information in it, and the model takes proper account of the geography of the farm in conducting the simulation. However it does this by storing information for each paddock in a database which simply understands each paddock as a management unit, but does not understand that paddock 3 is north-west of paddock 1 and contiguous with it. Such information is not necessary for a model of this kind, and would only add superfluous detail.

PossPOP

This is a model of the Australian brushtail possum in New Zealand, where it has become a wildlife reservoir for bovine tuberculosis. The modelling work is part of a larger study

of the epidemiology of the disease, which provides the model parameters. The model needs to have substantial ecological content in order to accurately represent the wildlife population, and will have information on the associated populations of farmed cattle and deer, to individual farm level.

It is still under development, and when complete will have a three-level nested structure. The lowest level is a single habitat type, and for New Zealand three habitat types have been identified as adequately representing the range of environments for possum population modelling at this micro-scale. As in any model formulation, this requires a compromise between the maximum achievable degree of realism and issues such as model execution time and availability of study findings which can be used to set parameters in the model. Within each of these habitat types a model of possum population dynamics and the epidemiology of disease can be run, varying the parameters to suit data for the specific environment, since each habitat supports different possum densities and influences the ecology of the particular possum populations.

Time patterns of ecological and epidemiological indices derived for each of the individual habitats will be used to predict behaviour in a larger habitat mosaic comprising a mix of habitats as derived from vegetation maps of the country, and at this level the model will be linked to data on farm boundaries, so that interactions between domestic livestock and the wildlife reservoir can be realistically considered in the modelling process. In addition, features which only become important at these larger scales, such as dispersal of older juvenile animals to distant locations, can be represented realistically at this meso-scale level of aggregation.

In order to predict the epidemiology of the disease at a regional level (thousands of square kilometres), output from representative habitat mosaic models will be fed to a macro-scale model in which major topographical features such as rivers and mountain ranges can influence the effectiveness of control policies. Within this format the cost-effectiveness of various control policies can be assessed in simulations covering 20 to 30 simulated years. Through the use of the hierarchical modelling approach the speed of the model can be kept quite fast while it maintains an adequate approximation to field reality.

The final version will have full linkage to the relevant GIS data on topography, vegetation type and other issues. Thus the model will be truly 'transportable' in that, if data on these features are available for another area, the model is designed to accept and operate with the new data. Model output will simply be treated as attribute data in a database file, equivalent to the physical attribute data used as input. It will therefore be possible to map expected infection prevalence or possum populations in space as well as in time, to show predicted trends under the influence of alternative control strategies.

The current version of PossPOP models the disease on a single habitat and also on a habitat mosaic covering 400 hectares, with the first model feeding data to the second. It is possible to examine tuberculosis control strategies at farm level using this approach, and it has allowed the solving of most of the major technical problems in formulating truly geographical models of populations. No insurmountable problems are seen in extending the approach to much larger areas, given the current capacity of GIS programs to provide efficient access to location and attribute data.

EpiMAN

This is a comprehensive decision support system designed for the emergency control of foot-and-mouth disease and other exotic animal diseases, should they ever enter New Zealand (Morris *et al.*, 1992). It comprises a database, geographical information system, expert system elements, and models for each of the major mechanisms of spread of foot-and-mouth disease. The model for airborne spread of FMD virus calculates the quantity of virus which would be produced by affected animals on an outbreak farm, then uses a meteorological air flow model to predict the concentration of virus at various distances downwind from the outbreak site, currently using a Gaussian dispersion model for the purpose. This is then overlaid on the GIS farm map and farms at risk of being exposed to virus are identified automatically by the GIS as those lying under the plume, differentiating those farms holding animals of various species which lie under a cattle-infective dose of virus from those which lie under the much higher sheep-infective dose. This ability to identify areas in one coverage (layer) of the GIS which are matched spatially to areas in other coverages and to the attributes of those polygons (for example, holdings of various livestock species) is one of the very powerful capabilities of a GIS which cannot be realistically replicated by any alternative approach. Allowances can also be made for a wider margin around the plume than the exact plume prediction would calculate. Although this technique has proved in practice to have valuable predictive capacity for foot-and-mouth disease outbreaks, the nature of the Gaussian plume method of predicting airborne virus transmission means that the calculations do not take true account of the three-dimensional topography over which the plume is passing. Newer techniques such as Lagrangian puff models (Dr T. Mikkelsen and co-workers, Department of Meteorology and Wind Energy, Ris National Laboratory, Roskilde, Denmark) can take this into account and can also more precisely account for specific features of weather conditions which may affect virus dispersion. They can also make use of output data from numerical weather prediction models as an alternative to using data from specific local weather recording stations. Such improved mathematical techniques can greatly enhance the predictive power of geographical models of virus dispersion, although limits on the accuracy of the biological data which can be supplied to the meteorological model means that their full power cannot always be captured for veterinary purposes. Nevertheless it appears that such models will progressively allow airborne spread of disease to be assessed in greater detail, as the importance of airborne spread of various disease agents achieves growing recognition.

EpiMAN also includes other geographical modelling features, such as a model of inter-farm spread by various mechanisms (Inter-Spread), which can be used both for real-time evaluation of likely outbreak development and as a training tool by creating realistic outbreak scenarios for transmission of the disease. A further model allows prospective evaluation to be carried out of various control options, such as ring vaccination and contact slaughter.

EpiMAN is not simply a series of models, but an integrated decision support system (DSS) which handles incoming data of many different types, links the data items to geographical locations through the GIS, guides management actions through knowledge-based priority setting systems, and provides up-to-date evaluations of progress in control procedures. Through the epidemiologist's workbench, it also offers a series of tools which

can be applied to the data to compare expected with actual trends, and where necessary modify the operation of the DSS to take account of new findings.

POTENTIAL APPLICATION TO AFRICAN TRYPANOSOMIASIS

The trypanosomiasis-tsetse fly complex is an ideal (although very challenging) application to which geographical computer simulation could be applied, probably most usefully as part of the development of a decision support system for control of the disease. It would be a long-term DSS, rather than a real-time emergency system of the EpiMAN type. Because the ecology of the fly and hence the trypanosomes is very dependent on landscape and climatic factors as well as host-related issues, modelling of large-scale control options could be a very powerful tool, utilizing a hierarchical model with a habitat-mosaic approach to handling the landscape diversity of African countries.

Models which lack a spatial dimension will have continuing difficulty in handling the geographical reality of this disease and the emergence of techniques for modelling on geographical surfaces with access to climatic and other data offers an ideal starting point for applying modelling at a practical level in the epidemiological study of such complex diseases.

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Statistical modelling of georeferenced data: mapping tsetse distributions in Zimbabwe using climate and vegetation data

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ABSTRACT

It is important to be able to predict the distribution and abundance of insect vectors of disease in order that intervention programs may be targeted at appropriate areas and control operations may be designed and executed in the most efficient manner. Climate and vegetation data are becoming more widely available, partly through the increased use of satellites for remote sensing. In this paper we compare and contrast a number of advanced statistical techniques that can be used to predict the distribution of tsetse flies in Zimbabwe. We consider the relative merits of the different techniques in helping us to make accurate predictions but also in helping us to understand the biological factors that determine the distributional limits of tsetse flies. The simpler methods, such as linear discriminant analysis and tree-based induction, tend to be less precise but easier to interpret biologically than the more sophisticated methods, such as non-linear discriminant analysis and neural networks.

INTRODUCTION

It is important to know the distribution and abundance of insects, especially those that are the vectors of disease. Eventually, we would like to be able to produce risk maps that tell us how the risk of disease varies over space and time. Such maps would be valuable for planning intervention strategies in epidemic situations and for planning control strategies in endemic situations.

Among the most important determinants of the distribution and abundance of insects are climate and vegetation. Many insects are limited in their distribution by high or low temperatures or by dry-stress. Even for haematophagous insects, vegetation cover is often

important for their survival. Furthermore, satellite-derived vegetation data may serve as a surrogate for climate data, when the latter is unavailable, since the vegetation might respond to the same climate variables as does the insect.

The general problem, then, is: given estimates of the distribution of an insect, for example, together with a set of climate- and satellite-derived data, all on a suitable raster grid, how can one best predict the distribution of insects? The problem appears to be fairly straightforward. One imagines a parameter space of several dimensions in which each axis corresponds to one environmental variable. A volume in this parameter space is then identified that encloses the values of the various parameters in which the insect vector or the disease, for example, occurs and excludes all those in which it does not occur. Unfortunately, this apparently straightforward procedure turns out to be difficult to handle with real data that do not satisfy the usual assumptions of normality and linearity that underlie most standard parametric statistical techniques. Furthermore, standard techniques, such as discriminant analysis, assume that the parameter space can be separated by a single linear function, an assumption that is rarely valid.

In recent years new mathematical techniques, including non-linear discriminant analyses, neural networks, decision tree induction methods and *k*-nearest neighbour analysis, have been developed to analyse multivariate data. In this paper we investigate the relative merits of these methods in helping us to identify the factors that determine the limits of tsetse fly distributions.

SOURCES OF DATA

There are, unfortunately, few places for which reliable maps of the natural distribution of tsetse flies as well as good climatic and vegetational data are available. In some places the distribution of the flies has been altered as a consequence of human interventions and in others as a consequence of biological events such as the rinderpest pandemic that swept through Africa at the end of the last century destroying most of the favoured hosts of tsetse flies and eliminating the flies from much of the country (Ford, 1971). Fortunately, maps of the pre-rinderpest distribution of flies are available for Zimbabwe. Figure 1 shows the distribution of tsetse flies in 1896 as deduced by Fuller (1923), Jack (1914, 1933) and Curson (1932) and reported by Ford (1971).

Tsetse Flies in Zimbabwe

The two species of tsetse flies that are found in Zimbabwe, *Glossina morsitans* and *G. pallidipes,* are both savannah species preferring open woodland to forested areas. At the end of the last century *G. morsitans* was overwhelmingly the dominant species of fly in Zimbabwe and the distributions can be taken as referring to this species alone. One belt of flies extended across the north of the country (along the Zambezi River) and another across the south of the country (along the Limpopo River) as shown in Figure 1. In other parts of Africa the distribution is more patchy and we are applying the methods that we have developed to the distribution of *G. pallidipes* and *G. morsitans* in eastern Africa where the distribution of flies is more complex than it is in Zimbabwe.

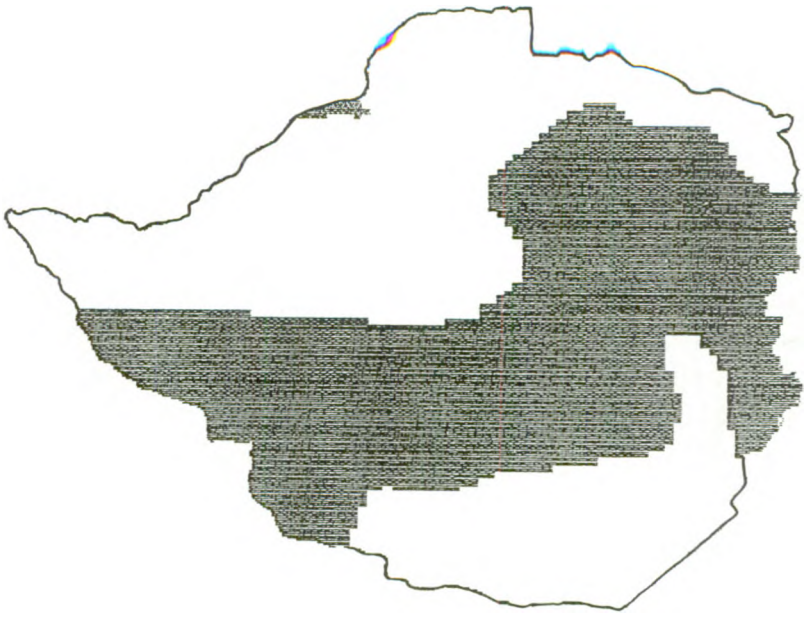

Figure 1. Map of Zimbabwe showing areas in which tsetse flies are believed to have been present and absent before the rinderpest pandemic in 1896. Light areas—present, dark areas—absent. The small black region in the north west is Lake Kariba.

Climatic Data

The climatic data were assembled by Booth *et al.* (1990). The available meteorological data for Zimbabwe were interpolated on a 5′ grid (about 10 × 10 km) using Laplacian smoothing splines (Hutchinson *et al.*, 1984). For each month of the year and for each of 4999 grid cells the elevation, rainfall, evaporation, maximum, minimum and mean temperatures were estimated.

The climatic data set alone has 420,000 data points and the first priority was to reduce the data to manageable proportions. The elevation, annual rainfall, evaporation and the following temperature variables were used*:

1. Maximum-mean-maximum temperature or XMX (average value of the daily maximum temperature for the hottest month).

2. Maximum-mean-mean or XMM (average value of the daily mean temperature for the hottest month).

* In the following definitions the last word refers to day, the last but one to month and the first to year. Maximum-mean-mean is therefore determined by taking the mean temperature for each day, calculating the mean value for each month and then taking the maximum of the resulting 12 values.

3. Mean-mean-mean or MMM (average temperature over the whole year).

4. Minimum-mean-mean or NMM (average value of the daily mean temperature for the coldest month).

5. Minimum-mean-minimum or NMN (average value of the daily minimum temperature for the coldest month).

Temperatures 1 and 5 give extreme values while temperature 2, 3 and 4 give the variation in the mean temperatures.

The elevation contours (Figure 2a) show the eastern highlands rising to 2000 metres and the high ground falling away to about 1000 metres from east to west and then falling away to about 500 metres to both the north and the south. The NMN temperatures (Figure 2b) almost reach freezing and the XMX temperatures (Figure 2c) reach 35 °C. The rainfall (Figure 2d) is very high in the eastern highlands, is lowest in the south and south-west of the country and does not vary greatly over the rest of the country. Typical values are about 500 mm per year. Evaporation (Figure 2e) is low in the eastern highlands and increases as one moves to the west which borders on the Kalahari sands.

Vegetation Data

The vegetation data are the monthly maximum value composites of the normalized vegetation index derived from the 8 km NOAA-AVHRR data for the years 1984 to 1989. The vegetation data were interpolated onto the same grid as the climate data and to reduce the size of the data set we used only the data for February and September which correspond to the highest (late wet season) and lowest (late dry season) values, respectively.

One Dimension

In one dimension it is easy to determine the optimal threshold value that divides places in which flies are present from those in which they are absent and the resulting threshold values with the corresponding number of correct predictions are given in Table 1.

The five temperature variables give the best overall predictions with NMM being the best of all, indicating that low temperatures are the most important factor in limiting the distribution of flies in Zimbabwe. The best prediction based on evaporation (Figure 3a) excludes flies in areas in which the evaporation is less than 1930 mm per year. However, the boundaries of the tsetse fly distributions lie along lines that run roughly from west to east while the evaporation and rainfall contours lie along lines that run roughly north to south. Using the range of NDVI values gives a better prediction than that based on evaporation (Figure 3b) but produces a more speckled distribution due in part to the inherently noisy nature of NDVI measurements and the extensive changes in vegetation cover brought about by human intervention since 1896. Although evaporation and the range of NDVI produce predictors of similar quality when judged by the proportion of grid cells for which the prediction is correct, one might prefer the prediction based on the vegetation index which, if one overlooks the speckled nature of the prediction, gives a better overall shape. Any criteria of goodness of fit should include reference to the spatial

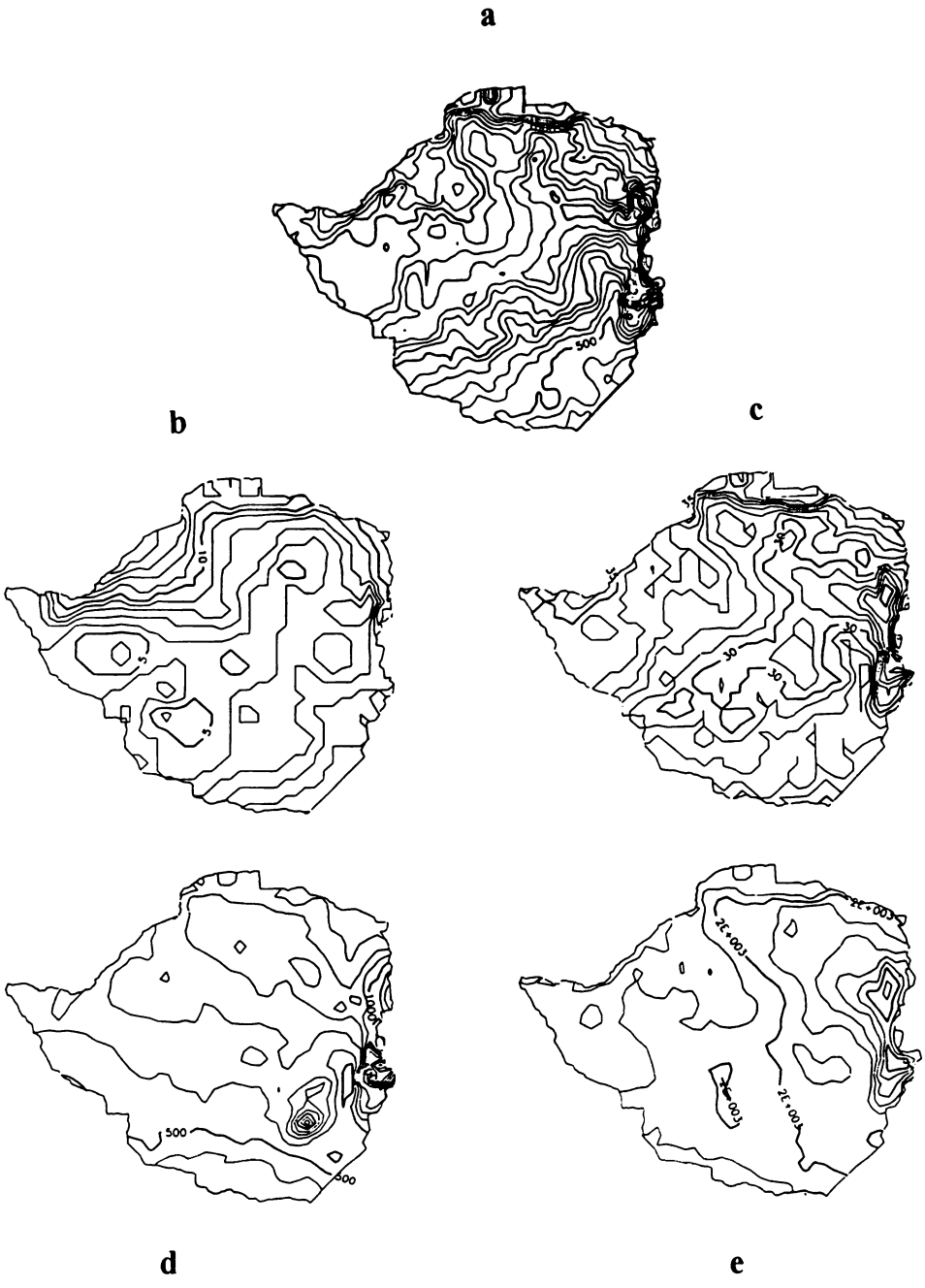

Figure 2. a) Elevation contours at 100 m intervals. **b)** Minimum-mean-minimum temperatures at intervals of 1 °C. **c)** Maximum-mean-maximum temperatures at intervals of 1 °C. **d)** Annual rainfall at intervals of 100 mm. **e)** Annual pan evaporation at intervals of 100 mm.

Table 1. Threshold values and percentage of correct predictions, *P*, for each of the variables used in this analysis. For the rainfall and the September NDVI, the flies are predicted to be present below the threshold values. For the other variables the flies are predicted to be present above the threshold values.

Variable	Threshold value	Percentage correct, P
NMM/°C	15.5	86
XMM/°C	24.5	83
XMX/°C	32.5	82
MMM/°C	21.0	79
NMN/°C	8.0	76
Range NDVI	0.22	71
Evaporation/mm	1930	69
September NDVI	0.18	66
February NDVI	0.39	64
Rainfall/mm	500	56

properties of the fit and cannot rely on a single overall statistic such as the proportion of correct predictions.

Many Dimensions

In many dimensions the analysis becomes more difficult because a multi-dimensional space can be divided in many different ways: by a linear surface, a curvilinear surface or even one or more isolated volumes.

Linear Discrimination

Standard linear discriminant analysis allows us to determine a linear function that separates the parameter space into regions where the flies are present and absent. The function is chosen to maximize the ratio of the between groups variance to the within groups variance assuming that the probability that an observation belongs to a given class follows a multivariate normal distribution with the same covariance matrix for all classes (Green, 1978).

Non-Linear Discrimination

In addition to the assumption of normality, standard methods of discriminant analysis also depend on assumptions of linearity that may not be valid. These limitations are largely overcome by non-linear discrimination based on projection pursuit regression. A direction vector is chosen in the parameter space and the independent variable (presence/absence)

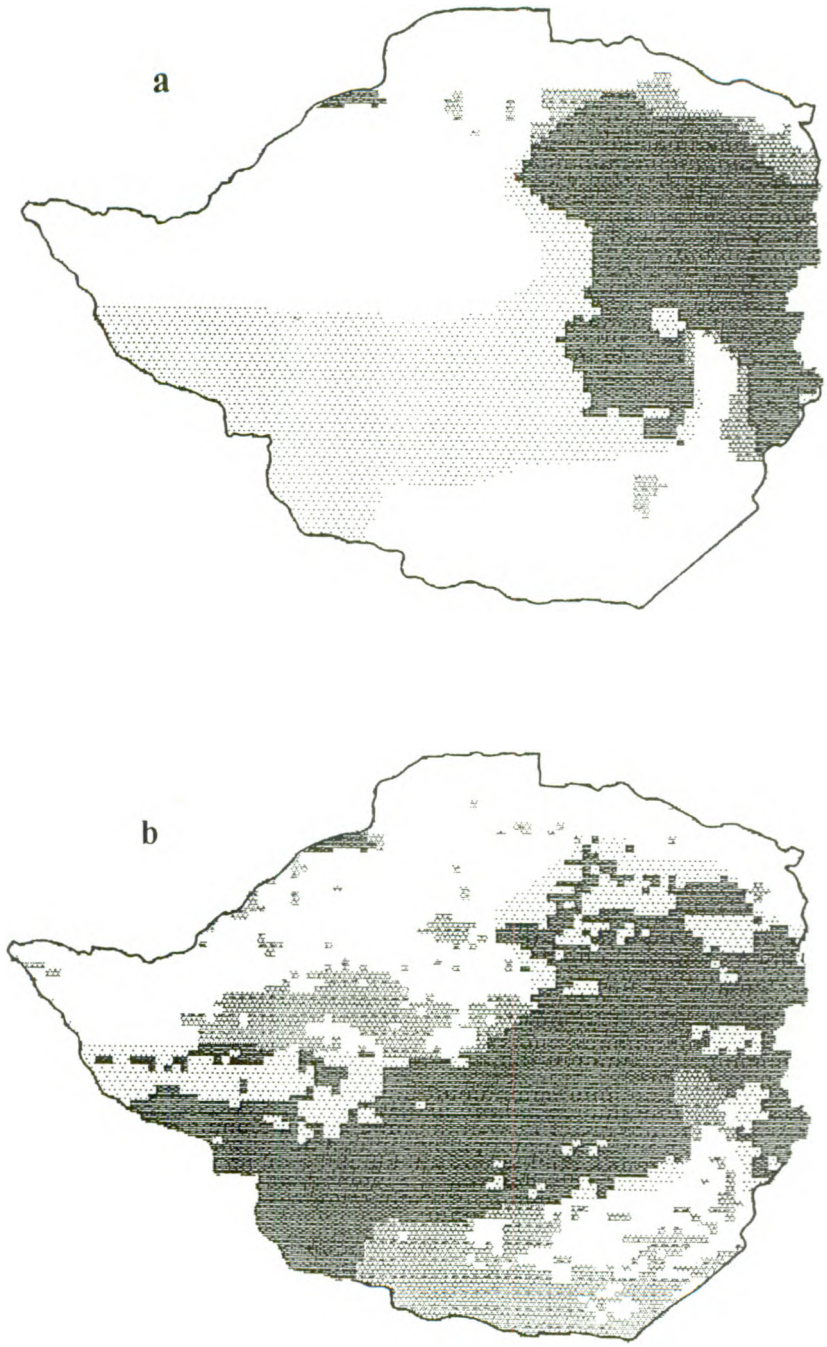

Figure 3. a) Predicted distribution of tsetse flies with a threshold value of 1930 mm/year for the pan evaporation. **b)** Predicted distribution of tsetse flies with a threshold value of 0.22 for the difference between the February and September NDVI values. White areas—flies present, predicted present; light shading—flies present predicted, predicted absent; dark shading—flies absent, predicted present; black areas—flies absent, predicted absent.

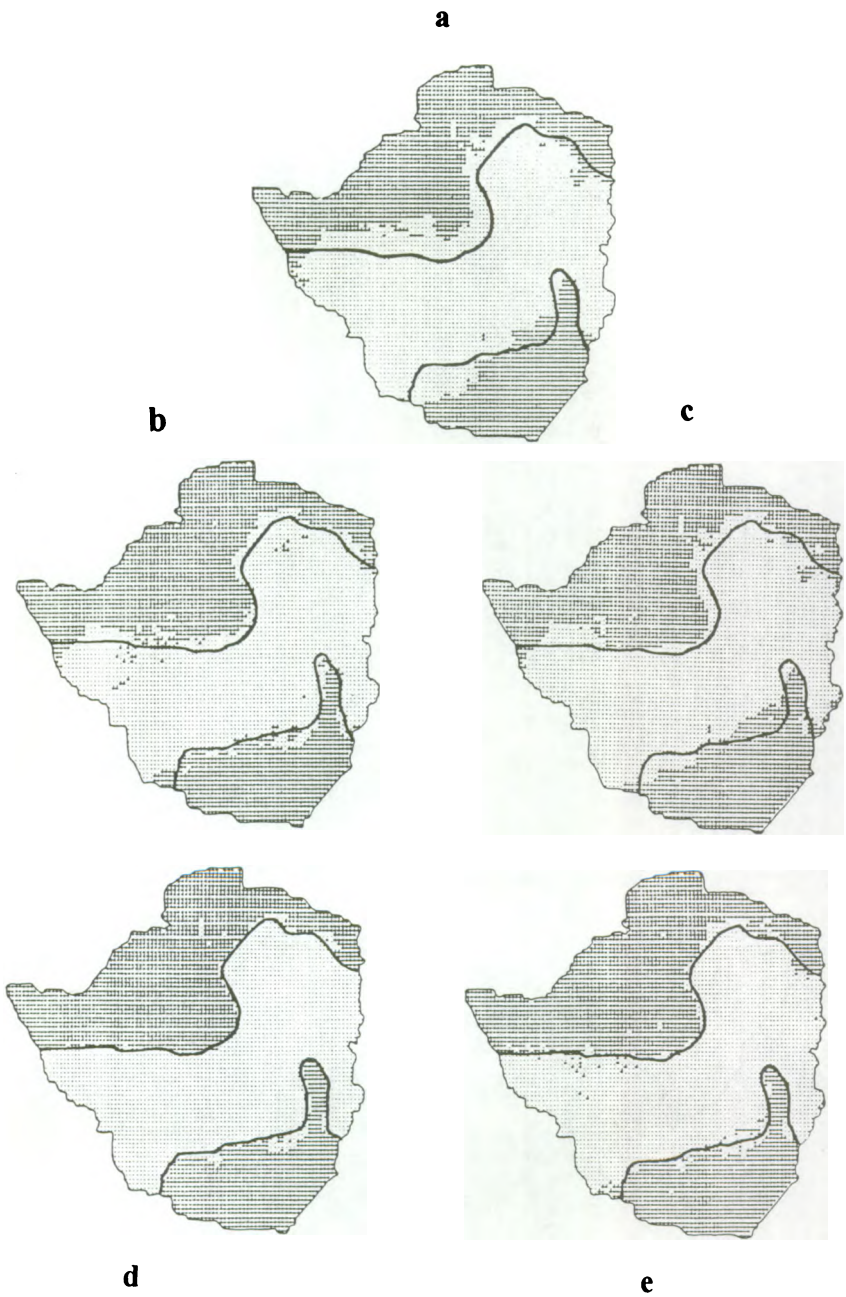

Figure 4. a) Predicted presence and absence of tsetse flies using linear discriminant analysis. **b)** Predicted presence and absence of tsetse flies using the projection pursuit regression discussed in the text. **c)** Predicted presence and absence of tsetse flies using the tree-based classification given in Figure 5. **d)** Predicted presence and absence of tsetse flies using the *k*-nearest neighbour analysis with *k* equal to 1 and using only the NMM temperature, the XMX temperature, the rainfall and the evaporation. **e)** Predicted presence and absence of tsetse flies using a neural network with 24 hidden neurons, starting with a seed of 2345. + indicates present, • indicates absent.

is plotted against the projection of the points in the parameter space onto this vector. The data are then smoothed using a numerical algorithm and this smoothing function is used to make the predictions. The direction of the vector is then varied and the smoothing process repeated until the best prediction is obtained. Another direction vector is then chosen and treated in the same way. The fraction of the unexplained variance in the data is used to determine the number of direction vectors to include in the regression.

Decision Tree Induction

Decision tree induction is an extension of the optimal threshold predictor described above. Each predictor variable is tested to find which one gives the best classification. Each of the two classes are then tested against each of the predictor variables to find the variable that gives the best discrimination in each class. The process continues until all observations are correctly predicted and the tree is then pruned to provide a reliable classification.

k-Nearest Neighbour Analysis

In *k*-nearest neighbour analysis a small integer *k* and a set of points that will serve as the training set are chosen. For each new point the *k* points that are closest to the new point in the parameter space are then identified and the new point is assigned to the class which is most common among these *k* nearest neighbours.

Neural Networks

Neural networks are layers of connected nodes. The first layer comprises the input to the system and the last layer the output. The number of input nodes is equal to the number of parameters in the fitting procedure and, since we have only two possible values for the output (presence/absence) there is one output node that can be either on or off. The input to each node is tested against a threshold to produce an output of 0 or 1. The output from each node in each layer is multiplied by a weighting factor and fed to the nodes in the next layer. The sum of the inputs to each node is then tested against a threshold and the procedure is repeated. Points in the parameter space are presented in random order to the network and the output from the network is calculated and compared with the observed values (present or absent). If the prediction is wrong the weights and thresholds are recalculated using a back propagation algorithm, a method of steepest descent, which minimizes the mean square error in the prediction. A weighting factor is used to control the amount by which the weights are changed on each iteration; small values of the weight will cause the algorithm to converge slowly while large values will cause it to oscillate.

RESULTS

From the 4999 grid cells for the data, a random sample of 1000 were used to train the various classifiers and the remaining cells were used to test the classifications.

Linear Discriminant Analysis

In addition to the variables given in Table 1 we used n_{15} the number of months for which the minimum value of the mean temperature was less than or equal to 15 °C.

The linear discriminant analysis gave the following model:

$$y = -2.04 - 0.45n_{15} + 0.11XMM - 4.85Sep + 1.58Feb$$

The flies are therefore excluded from cold areas in which many months have mean minimum temperatures less than 15 ÉC and the maximum value of the mean temperature is low, and from very wet areas in which the September (dry season) NDVI is high or dry areas in which the February (wet season) NDVI is low. For the training set 88% of the predictions were correct, for the test set 87% were correct. The predicted distribution of flies is given in Figure 4a. Although the overall shape is reasonably good, the boundaries are not picked out very precisely.

Non-Linear Discrimination: Projection Pursuit Regression

Using projection pursuit regression the fraction of the unexplained variance is used to determine the number of projection vectors to include and the value chosen was 5. For the training set 95% of the predictions were correct, for the test set 92 and 93% were correct.

The final model gives some weight to all of the variables and for each projection a non-linear transformation of the projection axis is used. Although the non-linear discriminant technique gives a better classification than the linear discriminant technique, the model effectively contains about 70 parameters making interpretation very difficult. However, comparison with the linear discrimination provides an indication of the limitations imposed by the assumptions of normality and linearity. Figure 4b gives the predicted distribution based on projection pursuit regression and comparing this with Figure 4a shows that the non-linear method picks out the northern limits more precisely, picks out the Sabi River valley more precisely in the north-east part of the Limpopo fly belt (in the south) and allows the flies to occupy regions further to the west in the Limpopo fly belt.

Tree-Based Model

Figure 5 shows the pruned tree-based classification. The top node indicates that if we assume that the flies are present everywhere then, in the training set, 498 out of 1000 grid cells are mis-classified. The first discrimination corresponds to the NMM (low temperature) classifier given in Table 1 and indicates that after this condition is applied 128 out of 1000 cells are mis-classified so that 87% of the cells are correctly classified. Using evaporation to reclassify the areas in which the flies are present (on the first criterion) increases the proportion of correctly classified cells to 89%. Using the XMX temperature to reclassify the areas in which flies are absent (on the first criterion) does not improve the classification but excludes flies from 262 cells while leaving 272 cells free to be reclassified. The best classifier for these 272 cells is rainfall and this increases the proportion of correctly classified cells to 90%. Reclassifying the cells in which flies are

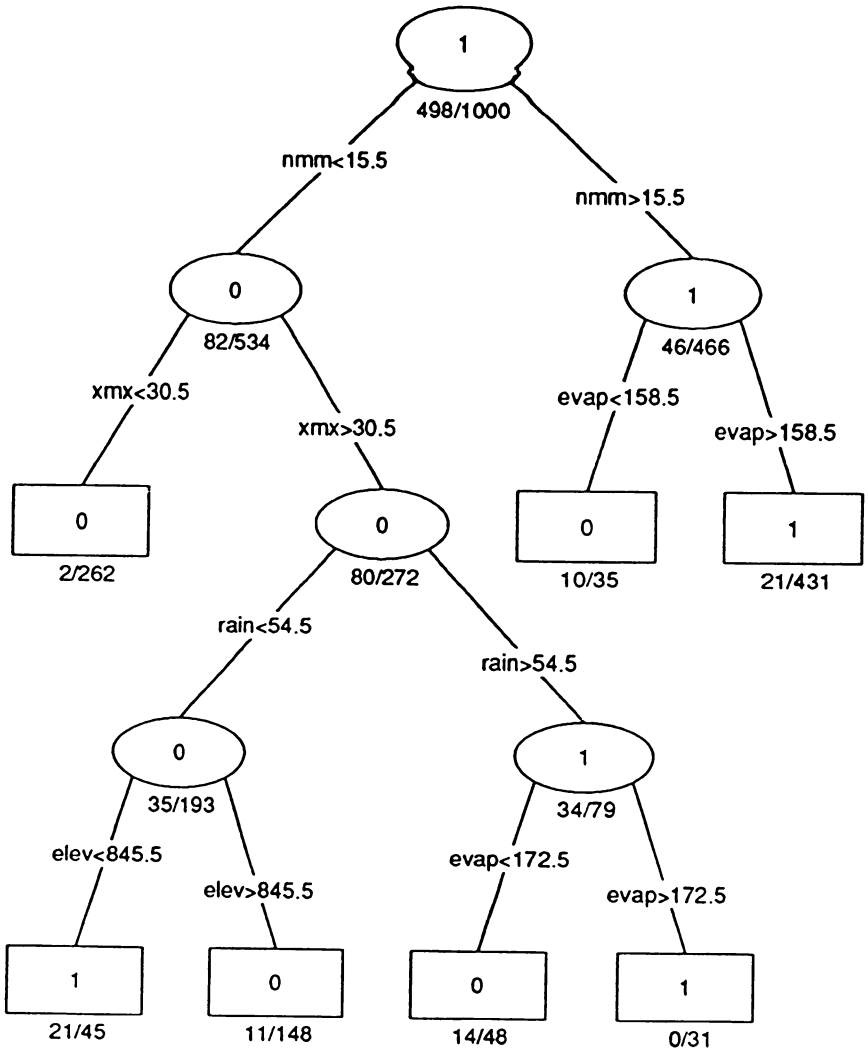

Figure 5. The pruned tree-based classification. Each ellipse indicates whether or not flies are present (1) or absent (0). The rectangles indicate the final classifications. The ratios indicate the proportion of mis-classifications at each node in the tree. The threshold values for successive nodes are indicated on the lines joining nodes.

present, using evaporation, and in which they are absent, using elevation, we get a final classification in which 92% of the cells are correctly classified. Applying this tree to the test set gives 91% correct predictions.

The predicted distribution of the flies using the tree-based classification is shown in Figure 4c. The tree-based classification is, like the linear discriminant analysis, easy to interpret biologically. It indicates that the overwhelmingly dominant factor is the low temperature threshold. Small, but significant improvements in the classification can be obtained using a combination of rainfall and evaporation. Where the flies should be

present, according to the low temperature limit, they should nevertheless be excluded in very wet areas where the evaporation is low. Where the flies should be absent, according to the low temperature limit, they may still be present if the rainfall is sufficiently high but not when the evaporation is very low.

k-Nearest Neighbour Analysis

After investigating the performance of the *k*-nearest neighbour analysis for different values of *k* it was found that the best error rate was obtained with *k* equal to 1. Each member of the test set is then put into the same class as its nearest neighbour (in the parameter space) in the training set. Using all of the available variables about 93% of the cells in the test set are classified correctly.

Using *k*-nearest neighbours the error rate on the test set was improved slightly by including only the environmental variables that were indicated as being the most important in the tree-based classification, namely the NMM temperature, the XMX temperature, the rainfall and the evaporation. The spatial distribution of the flies predicted on the basis of the *k*-nearest neighbour analysis is shown in Figure 4d. It gives the highest proportion of correct predictions and does even better than the non-linear projection pursuit regression. Like the latter, however, it does not, in itself, help us to interpret the data biologically.

Neural Network Analysis

Networks with a single hidden layer containing 6, 12 and 24 neurons were used. Random initial weights were chosen and for each network three runs were carried out using different random number seeds. Between 93 and 96% of the predictions were correct except for one run in which the network became trapped in a local minimum and only 86% of the predictions were correct. Figure 4e shows the predictions based on the neural network with 24 hidden neurons and the overall classification is very good. Unfortunately, the predictions of the neural networks are also difficult to interpret biologically.

DISCUSSION

We have a range of techniques that we can use to fit the distribution of tsetse flies to the environmental variables and these techniques can of course be used for any environmental variables and for any observed distribution. Eventually we hope to understand the biology of the organism whose distribution we are trying to explain sufficiently well that we can simply define criteria for the presence or absence of the organism and make predictions accordingly. We would then have a set of rules that we use to define a volume in our variable space of any complexity that we choose as has been done in the world-wide classification of vegetation types by Woodward and Williams (1987) and in identifying areas within Zimbabwe suitable for particular tree species (Booth *et al.*, 1990). Before we

reach that stage, however, we need to be able to use our data to help us to identify variables that are likely to be significant and to determine threshold values for such variables.

Probably the most useful way to begin is to consider each variable separately in order to decide which single variables are likely to be the most important and to decide if more than one threshold is suggested by the data for a particular variable.

Generally we will of course want to include more than one environmental variable and the simplest way to proceed is to use a linear discriminant analysis. If a particular variable seems to require more than one threshold, it is likely that the discriminant analysis will have difficulty producing a good prediction using that variable. At this stage we might examine the spatial distribution of the relevant variable and, if necessary, fit different models in different environmental regions. For example the highlands in the east of Zimbabwe are too wet for the flies while the Kalahari sands in the west of Zimbabwe are too dry for the flies. We might therefore consider dividing the country along a north south line and then analysing the eastern and the western regions separately. The larger and the more diverse the geographical area under study, the more likely it is that splitting the region up will help. An advantage of the non-linear methods of analysis is that they should be able to deal directly with problems of this nature without having to fit different models in different places.

The next most useful analysis involves carrying out a tree-based classification. While the discriminant analysis divides the parameter space over a hyperplane, the tree-based classification divides the space into a series of nested hyper-rectangles. This too is done in a forward stepwise manner including at each successive branching the variable that gives the greatest improvement in the number of correct predictions. This provides a useful contrast with the linear discriminant analysis. If the two methods identify quite different variables as being important one should examine the data and try to determine the reasons for this.

If the classification is not very good or if one is concerned about the validity of some of the assumptions, we can use a *k*-nearest neighbour analysis. This has the advantage of being simple to carry out and is likely to give a good fit to the data. Comparing the linear discriminant analysis and the tree-based classification with the *k*-nearest neighbour analysis should give some idea as to how much we are likely to be able to improve on the simple analysis schemes using more sophisticated techniques. The disadvantage of the *k*-nearest neighbour analysis is that it affords us no biological interpretation. However, if we are concerned to use our predictions simply as part of a management or planning operation, it may be that this is in fact the best method to use.

If we still feel that it should be possible to improve the prediction further, the next step would be to carry out a non-linear projection pursuit regression. Again one is unlikely to be able to use the fit to interpret the data biologically but it does tell us if the limitations imposed by the more restrictive assumption of the simpler techniques are important. And again, if the purpose was simply to use the predictions in a management or planning context this may be all that we need.

The final possibility is to use neural networks. These are very powerful but also the most demanding on computing time and the most difficult to execute and interpret. A neural network of sufficient complexity can pick out regions of parameter space of essentially any shape or form. However, the study of neural networks and their application to problems

such as this is still in its infancy. The neural network took several orders of magnitude longer to converge than even the non-linear discriminant analysis. Many flexible methods of discrimination are currently under development and these will incorporate the best features of the currently available methods.

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APPLICATION OF MODELLING

The development and application of models in the planning and implementation of reduced and strategic-minimal tick-control strategies in Zimbabwe

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ABSTRACT

Intensive dipping of cattle for tick control was introduced in Zimbabwe about 80 years ago as a control measure for East Coast fever caused by *Theileria parva*. The dipping policy was strictly enforced and by the mid-1950s had resulted in the apparent eradication of the more virulent forms of *T. parva* and the effective control of other tick-borne diseases. However, dipping was disrupted during the pre-independence war in the 1970s and large numbers of susceptible cattle died following exposure to tick-borne diseases. Since independence the costs of dipping have escalated considerably.

The epidemiological implications of and high costs associated with intensive dipping have led to a re-evaluation of Zimbabwe's policy on the control of ticks and tick-borne diseases. Recent research on tick population dynamics, production losses caused by ticks, the susceptibility of different cattle breeds to tick infestation and the epidemiology of tick-borne diseases has provided sufficient data to model tick-control strategies. At the same time, the integration of tick distribution data and other variables such as climate and vegetation, by means of geographical information systems (GIS), has allowed tick-control zones to be defined. Most research has been directed towards the two most important tick pests of cattle in Zimbabwe, *Rhipicephalus appendiculatus* and *Amblyomma hebraeum*. Cost effective control strategies for *R. appendiculatus* have been identified and simulated using a tick population model, T3HOST. Also defined has been an economic damage threshold for *A. hebraeum*.

Specific costed control strategies for exotic taurine and indigenous sanga cattle have been recommended for each tick-control zone. An important potential problem has also been identified using GIS in combination with a climate-matching model, CLIMEX. Namely, large parts of Zimbabwe which are currently free of *A. hebraeum* are climatically suitable for the survival of this species. As a consequence there is a risk of *A. hebraeum* (the vector of heartwater caused by *Cowdria ruminantium*) spreading if dipping frequency is reduced. Notwithstanding this risk the Government of Zimbabwe has begun to implement strategies involving reduced or strategic-minimal dipping. This revised dipping policy has resulted in considerable financial savings and does not appear to have caused any marked increases in production losses caused by ticks or in the incidence of tick-borne diseases. However, the changes in dipping frequency have occurred during a period of extreme drought when tick abundance has been very low, and as a consequence it is too early to assess realistically the impact of the new strategies.

* Deceased.

INTRODUCTION

Economically important tick-borne diseases of cattle in Zimbabwe include heartwater caused by *Cowdria ruminantium,* theileriosis (January disease) caused by *Theileria parva,* anaplasmosis, caused by *Anaplasma marginale* and babesiosis caused by *Babesia bigemina.* The control of these diseases has, for the past 80 years, been based primarily on the control of their tick vectors by dipping. Intensive dipping of cattle was made compulsory in 1914 to control East Coast fever (ECF), a virulent form of *T. parva* infection that had been introduced to southern Africa from eastern Africa in 1901/1902. Although ECF was considered to have been eradicated by 1954, the intensive dipping policy continued to be enforced as a control measure for the other economically important tick-borne diseases (Lawrence and Norval, 1979). Intensive dipping proved extremely effective in the control of *Amblyomma hebraeum,* the main vector of heartwater, and by the early 1970s the tick had been eradicated from large areas of the country (Norval and Lawrence, 1979). Control of *Rhipicephalus appendiculatus,* the vector of theileriosis, by means of regular dipping was the only control measure available against January disease (Lawrence and Norval, 1978). Babesiosis, transmitted by *Boophilus decoloratus,* and anaplasmosis, transmitted by a variety of tick species and biting flies, were also considered to be effectively controlled by intensive dipping (Matson, 1966).

The first major problem with the intensive dipping policy was encountered between 1973 and 1979, when the dipping service in the communal lands (then known as the Tribal Trust Lands) was progressively disrupted by the guerilla war that preceded independence. One million of the approximately three million communal land cattle were estimated to have died as a result of tick-borne diseases during this period (Norval, 1979). The cause of these losses was the exposure of non-immune cattle to tick-borne diseases following the resurgence of tick populations. Immunity to tick-borne diseases in many of the communal land cattle herds had been lost because effective tick control over many decades had interrupted the natural transmission of infection to young animals (Lawrence *et al.,* 1980). The communal land cattle that survived into the 1980s were mostly immune to tick-borne diseases; endemic stability had thus replaced the instability that had existed prior to disruption of dipping (Norval, 1981a; Norval *et al.,* 1983, 1984). The experience of the 1970s thus provided a dramatic and costly illustration of the inherent danger of creating endemic instability by intensive dipping.

When peace returned to Zimbabwe after independence in 1980, there was considerable popular pressure to restore the communal land dipping service because people had associated the cattle losses during the war with lack of dipping. Hence, for political rather than scientific reasons, intensive dipping was resumed in the communal lands in the early 1980s. Fortunately, the level of tick control achieved during those years was not such that endemic stability was disrupted on a wide scale (Norval *et al.,* 1992a). Cost became the principle obstacle to achieving intensive dipping throughout the communal lands. The costs of acaricides, labour, transport and materials for building and maintaining dip tanks increased at a much higher rate than the prices paid for cattle and their products. In the commercial sector the increasing costs were borne by individual farmers but in the communal lands, where dipping was completely subsidized, it was the government that had to make progressively more funds available to maintain the service. By 1988/1989 the

total annual expenditure by government on communal land dipping amounted to US$ 9.3 million (Z$ 18.5 million), which constituted 57% of the total budget of the Department of Veterinary Services (excluding expenditure on tsetse and trypanosomiasis control) (Perry *et al.*, 1990a; Norval *et al.*, 1992b)*. Perhaps inevitably, annual increases in the government's communal land dipping budget did not keep pace with cost increases and by 1984 it was clear that intensive dipping (i.e. 45 immersions per annum) could not be sustained.

Since the epidemiological and economic implications of intensive dipping have become apparent, the Government of Zimbabwe has made a commitment to re-assessing the role of intensive dipping in the control of ticks and tick-borne diseases and has begun to implement revised control strategies. Modelling has played a role in the development and simulation of alternate tick-control strategies. This paper reviews the development and application of models in the planning and implementation of reduced and strategic-minimal tick-control strategies in Zimbabwe.

DATA USED FOR MODELLING

The development of models from which tick-control strategies can be derived is obviously dependent on the existence of relevant data. Such data were not available prior to 1980. The research required to produce the data necessary for modelling was initiated by the Government of Zimbabwe shortly after independence, and has continued until present. Significant inputs to this research have also been made by FAO/DANIDA, USAID, ILRAD and ACIAR.

Tick Population Dynamics

Research has been directed primarily towards the two most important tick pests of cattle in Zimbabwe, the brown ear tick, *Rhipicephalus appendiculatus* and the southern African bont tick, *Amblyomma hebraeum*. Studies on the seasonal occurrence of *R. appendiculatus* in the high rainfall highveld and *A. hebraeum* in the low rainfall lowveld were carried out by Short and Norval (1981) and Norval *et al.* (1991), respectively. The development rates, fecundity and survival of *R. appendiculatus* under field conditions in the highveld, as well as the survival and behaviour of the unfed stages of this species, were studied by Short *et al.* (1989a, 1989b). The host-finding behaviour of *A. hebraeum* and the role of the male-produced attraction-aggregation-attachment pheromone (AAAP) in the ecology of this species have been reported by Norval *et al.* (1989a, 1989b).

Production Losses Caused by Ticks

Although the primary reason for intensive tick control has been the control of tick-borne diseases, a secondary but important reason for tick control has been to prevent production

* Total expenditure was derived from all costs, direct and hidden, associated with dipping. This differs from the 1988/1989 amount of Z$ 9.2 million provided by the Director of Veterinary Services, Dr. S.K. Hargreaves, which only takes direct costs into account (see Figure 1).

losses in cattle. It was widely believed that without protection from acaricides cattle would be overwhelmed by ticks. A series of field experiments, funded by FAO/DANIDA, was therefore carried out to quantify the production losses caused by *R. appendiculatus* and *A. hebraeum*. The aim was to define damage coefficients (loss caused by the successful feeding of a single tick), which could be used in models to estimate the overall losses caused by tick infestations.

No significant production losses were found to be caused by the immature stages of either *R. appendiculatus* (Norval *et al.*, 1988) or *A. hebraeum* (Norval *et al.*, 1989c). However, fairly large production losses were caused by the adults of both species. These losses amounted to 4.4 g of live-weight gain (LWG) (Norval *et al.*, 1988) or 7 g of milk (R.A.I. Norval, R.W. Sutherst, J. Kurki, J.D. Kerr and J.D. Gibson, in preparation) per engorged female with *R. appendiculatus*, and 10 g of LWG (Norval *et al.*, 1989c) or 6 g of milk (R.A.I. Norval, R.W. Sutherst, O.G. Jorgensen and J.D. Kerr, in preparation) per engorged female with *A. hebraeum*. The relationship between infestation size and screw-worm fly *(Chyrsomya bezziana)* strikes were recorded for both *R. appendiculatus* (Norval *et al.*, 1988) and *A. hebraeum* (Norval *et al.*, 1989c). With both tick species screw-worm became a problem only when cattle were very heavily infested with the adult stage.

Tick Susceptibility of Cattle Breeds

The tick susceptibility of the indigenous (sanga) and exotic (taurine and zebu) breeds of cattle and their crosses that occur in Zimbabwe have been studied by Norval *et al.* (1989c), Fivaz *et al.* (1992) and R.A.I. Norval, R.W. Sutherst and J.D. Kerr (in preparation). The three studies yielded consistent findings; namely, that sanga breeds (Mashona and Nkoni) carry much smaller numbers of all tick species than taurine breeds. Exotic zebu cattle (Brahman) also exhibit considerable tick resistance, approaching that of the sanga breeds. Cross-bred cattle are of intermediate resistance. These findings conform with those of similar studies carried out in South Africa (Rechav and Zeederberg, 1986; Spickett *et al.*, 1989; Rechav *et al.*, 1991; Scholtz *et al.*, 1991).

Epidemiology of Tick-Borne Diseases

The distribution and prevalence of babesiosis, anaplasmosis and theileriosis in Zimbabwe were recorded in serological studies carried out in the early 1980s (Norval *et al.*, 1983, 1984, 1985). The three diseases were found to be widely distributed throughout the country. Endemic stability for *B. bigemina* (herd prevalence rates of antibodies of over 80%) occurred at three-fifths of the localities sampled in communal lands and on one-quarter of the commercial farms sampled. *Babesia bovis*, which had been introduced to Zimbabwe with *Boophilus microplus* from Mozambique in the 1970s, disappeared from the country along with *B. microplus* during the drought years of 1981–1984 (Norval *et al.*, 1983, R.A.I. Norval, R.W. Sutherst, G.F. Maywald and B.D. Perry, submitted for publication). Antibodies to *A. marginale* occurred commonly in both communal and commercial farming areas, but no clearly defined association was established between detectable antibodies and endemic stability. The theileriosis study results were also difficult to

interpret, as disease outbreaks occurred in some areas where antibodies were detected but did not occur in others where prevalence rates were similar or higher. The existence of strains of *T. parva* of varying virulence and serological cross-reactions between *T. parva* and the relatively benign *T. taurotragi* are the likely causes of these anomalous findings (Koch *et al.*, 1988; Koch, 1990). Heartwater was not included in the surveys of the early 1980s because at that time no reliable serological test existed for the detection of antibodies to *C. ruminantium*. However, Norval (1981b) was able to transmit heartwater using engorged nymphs of *A. hebraeum* collected from healthy cattle in communal lands, providing indirect evidence of endemic stability. More recently, de Vries *et al.*, (1993) have shown that the occurrence of antibodies to *C. ruminantium* in cattle in communal lands is closely linked to the presence of *Amblyomma* ticks.

A second serological survey was carried out in communal lands in 1991 to determine the epidemiological states that currently exist for tick-borne diseases. The sera are at present being screened for antibodies to *B. bigemina* and *A. marginale*. The results should show where endemic stability and instability exist, and so provide a guideline as to where immunization against tick-borne diseases should accompany reduced dipping frequency.

Tick Distribution, Climate and Vegetation

Data on the distributions of tick species in Zimbabwe were obtained from a series of papers published between 1981 and 1987 by R.A.I. Norval and others in the *Zimbabwe Veterinary Journal* and *Tropical Animal Health and Production*. The data were recorded during a national tick survey, conducted between 1975 and 1985.

Climatic data were obtained from the Department of Meteorological Services of Zimbabwe. Vegetation maps of Zimbabwe were supplied by the National Herbarium, Harare. The amount of vegetation cover in different seasons, agroecological zones and farming systems was derived from the satellite-derived Normalized Difference Vegetation Index (NDVI) (Lessard *et al.*, 1990; Perry *et al.*, 1990b). This spectral vegetation index quantifies the level of photosynthetic activity (i.e. greenness) of vegetation.

TICK-CONTROL ZONES

The intensive dipping policy in Zimbabwe had, since its inception, been applied with equal vigour to both high and low rainfall areas. No allowance was made for the fact that the number of tick species present on cattle, as well as overall tick abundance, decreased from high to low rainfall areas. Norval (1981a) suggested dividing the country into zones based on rainfall, and applying appropriate tick-control strategies in each zone. He defined four zones and recommended control strategies ranging from intensive dipping and immunization to control tick-borne diseases (in the zone receiving highest rainfall) to minimal tick control and the maintenance of endemic stability (in the zone receiving lowest rainfall). Perry *et al.* (1990a) re-defined the tick-control zones for Zimbabwe on the basis of current distribution of tick-borne diseases. However, as noted by Norval *et al.* (1992a) the distribution of tick-borne diseases, in particular heartwater, are not static and can be expected to change with changes in vector distribution. Geographical models of potential

vector distribution are therefore essential in establishing realistic tick-control zones, particularly if changes in tick-control policy or other factors such as altered land use or the translocation of wildlife hosts are likely to cause changes in the distributions of tick species.

The climate-matching model CLIMEX (Sutherst and Maywald, 1985) is being used to determine the climatic suitability of Zimbabwe for *R. appendiculatus/R. zambeziensis* (B.D. Perry, R.L. Kruska, R.A.I. Norval, D.J. Rogers and U. Ushewokunze-Obatolu, in preparation), *B. decoloratus/B. microplus* (R.A.I. Norval, R.W. Sutherst, G.F. Maywald and B.D. Perry, submitted for publication) and *A. hebraeum/A. variegatum* (Norval *et al.*, in press).

The recorded distributions of *R. appendiculatus, R. zambeziensis* and *B. decoloratus* match fairly closely their predicted distributions, indicating that these species are unlikely to spread appreciably if management practices change. A limited spread of *R. appendiculatus* into a predicted unsuitable area did however occur during a period of above average rainfall between 1973 and 1983 (Norval and Perry, 1990), showing that CLIMEX predictions based on long-term climatic averages may be insensitive to short-term changes in climatic suitability. *Rhipicephalus appendiculatus* may also be absent from overgrazed habitats within areas of predicted climatic suitability, due to the destruction of the microhabitats necessary for its survival (Norval, 1977; Norval *et al.*, 1992a). Theileriosis is therefore absent from many of Zimbabwe's communal lands that are climatically suitable for the vector *R. appendiculatus*.

Although CLIMEX predicts that the higher rainfall areas of Zimbabwe are suitable for the survival of *B. microplus*, the species has never become permanently established in the country. Norval *et al.*, (submitted for publication) are of the opinion that the interaction of drought, the restoration of dipping and interspecific competition with *B. decoloratus* (Norval and Sutherst, 1986), a species which is better adapted to survive in cold and dry conditions, were the factors that contributed to the disappearance of *B. microplus* from Zimbabwe in the early 1980s.

ClIMEX has been of greatest value in predicting the potential distributions of *A. hebraeum* and *A. variegatum* (another vector of heartwater) in Zimbabwe. At present *A. hebraeum* is confined largely to the dry southern lowveld and *A. variegatum* to the dry northwest and Zambezi valley. Perhaps surprisingly, these are the parts of the country which the model predicts are the least suitable for the survival of the two species. Predicted climatic suitability for both species increases with increasing rainfall. The apparently anomalous distribution patterns of the species have been investigated by Norval *et al.*, (in press). The authors have found that the current distributions of *A. hebraeum* and *A. variegatum* coincide with the distributions of the main wildlife hosts of the adults of the species. It is known that *A. hebraeum*, and probably *A. variegatum*, can be eradicated by intensive dipping of cattle if no alternate hosts for the adults are present (Norval and Lawrence, 1979). However, eradication cannot be achieved if dipped (uninfested) cattle share the same pastures as alternate hosts infested with males because attached males emit a pheromone (AAAP) that attracts the unfed nymphal and adult stages to the host on which they are present (Norval *et al.*, 1989a, 1989b). The unfed stages are not attracted to uninfested hosts. The conclusion drawn by the authors is that *A. hebraeum* and *A. variegatum* have the potential to spread to the higher rainfall areas of Zimbabwe if

intensive dipping is relaxed or if wildlife hosts are introduced to these areas (this is occurring with the increasing popularity of game ranching). In the past five years, *A. hebraeum* has become established at several foci in the higher rainfall areas but there has been no recorded spread of *A. variegatum*. Outbreaks of heartwater have been recorded in some of the newly established foci of *A. hebraeum*.

We believe that the concept of tick-control zones is sound but further research using GIS, which incorporates data on parameters such as the distribution of tick species, climatic suitability, vegetation (type and density), cattle density, distribution and abundance of alternate hosts, acaricide usage and disease prevalence is required to realistically define such zones. The zones defined by Perry *et al.* (1990a) are currently being used by the Government of Zimbabwe for planning purposes, but their usefulness will obviously diminish if or when heartwater and its vectors become widespread in the higher rainfall areas or if *B. microplus* and *B. bovis* are reintroduced.

MODELLING TICK-CONTROL STRATEGIES

Floyd *et al.* (1987) used a tick population dynamics model, T3HOST (Maywald *et al.*, 1980), to design control strategies for *R. appendiculatus* for the highveld of Zimbabwe. The model was used to simulate strategies based on a three-month period of intensive tick control. The periods of strategic tick control that were predicted to be most effective against *R. appendiculatus* were those directed against the adult stage (December–February and January–March). Floyd *et al.* (1987) were also able to predict, using the damage co-efficient for *R. appendiculatus*, that the most cost-effective strategies are those directed against the adult stage in January, February and March. The authors based their estimations on an average tick-control cost of US$ 0.30 per animal per dipping, the value of beef at US$ 1.2 per kg and a dipping efficiency of 70%; the cattle involved were of the tick-resistant sanga breed. R.B. Floyd, J.R.A. Colborne, R.A.I. Norval and R.W. Sutherst (in preparation) have subsequently used the T3HOST model to simulate control strategies for *R. appendiculatus* on taurine and sanga cattle in the tick-control zones defined by Norval (1981). Their findings indicate that longer periods of strategic tick control are required to achieve cost-effective control of *R. appendiculatus* on taurine cattle than on sanga cattle. On taurine cattle, the longest period of strategic tick control is required in the zone receiving the highest rainfall and the shortest period in the zone receiving the lowest rainfall. On sanga cattle, no tick control at all is required in the zone receiving the lowest rainfall.

Rhipicephalus appendiculatus, which has a strictly seasonal pattern of occurrence in Zimbabwe (Short and Norval, 1981), lends itself to control by applying acaricides *strategically* in a given season to control a particular life-cycle stage. *Amblyomma hebraeum*, on the other hand, does not have a clearly defined pattern of seasonal occurrence (Norval *et al.*, 1991) and so cannot be controlled efficiently by strategic acaricide application. Meltzer and Norval (1993) have therefore proposed the control of *A. hebraeum* by *threshold* acaricide application. The authors have defined an economic damage threshold, using the damage coefficient for *A. hebraeum*, where the value of the losses caused by an infestation is equal to the cost of applying tick control. Control of *A. hebraeum* is recommended only when the economic damage threshold is exceeded

(i.e. when the value of production losses is greater than the cost of tick control). The threshold is determined by the producer price of beef (or milk) and the cost of tick control (acaricide, labour etc.). For example, when the producer price of beef was Z$ 1.63/kg (US$ 0.33/kg) and the tick-control cost was Z$ 0.29/head/dip (US$ 0.06/head/dip), the threshold was 18 standard female ticks/head/week.

At present there is little overlap between the distributions of *R. appendiculatus* and *A. hebraeum* in Zimbabwe, and so it is feasible that strategic tick control can be applied in areas infested with the former and threshold tick control in areas infested with the latter. However, strategies will have to be revised if *A. hebraeum* becomes widely established in areas infested with *R. appendiculatus*.

PLANNING AND IMPLEMENTING CONTROL STRATEGIES

In 1984 the Department of Veterinary Services of Zimbabwe announced that it was abandoning the policy of intensive dipping in the communal lands (Thomson, 1985) and since that time there have been progressive reductions in the frequency of communal land dipping. In an attempt to rationalize the movement away from intensive dipping, Perry *et al.* (1990a) provided recommendations for alternative tick-control strategies for Zimbabwe's communal lands. These alternative strategies were:

a) Reduced dipping, involving fortnightly dipping in the summer months and monthly dipping for the rest of the year (equivalent to 21 immersions annually).

b) A combination of strategic (weekly dipping during the summer months, equivalent to 12 immersions, supplemented by natural or artificially induced herd immunity to tick-borne diseases) and minimal dipping (equivalent to four acaricide immersions) during the rest of the year.

The T3HOST simulations of the control of *R. appendiculatus* (described earlier) provided the theoretical basis for reduced and strategic-minimal dipping, which were aimed at achieving effective control of adults of this species during summer. Minimal (or threshold) dipping was aimed at the control of *Amblyomma* species, in areas that were not infested with *R. appendiculatus*.

For each control strategy, target populations were identified by zone, and projections of the likely consequences were made. It was assumed that there would be no significant changes in disease risk or on the effects of livestock production by moving from intensive to either of the two alternative strategies. It was also assumed that the alternative strategies would be applied after a transitional period of reduced dipping.

The costs of applying the alternative strategies, compared to intensive dipping, were projected over a 20-year period. Discounted at 14%, reduced dipping was estimated to cost 45% less than intensive dipping and strategic-minimal dipping 62% less.

The transition from intensive dipping to reduced and strategic-minimal dipping, which had already begun in 1985 out of economic necessity, has now for all practical purpose been completed. In presenting the results of a 1989 survey, conducted to determine the frequency of communal land dipping, Barrett (1991) reported the following information. 'Most dips operated for between 17 to 25 times annually. Weighted according to number of cattle presented at each dip, the average dip operated for 20.7 occasions in 1989. The average turnout at dipping days was 82 percent of the cattle census, so that for the overall

herd the average number of dip treatments in 1989 was 17.0.' Since 1989 the dipping frequency has declined even further due to economic constraints and a prolonged drought, which has reduced the availability of water for dipping in many areas (S.K. Hargreaves, personal communication).

The report by Norval *et al.* (1992a) that *Amblyomma* ticks and heartwater are likely to spread into communal lands in the higher rainfall areas if dipping frequency is reduced, has been a cause of considerable concern to the Department of Veterinary Services. However, a decision has been made to continue to implement reduced and strategic-minimal dipping (S.K. Hargreaves, personal communication). The spread of *Amblyomma* ticks is being monitored and appropriate control measures are being applied where and when heartwater becomes a problem.

Research is being conducted in Zimbabwe by the University of Florida/USAID/SADCC/Heartwater Research Project on the development of a pheromone-based control system which is specific for *Amblyomma* ticks, as well as improved heartwater vaccines (Norval *et al.*, 1992c). Progress in either or both of these areas will obviously be of considerable value in dealing with *Amblyomma* and heartwater problems in the future.

EFFECTS OF ALTERNATE DIPPING STRATEGIES ON THE CONTROL OF TICKS AND TICK-BORNE DISEASES

The reduced dipping frequency in the communal lands has not resulted in any obvious decline in cattle productivity due to increased tick infestation or in any increases in the reported incidence of tick-borne diseases (S.K. Hargreaves, personal communication). There has also been no apparent increase in the incidence of tick-associated screw-worm fly strikes. However, it should be noted that the reductions in dipping frequency have occurred to a large extent during a period of prolonged drought (1988–1992), which has caused tick populations to decline to extremely low levels.

DISCUSSION

The transition from intensive dipping to reduced and strategic-minimal dipping in Zimbabwe appears to have been successful in that it has not been accompanied by obvious declines in cattle productivity due to tick infestation, increased frequency of screw-worm fly strikes or increased losses from tick-borne diseases. During the transition period, cattle numbers in the communal lands actually increased by 19.5% from 3.4 million in 1984/1985 to 4.2 million in 1990/1991 (Figure 1). However, as stated earlier, the transition has occurred during a period when tick challenge has been low due to a succession of droughts. Measurement of the overall success of the alternative tick-control strategies, in terms of cattle productivity and tick-borne disease incidence, must obviously be deferred until after several years of normal or above average rainfall to ensure that a realistic assessment is made. In the meantime, tick infestation levels and losses due to tick-borne diseases should continue to be monitored. If increased losses do occur at any time, it may become necessary to revise and modify the control strategies.

The low incidence of tick-borne diseases in communal land cattle during the transitional period also indicates that the assumption made by Perry *et al.* (1990a), that the transition

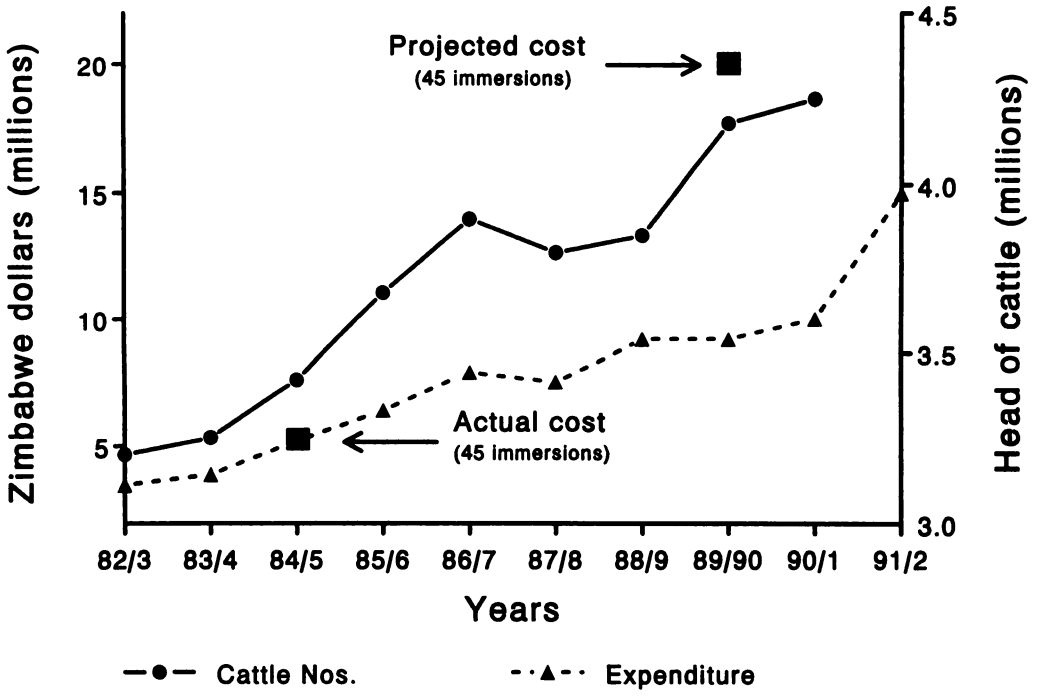

Figure 1. The changes in cattle populations and expenditure on tick and tick-borne disease control in the communal lands of Zimbabwe over the period 1982/1983 to 1991/1992.

from intensive to reduced or strategic-minimal dipping would not significantly alter the tick-borne disease risk, was correct. The endemic stability that existed in the communal lands in the early 1980s was obviously not disrupted on a wide scale by the implementation of intensive dipping between 1980 and 1984.

To date, the most tangible benefit of reducing the frequency of dipping in the communal lands has been cost saving. During the transition period dipping costs have increased considerably, and as a consequence annual expenditure by the Department of Veterinary Services on communal land dipping has increased steadily (from Z$ 6.5 million in 1985/1986 to Z$ 15.0 million in 1991/1992) despite the reduced frequency of dipping (Figure 1). Assuming a dip tank attendance of 82% of cattle (as recorded by Barrett in the 1989 survey), the dipping cost per head has increased by 325% from Z$ 0.04 in 1984/1985 to Z$ 0.13 in 1988/1989. According to the Director of Veterinary Services of Zimbabwe, Dr. S.K. Hargreaves, intensive dipping would have been impossible to sustain through the 1980s because of cost factors alone. This point has been illustrated in Figure 1, where the actual cost of intensive dipping in 1984/1985 (the last year that it was enforced) has been compared to the projected cost of intensive dipping in 1988/1989, when the survey on dipping frequency was carried out (Barrett, 1991). The actual cost in 1984/1985 was Z$ 5.3 million and the projected cost in 1988/1989 was Z$ 20.0 million. When the projected cost of intensive dipping in 1988/1989 is compared with the actual expenditure of Z$ 9.2 million, it can be seen that the saving incurred by the alternative strategies amounts to Z$

10.8 million (54%). This amount saved by the combination of reduced and strategic-minimal dipping for 1988/1989 compares well with the projected savings published by Perry *et al.*, (1990a). Hence, based on cost saving, the implementation of the alternative tick-control strategies in Zimbabwe's communal lands can be considered to have been extremely successful.

As the alternative tick-control strategies proposed by Perry *et al.* (1990a) were based on the results of modelling, it can be concluded that modelling has played a useful role in rationalizing tick-control policy in Zimbabwe. Although the implementation of the strategies has been somewhat haphazard and driven as much by economic reality and the availability of water for dipping as by scientific planning, the existence of a framework for change has given the Department of Veterinary Services the confidence to proceed with its policy of reduced dipping. The importance of this last point cannot be over emphasized.

The rationalization of Zimbabwe's communal land tick and tick-borne disease policy is obviously far from complete and an important role for modelling clearly exists in the refinement of the policy. For example, if the precise relationship between vegetation cover and the survival of *R. appendiculatus* is determined and included in a geographic model, it may be possible to further reduce dipping frequency in many overgrazed communal lands. Modelling will also be a necessity in determining how best to deal with the *Amblyomma*/heartwater threat to the higher rainfall areas. The question that requires an answer is whether it will be more economical to continue to exclude *Amblyomma* ticks by means of acaricides or to control heartwater by immunization as it spreads. Another role for modelling will be in the design of appropriate tick and tick-borne disease strategies for Zimbabwe's commercial farms, many of which are stocked with tick-susceptible taurine cattle and still practise intensive dipping.

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Practical experiences in using models for tick control in Malawi

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The control of ticks and tick-borne diseases in Malawi has for a very long time been governed by legislation which requires all animals within a radius of 8 km from a dip tank to be compulsorily dipped in a suitable acaricide every week throughout the year. This is carried out in over 360 dipping tanks constructed and maintained by the Malawi Government. This is uniform for the whole country where arsenic trioxide has continued to be used. In recent years it has become increasingly difficult to sustain such an intensive dipping program because of high costs of the acaricides. This, coupled with an increased awareness of the effects of chemicals on the environment, has led the Malawi Government to review its current policy in favour of cost-effective methods suitable to the different ecological zones without undue risks to the cattle industry from ticks and tick-borne diseases.

Surveys have shown *Amblyomma variegatum, Boophilus microplus* and *Rhipicephalus appendiculatus* to be the major tick species to be targeted for control, but with varying relevance in different ecological zones. After initial testing for agreement, the climate-driven computer model CLIMEX was used to map out favourability distributions for these three species in the different ecological zones throughout the whole country and this allowed potential different approaches for their control to be identified. For *R. appendiculatus* these approaches have been tested and refined using the computer model T3HOST and are now undergoing validation through field trials before specific recommendations can be made to the government.

Using spreadsheet models, the relative costs of using different acaricides under different dipping regimes were compared. Suitable replacements for arsenic trioxide have been suggested and the dipping regimes for their economic utilization also recommended to the government.

So far the indications are that the most economic approach to tick control in Malawi is not dipping at all in some ecological zones and limited dipping in others for the indigenous cattle and incorporation of immunization with limited dipping for cross-bred cattle kept under the smallholder production system of husbandry. However, the exact dipping regimes to be finally adopted will be determined after the field trials, at which time the government will consider changing its basic legislation on tick control.

Application of models to screwworm eradication programs

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ABSTRACT

Screwworms *(Cochliomyia hominivorax,* Diptera: Calliphoridae) were eradicated from the United States with E.F. Knipling's 'demonstrative' model that related the relative mating proportions of wild and sterile insects to population fertility and predicted population trends in subsequent generations. *Ad hoc* correlations between treatments applied and experimental results obtained on Sanibel Island, Florida, in 1952–1953, Curacao, Netherlands East Indies in 1954, and the Florida mainland in 1957 provided a conceptual guide for the eradication campaigns from 1958 until 1967. Many mathematical models have since been proposed that relate pest insect population density at some future time to density, fertility, net reproduction rates, intrinsic reproduction rates, density dependent survival and frequency dependent matings at the present time. Both deterministic and stochastic formulations have been presented, but none has been adapted for use in screwworm eradication programs. A regression model, based on empirical field data, predicts frequencies of sterile matings in the target native populations given sterile fly release indices and estimates of native fly densities. This model is used in central America to help interpret field trials of new screwworm strains for mass production and release and to monitor the efficiency of sterile fly dispersal operations. Even now there is no model that predicts screwworm abundance from estimates of host animal densities, screwworm age structure, or screwworm fertilities and densities. Analysis of sterile fly release experiments, however, hints that density-dependent sterile mating rates obtain in screwworm flies, similar to those demonstrated in tsetse by Rogers and Randolph (1984).

A practical simulation model developed by Foster and colleagues at CSIRO in Canberra is used to evaluate the effects on natural populations of genetic methods of controlling sheep blowflies, *Lucilia cuprina* (Diptera: Calliphoridae). There also are simulation models for tephritid fruit fly pest species. In practice, however, action agencies seem usually to rely on experience and overkill to achieve goals; practical criteria, not hypothetical models, are generally used to evaluate the results. Treatments are confounded; cause and effect cannot be scientifically or unambiguously demonstrated. Thus field data about the target populations as they respond to treatments may not be collected, and much useful information is lost.

INTRODUCTION

In 1955 when Bushland, Knipling and Lindquist informally planned to attempt screwworm eradication in Florida (Knipling, 1955, 1959; Lindquist, 1955), the application of mathematical modelling to predicting the outcome of intervention was not a standard operating procedure.

But Knipling (1955) used a model that predicted trends in a 'theoretical' population of virgin female insects during generation by generation releases of sterile males. The purpose of the model was to demonstrate the principle that underlay the eradication of

screwworm flies, *Cochliomyia hominivorax,* from Curacao, an island of 440 km^2 in the Netherlands Antilles (Baumhover *et al.,* 1955), by the sterile insect technique (SIT). Taken with Baumhover and colleagues' accomplishment of eradication, Knipling's model convinced skeptical officials to support the establishment of an eradication program in Florida with results that have often been described (Baumhover, 1966; Knipling, 1959; Bushland, 1971). The mechanism of population suppression by SIT is that wild females mated to released, sterile males become inseminated with sperm bearing dominant lethal mutations and their eggs do not hatch. Sterile flies of both sexes are released in screwworm eradication programs; the irradiated females do not undergo vitellogenesis and it is assumed that they have a negligible role.

In this paper I shall relate how Knipling's model was used during the screwworm eradication campaigns in southwestern USA and Mexico. I shall also refer briefly to some other models that, in my opinion, have some bearing on operations in eradication programs.

KNIPLING'S MODEL

Knipling's (1955) original formulation was drafted to examine theoretical expectations and feasibility of insect control by the release of sterile males.

Given a 'stable' population closed to immigration, of uniform age structure, discrete generations, a constant *per capita* reproductive rate, and the release of sterile males in such a way as to achieve insemination of virgin, wild females in proportion to their frequencies relative to wild, fertile males, Knipling showed that population suppression accelerated if sterile insect releases were kept constant. A later formulation allowed reproductive success to vary with population size; a fivefold rate of increase per generation was assumed until a population reached an arbitrary, stable level, at which growth ceased. Knipling's formulation (Table 1) takes the form of a spreadsheet and can be used as such with any microcomputer and commercially available spreadsheet program. It is intuitively obvious and simple to use and therefore appealing and useful to personnel in action agencies.

This conceptual model provided the principles upon which the USDA and the Mexico-US Commission planned their eradication operations and interpreted the results. Efforts were made to reduce native populations by chemical and cultural methods. Sterile fly production was maintained at the greatest possible levels. Once a 'barrier zone' on the US-Mexico border had been established, expensive sterile fly packaging and distribution costs were reduced by packing ever greater numbers of flies, cheap to produce, in large containers and distributing them from C-45 and C-47 aircraft flying lanes set 8 or 16 km apart. For example, sterile flies were applied at low average densities and distributed in swaths 16 km apart to areas where screwworms were undetected north of the 'barrier'. Because the threat of screwworm infestation had greatly declined, vigilance was reduced and decreased the probabilities of detection. In short, every effort was made to intensify application of sterile flies to areas of greatest infestation at the expense of areas where detections were scarce and scattered; 'overflooding' was thought to be the key variable, and reliance was placed on mere numbers of sterile flies released. When such overkill tactics failed, as they seemed to do in the continuous epidemic of 1972–1976, the failure was attributed by senior program personnel to factors beyond their control. The epidemic was attributed to weather unusually

Table 1. Knipling's model showing expected insect population sizes after releases of sterile male insects. A net per capita reproduction rate of 5× per generation is assumed.

Natural population N_t	No. sterile males released	No. Ratio, *S:F*	Natural fertile matings	population N_{t+1}
1,000,000	9,000,000	9:1	100,000	500,000
500,000	9,000,000	18:1	26,316	131,580
131,580	9,000,000	68:1	1,907	9,535
9,535	9,000,000	942:1	10	50
50	9,000,000	180,000:1	≈ 0	≈ 0

favourable to screwworm survival, ranching practices that allowed many screwworm cases to go undetected and untreated, and possible genetic changes in the native populations that conferred a degree of assortative mating (Bushland, 1974, 1975). Commentators in the academic community suggested that there was production of factory-adapted flies that did not fly or 'compete' in cooler temperatures in the field (Bush and Neck, 1976).

The early success of SIT generated much practical and theoretical research, including numerous mathematical models. I shall mention only a few here, but first must say that, to my knowledge, none were used in evaluating screwworm eradication operations.

Many population phenomena were ignored in Knipling's model. Naturally, scientists were interested in investigating the effects of immigration, density-dependent population growth, predation, multiple matings, etc. on SIT, but actual experiments to do so are difficult to arrange. Mathematical models, however, allow simulation and many algebraic models have been used to explore these questions.

A deterministic model and a probabilistic model that generalized the properties of Knipling's model were put forth by Costello and Taylor (1975). These workers developed their models to capture Knipling's observation that frequencies of sterile matings increase inexorably as target populations decline, providing that sterile male releases are continued. Costello and Taylor also used the Curacao field data (Baumhover *et al.*, 1955) to develop and test their models. Model variables include an environmental carrying capacity (the 'K' in logistic population growth), net reproduction rate, initial population size, and sterile male numbers. Time is treated as a continuous variable for populations that breed continuously and have overlapping generations. The model predicts the probable mean time (in insect lifespans) to extinction. The interesting properties include a sharp threshold in the numbers of sterile males released, below which extinction will not occur and above which additional steriles have little effect. This 'threshold' between success and failure seems to have occurred in practice in Curacao and the southwestern USA. Also interesting is that reduction of a hypothetical pest population before steriles are released had no effect on time to extinction in the simulations. The stochastic formula itself is opaque, and some of its variables seem not to have been defined explicitly. Moreover, the authors wrote that the algorithm for computer simulation was difficult, so one cannot easily use Costello and

Taylor's models. Prout (1978) examined the joint effects of SIT and immigration of fertile females on density-regulated populations with discrete generations. Effects of sterile male and female releases on density-dependent growth in continuous populations have also been simulated (Barclay and Mackauer, 1980).

Barclay (1982) simulated the effects of competitiveness of sterile males on sizes of fertile female populations. Density and frequency-dependent competitiveness were treated also. Horng and Plant (1992) studied the role of lek mating on control of wild populations by SIT, with particular reference to fruit flies. It is noteworthy that few of these studies made reference to field data nor were the models tested against data. What uses, if any, do field workers make of models?

An important model by Ito (1977) was predicated on logistic population growth, multiple matings, and a Poisson distribution of sterile and fertile matings. The model was developed from population data on the melon fly, *Dacus cucurbitae* (Diptera: Tephritidae), and was used in a very practical way to estimate the numbers of sterile flies to be released to achieve melon fly eradication on Kume Island (near Okinawa). Many more sterile males were required to achieve sterile matings than were suggested by the model. Estimates of fertility among wild females and other ecological estimates showed that sterile matings were less than expected because of mortality among the pupae and teneral adults and because sterile males did not distribute themselves spatially in such a way as to encounter wild females. Thus, Ito's model suggested that sterile fly wastage was great and provided important hints about where the problems occurred. Continuous exchange of views between modellers and field biologists before and during a project can make for much more rapid progress than working in sequence.

The sheep blowfly project at CSIRO has routinely used models to evaluate relative costs and feasibility for successful control or eradication by various genetical methods (e.g. GENCON, Foster *et al.*, 1988). The methods include SIT, the release of strains carrying various pericentric inversions, compound chromosomes, and reciprocal translocations singly or in combination. GENCON has also been used to help interpret the results of field tests of genetical control methods (Foster and Smith, 1991).

In an active eradication program, producing sterile flies, packaging them, distributing them over vast geographical areas, following up case reports of screwworm myiasis, site inspections, and so forth, consumes most energies of an institution. Few resources were allocated to long-term research efforts. There are many possibilities to be considered when eradication progress suddenly stops; enormous pressures ensure that most effort will be devoted to 'quick fixes'. Systematic and thorough investigation often will be the method of last resort. I have already mentioned explanations for the screwworm epidemic of 1972–1976. My participation in the eradication program led me to examine critically the hypotheses favoured by the leadership and other, less appealing, explanations as well. I begin with the somewhat diffuse genetical argument that was put forth and show a working model I developed for the USDA to examine the question. This simple, empirical model says nothing about eradication or failure, but can be (and has been) used to evaluate candidate strains of screwworms for mass release and other questions that arise in day-to-day eradication campaign activities.

Natural selection would greatly favour premating isolating mechanisms between released, sterile screwworms and native flies. Premating isolation has therefore been predicted by commentators and is, even now, continuously searched for by screwworm

program entomologists. Screwworm outbreaks in the southwestern USA and northern Mexico indeed have been attributed to assortative mating (Bush and Neck, 1976), speciation (Richardson *et al.*, 1982), and climate (Readshaw, 1985). How can these be demonstrated? There is a substantial body of evidence that has an important bearing on the issue of premating and sexual isolation among screwworms.

This body of evidence is the estimates of sterile mating rates among native females, and data have been collected since 1952 with Baumhover's experiments on Sanibel Island, Florida, to more recent observations in Guatemala in 1986. Reproductive isolation between released and native screwworms should be reflected in sterile mating frequencies whatever the cause of isolation. The procedures used in these field evaluations of SIT include releasing sterile flies over large areas for many weeks. Sterile mating frequencies were estimated by the daily collection of screwworm ovipositions from penned, sentinel sheep. Hatched egg masses signify a mating between wild flies, unhatched egg masses signify matings between released males and native females. Released females do not become gravid and therefore do not oviposit.

Table 2 shows the mean observed sterile mating rates in the field unadjusted for different sterile fly release rates, target population densities or other variables. It would seem that large differences existed among strains. These data might support the idea of 'strain deterioration' (Bushland, 1974, 1975; Knipling, 1979). Are these differences related to their heritable competitiveness? An objective method of comparison would be helpful and an attempt was made to develop one (Krafsur, 1985).

Five continuous variables were recognized in attempting to compare objectively numerous field experiments involving sterile male releases. Of principal interest was the dependent variable, sterile mating frequency, **Y**. Independent, presumptively explanatory variables included the *dose rate* **X1**, the mean number of males released per unit area per week; *missile rate* **X2**, which is the mean number of fly cartons per unit area per week; *swath width* **X3** is the mean distance between adjacent flight lanes; and an estimate of native *population density* **X4**. The effects of categorical, discrete variables also were investigated. These included *regions* in which sterile fly releases were performed and the *strains* of flies released. Five regions were recognized: (1) Curacao, (2) Florida, (3) the Edwards Plateau of Texas, (4) semiarid regions of Texas, Tamaulipas, Sinaloa and Yucatan, Mexico, and (5) the tropical humid regions of Mexico (Veracruz, Chiapas) and Guatemala. Data were available representing the effects of releasing 12 strains of screwworms.

Expectations in sterile mating rates are based on historical experience. The empirical model takes the form:

$$\begin{aligned}\%\ \text{sterile matings} = {} & \text{constant} + \text{effect of region} + \text{dose effect} \\ & + \text{missile effect} + \text{swath width effect} \\ & + \text{native population density effect} + \text{error}.\end{aligned}$$

Regression and analysis of variance methods were used to evaluate the data and fit the model.

$$\text{ARCSINE}\ \sqrt{Y} = 48.1 + \mathbf{REGION} - 0.02(\mathbf{X1}) + 8.8(\mathbf{X2}) - 1.1(\mathbf{X3}) - 19.2\ \text{LOG}(\mathbf{X4}),\ R^2 = 0.82.$$

When *region* is ignored, $R^2 = 0.71$. The 95% confidence limits for **Y** are ± 13.5.

Table 2. Average percent sterile matings observed and corrected for the effects of sterile fly dose rate, missile rate, and target population densities.

Percent sterile matings Strain released	Uncorrected	Corrected*
A-81	41.6%	40.2%
APHIS	10.3	41.3
ARICRUZ	55.1	29.1
CH-85	26.2	24.8
DE-9	71.4	43.7
FF8	20.1	23.8
FLORIDA	43.6	46.7
KERRVILLE	46.7	30.9
009	36.7	21.6
TEXMEX	16.9	36.5
V-81	32.0	28.5
VF-84	44.7	47.6

*least square means. $F = 1.41$, $df = 11$, $P = 0.23$.

This provisional model incorporates all variables except strain. The effects of region ($P = 0.004$) and the continuous variables ($P \leq 0.0045$) were statistically highly significant. All the variables were separately or together significantly associated with sterile mating rates. It seems that sterile mating frequencies increased as the dose rate, distance between flight lanes and target population density decreased. A high missile rate was associated with high sterile mating rates, while a high dose rate was not!

The observed sterile mating rates in different experiments can be adjusted for the effects of the continuous variables and then compared. When this was done, no strong differences were obtained among strains of flies released. It seems that strain effects were small with respect to the continuous variables (Table 2). For many years there was controversy over strain deterioration, mating types, and geographical races, and much expense was incurred in collecting wild material, constructing new strains, and developing them for mass propagation.

The adjusted regional means were significantly different (Table 3). Ecological studies in Mexico suggest that dispersal of released flies is considerably less in well-forested areas than in open savanna woodlands (Krafsur and Garcia, 1978; Krafsur *et al.*, 1979, 1980). Experience shows that sterile fly releases in tropical humid environments elicit lesser sterile mating rates, and this may become increasingly important as the program continues further into Central America.

The regression equation can be used to provide an assessment of program effectiveness independently of reported screwworm case incidence in domestic animals. The model provides an objective method to evaluate sterile mating frequencies by comparing them with their expectations. And it can be used to optimize sterile fly releases with respect to cost and predicted effectiveness. Like all multiple regression models based on historical

Table 3. Mean sterile mating rates in geographical regions as observed and as corrected for effects of continuous variables related to sterile fly releases.

Region	Observed	Corrected*
Curacao	43.2%	19.8%
Florida	44.7	43.6
Edwards Plateau	48.4	37.5
Semiarid†	35.8	41.9
Tropical Humid‡	27.3	24.5

*Least square means. $F = 4.77$, $df = 4$, $P = 0.004$.
†<< 1100 mm rainfall annually (south Texas, Tamaulipas, Sinaloa, Yucatan).
‡>> 1750 mm rain annually (Veracruz, Chiapas, Guatemala).

observations and unplanned comparisons, predictions from applying the model should be viewed with much caution. The large error in Y testifies how limited this model is. The regression model does not predict trends in target population density. But it is interesting that when sterile mating rates estimated in the field exceed *c.* 70%, densities of the target screwworm flies become too low to measure (e.g. Baumhover *et al.*, 1955; Krafsur and Garcia, 1978). Rogers and Randolph (1984) observed a likely threshold sterile mating rate in tsetse flies of *c.* 60–70% when fitting a density-dependent model. Of course, screwworm reproductive biology is very much different than that of tsetse. Rogers and Randolph show how to estimate changes in population density (N_{t+1}/N_t) given the net rate population increase (λ) and an exponent *b* that describes the strength of density-dependent regulation (Maynard-Smith and Slatkin, 1973). Values of N_{t+1}/N_t for different fertility rates show that change is very sensitive to *b*, and only weakly sensitive to λ. It is high time that some effort was devoted to understanding how density-dependent mechanisms may work in screwworms.

The field data afford rough estimates of sterile male competitiveness in the various experiments. Coefficient **c** expresses competitiveness of released *R* to wild *W* males $cR:W$. Let the probability of sterile mating $P = cR/(cR+W)$. This rearranges to $c = PW/(1-P)R$. *P* was estimated by the fraction of ovipositions that did not hatch, *R* was taken as the sterile male release rate (males km^{-2}), and *W* was estimated by oviposition densities. Note that *R* actually is sterilized puparia stuffed in boxes and will therefore overestimate the actual number of flies surviving release. *W* is much smaller than the numbers of wild males because many females do not live long enough to oviposit, those first doing so on day 7 of adulthood and at three-day intervals thereafter (Krafsur *et al.*, 1979; Thomas and Chen, 1990). Estimates of sterile male competitiveness were made for the 42 data sets. I adopted $\log_{10}(100 \times c)$ as the estimator of competitiveness. Note that least squares regression of any function of **c** on sterile male density *(R)* is invalid, because **c** itself incorporates *R*. Pearson correlation coefficients were instead calculated and the results are set forth in Table 4.

The negative relation between sterile mating rates and dose rates observed in the multiple regression model now becomes even more emphasized (Figure 1). Competitive-

Table 4. Pearson correlation coefficients between sterile male competitiveness (log[100 × c]) and other variables.

Variable	Sterile dose rate	Missile Rate	Swath width	Log population Density
Correlation	–.79	0.34	–0.58	–0.29
Significance	0.0001	0.027	0.0001	0.065

ness of the released males seemed to vary inversely with their abundance, as suggested in tsetse by Rogers and Randolph (1984). The positive relationship of **c** with missile rates and negative relationship of **c** with swath width shows that competitiveness is positively related to the chances of placing sterile flies near breeding sites. This confirms an explicit assumption of Knipling (1955) with regard to SIT feasibility that 'adequate dispersion of the released sterile males must be obtained'. Both experimental (Krafsur and Garcia, 1978; Krafsur *et al.*, 1980) and observational evidence (Krafsur, 1978) and the present data

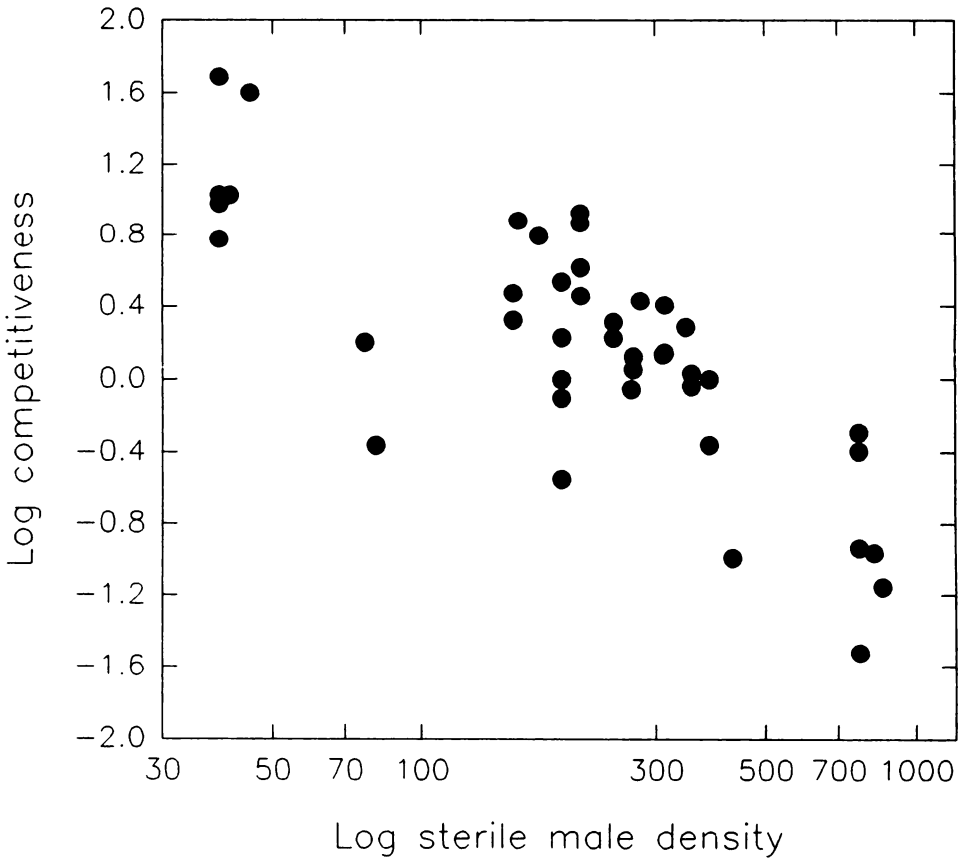

Figure 1. Scatterplot of competitiveness on sterile male density from field observations in Sanibel Island, Florida, in 1952 to Guatemala in 1986.

suggest that the effectiveness of SIT is enhanced by maximizing the chances of putting sterile males into actual or potential breeding sites. Sterile male field trails (1952 to 1976, Curacao, Florida, Mexico and Texas) gave no evidence that sterile males disperse very far from their original release sites. Sterile females, on the other hand, move considerable distances, and it has been implicitly assumed that males do also. The overkill release strategy once used by program officials was probably counterproductive and helps to explain the 1972–1976 screwworm outbreaks. Different release methods were adopted in 1977 in Texas and 1979 in New Mexico and Arizona; progress in eradication since has been interrupted only by organizational and political matters.

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Potential for application of current models for the improvement of helminth control: advantages, limitations, shortcomings

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ABSTRACT

Mathematical models are simply a means of representing and manipulating something that would not otherwise be accessible. They are aids to thought and, if properly constructed, excellent tools for communicating and explaining ideas. There have been many models for the population biology of the common trichostrongylid infections of cattle and sheep. Almost all of them have been constructed in order to design more effective strategies for parasite control. Very few of them have been widely used. There are a number of reasons for this. For example, most were constructed before the personal computer revolution and so were restricted to mainframe format. There was little need to render the models 'user-friendly' because they were used mainly by the model builder. Such models intimidate and deter those who might plausibly be called upon to interpret the results to producers (e.g. veterinary practitioners, government extension agents and pharmaceutical technical services representatives).

With the advent of battery-driven laptop computers, it has become possible to conceive mathematical models that can be taken directly to the producer. One such model is PARABAN, a model for the population biology of several common trichostrongylid nematode parasites of cattle. Experience in implementing PARABAN in South American countries and elsewhere has revealed that such models can be usefully employed to help explain parasite control strategies to producers. To be successful, the model must have a clear, 'user-friendly' screen display, it should not appear to be 'too technical' and it should present the results using local terminology and in a format that is intelligible and familiar to the user. Considerable care should be taken to allay the fears of users who are not computer literate or who might view the model as a threat to their livelihood. It should be emphasized that the model is merely a tool and that the model results represent our 'best conjecture' about what is likely to happen. Particular attention should be paid to training potential users. The limitations as well as the strengths of the model should be dealt with in detail so that the model results can be presented to the user in an appropriate context without inflated expectation or unwarranted cynicism.

INTRODUCTION

'Right Decisions'

A colleague of ours recently remarked that physical scientists do not talk about modelling, they just do it. He meant merely that modelling was such an accepted and integral part of

their activity that questions of utility simply do not arise. Such is not the case in the biological sciences. It is a peculiar conceit of many in our field that the systems with which we deal are too complex to be modelled; models and modelling have to be justified on a continual basis unless the thing being modelled seems to fall with the province of the physical scientist (e.g. transmission of nerve impulses). This paper begins with the proposition that modelling is an essential adjunct to any scientific endeavor. A model is merely a way of representing and manipulating something that would not otherwise be accessible. Models are aids to thought, and it is precisely because biological scientists deal with complex systems that they require models.

The particular kinds of models that are dealt with in this paper are guides to future action, devices that assist in the decision-making process. This being the case it is worth defining at the outset what we mean by a 'right decision'. A right decision is not a decision proved correct by subsequent events but rather a decision that was arrived at by using all the relevant information in the most rational manner. Implicit in this definition is the notion that we do not know all there is to know about the system in question but that it is necessary to come to a decision anyway. The model is merely an attempt to ensure that we use what we do know in the most effective manner possible. In a thoughtful and provocative chapter on the role of models in a practical context, Botsford and Jain (1992) recount the argument between Slobodkin and May. May took the view that the 'choice was not between perfect and imperfect advice to managers but between crudely imperfect advice and no advice at all'. Slobodkin replied 'that it was by no means obvious that "crudely imperfect advice" from a supposed expert is more or less valuable than no advice at all'. But this is mere sophistry.

Managers make decisions all the time because they are obliged to. No responsible manager takes a uniformed decision and so what matters is the quality of the information. May accepts that all advice, including that engendered by models, will be imperfect. But models and the activity of modelling, by their very nature, have a better chance of providing good advice if for no reason other than that they expose all the relevant arguments in a form that is amenable to review and criticism. Nevertheless, despite the fact that modellers have faith in the usefulness of their activities, models are frequently greeted with distrust by those they are meant to assist. If models are to be applied effectively, we must dispel this apprehension. This article reviews the problem and draws in particular on our experience of implementing a model for the control of bovine helminthiasis in South America.

COMPLEXITY AS AN OBSTACLE TO MODEL BUILDING

The question frequently arises whether it is even possible to build a useful model of helminth infections. A cursory examination of the literature reveals systems of bewildering complexity. Laboratory and field reports paint a picture of free-living stages that are exquisitely sensitive to variations in temperature, moisture and partial pressure of oxygen, and of a parasitic phase that still has yet to yield up even a small fraction of its secrets. Surely, the argument goes, we cannot build a useful model in the face of all this complexity. The best way to answer this is to refer to what has been achieved in the absence of a formal mathematical framework. Effective control strategies have been devised and even more effective strategies are emerging

all the time even in the absence of mathematical models. This has been possible because most of what we observe in the field can be explained in terms of a relatively small number of population processes. By focussing on these simple conceptual models and ignoring the rest, it has been possible to formulate interventions that work.

Mathematical models are feasible for exactly the same reason, we are dealing with a tractably small number of very influential population processes that are easily represented in mathematical formats. But if the simple conceptual models work, why do we need mathematical formulations? The conceptual models that have led to such significant advances in parasite control as strategic dosing programs like WORMKILL (Dash, 1986) are expressed (often incompletely) as qualitative statements. Confidence in these statements grows as they are tested in field trials and forms the basis for generalizations about strategies that are likely to work in as yet untested contexts. Unfortunately, the qualitative nature of the conceptual models makes them increasingly vulnerable to criticism as the argument shifts to contexts more and more removed from those in which they were originally tested. A good example is how one might implement the prophylactic dosing strategies against bovine nematode infections that have proved so successful in the intensive, seasonal grazing systems of Europe in the extensive, year-round systems of South America. Quantitative models are less vulnerable to this kind of criticism because we can be more certain that we have taken full and objective account of all of the most relevant factors. Our confidence is based on the requirement that model performance be tested at a variety of levels. There are two principal phases to testing model performance. The first occurs during model development (model validation) and the second occurs when the model is first introduced to the users (beta testing).

MODEL VALIDATION

Validating realistic models turns out to be very difficult. The problem we face is the same as that encountered when trying to measure the sensitivity and specificity of a diagnostic test . . . what do we use as a gold standard? A useful 'rule of thumb' is that the model should generate patterns that an experienced field worker would regard as typical. The merit of this apparently subjective criterion is that the mental models of parasite epidemiology we all carry around with us are uncluttered by the nuances of fine detail. With respect to the models dealt with later in this paper, it is the major patterns and trends we are interested in, not the detail. In part this represents a deliberate compromise between precision and tractability. But, rather more, it represents a growing conviction that there is clear tendency in the literature to over-interpret the ups and downs of field data. The vagaries of chance play a far greater role in the patterns we see than most of us like to admit. Because of this, it is important to use additional criteria in the validation process. There are three main steps.

Construct Validity

The first thing to do is to make sure that the mathematics in the model adequately reflects and encompasses the known biology. One tries to make the model a comprehensive and

accurate embodiment of current hypotheses about the way in which the parasites interact with their environment.

Testing Elements of the Model

Having made sure that the basic architecture of the model stands up to scrutiny, we can then examine its constituent elements. The best way to do this is to compare model output with the results of laboratory experiments. However, it is frequently the case that one has used the laboratory data in the first place to estimate the model parameters. This presents a problem because it is clearly not legitimate to use those same data in any subsequent test of model validity. Often suitable independent experiments are simply not available—but when they are, they provide a very exacting test of the model adequacy. Some examples of this can be found in the companion paper (Smith, 1992). Unfortunately, the opportunity to carry out that kind of comparison does not arise very often. Usually, one has to rely on field data, and in this case one cannot test constituents of the model. Instead, one must test the entire model.

Testing the Entire Model Against Field Data

We have already alluded to our reservations concerning the adequacy of field data as a criteria for model performance, nevertheless, a decent fit between field data and model predictions is almost the only test of model validity that wins general acceptance. It is not a very good one though. In the laboratory, we frequently have some idea about the precision and reliability of our measures. Often we can transform our counts into something approaching absolute values and we are able to take sufficient samples to be sure that we have a good estimate of the mean. That is not usually the case in the field. There we deal with relative rather than absolute measures and it is wise to be cautious about accepting the calculated means too uncritically. For example, trichostrongyle worm counts and egg counts typically exhibit highly overdispersed frequency distributions. The number of samples required to estimate the mean values accurately is far more than can be managed given normal constraints.

The problem is further compounded because we do not know quite what it is we are measuring. Studies of bovine helminthiases, for example, often involve faecal egg counts. Indeed, many studies measure no other indicator of parasite abundance. Unfortunately, very few of these distinguish between the various trichostrongyle eggs counted. This presents a problem for the modeller. Natural infections are multispecies assemblages whereas all current models of gastrointestinal infections of ruminants deal with only one parasites species at a time. The pattern of egg counts generated by the model pertains only to that species and not to the assemblage of species that is actually present. We illustrate the difficulty this presents in Figure 1. Some years ago Borgsteede (1984) undertook a study in the Netherlands in which he attempted to differentiate between the relative contribution of each species to the overall 'trichostrongyle type' egg count in infected animals. As Figure 1 shows, *Ostertagia* peaks quite early in the counts, whereas something like *Trichostrongylus* peaks much later. The qualitative differences between the curves are

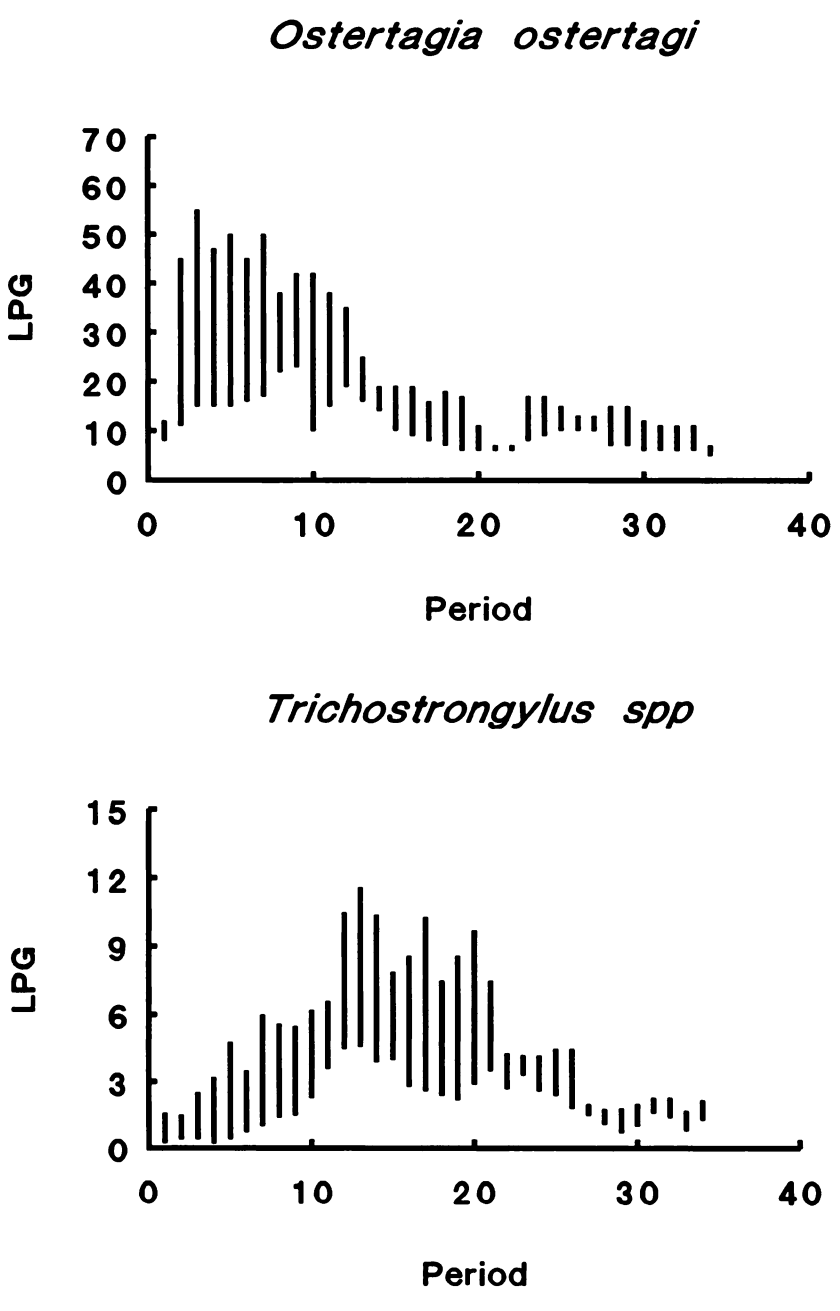

Figure 1. Larvae per gram (LPG) of *Ostertagia ostertagi* and *Trichostrongylus* spp. in the feces of calves collected over successive two-week periods. The eggs were incubated and the larvae cultured to the third larval stage for identification.

relatively unimportant if one species always predominates and the model happens to concern that species. But if the species are there in roughly equal numbers, or if one takes over from the other as the season progresses, a detailed comparison between observed numbers for the mixed species assemblage and predicted numbers for a single species model is impossible. Some examples in which model predictions are compared with independently obtained field data are given later in the paper.

BETA TESTING

The software which implements the model is first introduced to the potential users during the beta testing phase. Beta testing has two functions: it reveals previously unrecognized flaws in model performance and it is the first phase of user acceptance.

The model must be exposed to the criticism of other modellers. This is done by means of published papers describing model architecture, conference presentations and by hands-on testing. A favourable appraisal can generate good word-of-mouth recommendations for the model; criticisms can be responded to; and errors and imperfections corrected. The next step is to approach those whose opinions influence the potential users. This includes academics, veterinarians and farming extension agents. Model demonstrations in the context of informal question and answer groups work particularly well but will not succeed unless there has been adequate preparation.

The credibility of the model often depends as much on the credibility of the presenter as it does on its own performance. Finally, the user group must be persuaded of the utility of the model and trained in its operation. Preparatory seminars and discussion groups are an essential first step here. The purpose of these sessions is to acquaint the users with the biological underpinnings of the model, its proper use, and the evidence that it does what it is supposed to do. Only then should the users get their first hands-on experience of model operations. Small, fully supervised training sessions work best. The prime purpose of the initial sessions is not to train the users in the commands which operate the model but rather to instil confidence that the model works. Inadvertent key strokes, hardware problems and the specification of unrealistic or impossible biological scenarios (not unusual amongst inexperienced users) erode model credibility very quickly. Finally, training sessions must include access to clear, written instruction manuals. Help screens are useful, but not easily utilized by those not used to computers.

It is important to request and respond to feedback at each step in the beta testing phase. It is also important to keep each group fully aware of the intended purpose of the model and this involves being very clear about its limitations as well as its strengths. Models are damaged as much by their failure to live up to inflated expectations as they are by poor performance in the face of realistic expectations.

POTENTIAL FOR APPLICATION OF CURRENT MODELS

Models are built to some purpose. All the existing models of helminth infections of veterinary importance were constructed with a view to increasing our understanding of the population biology of the parasites, and all of them were designed to assist in some aspect of parasite

control (Smith, 1992). Nevertheless, the capabilities and specificity of these models vary enormously, and deliberately so. Most deal with just a single parasite. One (PARABAN) deals with a whole family of parasites. Some models are useful only in establishing general rules for treatment, others are more sensitive to local fluctuations in climate and management and are useful in designing area-specific strategies for parasite control.

The two models we consider here address different, but linked, problems. The first model, which deals with strategies to impede anthelmintic resistance, is typical of models which address important practical issues but which are expressly written to communicate ideas to other specialists. In such cases, there is often no systematic attempt to inform those who might benefit most by the ideas generated and tested in the model. This model will serve as a contrast to the second which was written to assist in the design and communication of control strategies for bovine parasites in extensive as well as intensive grazing systems. From its initial conception, this latter model was intended to inform those who have to make decisions about how often to treat and when. Its development followed that outlined in the opening sections of this paper since it was important that the model gained acceptance at all levels of expertise. In neither of these models is there any pretense that they precisely mimic the course of events on this or that farm, but both were expressly designed to provide a rational basis for deciding between competing strategies and this they do very well.

Anthelmintic Resistance

The evolution of anthelmintic resistance is an important impediment to the economic control of gastrointestinal strongylid nematode parasites of sheep, goats and horses and there is recent evidence that it may become a significant factor in the control of gastrointestinal parasites in cattle (Smith, 1990a). We cannot expect to avoid the problems caused by anthelmintic resistance merely by replacing old drugs with new ones. We must manage anthelmintic resistance using the drugs we already have to hand. There is general agreement that regimes involving infrequent treatments of only that fraction of the host population most at risk will impede the spread of anthelmintic resistance but such a strategy may not achieve the production benefits required in the market place. As an alternative, resistance management programs involving more than one kind of anthelmintic preparation have been suggested, but the literature is replete with conflicting claims about the efficacy of each of the competing strategies. Le Jambre *et al.* (1978) recommended using a single anthelmintic for as long as it remained effective and then switching to an alternative; Prichard *et al.* (1980) recommended slow rotation of alternate drugs, a strategy that might be particularly effective if one drug selects against resistance to the other; and Dash (1986) recommended using mixtures of anthelmintics.

There have been several models which address anthelmintic resistance in parasites of veterinary importance (Gettinby *et al.*, 1989; Barnes and Dobson, 1990; Smith, 1990a) but only one (Smith, 1990a), which was specifically designed to distinguish between sequential, rotational and simultaneous drug treatment strategies. The basic model was typical of an extensive family of similar models that have been successfully used to evaluate anthelmintic control strategies against various nematode parasites of man and his domestic animals

(Anderson, 1986; Smith *et al.*, 1987). It consisted of two coupled differential equations. The first equation described changes in the abundance of the free-living infective larvae and the second changes in the abundance of the sexually mature parasitic adults. The life cycle was direct and the parasite was assumed to be naturally regulated by a density-dependent constraint on the survival of the sexually mature stages. The model assumed that resistance to any given drug was determined by a single major gene comprising two alleles at a single autosomal locus and that resistance to drugs with different modes of action was determined by loci on different chromosomes. The assumption that resistance is determined by a single major gene is almost certainly a simplification but recent work on mechanisms of resistance suggest that the system may not be as genetically complex as once thought (Pritchard, 1990). Finally, the persistence of mutations conferring resistance, despite their deleterious nature in the absence of treatment, was assumed to be the result of heterozygote advantage operating on the survivorship of the free-living stages.

Extensive simulation studies using this model revealed that sequential and rotational strategies were very poor at impeding the spread of anthelmintic resistance. The simultaneous application of two drugs with different modes of action was always the better strategy (Figure 2). The reason is relatively simple, the simultaneous strategy works because it increases the potency of each individual treatment. Parasites resistant to drug A are killed by the simultaneous application of drug B. Unfortunately, the simultaneous strategy is more expensive than either the sequential or rotational strategies and meets with considerable consumer resistance.

The model just described has been criticized for representing the population biology of the free-living phase of the parasite life cycle in too simplistic a manner. This was a deliberate strategy to ensure the genetic mechanisms remained unobscured. Perhaps a more telling criticism is the lack of attention given to the distribution of parasite genotypes amongst the host population. Indeed, this model explicitly avoided the problem by assuming that the host population consisted of only a single host! The difficulty arises because it is unlikely that the distribution of genotypes will be identical in every host in the population and it becomes increasing difficult to estimate the frequency of the all possible mating combinations and thus the frequency of given genotypes amongst the offspring. None of the models cited above deals with this issue and the consequences of unequal distributions of parasite genotypes remain unresolved.

PARABAN

PARABAN is a model for the common trichostrongylid infections of cattle (Smith, 1990a; G. Smith and J. Guerrero, unpublished data). The principal purpose of PARABAN is to help design and communicate effective parasite control strategies. PARABAN is unique in that it uses the same model framework for each of a whole assemblage of parasites. This model exploits the finding that the population processes that regulate and control parasite abundance in the parasitic phase of the life cycle are essentially identical across all the species of interest (Smith, 1992). Moreover, it also assumed that there are negligible differences in the biology of identical species in different geographical locations. This means that if PARABAN works in the sandhill regions of Nebraska, it should also work

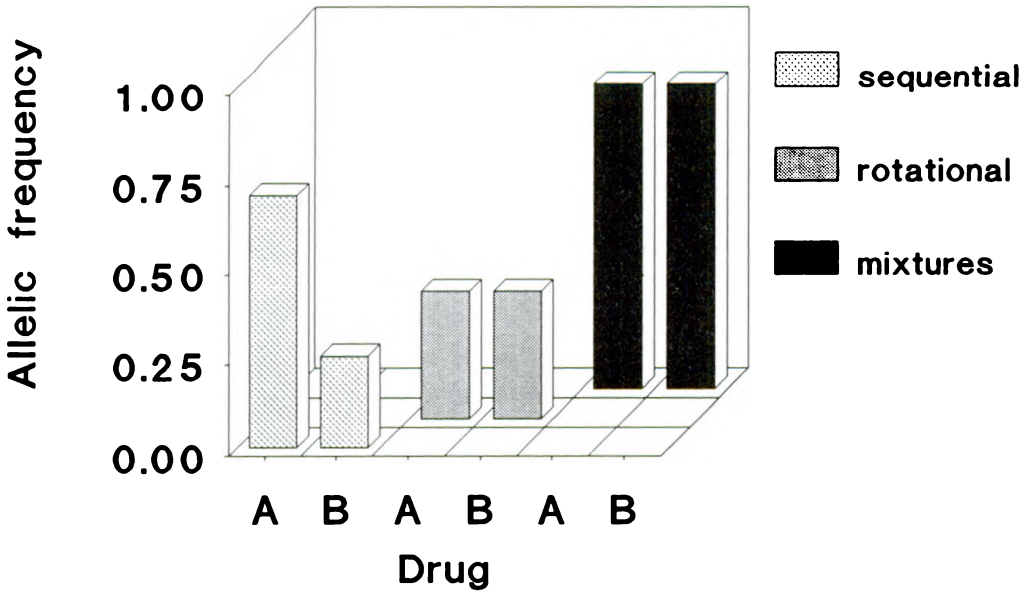

Figure 2. Allelic frequencies of alleles for susceptibility to two drugs following the completion of a sequential, rotational and simultaneous strategy. The same number of doses of each drug was given over the same time period in each case (Smith, 1990a.

in, for example, the Chiahuahuan deserts of Texas, the marshes of Louisiana, the Cerrado region of Brazil, the humid Pampas of Argentina or the meadows of Europe. As a result, the user interface is designed so the user can specify the details of almost all the common intensive and extensive management systems. PARABAN deals with a range of parasites *(Ostertagia ostertagi, Cooperia* spp., *Trichostrongylus* spp. and *Haemonchus axei).* The most studied of these is *O. Ostertagi* and so in order to illustrate PARABAN's potential and provide the greatest contrast of management types and climate, we present the result of two simulations: one for an intensive replacement heifer system in the Netherlands and one for an extensive cow-calf system in Buenos Aires Province in Argentina. We emphasize that the data used in the comparisons were collected entirely independently of any work on the model and so provide a true independent test of the model's value.

The Netherlands

The first trial dealt with an intensive replacement heifer system in the Netherlands (Eysker, 1986). Since Eysker logarithmically transformed his data before presentation, we have similarly transformed the results of the simulation to make the comparison easier (Figures 3 and 4). Eysker also distinguished *O. ostertagi* from all the other parasites present so the data shown refer to *O. ostertagi* alone. The trial involved groups of calves first turned out onto

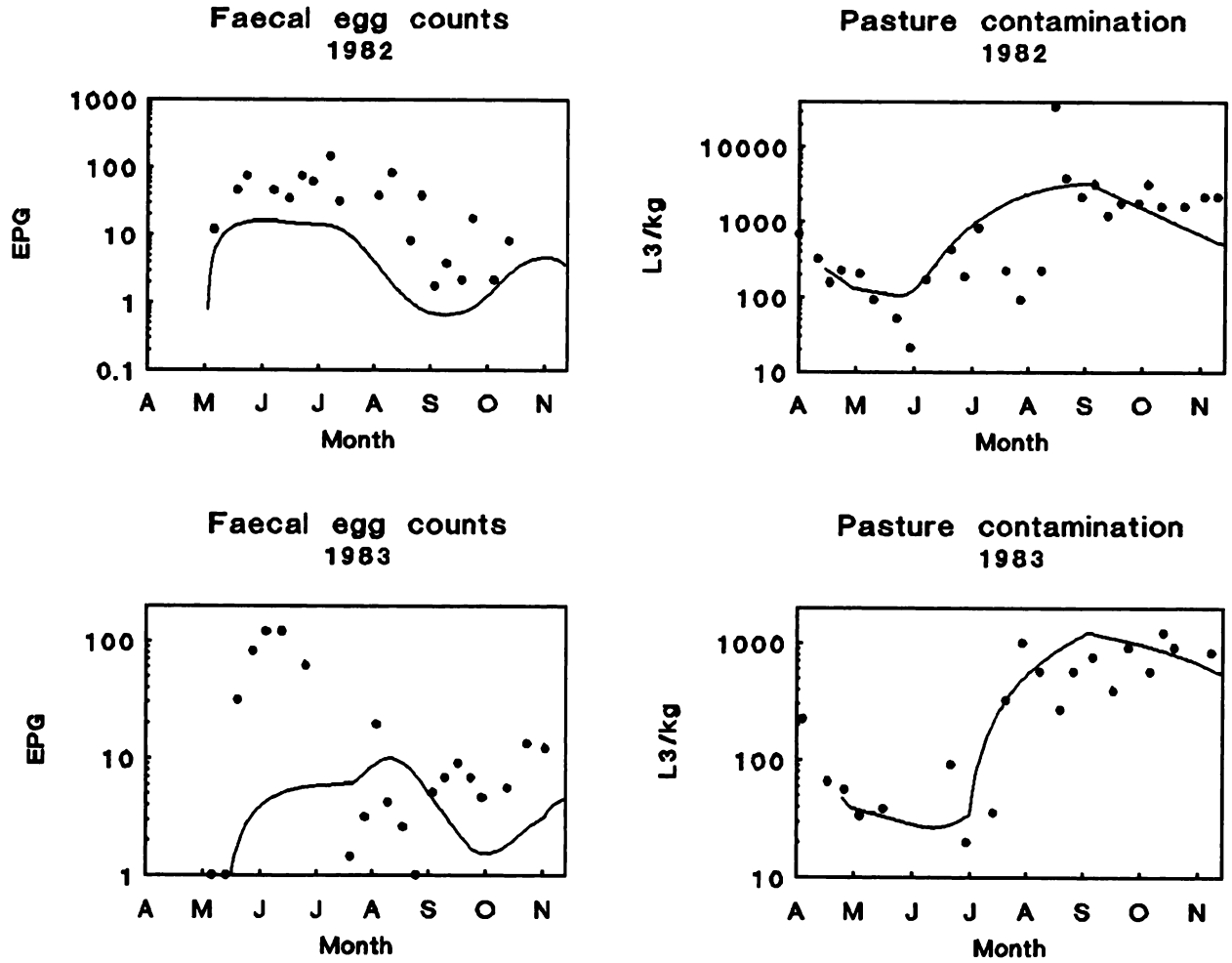

Figure 3. Observed (●) and predicted (solid line) faecal egg counts and pasture larval counts in two successive years. Calves were turned out in April 1982 and May 1983 and set stocked (0.5 calves/hectare) until the end of October in each case. Data from Eysker (1986).

pasture in the spring and set stocked until housing in the autumn. One group of calves was left untreated, the other was treated once three weeks after turnout with ivermectin. Figure 3 compares observed and predicted faecal egg counts in untreated groups in 1982 and 1983. With the exception of the egg counts in 1983, the correspondence between observed and predicted trajectories is fair to excellent. The midsummer rise in pasture larval contamination is particularly clear in both years. It might not be immediately obvious why there is such a good fit for the pasture larval contamination in 1983 given the rather indifferent result we obtained for the egg counts. The reason is simply that the pattern of pasture larval contamination depends far more upon the effect of climate on the development and mortality of the free-living stages than it does on the rate of recruitment of eggs. When Eysker treated the calves early in the grazing season, he hoped to eliminate the early surge in egg output, which he most effectively did. Figure 4 shows that PARABAN predicted the same result.

Argentina

Steffan and Entrocasso (1991) were interested in testing a prophylactic treatment strategy in calves in the Humid Pampas of Argentina. Postmortem analysis of the worm burdens in the control calves revealed that *O. ostertagi* and *Trichostrongylus* spp. were equally represented. The principals were treated once at weaning with fenbendazole and then three times with ivermectin 3 weeks, 8 weeks and 13 weeks later. The principals and controls were maintained on separate pastures. Pasture larval counts and faecal egg counts were carried out at regular intervals. The results are presented in Figure 5. The data exhibit the variance typical of such trials and so a fitted fifth order polynomial was used to summarize the general trends and the model results compared with the fitted line. The most obvious feature was that the simulated trajectories are below the fitted lines. This is to be expected though, since the model is concerned only with *O. ostertagi* whereas the fitted line represents a mixed species infection. More importantly, the simulation and the fitted line follow the same temporal trajectory in both the treated and untreated groups indicating an excellent correspondence with regard to the dynamics of the infection.

It is worth emphasizing here that the same model was used in both simulations, only the climatic parameters and management details were differently specified. There were some discrepancies between observed patterns and the simulations, particularly with regard to the egg counts in the Netherlands study. This is to be expected if for no other reason than that there are limits to the accuracy with which we can specify the climatic and management details prevailing during the actual trial. What is important, and what constitutes the acid test for the model is that PARABAN worked well enough that we should have been able to predict the result of each control strategy in the absence of prior knowledge of the outcome. This is what the model was designed to do.

ADVANTAGES, LIMITATIONS, SHORTCOMINGS

We have presented two models for helminth parasites which seem to us to typify the potential application for helminth models. One dealt with anthelmintic resistance, prob-

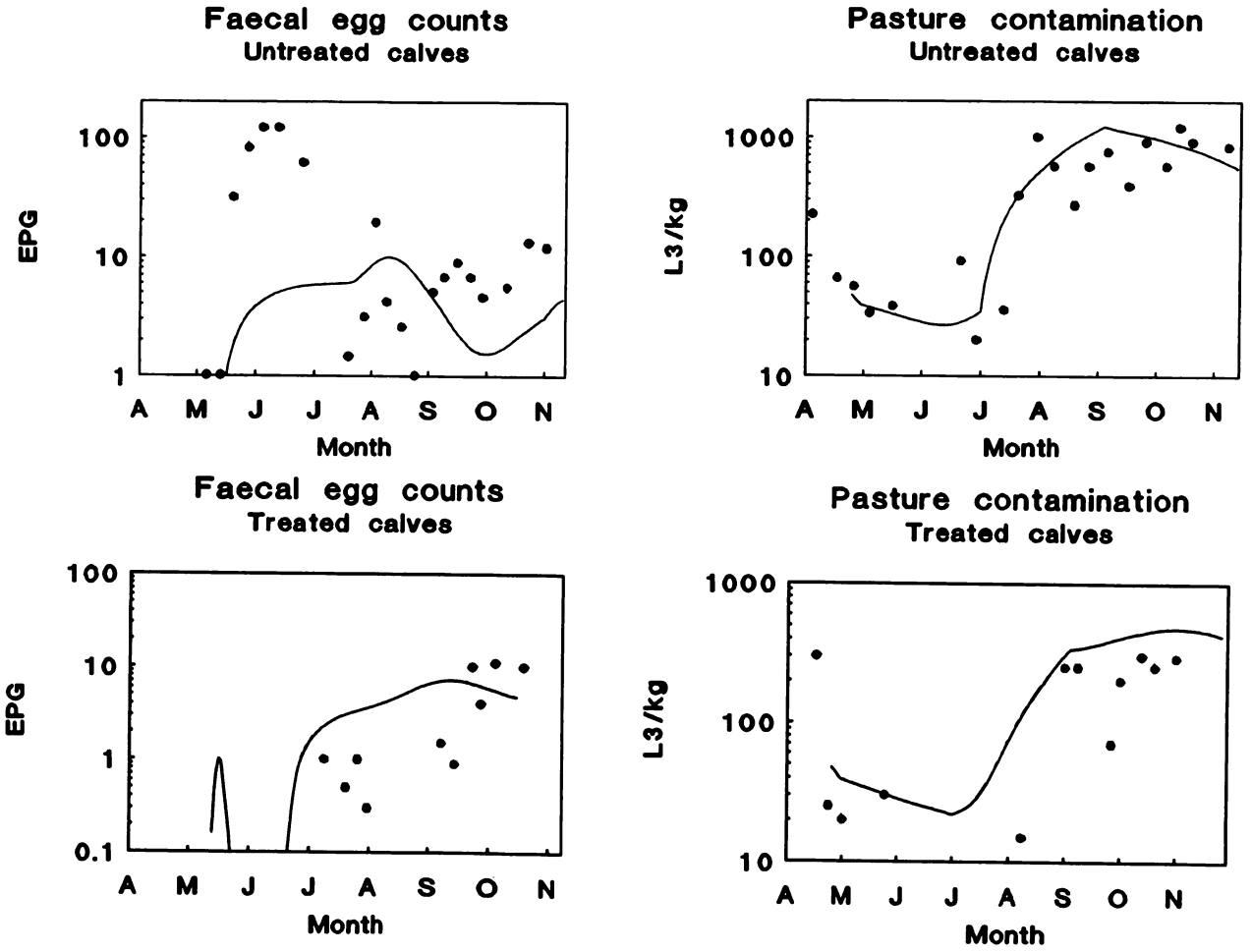

Figure 4. Observed (●) and predicted (solid line) faecal egg counts and pasture larval counts in 1983. Principal and control calves were turned out on separate pastures in May and set stocked (0.5 calves/hectare) until the end of October. The principals were treated with ivermectin three weeks after turnout. Data from Eysker (1986).

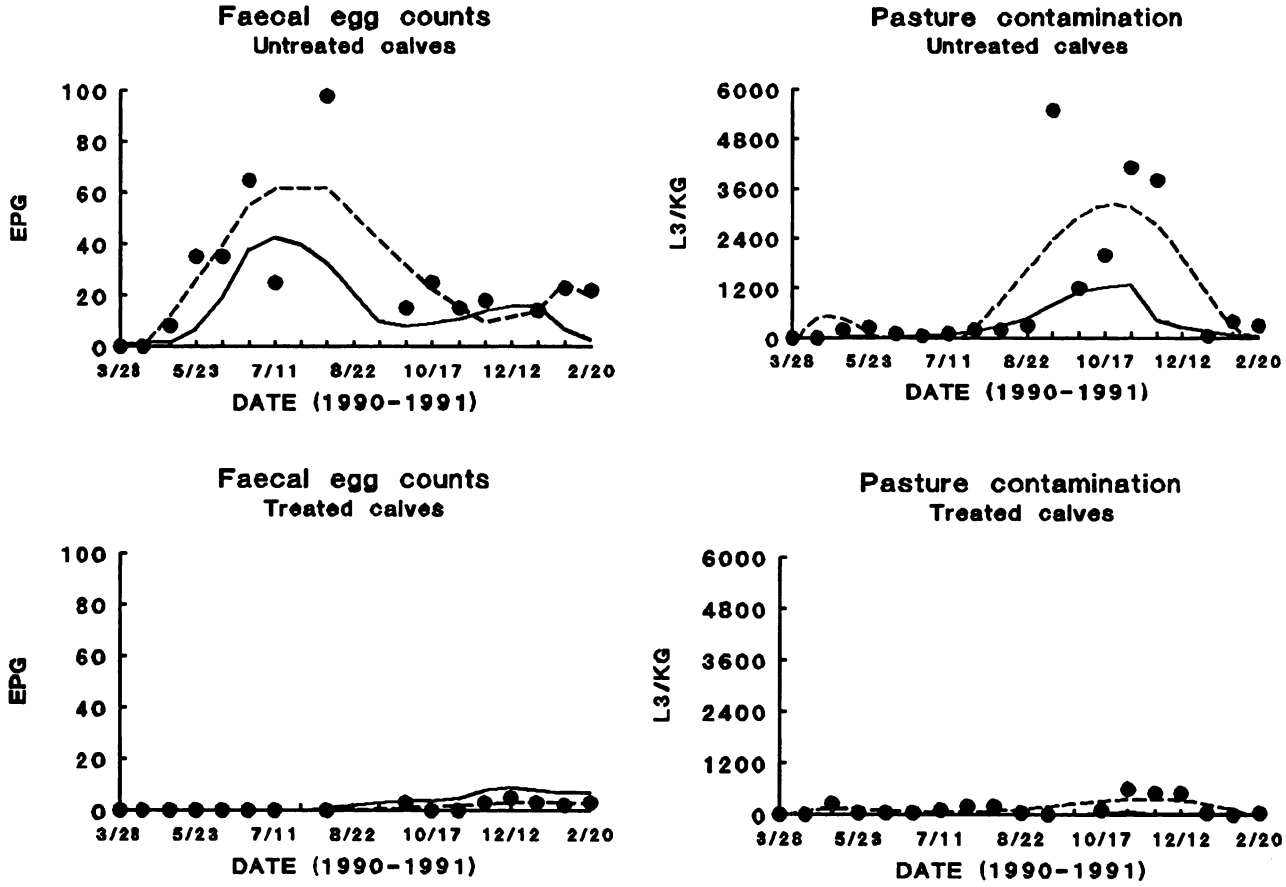

Figure 5. Observed (●) and predicted (solid line) faecal egg counts and pasture larval counts in calves in Buenos Aires Province, Argentina. The calves were born in August 1989, weaned in March 1990 and maintained at a post-weaning stocking density of 2.7 per hectare. The dashed line is a fifth order polynomial fitted to the observed counts. Note that observed counts include both *O. ostertagi* and *Trichostrongylus* spp. whereas the predicted line is for *O. ostertagi* only. The principals were treated with fenbendazole at weaning and then with ivermectin 3, 8 and 13 weeks later. Data from Steffan and Entrocasso (1991). Figure redrawn from Smith and Guerrero (in press).

ably the most important potential impediment to successful parasite control, and the second dealt with the design of effective parasite control strategies, still a contentious issue in extensive grazing systems. The first was intended to communicate information to other specialists, the second was intended to be used in producer group meetings in a variety of countries to elicit and guide discussion about the efficient use of anthelmintics. The first had only to satisfy the usual criterion of peer review in academic journals whereas the second had to undergo in addition the kind of testing and introduction procedures that are generally associated with commercial software. Our experience shows that the successful application of a model intended to be used by those other than the model builders is critically dependent on procedures that build confidence in the intended user group. The users must be confident that the model does what it is meant to do and confident that they can themselves use it effectively in the absence of supervision. We believe that the principal usefulness of these models is that they are both effective aids to thought. But both models represent a compromise between detail and tractability and this limits what it is reasonable to expect them to do.

The model on anthelmintic resistance was designed to investigate a very specific problem and its uncluttered two-equation format reflects that very singular purpose. PARABAN, on the other hand, is considerably more complex, but here too considerable care was taken to eliminate detail unnecessary to its intended function (Smith and Guerrero, 1993). Although we have used the word prediction when referring to model results, perhaps we can express our purpose more clearly when we say that model results are intended to represent our very best conjecture about what is likely to happen given a particular set of circumstances. Neither model is intended to stand alone. Continuing experience with PARABAN buttresses our early impressions that it is a very good mimic of parasite population biology, but this not withstanding, we resist any attempt to use it uncritically and insist that its proper purpose is to elicit informed discussion about parasite control in a *regional* context. There is no pretense that PARABAN can accurately mimic the nuances of parasite trajectories on this or that ranch. Indeed, given our current state of knowledge, this would be a recklessly ambitious objective for any model. Nevertheless, PARABAN is able to rank competing strategies in a convincing rank order of efficacy and that, for our present purpose, is sufficient.

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Initial practical experiences in using epidemiological modelling in Costa Rica

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ABSTRACT

The animal production process includes production factors such as soil, feed, labour and animals. Disease as part of this process reduces potential factor sources and increases costs. To optimize production, the factors involved in the disease presentation have to be elucidated and controlled. Updated and accurate data are necessary, but in developing countries information on disease incidence, prevalence, potential causal factors are rarely available. Different sampling strategies can be used to deal with this lack of information. Cross sectional studies using convenience and random samples can be used to estimate regional or national parameters. Recently decentralized computerized farm monitoring packages have become widespread in developed countries and in some developing countries. This information can be used in epidemiological modelling to determine the consequences of various biological variables and management strategies concerning different aspects of the animal production process. Three different examples of the applications of epidemiological modelling in Costa Rica are given; in the first, convenience sampling was used to gather data on bovine trichomoniasis and a simulation model was developed. The model was validated and different control strategies tested. The second example uses data from a random national survey developed by the Ministry of Agriculture in Costa Rica. Biological and geopolitical areas were assessed as potential factors involved in the occurrence of bovine anaplasmosis and babesiosis, using spatial autocorrelation analysis and risk assessment. Finally, using prospective data a deterministic economical model was designed to evaluate the economical impact of diarrhoea and respiratory disease in commercial dairy calves. A Monte Carlo simulation was applied to the model to determine the range of potential outcomes in an average farm with 25 calves.

INTRODUCTION

Changing global trading patterns, such as the free trade between Mexico, USA and Canada, is demanding higher production efficiency and quality of agricultural production in the Central American area. At the same time, there is a demand that farming activities encourage sustainable ecological and socioeconomic development.

This ecological and economical situation is forcing livestock production systems in Costa Rica to intensify in order to allow reforestation of degraded areas and still produce sufficient food for a rapidly increasing population. It is in this context that a joint effort between the production, academic and official sectors is necessary to improve the efficiency of natural, human and capital resources in livestock production systems. I will address in this paper the role of modelling in our project in developing of knowledge,

information, resources and tools to optimize the Costa Rican livestock production systems. First, there is a brief description of the development of a farm monitoring system in pilot projects (under the control of the unit). An illustration of modelling as a tool in the farmer's decision-making process and in our research activities is then provided.

INFORMATION SYSTEM

The information system was established in a decentralized, farmer-oriented manner, and comprised a data collection and processing unit using a personal computer and VAMPP software (Noordhuizen, 1984. This provided farmers with a user-friendly recording system and immediate feedback of information to support farm management. Farms were visited on a weekly basis by technicians of the pilot projects, when information from the farmers' daily report was entered in a portable computer and processed, providing the farmer with management action lists. This procedure gave appropriate and timely information to the farmer in terms of quantity, quality and format and provided our unit with validated and standardized data. The feedback stimulated the farmers and farmers' advisors for continuation and correction of incomplete data.

The information was centralized and the resulting databases allowed individual (animal), aggregate (herd) or area (region) analyses, limited by production, health and reproduction criteria and other variables such as breed, body condition, parity, etc. This procedure was very useful for applied epidemiology research to support programs in herd health and generate statistics of the region. Information was also generated for extension, teaching and research. It was in this area where the epidemiological modelling was a useful tool. Modelling was applied to define research objectives and current knowledge of the production systems. It also was a helpful tool to identify significant gaps in knowledge.

User Characteristics

A total of 30 stations (computers with software) were using the system. Sixteen of these were owned by farmers servicing their own farms, six stations were administered by veterinary practitioners and eight stations were operated by farmer organizations, technicians or other farm consultants.

All microcomputers were used to run other specific applications (accounting) or non-farming applications (spreadsheets, word processing, etc.). All non-farmer VAMPP stations gave other services to the farmers such as emergency attention, veterinary visits, extension programs or general services (sale of veterinary drugs, nutritional advice, etc.). Several brands of computers (17 PC-AT compatible and 13 PC-XT compatible) with a wide range of configurations were used. The disk space required for the package was in all cases less than seven megabytes. At 28 stations the animal health and production data was collected through farm visits or mail systems with a frequency of less than 30 days. The reports for the farms were generated with intervals of less than 30 days in 14 stations, while in the remaining stations reports were generated in periods greater than 30 days.

Table 1. Available records from the VAMPP database from 221 farms.

Types of records	Number of records
Individual milk recordings	132,122
Inseminations	52,943
Reproductive examination	42,654
Calvings	32,418
Animal identification	26,024
Drying off	10,120
Services and heats	9,597
Young stock body weights	9,192
Disease events	7,733
Culling	4,681
Body condition scores	2,351
Cows to be kept open	561

Farm Characteristics

Out of 221 farms initially approached, 192 farms were actively using the package. A farm inquiry was conducted at 132 of these farms, resulting in the following information: the information system is most prevalent in specialized dairy farms (87 farms; 66%); 42 farms were recording information from dual purpose cattle and three farms from beef (cow-calf) cattle. Most of the farms (84%) were smaller than 200 hectares. All farms received technical assistance from public or private veterinarians, animal scientists or others.

The Database

The integrity of the database was evaluated and no physical or logical errors were found. The database contained information on 26,024 cows and heifers including 32,418 registered calving dates and history. Examples of other records are shown in Table 1.

Based on the information system integrated with the herd health programs in the pilot projects, modelling has been applied to aid in the decision-making process. Three examples are described in the following pages.

Model 1. The transmission of *Tritrichomonas foetus* in Costa Rica: an epidemiological simulation model

INTRODUCTION

Trichomoniasis, and its association with infertility has been recognized worldwide as a major cause of infertility in naturally bred cattle (Johnson, 1964; Clark *et al.*, 1974; Wilson

et al., 1979; BonDurant, 1985). In published surveys, the percentage of infected bulls varied from 7 to 15.8% (Skirrow and BonDurant, 1988; BonDurant *et al.*, 1990). In a recent cross-sectional survey in Costa Rica, the prevalence of *Tritrichomonas foetus* infection was determined in bulls of two major cattle-producing regions (Perez *et al.*, 1992). Herd prevalence rates of 6.74% (6/89) and 15.87% (10/63) and bull prevalence rates of 3.92% (6/153) and 6.22% (14/225) were detected. Within-herd prevalence ranged from 50 to 100% of bulls (mean = 83.3%; median = 75%) in one region and 12.5 to 100% (mean = 39.39%; median = 29.16%) on the other.

For infected herds, in the Tilaran region, the median herd size was one bull (range 1–2) and for uninfected herds it was three bulls (range 1–14). A median herd size of four bulls (range 1–13) was found in San Carlos both in infected and uninfected herds.

Three risk factors for bull infection were identified using binomial logistic regression for distinguishable data: age (> 4 years), breed *(Bos taurus)* and whether the bull was in service at sampling. The venereal nature of the disease and the high prevalence indicated that trichomoniasis could have a serious economic impact on cattle production in Costa Rica.

Model Construction

Stella software was used to simulate the transmission and persistence of *T. foetus* in dual purpose and cow-calf herds. A flow diagram of the typical cow-calf production system in Costa Rica, including a subsystem of bovine trichomoniasis, was constructed (Figure 1). A combination of the Reed-Frost model for the transmission and Anderson and May model for the duration of infection and immunity was used based in the following assumptions:

- The simulation covered 96 weeks.
- There are three groups of susceptible animals (first calving heifers, cows with a calf suckling and open cows), all included into the category of susceptible cows in the model.
- There is no seasonal breeding.
- The annual mortality rate is 10%.
- The annual culling rate is 15%.
- It was assumed that 10% of the herd culling rate was in infectious cows due to infertility, and 5% was in immune cows due to other causes.
- The infection rate was calculated using the Reed-Frost equation.
- An infected cow stayed as a diseased animal during three oestrus cycles (nine weeks) (Abbitt, 1980).
- A cow lost her immune status beginning at the 5th week until the 80th week (Clark *et al.*, 1983). In the model, this was assumed to occur randomly between 5 and 80 weeks.
- *Bos taurus* bulls are the predominant breed in dual purpose herds, and have a 4.58 times greater odds of being infected with *T. foetus* (Perez *et al.*, 1992), also the *B. taurus* bulls accomplished an increased number of matings in the same period of time as compared with *B. indicus* bulls (Galina and Arthur, 1991).
- The effective mating contacts were assumed to be random, being one to five in *B. taurus* and one to two in *B. indicus*.

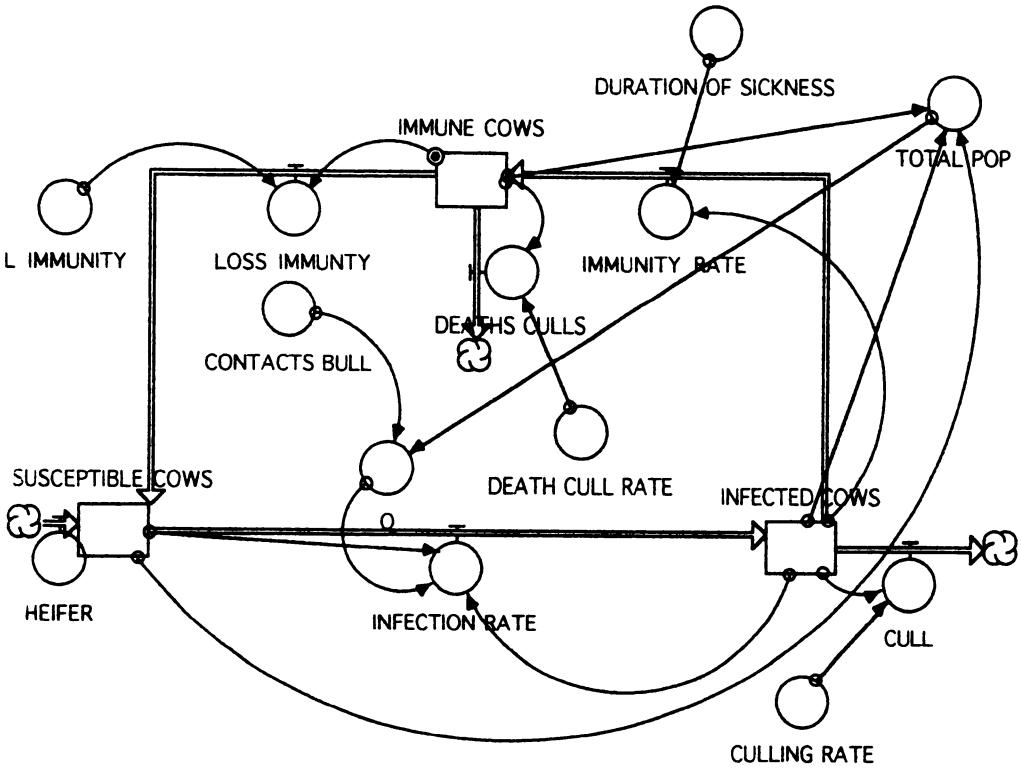

Figure 1. A flow diagram depicting trichomoniasis in the cow-calf production system of Costa Rica.

- Cows are equally susceptible to infection.
- Prevalence of *T. foetus* infection is consistent with field observations for these herds (Perez *et al.*, 1992

RESULTS AND DISCUSSION

The results of the model in both types of herds (beef, dual purpose) are compatible with the behaviour of the disease under field conditions (Figure 2). Cows without previous experience of infection are highly susceptible to *T. foetus* infection. The susceptibility to re-infection is related to the time that has elapsed since resolution of their previous infection. The progressive loss of the immunity that follows resolution of infection in cows was demonstrated by the model. This situation leads to difficulty in tracing trichomoniasis in a herd, because the infection is persistent so that the rate of new infections is balanced with the rate of recovery. Using the model, two possible control strategies can be tested: 1, Interrupt the transmission of the disease, 2. Eliminate infection from diseased animals.

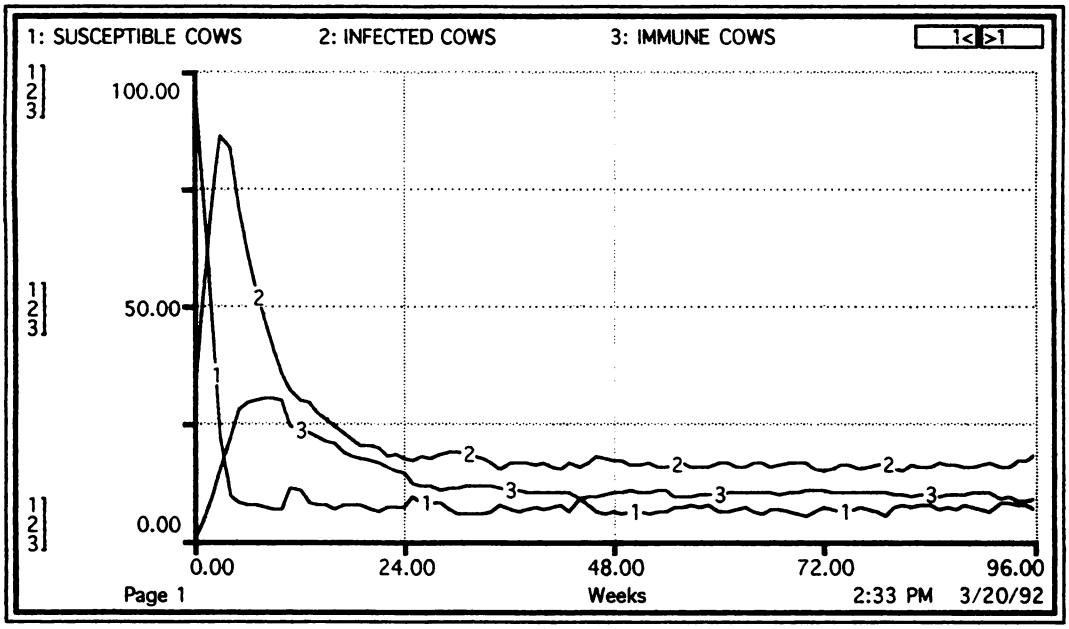

Figure 2. The prevalence of trichomoniasis in a herd predicted by the model for a 96-day period.

The first strategy can be achieved through abolishing natural mating. This possibility was not tested in this study. The second strategy, eliminating infectious cows, was not very effective. A variable number of infected cows persisted in the herds. Different prevalences and culling rates were tested and the results indicated that increasing the culling rate of infected cows was not effective. This model suggests that a good method of control of trichomoniasis is reducing the transmission through the control of the bull infection and cull only non-pregnant cows.

Model 2. Early calfhood morbidity and mortality in Costa Rican tropical cloud-forest dairy farms: an economical analysis

INTRODUCTION

Although of primary importance for the farmer and the herd health practitioner, the economic loss associated with calf morbidity and mortality in Costa Rica is unknown. Decision analysis is a technique designed to approach decision-making under conditions of uncertainty. For this reason it is inherently adapted for herd health problems. One form of decision analysis, decision-tree analysis, is suitable for solving sequential problems. The components of a decision tree are alternatives, probability values for the outcomes resulting from various decisions, and the monetary value associated with these outcomes or decisions.

The economic aspects of diarrhoea, respiratory disease and death in calves from birth to the third month of age in dairy farms in a tropical cloud forest environment was evaluated using a decision-tree structure.

MATERIALS AND METHODS

Study Population

Dairy farms

The entire northwestern milkshed of the central plateau (San Jose and surrounding area, Poas Pilot Project) was selected for this study. The farms were selected for study if they had more than 10 milking cows, if female calves were raised on the premises and if the owner was willing to cooperate.

Data Collection

A standardized wall chart was provided for prospective recording of events for the 42 out of the 52 participating farms. Only live female calves seen by the owner, calf keeper or manager were considered and individual information for each calf was recorded during the first 90 days of life, including death and clinical disease events. Data collection started in February 1987 and ended in May 1988. Of the 1116 female calves born during the study, 928 were Holsteins and 188 were Jersey. Of all calves born, 41.2% were born during the dry season and 58.8% during the rainy season. A description of the calf-management variables and its association with morbidity and mortality on the 42 farms has been presented elsewhere (Perez *et al.*, 1992).

The Disease Model

The model contains the probabilities that a calf will have scours, respiratory disease or die in a given age interval. All the assumptions and probabilities were drawn from a previous prospective study (Perez *et al.*, 1992). Any calf can follow one of two routes: survival or death, with the probability of being in one of these states being conditioned on having followed a certain pathway. The decision-tree therefore was formulated to evaluated the different pathways and monetary values associated with them. There were five 'decision' nodes for the scour model and four nodes for the respiratory disease model: breed node (Holstein or Jersey); the disease node (respiratory disease, yes or no and diarrhoea, yes or no); the treatment node; second event of diarrhoea node and the treatment for the second episode of diarrhoea. The diagram was initiated when the calf was born and each branch terminated when the calf died or survived to three months of age. For the calf, each event (disease or no disease, death or no death) was associated with a certain probability and a economic value. The expected monetary value for a given event was calculated as the product of the probability of the event and its associated economic value. Thus the model

provides an estimate of the economic return per calf in each of the possible pathways that can be followed. The expected monetary values (or expected monetary loss) of each possible outcome is then the sum of the products of the monetary value (loss) of each outcome and the probability of that outcome occurring. Using the tree, it is possible to determine the 'optimal path' that a calf can have, given the occurrence of a preceding event. This method is referred to as a folding-back procedure. When all possible paths are included it is possible to determine the economic cost associated with them.

Conditional Probabilities

The respective conditional probabilities of first scour presentation and respiratory disease were assessed using a Cox Proportional Hazard method, stratified by breed. Each model used the potential risk factor associated with the outcome as covariate. The conditional probability for second scour presentation was assessed using PROC FREQ in SAS (SAS, 1989) for the calves that suffered a second episode of diarrhoea. The conditional probability of death given first scour was also assessed with the Cox method and the conditional probability of death given two episodes of diarrhoea was assessed with PROC FREQ. The respective probabilities for respiratory disease or death given a respiratory disease were assessed using Cox Proportional Method.

Economic Values

The average price of a female calf at 12 months of age in these farms was estimated to be $850. Input costs were estimated as $85.65 for feed costs (milk for three months plus some roughage and mineral salts) and $33.60 for non-feed cost (labour, bedding, equipment). This resulted in a net value of $730.75 and an average monthly return of $60.7 totalling $182.69 in three months. For purposes of the model the net return of a female calf was considered to be $185. Fixed costs were not considered. The first diarrhoea presentation is a mild form of scours. It is treated by removing the milk and feeding only water and electrolytes with activated charcoal. The cost for the three-day treatment for diarrhoea was calculated at $2.50. Repeated episodes of diarrhoea increased the cost to $5.00.

The cost associated with respiratory disease in these herds was calculated to be $10.00, due to intensive antibiotic therapy for five days; some cases are also treated with expectorants and electrolytes. No reduction in weight gain was assumed for either diarrhoea, or respiratory disease unless the animal died.

Application of the Model

A deterministic model was run to evaluate the average or expected return per calf. To model the range of potential outcomes, a stochastic Monte Carlo simulation was used considering an average sized farm with 25 calves.

RESULTS AND DISCUSSION

To perform the economic analysis for the clinical events during the three-month study period, we divided it into sub-periods that represented better the biological reality, using the periods of higher incidence of diarrhoea or respiratory disease for calculation of conditional probabilities. However, to fit any particular problem the nature of these periods can be changed.

The crude incidence rate in the 90-day period for diarrhoea was 36.6%, and mortality was 4.8%. Seasonal differences between morbidity and mortality rates were not statistically significant. Calves were at highest risk of scours during the first two weeks of life. In a previous study in these herds *Escherichia coli*+K99 and rotavirus were isolated, and both agents are associated with diarrhoea during this age. The highest risk for respiratory disease occurred between the third and sixth week in life in Holsteins and the third to fourth week in Jerseys and in both breeds decreased with increasing age.

The average total expected return in surviving calves ranged from $167.70 in the best scenario of a calf suffering one episode of diarrhoea to the worst scenario of $136.80 with a calf suffering two episodes of diarrhoea. The range of potential loss varied from $17.7 to $48.2 per calf. In the respiratory disease model the losses ranged from $28.5 to $32.2. However, the above figures are deterministic and average expected values. In order to examine the range of potential outcomes it will be necessary to make a stochastic model. Using random probability values, the individual animals can be simulated through the tree and summarized according to the monetary value of the path and the number of times that the path was taken. In the best scenario, a calf without diarrhoea and surviving the study period occurred 12.46 times (51%). The worst scenario (death of the calf) occurred 3.4% of the times with a loss that ranged from $185 to $192.50, depending on the number of episodes of diarrhoea. One case of diarrhoea occurred in 38% of the calves with a given a loss of $2.5. Two episodes of diarrhoea occurred in 7% of the calves with a loss of $7.5. In the respiratory disease model, the best path of surviving without respiratory disease happened 92.6% of the time; the worst scenario of total loss (death) happened 2.7% of the time giving a loss of $195. A calf with one episode and surviving happened the 4.7% of the times.

Management is dynamic and complex and therefore its impact must be constantly evaluated. The herd health practitioner must evaluate his/her recommendations for a preventive protocol in calf health and growth on an economical basis. The use of a suitable model like the one described in this report can make the evaluation of the economic impact of morbidity and mortality rates in the dairy farm much simpler and serve to evaluate the herd health protocol. In this situation, the economic loss due to mortality and to calves suffering two episodes of diarrhoea are the worse scenarios given. Combining the information given by these models with the risk assessment performed by epidemiological studies will give the practitioner the tools for economically optimal husbandry advice to the farmer in raising the young stocks. For example in our case, raising Holstein calves in single pens with wood-slat flooring showed a positive economical impact in these dairies by a reduction of the losses due to calf mortality and treatments. The greatest restriction of these models is if no valid up-to-date data exists. In this case, they will be inaccurate and not reflecting the actual situations of the farms under various management systems.

Due to that reason an accurate on-farm surveillance system in combination with a strong analytical epidemiological interpretation is necessary. Finally the simplicity of the tree structure and the analysis performed here makes it easy to demonstrate to the farmer the attention that is necessary in the calf rearing.

Model 3. Sero epidemiological studies on anaplasmosis and babesiosis in Costa Rica: spatial autocorrelation analysis and ecological risk assessment

INTRODUCTION

Anaplasmosis, babesiosis and their tick vectors were studied in Costa Rica by the Ministry of Agriculture and Livestock in collaboration with FAO from 1977 to 1980. Different rates of seroconversion against anaplasmosis and babesiosis were determined, and economic annual losses due only to death of adult cattle were calculated to be US$ 64,000 (McCauley and Perez, 1980). Livestock production systems in the country vary according to ecologic life zones, natural sets of landscapes ranging from swamps to ridge tops in which equivalently weighted divisions of the three major climatic factors (heat, precipitation and moisture) are considered (Holdrige, 1967).

Ecological comparison of areas can be useful in the investigation of potential factors involved in the serological status of cattle to tick-borne diseases (Deem *et al.*, 1993). Environmental factors could have a considerable influence over the incidence of diseases in animals (Gettinby and Byrom, 1991). In vector-borne diseases humidity, rainfall and temperature are all factors which can modify the transmission rate.

The aim of this study was to determine the seroprevalence of *Anaplasma marginale*, *Babesia bigemina* and *B. bovis* in Costa Rica and to study some geographical, ecological and management factors which could influence the epidemiology of the infection.

MATERIALS AND METHODS

Study Population

A serum bank, created by the National Brucellosis Control Program during 1991, was used to provide data for this study. It consisted of approximately 4000 sera collected from farms in each of the sevem provinces in Costa Rica which were selected by a stratified random sample design used by the 1982 national livestock survey. The following information was available for each serum sample: herd size, farm size, farm type (dairy, dual purpose, cow-calf) and location of the farm. Each sample was classified by ecological life zone (Holdrige, 1967). A proportional random selection by number of head within an ecological area was obtained, using an expected prevalence of 50%, an error level of 5% and a confidence level of 99.5%. A minimum sample size of 689 sera was calculated. We selected 717 sera to allow for loss, contamination or otherwise unsuitable sera (Table 2).

Table 2. Sampling distribution and seroprevalence (%) of sera-sampling by ecological area, Costa Rica 1990–1991.

Ecological zone	No.	Percent	*Anaplasma Marginale*	*Babesia bigemina*	*Babesia bovis*
Tropical dry forest, moist transition	74	10.3	72	51	55
Tropical moist forest	180	25.1	71	56	53
Tropical moist forest, perhumid transition	10	1.4	70	70	20
Tropical moist forest, permontane transition	43	6.0	76	35	44
Tropical wet forest	37	5.2	81	67	62
Tropical wet forest, permontane transition	43	6.0	76	67	51
Permontane moist forest	20	2.8	65	55	90
Permontane moist forest, basal transition	24	3.3	66	37	83
Permontane wet forest	70	9.8	74	53	57
Permontane wet forest, basal transition	191	26.6	68	56	50
Permontane rain forest	2	0.3	100	0	0
Lower montane moist forest	3	0.4	66	0	33
Lower montane wet forest	8	1.1	87	87	87
Lower montane rain forest	9	1.3	77	78	11
Montane wet forest	1	0.1	0	100	0
Montane rain forest	2	0.3	100	100	100
Total or mean	717	100.0	72.4	55.4	54.1

Serological Assay

Sera were stored at –20 °C until tested for antibodies against *A. marginale* using rapid-card agglutination test as prescribed by the manufacture (Brewer Diagnostic kit, Wescott and Dunning, Inc). The indirect fluorescent antibody test (IFAT) as described by Payne and Scott (1982) was used to detect antibodies to *B. bigemina* and *B. bovis*. Results of both serological tests were recorded as either positive or negative.

Statistical Analysis

Descriptive analysis

The units of analysis were either geopolitical area (canton), ecological life zone or the individual animal. Means, standard errors, and medians were calculated using PROC UNIVARIATE in SAS (SAS, 1989). Continuous variables were categorized using quartiles. Crude odds ratios were calculated for risk factors using PROC FREQ in SAS (SAS, 1989), using the first category of each variable as the reference level. For variables with three or more levels, each level of the variable was compared with all other levels together as a reference level.

Spatial analysis

Spatial analysis can test the significance of geographical patterns in disease distribution describing them as either clustered, random or dispersed. In theory a random distribution

is one in which the prevalence of an area is in no way influenced by other areas. A cluster distribution will be one in which some pattern in the location of the prevalence exists. A dispersed distribution would be one in which the prevalence is evenly and systematically distributed throughout the study areas. When binary data are available, a second order nearest neighbourhood analysis (Getis and Franklin, 1987) can be executed. With non-binary data such as continuous or ordinal values the method developed by Moran (1950) can be employed. The Moran's index or spatial autocorrelation coefficient tests two possible null hypothesis: (1) normality and (2) randomization. The normality hypothesis assumes a free sampling (sampling with replacement) and is employed when *a priori* probability is considered, i.e. based on information inferred from a larger area. The randomization hypothesis assumes a non-free sampling (sampling without replacement). No reference is made to outside factors. In this study the spatial autocorrelation index using the Moran's coefficient was employed to test the null hypothesis of randomization (Ebdon, 1985).

Risk assessment

Ordinary logistic regression can be used to model herd rates as binomial proportions. The use of this model requires that herd proportions are independent and binomially distributed. These assumptions can be violated by the presence of unmeasured or unmeasurable covariates such as genetics, climate and management. Thus two herds having identically measured covariates (in our case same herd size or belonging to the same life zone), may have different true rates due to differences in unmeasured covariates. This type of extra-binomial variation can be modelled by logistic regression with random effects (Curtis *et al.*, 1993). A second assumption that can be noted is that of within-herd independence, which is likely to be violated due to lateral transmission and clustering of cases within herds. The logistic regression with random effects can also be used to model this type of data. Logistic regression analysis using a logistic binomial for distinguishable data model was performed using EGRET (SERC, 1990). In the multivariate analysis all subsets of variables (farm size, herd size, type of production system and ecological life zone) were used, the reference level for the variables with three or more classes was chosen using the lower level of each category.

RESULTS AND DISCUSSION

The seroprevalence of anaplasmosis and babesiosis are listed in Table 2. These results indicate that *A. marginale, B. bovis* and *B. bigemina* were widespread in the country. Even though these sera were originally selected as part of the brucellosis control program, the stratified random sample obtained by separating the population elements into life zone groups (strata), and then independently selecting a random sample for each strata, allowed us to obtain an unbiased estimator of the population mean and variance making this study representative of the national prevalence by ecological area. The serological tests for anaplasmosis and babesiosis are epidemiologically unrelated with the primary purpose of the sampling *(Brucella abortus).*

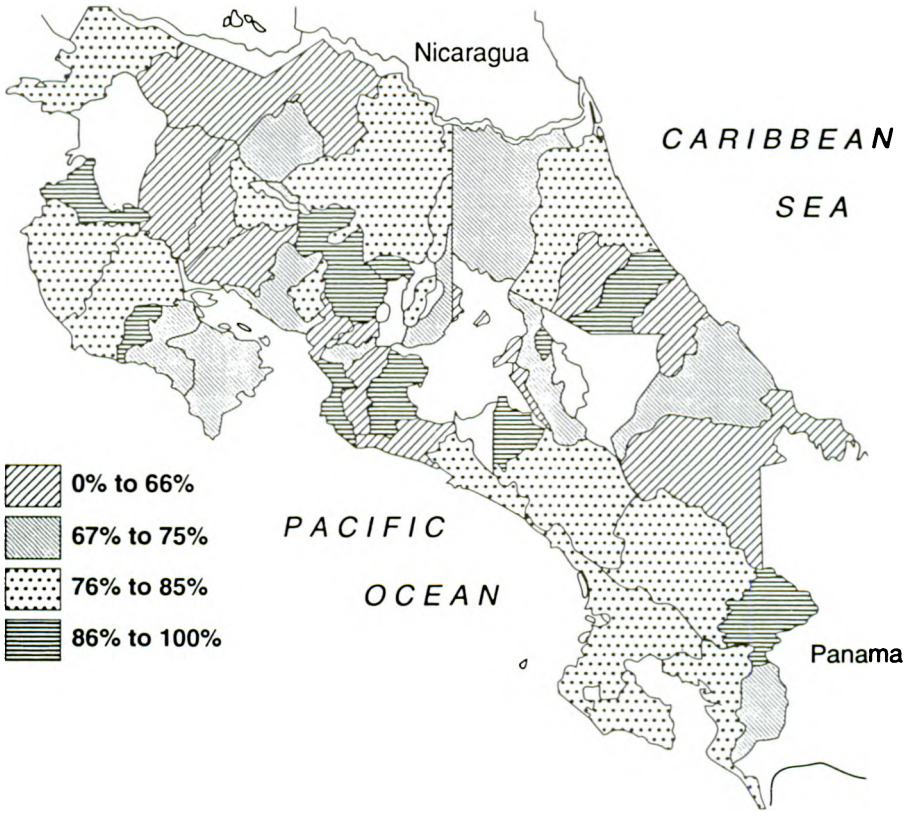

Figure 3. Distribution of sero-reactors to *Anaplasma marginale* in different geographic areas of Costa Rica, 1990–1991.

Transmission of the diseases studied in this work were principally by the tick *Boophilus* spp. (Young, 1988; Lawrence and de Vos, 1990). Anaplasmosis can occur in the absence of babesiosis with transmission influenced by other genera of ticks or other insects and mechanical agents (Callow, 1984). Differences between seroprevalences could then be explained by the favourability of certain geographical areas for the ticks and other vectors due to direct effects of the climate and vegetation on the free-living stages of the potential vectors and indirect effects of the climate on the resistance of the cattle. The latter could be the explanation of the results of the spatial analysis where the resulting statistically nonsignificant z value of 0.838 ($I = 0.069$), $P < 0.42$ for anaplasmosis, and 0.947 ($I = 0.083$), $P < 0.94$ for *B. bigemina* failed to reject the null hypothesis of randomness, implying a random distribution for seroconversion against *A. marginale* and *B. bigemina*. On the other hand the z value of 2.314, $P < 0.03$ for *B. bovis* ($I = 0.235$) indicated a clustered distribution for seroprevalence against *B. bovis*. Possibly bordering cantons shared similar ecological and management factors favourable to the transmission of *B. bovis* (Figures 3, 4 and 5).

The results of the spatial analysis were corroborated by the risk assessment using the random effects models. With one exception, no statistically significant association

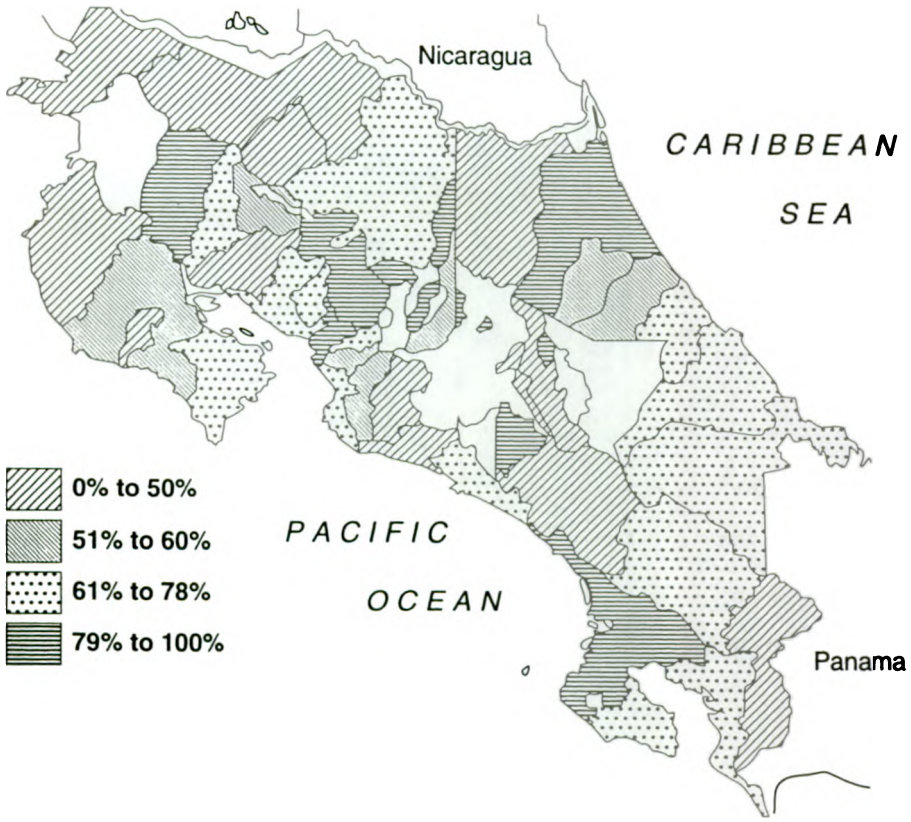

Figure 4. Distribution of sero-reactors to *Babesia bigemina* in different geographic areas of Costa Rica, 1990–1991.

was found between any of the farm characteristics under study or geographical area and the seroprevalence of *A. marginale,* or *B. bigemina.* Only medium size farms (76–150 heads) had an increased odds of seropositivity of *B. bigemina* (OR = 2.56, 95% CI of 1.13, 5.82). These results suggest that Costa Rica is a homogeneous, endemic environment with respect to transmission of these infections (Mahoney and Ross, 1972).

However for *B. bovis* two ecological areas, Premontane Moist Forest transition to Basal (PMFB) and Premontane Moist Forest (PMF), were associated with a significant higher seroprevalence. The PMF showed an odds of 11.8 and PMFB an odds of 15.3 respectively agreeing with the spatial analysis of clustered presentation (Figure 5). The Tropical Moist Forest showed a P-value of 0.07 and a protective odds ratio of 0.09. These three ecological life zones covered 24 of the 52 cantons of the country, with areas of high and others of low seroprevalence as shown by the spatial analysis (Figure 5). There are differences of maintenance transmission thresholds between species of *Babesia,* given by the tick bites per day, infection rates in cattle and inoculation rates from differences in the transovarial transmission rate. *Babesia bovis* is transmitted to cattle

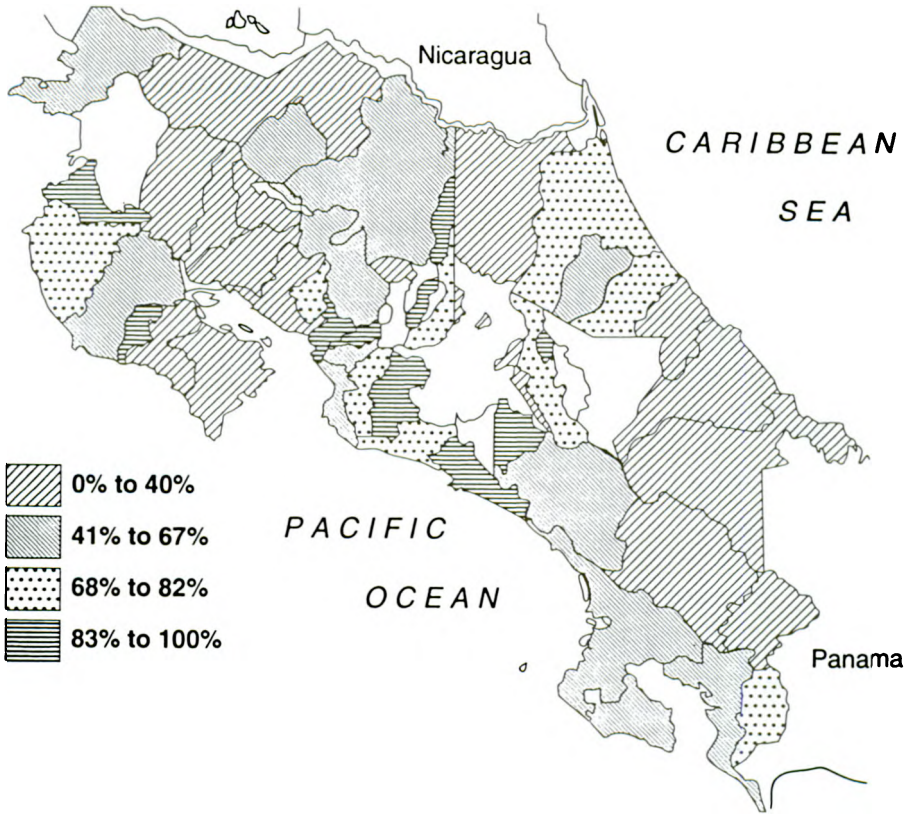

Figure 5. Distribution of sero-reactors to *Babesia bovis* in different geographic areas of Costa Rica, 1990–1991.

by infected larvae (Riek, 1964), and *B. bigemina* is transmitted by nymphs and adults (Riek, 1964; Dalgliesh *et al.*, 1978). Inoculation thresholds for *B. bovis* vary from one geographical location to another depending on the tick activity. On the other hand inoculation thresholds in *B. bigemina* vary less from one location to another (Haile *et al.*, 1992). These differences in thresholds can create as in our case zones of risk (Smith, 1983) where the cattle would be in danger of suffering the disease. Smaller farms (< 40 ha) showed an increased odds of infection as well as farms with more than 40 head, apparently indicating that farms with larger stocking rate (heads/ha) has an increased odds of seroconversion.

These results suggest two foci of seroconversion in the country for *B. bovis*. One is located mainly in the province of Guanacaste (dry pacific region) where cow-calf enterprises predominates. The annual precipitation in this region ranges from 1000 to 2000 mm, and the average temperature is 24 °C. The other is located in the lowlands of the provinces of Alajuela, Heredia and Limon (Tropical Moist Forest, low seroconversion area) with an annual precipitation of 2000 to 4000 mm and temperatures higher than 24 °C degrees. In this region, dual-purpose and milk enterprises are common.

CONCLUSION

It is evident for us that in the stage that we are in now the use of modelling has a direct benefit for research and developmental work. Until now we are testing if our field investigations are appropriate for modelling. We believe that the data recovered in our pilot projects are good enough for a clear understanding of the behaviour of the production systems, allowing a detailed knowledge for the model construction. Our next steps will be:

- To develop and validate models in different components of the productions systems (i.e. young stock rearing, reproduction) to determine economical optimum.
- To generate methodologies that can be used by the farmers or advisers.
- To generate methodologies for the researchers.
- To estimate economical losses and potential causal factors.

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Session discussion

Several speakers stressed the importance of validating models. However, it was stressed that careful assessment should be exercised as a model that fails validation under some circumstances might be a very good model under other circumstances, and may raise important questions on the biological processes involved. Validation starts when models are constructed and includes three steps: a) verification of the code in the program; b) verification of the basic output (does it match the expectations?); c) sub-system evaluation, test sub-systems of the model (e.g. it should be possible to reproduce properties which have not been forced by the model). Finally it is important that field data are used for testing the model. It was recommended that statisticians should assist in developing validation methods, as there is no difference in principle between testing hypotheses and testing models. It is also useful to compare different models for the same subject, to see to what extent model behaviour depends on the modelling technique/architecture as opposed to the biological assumptions. Validation must include training of the intended user in order that they can properly assess comparisons.

Concern was expressed about the availability of current models for ticks and tick-borne diseases, and the importance of having access to the structure of existing models before developing new models was stressed. A feeling was expressed that where models cannot be made public, scientific principles are violated. The question was raised as to whether models which are expected to be used in the public domain should be made widely available with full documentation. It was, however, pointed out that some models are commercial products and one cannot always expect complete documentation. However, it is possible to make such models accessible, through the provision of user control over variation in parameter values. The main concern raised was that the user might pervert the model, and misrepresent its intended use.

It was discussed as to whether a general model for tick control was a realistic proposition. Experiences from Zimbabwe were tabled; they indicated that the losses caused by ticks are often due to a single species in a certain area, and that regional and local differences may not be well accommodated in a general model.

For the development of new models, many people considered it important that the modellers work in close collaboration with the field workers, particularly in the stage of study design otherwise contradictions between model behaviour and field observations cannot be dealt with in a timely manner. When existing models are used it is important that the user contact the developer for guidance. Funding agencies should make sure that the modelling component is included in the grant applications.

The question of integration of the various kinds of models on livestock production, parasitic diseases etc. was brought up; several modellers considered that although it is technically feasible, it is a risky business unless there is very close collaboration between the different developers. An option is to rewrite someone else's model and integrate a livestock model with say a disease model. Concern was expressed that

unknown interactions could be a limitation but model validation might reveal such unknown interactions.

The cost of and funding for modelling was discussed and a general feeling was expressed by the modellers that few people were aware of the costs involved and users often expected to get the models free of charge. The opinion was expressed that costs could be reduced by making more use of adapting existing models.

The potential benefit of having a list of models and a roster of modellers was discussed. It was felt that a roster of modellers would be useful. It was also proposed that an electronic bulletin board should be established in order to exchange information (e.g. Net-News). Doubt was expressed as to whether this would work in the field but several participants reported successful experiences with e-mail in remote places, and it was considered that the trend to increased use of e-mail would continue.

COLLECTION, COLLATION, ANALYSIS AND DISSEMINATION OF DATA ON VECTOR-BORNE AND OTHER PARASITIC DISEASES

Collection, collation, analysis and dissemination of data on vector-borne and other parasitic diseases

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ABSTRACT

Disease modelling frequency has been criticized due to the numerous assumptions that typically go into the construction of a model. This criticism is no doubt significantly linked to the paucity of appropriate data available to the modeller. Given this deficiency, how can international agencies such as the Food and Agriculture Organization (FAO) and the International Laboratory for Research on Animal Diseases (ILRAD) assist the modeller in obtaining data in a form necessary to construct, verify and validate a vector-borne or other parasitic disease model.

Before identifying the requisite data, it is necessary to establish the system being modelled, the hypothesis being tested and the intended audience. Models designed to mimic zoonotic infections require not only demographic information on human populations, but also frequently comparable data on wildlife and domestic animal populations. Such information would include—but not be limited to—density, movement, reproductive rate, death, prevalence and incidence or infestation rates and levels in the respective populations. Host-specific information such as age, sex or breed-specific risk or susceptibility needs to be identified and quantified if existing. Once the host populations have been identified, similar demographic data as well as maturation rates are required for parasite and vector populations. In addition, climatic and control specific susceptibility data are critical to permit modelling of these later populations.

There is need for long-term data collection if the modeller is to attempt to perform a time series analysis of data in order to account for seasonal, cyclic or secular trends in the respective populations and infection patterns. Collection and presentation of information in a temporal form could be greatly enhanced by the addition of spatial dimension, whether it is through satellite imaging of soil or vegetation types of mapping of populations.

For both parasitic and vector-borne diseases, it is important to determine the level of aggregation or clustering of infection or infestation within the population of interest. Such data could be collected from both the laboratory and field. Data such as that discussed above could be useful to the modeller, whether or not it has been analysed, if it is available as either an ASCII file, or as a data base.

INTRODUCTION

Disease modelling frequently has been criticized due to the numerous assumptions that typically go into the construction of a model. This criticism is no doubt significantly linked to the paucity of appropriate data readily available to the modeller. Typically, a modeller will rely on data available in the literature for initial parameter estimates necessary to

construct the model. Given this deficiency, how can international agencies and research institutes such as the Food and Agriculture Organization (FAO) and the International Laboratory for Research on Animal Diseases (ILRAD) assist the modeller in obtaining data in a form necessary to construct, verify and validate vector-borne or other parasitic disease models?

One view of what an epidemiological model is was given by Anderson (1976) when he said it was to '. . . describe temporal changes in the number of susceptibles, infected and recovered or immune hosts within a population, and depend on a few parameters which specify the nature of the incubation and infectivity period and the rate of transmission of disease'. If it were as simple as the quotation implies, the data needed for model construction would be limited. However, as discussed below, it is not often simple and additional data must be collected in order to avoid misinterpretation of model results, or mis-specification of model parameters.

Lamenting inaccuracies of parasite models, Anderson went on to state that: 'Unfortunately . . . very few field or laboratory studies have yielded quantitative estimates of the population process such as infection rates, rate of host mortality caused by parasite infection or even survival rates of the various stages in the life cycle . . . . The paucity of our knowledge is no doubt due to the complexities of parasite life cycles, but the lack of experimental and field information is also a direct lack of the intimacy of the relationship between host and parasite'.

The purpose of this paper is to discuss the need for collection, collation, analysis and dissemination of appropriate (useful in modelling of parasitic and vector-borne diseases) data. The focus will be on the collection and analysis of these data. In the section on analysis, in addition to a limited discussion of some of the appropriate techniques which could be used, some of the errors encountered in the analysis of epidemiologic and production data will be highlighted.

COLLECTION

Before identifying the requisite data, it is necessary to establish the system being modelled, the intended goals or objectives, the hypothesis being tested and the intended audience for which the model is being constructed. Models that are developed to better visualize a system may be satisfactorily completed when the modeller has constructed a basic flow diagram representing the system. Typically, however, the modeller constructs a model that is to be used either to understand the basic components of the system, or for predictive purposes.

Data needs may also be determined after the initial model has been constructed. That is during the model verification and validation stages, it often becomes apparent that due to the responsiveness of the model to changes in a given parameter, additional data may be required to more accurately estimate the parameter which may allow the model to perform more realistically.

Data may be in several forms: production, health, nutrition and other inputs and outputs; economic, border and farm-gate prices, demand and supply elasticities, and accounting or shadow prices; health, efficacy of vaccine, acaricide and chemotherapy; climatic,

temperature, relative humidity, evaporation, and rainfall; topographic, altitude, vegetation and land use; demographic, host, vector, and parasite population dynamics, including spatial distribution and movement; and laboratory, serological, and DNA fingerprinting.

Since data used to estimate model parameters, out of necessity, are often secondary data, i.e. collected by someone else or for another purpose, it is important that they be well understood by the modeller. An example of this necessity for a more critical understanding of the data is the interpretation of serological data. Serological results are dependent on test sensitivity, specificity and prevalence (Figure 1). As any of these parameters change, interpretation of test results will change. Specifically, a test result may either be correctly or incorrectly interpreted as test positive or negative. Measures of these interpretations are referred to as the predictive values of the test. For example, the predictive value (+) of a test is the probability of an individual being infected (D+), given it has a positive test result (T+). This is expressed as a conditional probability, P(D+|T+). As can be seen in the figure, assuming a test sensitivity and specificity of 90% each, the interpretation (predictive value (+) of a positive test result varies, depending on the prevalence, which may be calculated from the apparent, or serological, prevalence, P(T+). Given these test parameters, although one can be confident, e.g 90% probability when the prevalence is moderate to high ($\geq$ 50%) and even 80% when the true prevalence is $\geq$ 30%, this predictive power falls off precipitously, e.g. only 50% when the true prevalence is 10%. This potential for misinterpretation of positive serological results therefore has the potential of being serious at low prevalence levels.

Data may be collected from long or short term, longitudinal or cross sectional, or retrospective or prospective in nature. Long-term data although in some cases essential, e.g. in time series analysis, is often prohibitively expensive in terms of both labour and monetary cost. However, long-term data collection is critical, if the modeller is to attempt to perform a time series analysis to account for seasonal, cyclic or secular trend in the respective populations and infection patterns. Time series analysis is also useful in quantifying parasite or vector development and maturation (Mullens and Lii, 1987).

Data needs also vary, depending whether the system being modelled is direct or indirect (involving definitive as well as intermediate hosts), and for a parasitic infection or infectious disease. These factors must be considered throughout the data collection and analysis process. Models designed to mimic zoonotic infections require not only demographic information on human populations, but also frequently comparable data on wildlife and domestic animal populations. Such information would include but not be limited to density, movement, and reproductive, death, prevalence and incidence or infestation rates and levels in the respective populations. Host-specific information, such as age, sex or breed specific risk or susceptibility needs to be identified and quantified if existing. Once the host populations have been identified, similar demographic data, as well as maturation rates, are required for parasite and vector populations. In addition, climatic and control specific susceptibility data are critical to permit modelling of these later populations.

The design of the method in which data are to be selected is an important step in achieving an answer to the proposed questions. Several types of sampling methods have been used in veterinary epidemiology, including stratified, random, stratified random, cluster and biased. As will be discussed in the section on analysis, the type of sampling

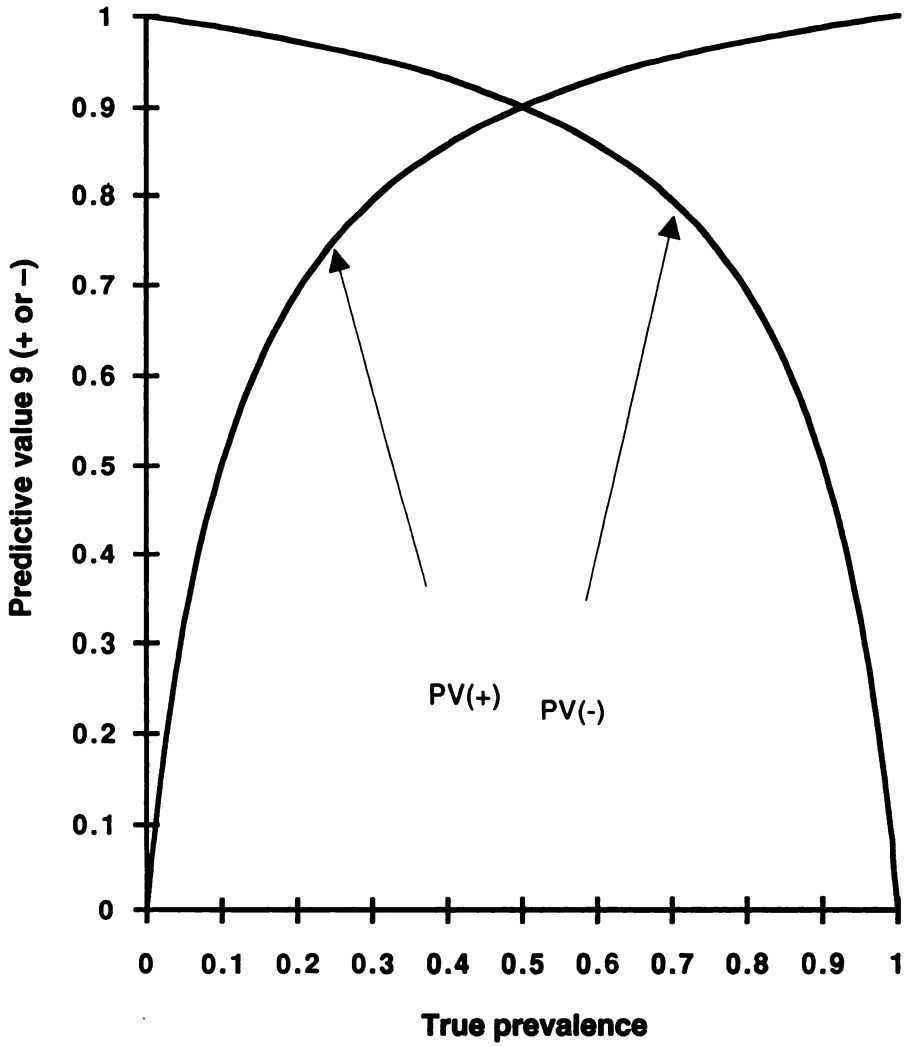

Figure 1. Predictive value positive (PV(+)) and predictive value negative (PV(–)), assuming sensitivity and specificity of 90% and a varying prevalence.

will also determine the type of analysis which is appropriate for use and the types of interpretations which may be drawn from the analysis.

COLLATION

Although computers have been available and heavily used in the developed world for several years, they have been in limited supply in many of the lesser developed countries. As a result, the data from these lesser developed countries typically exist on paper. This

problem is also typical of animal health data collected by organizations such as FAO. It is critical that if these data are to utilize modern statistical techniques, that they be coded and entered into appropriate digital databases. It is unrealistic to assume that data would be disseminated, much less evaluated by modellers, if it were not available in a computerized form.

In addition, to be useful, data should be in a form appropriate for statistical analysis. Appropriate forms would be either as ASCII, database, or spreadsheet files. In one of these forms, the contemporary modeller would have the capability of easily importing and analysing the data. Necessary data validation and checking for errors in the data should be performed both prior to and after data have been obtained by the modeller. Frequently, after data have been collected and coded into the computer, it may take weeks before the data are in a form amenable to analysis. It is important, therefore, that during the early stages of study design, data collectors and analysts get together and design proper questionnaires and databases, in order to minimize the task of organizing the data in a form in which it may be analysed.

Once the data have been computerized, the next step in the process is compiling it in the form necessary for analysis. This often includes transformations of the data, such as arcsin transformation of percentages, or other distribution transformations to conform to the assumption of normality, if that is a necessary assumption for the analysis. Once the transformations have been performed, the data are often re-categorized from continuous data to other forms such as categorical or nominal data. The classification, or cut points used to determine the classification, should have sound biologic criteria for making such selections.

ANALYSIS

The type of analysis needed for epidemiological modelling will depend on the question of interest. Appropriate analyses could include case-control or cohort studies, or they may focus on the quantification of the estimation and significance testing of specific population and disease dynamics parameters. Analyses may also be made in order to specify the appropriate distribution of these parameters to be used in a simulation model.

Analytical techniques which have probably been underutilized in epidemiological models include logistic regression and survival analysis. These techniques enable the analyst to determine relevant risk factors which should be included in the model (logistic regression) and predicted time to the occurrence of a particular event, which may include the potential confounding of a time dependent covariate (survival analysis). Among these parameters are: 1) population—birth, death, maturation and migration rate, and 2) disease—transmission, incubation, latent and infectious periods.

Additional tests that have been discussed in this workshop include time series and spatial statistics tests. The time series analyses would be important in both modelling the growth and activity of the host, parasite and vector populations. For example, it is important to know the timing of the infective larval stage of a parasite in order to determine what action should be taken to insure that newborn lambs are at reduced risk of infection.

Spatial statistical tests are important due to the fact that the distribution of individuals (hosts, vectors and parasites) is rarely of the random form which is often assumed during at least the initial stages of model construction. Just as it was important to consider age and sex, in order to avoid any potential confounding which may occur in an analysis, it is necessary to also consider potential confounding which may arise from assuming a spatial (as well as temporal) distribution. Several methods are available which could asses the level of dispersion, or clustering, in a population. These include tests for autocorrelation of areal and point data, using among other techniques nearest neighbour analyses.

Data should be analysed with respect to its proper distribution. Many statistical tests (parametric) assume data are normally distributed. However, this is often not the case for data used in estimating parameters in epidemiological models. Frequently these data are distributed as binomial, negative binomial, or Poisson random variables. Calculation of the means and variance of such variables would give erroneous model results. This would also negate the possibility of using the simpler deterministic type models instead of the more complex stochastic or Monte Carlo models, which depend on the ability to assign random distributions to numbers.

Case- and cause-specific fatality and morbidity rates, as well as attributable risk for the infection should be calculated. These rates should all be adjusted for differences that exist in age, sex, breed, or species, of the host, vector or parasite.

Confounding

One of the most frequent explanations of the occurrence of bias in epidemiological studies is that of confounding. Martin *et al.* (1987) explained it as follows: 'As a working definition, a confounding variable is one associated with the independent variable and the dependent variable under study. Usually, confounding variables are themselves determinants of the disease under study, and such variables if ignored can distort the observed association. Preventing this bias is a major objective of the design and/or analysis of observational studies'. The most common sources of confounding include age, sex, breed and location. Cattle of a particular breed tend to be more trypanotolerant than others. Calves are more susceptible and will have a lower seroprevalence than adult cattle. Therefore, when doing a seroprevalence study or attempting to assess risk factors, it is important to take this biologic knowledge into consideration when designing a study as well as during the analysis. Three methods of dealing with confounding are exclusion, matching and analytic control, or stratification. Through these methods, the analyst may either control or adjust for potential confounding, or through exclusion focus on a single group, e.g. a single breed, and in that way avoid bias through confounding.

Repeated Measures

Another statistical problem that may occur with data that have been serially collected, as mentioned above, is that of multicollinearity (Vågsholm, 1989). Presence of multicollinearity in the data will lead to an inflation bias of the variance of the parameter estimate.

In a multivariable analysis, this bias may result in either an increased or decreased estimate of the variance and hence a decreased or increased estimate of the statistical significance of the parameter coefficient. The result could therefore be incorrectly concluding that a parameter is statistically significant when it is not, or not statistically significant when in fact it is (Mousing *et al.*, 1988; Carpenter *et al.*, 1988). In either case, this potential bias resulting from autocorrelation should be considered and adjusted for when present.

Simultaneous Equation Bias

In estimating model parameters, it is essential that the analysis reflects the fact that the data, as with the model we may attempt to construct, are collected from and therefore intended to represent a system and are therefore not independent of that system (Working, 1927). One of most commonly overlooked examples of this in veterinary medicine deals with the case of simultaneous equation bias. This bias implies that our model, or system, consists of outcomes, referred to as endogenous variables, that are a function of explanatory variables, often referred to as exogenous variables. However, additional relationships may exist whereby not only the traditional exogenous variable explains variability of the endogenous variable, but, in addition, there may be additional variables, for example either current or lagged endogenous variables which also significantly effect the system being analysed.

A simultaneous equation, and its associated bias may occur in one of three ways: 1) presence of true biological interactions, e.g. disease and production; 2) aggregation of observation periods, when data are collected; and 3) multiple-output production processes, e.g. milk and calves.

An example of simultaneous equation bias is seen with the relationship between a parasite population and an associated control measure, pesticide application. The primary objective of a model may be to evaluate the efficacy of pesticide application on a parasite-infested population. Classical regression would have a model specified as parasite population as a function of, among other things, pesticide application. However, inherent in this equation is the fact that pesticide application is a function of, among other things, the perceived risk of an individual or the population being infected. Therefore, two endogenous variables exist in this simple system, parasite population numbers and pesticide use. The bias arises because one of the endogenous variables, pesticide use, is not independent of the error term. The resulting bias will be in the estimate of the coefficient in the equation used to estimate parasite population. The bias may give an increased or decreased estimate of the risk. For example, although biologically, we know that the application of a pesticide, discounting drug resistance, will act to decrease the population size. However, through statistical analysis, it is likely that pesticide use will be associated with an increased risk of infestation, or an increased population size. This is due to the fact that instead of measuring the impact of the pesticide, we are instead measuring the decision makers' response to a problem.

Traditional analysis, e.g. ordinary least squares regression analysis, of the data of such a system could lead to serious mis-specification of the model and consequently misinterpretation of the results (Vågsholm *et al.*, 1991). Alternative methods, e.g. three-stage least

squares analysis, are available in biostatistical or econometric software packages and will eliminate such bias.

DISSEMINATION

Once the appropriate data have been collected, collated and analysed, what is the appropriate form(s) in which they should be disseminated? Meaningful dissemination of these data and analytic results could occur in at least two ways. The first is to make the data available, in a collated from, to all interested scientific researchers. This method has recently been adopted by the National Animal Health Monitoring System, which is a livestock health surveillance system operated by the United States Department of Agriculture (USDA-APHIS/VS). It is provided to interested researchers, primarily at US universities, on magnetic tapes in a SAS format.

A second method of data dissemination would be through publications. These could occur either through proceedings of conferences or workshops, refereed journals, books or annual reports of institutions such as ILRAD or FAO.

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GENERAL DISCUSSIONS AND RECOMMENDATIONS

General discussions and recommendations

Following the conclusion of the presentation sessions, workshop participants divided into two discussion groups. The first group discussed modelling of three biological processes involved in vector-borne and other parasitic diseases, namely immunogenetics, parasite transmission and livestock production and ecology. This group also considered issues relating to modelling science in general. The second group took a different approach and considered the modelling needs within the three major disease complexes of relevance to the workshop, tick-borne diseases, trypanosomiasis and helminthiasis. The two groups were then reunited to rationalize their deliberations and develop appropriate recommendations.

Discussion series I

IMMUNOGENETICS

There was a vigorous discussion on the approaches to and possibilities of modelling infection, immune responses and vaccine design. The meeting then focused on the modelling of *Theileria parva* infection within the host and a simple model for the cytotoxic T lymphocyte (CTL) response was outlined. The possible effect of a vaccine based on a sporozoite antigen (p67) of *T. parva,* to which the response detected is thought to be antibody mediated and mainly infection blocking, was discussed. The case was put strongly that it was possible to quantify rates of infection and immunity processes and quantify the relationships between processes. Models can and have been developed for infection and immune responses and they can be valuable aids in exploring vaccine approaches. Even if models are not particularly accurate initially with regard to infection and immunity, they are powerful tools for exploring and explaining mechanisms, and raising questions to be answered by experimentation. It was recommended that ILRAD explore modelling approaches to evaluate immune responses to *T. parva* with a view to supporting vaccine development strategies.

The double expressor model for immune response-driven antigen variation in trypanosome infections, presented in the Host-Parasite Interaction session, was discussed in relation to rates of development and possible differences in responses between N'Dama and Boran cattle. The *in vitro* expression of antigenic variants could provide important information invalidating the theoretical basis of this model.

Differences in parasitaemia profiles between N'Dama and Boran cattle were described by ILRAD scientists and questions were raised as to whether these differences would be due to differences in parasite replication rates. This could be tested in the model.

Further discussion on trypanosomiasis and the responses of trypanotolerant cattle populations identified a range of variables which could and should be modelled, such as

primary response affinity of antibodies and rates of development of antigenic variants. The task of obtaining the full range of antigenic variants of any particular stock (or clone) for the latter was considered daunting.

There was some discussion amongst immunologists as to the likely mechanisms underlying resistance to trypanosomiasis in different cattle populations.

Significant improvement in understanding of the role of a modelling approach and its potential for investigating and explaining biological problems at a molecular or cellular level was an important outcome of the workshop and a closer interaction between biologists and modellers was encouraged by all participants.

PARASITE TRANSMISSION

The discussion started by considering whether it would be possible to model the important components of parasite transmission in both tick-borne diseases and trypanosomiasis with a single model. The view was expressed that this could be achieved for many aspects of the transmission of vector-borne infections, simply by varying a standard set of parameter values in the model. The discussion then considered what types of problems could be addressed by such 'generic' models.

The view was expressed that these could effectively examine the comparative importance of different parameters in the dynamics of disease transmission (such as the relative importance of carrier status in determining tick infection rates under different conditions of endemic instability in *T. parva* infections), but that they would not address some of the more fundamental questions which constitute much of ILRAD's research. For these questions (such as the level of vaccination coverage required to protect different populations under specific conditions), more complex simulation models may be necessary.

Ways of further developing and validating the presented model for *T. parva* (developed by Medley and colleagues) were discussed. It was recommended that available data sets of theileriosis dynamics from eastern Zambia (Berkvens) and Zanzibar (Woodford) should be applied to the model, along with future data sets currently under collection in coastal and highland Kenya.

The suitability of the model T3HOST as another starting point for modelling tick population dynamics was discussed. Some of the group were or the opinion that it was the most realistic of the available tick dynamics models, but its lack of general availability constrained independent verification of that by modellers. Doubt was expressed in some quarters that it would serve as a panacea for modelling tick dynamics, let alone parasite transmission.

Possible collaborations were then discussed. There was an optimistic sentiment expressed by the modellers that existing comparative approaches in use for other vector-borne infections could easily be applied to tick-borne diseases, and various ways of achieving this were tabled. These included the setting up of specific collaborative arrangements for different processes with particular modelling groups and the option of widely distributing available data to all modellers, who would then each explore them with their own approaches.

LIVESTOCK PRODUCTION AND ECOLOGY

The group recognized various areas that require strengthening if modelling systems are to be used to support the development of sustainable agricultural production systems in developing countries. There is an immediate and priority need to address the lack of data in certain areas; to quantify the economic losses due to morbidity and mortality from target diseases; to identify appropriate epidemiological studies, particularly in regard to disease transmission levels in various ecological situations; and to identify the availability of data sources that may be useful to modellers.

In order to address these areas, it was recommended that FAO integrate more closely the activities within the Animal Production and Health Division and, in collaboration with ILRAD, ILCA and others, further computerize its data management systems making appropriate use of GIS, remote sensing and modelling.

It was also recommended that FAO/ILRAD/ILCA and other relevant international agencies, in collaboration with national institutions, support the adaptation of existing models on epidemiology and control of parasitic diseases and livestock management to African conditions.

The group considered that these organizations should promote and provide support for strengthening the capabilities of national veterinary services in data gathering and where possible standardized equipment and procedures should be adopted.

Finally, it was recommended that FAO examine ways to retrieve and collate historical data on livestock production systems making databases more accessible for modelling.

MODELLING APPROACHES

The perceived modelling requirements of ILRAD and FAO were discussed. Both organizations clearly have a variety of needs for modelling, but these need to be prioritized. ILRAD participants identified some specific needs and examples of these are:

- immune responses against trypanosomes and *Theileria;*
- antigenic variation;
- the pathogenesis of anaemia;
- transmission dynamics of parasites;
- host-parasite interactions;
- disease impact assessment; and
- evaluation of alternative control options.

FAO identified other needs, particularly in the area of livestock production models and the delivery of interventions. The group considered that there is scope for ILRAD and FAO to collaborate further in the design of decision-support systems and control strategies based on models. It was recommended that FAO gives priority to the development and transfer of models which will directly enhance livestock production, and that FAO promotes awareness of the value of proven modelling systems.

The review of modelling procedures appropriate to meet these requirements were considered and it was the general feeling that analytical procedures appear to be appropriate for parasite transmission and immune response studies, whereas simulation/database/spreadsheet

models are more suitable for the areas of livestock production, vector population dynamics and disease control. In an attempt to identify relevant approaches, it was stressed that simple approaches should be undertaken initially which could increase in complexity as the problem and solution demanded. It was considered very important to have modelling under consideration at an early stage in project development. It was recommended that ILRAD and FAO consult with other centres of excellence in developing and promoting models.

It was noted that model development is time consuming and is undertaken against a background of rapidly changing technologies. Solutions and methods will have a finite generation time. It was recommended that different techniques be used to address similar problems and that the use of generic models be explored where possible in order that effort invested in modelling one disease may be applied to others.

Data requirements are often only known once model construction has been initiated. The group considered that models should be initiated where possible on the basis of existing data. For model development, database collection should focus on spatial and temporal data that will enable models to be tested over a range of circumstances. It was recommended that FAO considers ways of making digital databases more widely and easily accessible.

The group noted that there are issues concerning ownership, accessibility and preservation of data which need to be addressed.

It was agreed that collaboration in model development, in terms of modellers and biological scientists, and in terms of ILRAD, FAO and other collaborators, should be initiated early in any project preparation phase. Most collaboration arises from individual contacts and in particular where there is a critical mass of resources. To assist this, some participants considered that the establishment and dissemination of registers of modellers and models, complete with status reports of model development, could be a valuable role for FAO. Finally, with respect to modelling approaches, it was recommended that FAO play a convening role in training people in the use of models, and contribute to the provision of resources for such training.

Discussion series 2

TICK-BORNE DISEASES

It was agreed that if good quality data are available it should be possible to model many aspects of the immune processes and the response to immunization. Models should, therefore, be further developed and attention focused on how to quantify processes in the immune response and the relationships between these processes.

Models have been developed, or are being developed, for relevant aspects of parasite transmission. In the face of changing tick and TBD control strategies and policies, this should be given priority.

It was the general opinion among the modellers that all models should be as simple as possible initially, growing in complexity as components are understood and others identified. This could eventually lead to the integration of disease transmission models, vector population dynamics models and livestock production models which when combined will form the basis for interactive decision support systems.

In discussing the deliberations on livestock production (above) it was considered necessary for governments to establish national priorities (in terms of diseases and other constraints) for future priority attention. The priorities should be based on benefits to be gained from available and potential control measures rather than value of theoretical losses. Specifically, in the case of TBDs, there is an urgent need to quantify both direct and indirect production losses (for both morbidity and mortality and the inability to use land or introduce improved cattle).

At all levels, both modellers and statisticians should interact with scientists in both the laboratory and the field. It was emphasized that for progress to be made, there is a need for greater understanding and respect of each other's disciplines.

TRYPANOSOMIASIS

There are certain specific research areas in ILRAD's trypanosomiasis research program that could be addressed through a modelling approach. The view was expressed that at present the development of diagnostics was not a priority area for modelling. Likewise it was considered that modelling of vaccine development should be left for another forum to discuss, given the limited progress in research on vaccine development.

The interest, therefore, focused on the possible modelling of chemotherapy and trypanotolerance which is of relevance to the following research areas.

- Trypanosome genetics, including relevant areas in chemotherapy, drug resistance, and marker identification.
- Parasitaemia and other aspects of trypanosome infection dynamics within the blood stream remains unclear and therefore controversial. Several of the modellers expressed an interest in working with these data.
- The role of trypanosome immunology in trypanosome population dynamics is still uncertain. It was suggested that research in the immunology field could benefit from modelling expertise outside ILRAD. Since there is a variety of alternative hypotheses on immune mechanisms, it might be best to consider collaboration with more than one group/individual.

In order to obtain a more complete picture of the epidemiology of trypanosomiasis, it was suggested that data from several representative field sites should be collected to study the relative role of different variables and parameters play in contributing to variations in infection transmission rates. This was considered by some to be a relatively easy exercise intellectually, but will clearly involve considerable thought and commitment at the field sites. The obtained data could be used subsequently for the construction of a model describing trypanosomiasis transmission at each field site.

The importance of more effective monitoring of livestock production systems in Africa was stressed and it was agreed that the ILCA/ILRAD Trypanotolerance Livestock Network could be utilized and possibly act as a prototype for similar networks for collecting and analysing data on trypanosomiasis impact to livestock.

Through the modelling of livestock production systems, it should be possible to develop decision-support systems (DSS). It is important to realize that DSSs can be targeted at individual farmers, communities of farmers, governments and donors. Recommendations

from a DSS to farmers may not necessarily be in the interests of ecosystems or societies on a long-term basis. It was considered that the Socioeconomics Program of ILRAD could make a major contribution to the development of DSS appropriate for these different client groups in the control of livestock diseases in Africa. It is also vital that national research and implementation organizations are involved at an early stage as partners in this development, and not just as recipients of the products of DSS analysis.

The importance of managing resources for sustainable production was discussed and it was agreed that FAO clearly has an important role in developing and promoting activities which would result in sustainable solutions to resource management. In this FAO has to address and resolve the conflict between the producers (as advised by the DSS analysis) and consumers (not only the broad society within which the producers live and sell their produce, but the world community). In the short term FAO is interested in the collection, collation and analysis of existing data sets and in developing the methodologies for analysing those data to establish the constraints and environmental impact of tsetse, trypanosomiasis and tsetse control throughout Africa.

HELMINTHS

Initially the discussion focused on the currently available models for the management of helminth control programs and the possible adaptation of these to African conditions. Some of these models (analytic differential equation models) are used for anthelmintic management strategies and they are not site specific or species specific, nor do they have a livestock management component. Others are simulation models. The modellers expressed their optimism regarding their future adaptation if sufficient databases are available.

The rapidly developing problem of anthelmintic resistance, which has reached emergency proportions in some areas of the world, was debated. Modelling in this area has been initiated in several institutions and existing models might be useful in the African context to predict the consequences of indiscriminate use of anthelmintics. It was recommended that this be pursued by FAO.

Among the alternatives to the use of chemicals to control helminths is breeding for genetic resistance to helminth parasites. Work is under way in several regions comparing the resistance qualities of indigenous breeds with those of exotic breeds; initial experiences in Australia indicate that modelling will be a useful tool in this discipline.

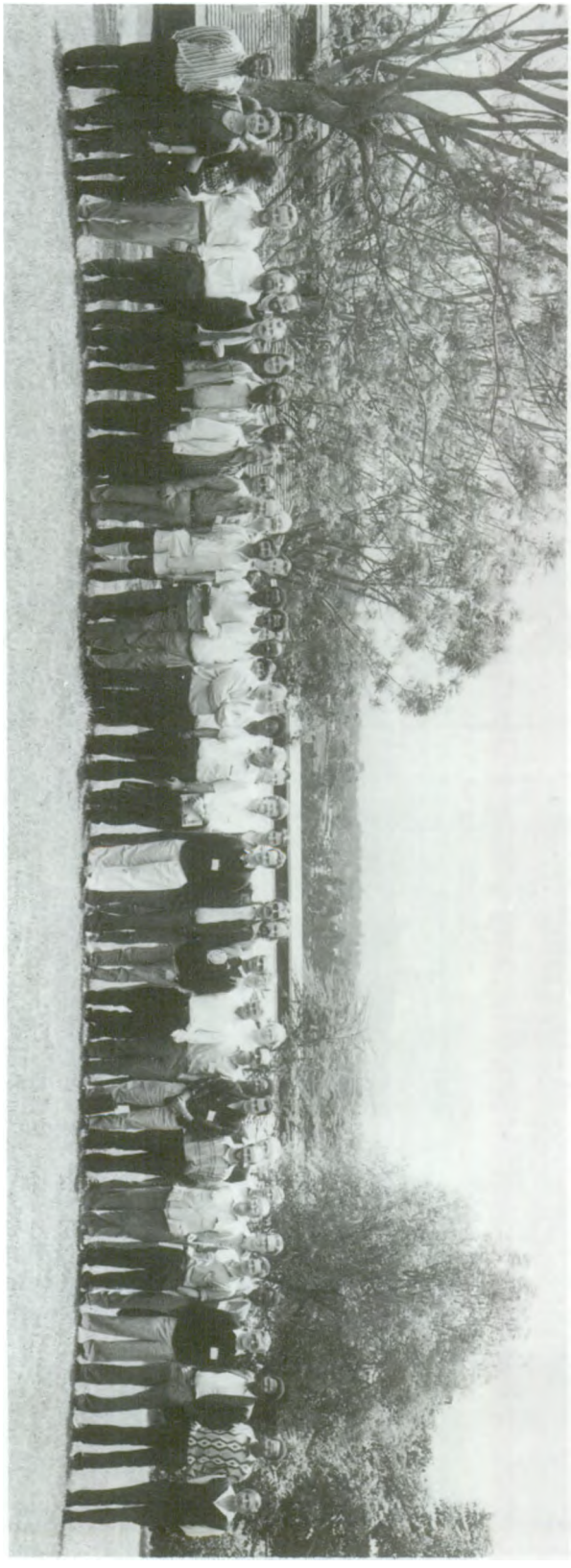
It was agreed that more knowledge was needed regarding the impact of helminth parasites in goats and modelling could be better utilized in order to obtain more understanding on the population dynamics of goat parasites.

The understanding of the interaction between different parasitic diseases in any one host is limited. The need for establishing data in this field and the potential use of modelling was discussed.

The importance of being able to integrate the models on helminth epidemiology and control with models on livestock production was stressed.

It was recommended that FAO support the ongoing development of models for determining the minimum effective use of anthelmintics in strategic control programs and the prevention of the development of anthelmintic resistance.

APPENDIX: LIST OF PARTICIPANTS



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