Modelling vector borne disease transmission

INTRODUCTION[1]

The computer program describe in this booklet models vector borne disease transmission such as dengue, Japanese encephalitis, malaria and filariasis. Such diseases are of major medical and veterinary importance and considerable resources are expended each year on a global scale in control programs. Although a general understanding of the way in which these diseases are spread has been known for many years, the large number of environmental and other factors which affect transmission rates, and the difficulty in quantitatively measuring some of the important parameters has made meant that control programs have largely been empirically designed. While many of these undoubtable produce substantial reductions in transmission, it is not clear that they have necessarily operating at the best efficiency. This complexity in the life cycle also means evaluation of pilot control projects is often difficult and there are many examples where inappropriate criteria have been used.

All understanding of transmission and the planning of intervention programs requires a model of transmission although it often not recognized that a model is being used. The simple qualitative statement "mosquitoes which bite people with malaria get infected and can transmit malaria to other people when they bite again" is a simple model for the transmission of malaria. This simple model illustrates a number of the important characteristics. Firstly, it provides a simplified description of what we postulate is happening in nature. Secondly, it is easy to imagine ways in which it could be tested: we could look for parasites in mosquitoes which have fed of malarious people and then see if these can transmit the disease to uninfected people. Thirdly, this model provides a practical basis for control programs: stopping mosquitoes from biting infected people, or stopping infected mosquitoes from biting uninfected people should control malaria.

Such a simple model has obvious limitations. For example, attempts to experimentally verify such a model would quickly indicate that not all mosquitoes could transmit disease. Such a simple model is incapable of quantitative analysis: it is of no assistance in answering the questions such as "How fast will malaria spread in a certain situation?" or "By how much will mosquito/man contact need to be reduced before malaria transmission will cease?". Experience has shown that such important and simple questions are quite difficult to answer. The accompanying model is designed to provide assistance in answering such questions without necessarily requiring the user to be familiar with the mathematics.

This approach is designed to make modelling accessible to non-experts, in the same way

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[1] This version of the program and notes were revised in September 2003 to accompany Saul A, (2003) Zooprophylaxis or Zoopotentiation: the Outcome of Introducing Animals on Vector Transmission is Highly Dependent on the Mosquito Mortality while Searching, The Malaria Journal. The original program and notes were written in September 1990 and were used as teaching material for a Master of Tropical Health Students at the Australian Centre for International and Tropical Health and Nutrition, Brisbane, Australia.

For this version, the underlying model remains unchanged, but the model has been translated from a stand alone DOS program to an Excel spreadsheet format. New instructions for use of the spreadsheet have been substituted in the notes. Minor changes in the remainder of the text have been made to correct typographical errors and to harmonize the terminology with that used in the accompanying paper.

For further information on the use of the program contact Allan Saul: asaul@niaid.nih.gov

that it is quite possible to drive a car without a detailed understanding of the mechanics of the internal combustion motor. However such an approach also has dangers. The results obtained by using such models are only intended as a guide and it would be useful to discuss details of planned trials with a competent epidemiologist before proceeding. In particular, the accompanying model is *deterministic*. It provides and average picture of what is likely to occur. Actual field observations tend to be dominated by stochastic, or chance, events. For example, this model may predict that on the average, 1.34 mosquitoes will bite a person per night. In reality, there would be 0, 1, 2, 3.... mosquito bites on a particular person on a given night and this random fluctuation needs to be considered when assessing if observed differences in measured parameters are real.

THE MODEL

A formal description of the model and symbols is given in

A Saul, **Zooprophylaxis or Zoopotentiation: the Outcome of Introducing Animals on Vector Transmission is Highly Dependent on the Mosquito Mortality while Searching**. *The Malaria Journal*, 2003

The model views the vector's behaviour as a series of feeding cycles. A suitable starting point is when a vector feeds on a vertebrate. After feeding, the vector will digest the blood meal then egg maturation will usually, but not always, take place. Typically, this occupies several days. The vector then seeks a suitable location to lay eggs and possibly following another resting phase once again actively seeks a new blood meal. The time from one blood meal to the next is the length of the feeding cycle (T_f). This model divides the feeding cycle into two parts. The time taken from feeding for egg maturation, seeking a suitable egg laying site, oviposition etc, up to seeking the next blood meal is assumed to be constant (T_{ov}). On the other hand the length of time it takes to find a blood meal (T_s), is assumed to depend upon the number of suitable animals (Y) and the rate at which mosquitoes are attracted to the animal (A). Furthermore, since many vectors have limited periods of activity, eg. a few hours at dusk, only during the night, if a vector fails to find a blood meal within this time (T_{ms}), then it is assumed the cycle is lengthened and searching will recommence the following day.

In any environment, it would be unusual for there to be only one type of vertebrate acting as a source of blood meals for the vector. For example, in malarious areas, in addition to humans, the anopheline vector may feed on domestic animals such as dogs, cattle, buffalo or pigs. These alternative blood meal sources have a major effect on the transmission. Vectors feeding on these animals cannot become infected during that feed, and infectious vectors will be unable to transmit the infection if they are diverted to feed on an animal which is not the vertebrate host of the disease. This model is able to accommodate up to three categories of animals, the host of the disease, animals which are able to act as alternative blood meal sources but are totally refractory to the disease and a "bait" population which can be either susceptible or not. These three categories allow almost all likely situations to be modelled. Examples of how these populations can be defined for specific situations are covered later.

A defined proportion (x) of the susceptible vertebrate population is assumed to be potentially infectious to the vector. However, different combinations of disease, host and vector can vary considerably in the efficiency with which the disease is transmitted to the vector. The model assigns a certain probability (k) that an individual vector will become infected upon feeding on an infectious host. Not all vectors that become infected (an in practical terms this assumes that there is some way of determining if a vector has been infected - eg. by examination for oocysts) go on to transmit the disease. Usually most vectors which have become infected will not survive long enough to transmit. The period that such a vector must survive is the extrinsic incubation period of the disease. Typically in vector borne diseases this is the time it takes for the disease organism to find its way from the vector gut to the salivary glands and is often accompanied by many rounds of pathogen replication. Even if and infected vector survives the extrinsic incubation period, then some will still fail to become infectious due to a variety of mechanisms such as midgut barriers which prevent the pathogen from properly maturing or migrating in the vector. The probability (v) that such surviving infected vectors become

infectious and are potentially capable of transmitting the pathogen to another vertebrate host can be specified in the model. In this model it is assumed that once a vector becomes infectious, it will remain so for life and be potentially capable of transmitting every time it subsequently bites a suitable host. It is also assumed that once a vector becomes infected, then further feeds on an infectious host will not alter the probability of that vector becoming infectious.

In addition to being able to divide the vector population into noninfected, infected and infectious categories, the vector population also can be divided into a series of ages. In this model it is assumed that a certain number of newly emerged vectors (N_0) come to feed for the first time each day. This definition is chosen over possible alternatives, eg the total number of emerging vectors per day, for two reasons. Theoretically, what happens to the vector before the first feed in generally of no consequence to disease transmission: what counts is the number feeding, and practically, the way in which these numbers are usually determined, is from collecting biting insects at some sort of bait. The remainder of the feeding population will be made up of vectors that have survived a varying number of feeding cycles. Vectors lead a precarious existence and run considerable risks of meeting death by misadventure e.g. in the form of predators or unfavourable microclimatic conditions leading to death by desiccation. In many vector populations, the evidence suggests that the probability of getting killed is so high that very few die of old age! In practice, this means that in these conditions there is no detectable age dependant mortality and so a vector which has survived 1 feeding cycle is just as likely to be killed during the next feeding cycle as a vector which has been lucky enough to have already survived 5 feeding cycles. Although there is evidence to suggest that age dependant mortality is a factor in some vector populations, for simplicity this model assumes no age dependant mortality.

This model subdivides the probability of surviving the feeding cycle into three parts. The model allows vector feeding on the bait population to have an increased mortality associated with this feed (M_f). This increased mortality would usually be due to some control measure such as the use of insecticide impregnated bed nets. The modeller can specify whether this increased mortality occurs before or after the vector actually feeds. If the vector dies after feeding then this still allows infectious vectors to transmit the disease. The second phase is the period following a feed to the start of searching for a new blood meal and a probability (P_{ov}) is associated with surviving this period which would usually include oviposition. The third period is the probability of surviving the search for the next blood meal. This model assumes that the probability of the vector being killed during this phase will depend on the time it takes searching and uses a mortality rate while searching (M_s) and the searching time to compute the probability of surviving this phase. The probability of surviving all three phases is the probability of surviving the feeding cycle (P_f).

The primary output of the model is an estimate of the host innoculation rate (HI). This is the number of infectious bites recieved per day by each individual in the susceptible population. The host innoculation rate depends upon the number of infectious hosts. The model also gives an estimate of the vecorial capacity. This is a measure of the potential transmission rate resulting from the presence of a single infectious host.

The model also gives predictions of a number of other parameters which are useful for measuring the transmission parameters and therefore for evaluating the validity of the model and for following the efficacy of control programs. These include the biting rates of the vector on the different vertebrate populations (e.g. H_{bt}); the proportion of vectors which feed on each vertebrate population (e.g. Q_h and usually estimated from a blood meal analysis of fed vectors); the probability of surviving the feeding cycle (P_f, estimated from parous rates or mark - recapture

experiments); the length of the feeding cycle; the proportion of infectious vectors (S, estimated, for example, in malaria transmission by the sporozoite rate in mosquitoes); the number of eggs laid each day by the vector population.

There are a number of limitations which need to be taken into account in interpreting the outcome of modelling. This model assumes that the conditions are stable. In field situations various local conditions will cause fluctuations in the numbers of vectors, the length of the feeding cycle etc. This model will give realistic values provided the populations are reasonable stable for a period of about one extrinsic incubation period i.e. usually a period of about 10 days. Models can be used to examine rapidly changing conditions e.g. where the vector population increases rapidly or where there is an epidemic of disease but may need to be written for the specific case (e.g. Kay et al 1987). Although this model in not applicable in this context, it can still give useful information, through the use of vectorial capacity, in measuring the potential of such outbreaks and looking at likely affects of control measures on decreasing such risk.

This model estimates the transmission rates. Unfortunately there is no universal formula for equating transmission with the amount of disease that will be present. This relationship will depend on such factors as whether susceptible hosts become chronically infected and whether there is significant immunity to the disease. In general, for situations where transmission rates are low, and the rate at which infected hosts clear the infection is much more rapid that the host inoculation rate, then the amount of disease in the community will be proportional to that inoculation rate. For some chronic infections, e.g. malaria in hyperendemic regions, moderate changes in the transmission rate may have no effect on the parasite positivity rate since this is controlled only be the rate at which people can clear the parasites.

One of the secondary outputs of the model, the number of eggs laid per day by the vector population, also needs to be interpreted for each situation. A control program which results in a decrease number of eggs may cause a subsequent reduction in the number of adult vectors emerging. Unfortunately there is no universal relationship. In some situations, where the number of eggs being laid exceeds the capacity of the larval habitat, then the number of emerging adults will not be affected by changes in egg laying. In other cases, there may be a direct relationship. This is more likely to happen where the size of the vector population undergoes rapid fluctuations.

This model can be used to predict the likely changes in a number of variables depending upon a range of input parameters. For example, the model may be used to estimate changes in the sporozoite rates, the probability of surviving the feeding cycle and the number of mosquitoes feeding per person per night following the introduction of bed nets. Whether such changes could be observed in the field will depend on the accuracy with which such parameters can be measured. This will depend on local conditions, especially the ability to collect sufficiently large sample of vectors. Such factors will need to be taken into account when using this model as a tool to assist in the evaluation of control strategies.

RUNNING THE MODEL

Download and save the Excel spreadsheet, Vector transmission model.xls. You are strongly recommended to set this copy as "read only". Particular examples can then be saved as new files without compromising the original.

The spreadsheet consists of a number of worksheets. The primary working worksheet and the only worksheet on which user entry occurs is the "Main" spreadsheet. The "Main" spreadsheet contains two entry panels: A "Primary parameter panel" and a "Graph parameter panel".

Values for all 18 parameters listed on the "primary parameter panel" must be entered. All data entry occurs in the blue cells. Definitions and hints for suitable values can be seen by positioning your cursor over the symbols in the green cells on this table. Note that the SB and DBF parameters are Boolean variables. They only take the values "true" or "false". Warning: this version does no error checking. You will be able to enter nonsensical values, e.g. negative values for all parameter, probabilities >1 (x, k, v) or non-boolean entries for SB and DFB.

As the primary parameters are changed, the spreadsheet updates the principle output measures of transmission (orange cells). In some cases, apparently impossible values will be seen. For example, even if there are zero non-host animals, a value for A_{bt} will be computed. This is the limiting value for A_{bt} as $Y_a \rightarrow 0$.

The simplest use of the model just uses the primary parameter entry to investigate individual combinations of the output parameters. However, the spreadsheet can also plot output parameters as a function of a continuously varying single input parameter at up to 6 values of a second input parameter. This is achieved though the "Graph parameter panel". The number of the parameter to be varied is chosen from the list and entered in the top blue cell with the minimum and maximum values for that parameter in the next two cells. The number for a secondary parameter is then entered in the top blue cell in the "Secondary parameter panel" and up to 6 values for this parameter.

As the primary and secondary graph parameters are entered, the spread sheet calculates a set of output graphs showing the relationship between the range of primary and secondary parameter variables and the 16 output measures defined by the model.

NOTE: for this part of the program, input parameters other than the primary and secondary graph parameters are derived from the "Primary parameter panel". Thus when using the graphing feature, you must first enter values in this panel. For the graph parameters, the values in the "Primary parameter panel" will be substituted during calculation from the values specified in the Graph parameter panels.

For convenience, the relationship between entomological inoculation rate for the human (host) population (in infectious bites per person per day) is displayed on the "Main" worksheet. In addition to this graph, each of the output measures is graphed on its own worksheet.

Warning: Worksheets a to f and column N on the Main worksheet are used by the graphing routine. Do NOT alter these.

EXAMPLES

This chapter gives some examples of how to specify values for the variables to model different situations. These examples are largely drawn from examples in malaria control but should serve as the basis for modelling other diseases.

Larvicidal programs

The primary effect of larvicidal programs will be on N_0, the number of newly emerged vectors feeding for the first time. Destruction of larval habitat may also increase Tov and decrease P_o, since the vectors may spend longer finding suitable oviposition sites.

Spraying programs

Spraying with residual insecticides and fogging kills resting insects, so this will decrease Po. If the spraying is carried out in the vicinity of the preferred feeding location, then the attractiveness of host may also be altered. E.g. spraying of houses to kill mosquitoes which rest indoors following a blood meal may also make the people less attractive to the mosquitoes if the spray has some repellent effect. In this case A_h may need to be modified.

Repellants

The use of repellents, untreated bed nets etc will have a direct effect on A_h etc.

Insecticide treated bed nets

Treated bed nets alter a number of factors. The easiest way to model it to treat the population protected by bed nets as the bait population. The bed nets will decrease A_b in two ways. They will impose a physical barrier and they may also have a chemical repellent effect. The bed nets may also kill mosquitoes coming to feed, so M_f will increase as the efficacy of the bed nets improves. When estimating the size of the change in these parameters you will need to take into account the proportion of time, the protected population will spend under the nets. The third parameter of relevance is whether those mosquitoes which will die as a result of contact with the treated nets die before or after feeding (DBF TRUE or FALSE).

Vaccines and natural immunity

There are several types of immunity that could be considered.

The effects of transmission blocking immunity, e.g. a malarial anti-gamete vaccine can be modelled by varying k. For a totally effective vaccine covering 100% of the population $k = 0$. Less effective vaccines covering smaller populations will have $0 < k < 1$.

A malaria pre-erythrocytic vaccine could be modelled by varying v. Malaria blood stage vaccines may have an effect on both v (decreasing the probability with which people become infected) and x, by decreasing proportion of people infectious, and possibly in some circumstances by decreasing k, where lower parasite burdens may lead to lower gametocyte levels.

Immunity which completely renders the host resistant to becoming infected (e.g. a vaccine against Japanese encephalitis B) and therefore becoming infectious, can be modelled by splitting

the host population into susceptible (retained as Y_h) and making the protected population the bait population, with $M_f = 0$ and SB = FALSE. By setting up the model this way, variables such as the human blood index can still be obtained for the whole population ($Q_h + Q_b$), x will refer exclusively to the susceptible population and the number of infectious bites on susceptibles H_{bt} is still available.

Note that this model will not estimate the number of susceptible hosts becoming infected as a result of infectious bites nor will it model the conversion of susceptible hosts to immune and therefore resistant hosts.

Zooprophylaxis

There will nearly always be effects of other animals on transmission whether part of a deliberate control program or not. The simplest effect is easy to model. Increasing numbers of alternative animals (Y_a) will divert vectors. Where there are two different species of alternative animal the bait population (with SB = 0 and $M_f = 0$) can be used for the second population. Where there are more than two significant species, then average values of Y_a and A_a can be used. In this case, these "averages" should be weighted so that the "average" Y_a x "average" A_a is the sum of the individual Y_{ai} x A_{ai}.
In more a complicated situation, the presence of alternative blood sources may have a significant effect on the time it takes for vectors to find blood meals. This will alter the survival per cycle, the length of the feeding cycle and the number of cycles per EIP.

Feeding catches

Vector abundance is often measured by biting catches. By setting Y_b equal to the number of collectors then B_{bt} is a direct estimate of the daily catch. In this case, and where collections will continue for an extended time, set $M_f = 1$ since all vectors coming to feed will be killed. In some situations, e.g. modelling bed nets, where the bait population is already in use, it may be possible to use Y_h as the bait population instead, but check that the proportion of vectors being caught by the collectors is not more than a few percent of the total or the average survival of the population will be affected.