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A model to simulate the impact of timing, coverage and transmission intensity on the effectiveness of indoor residual spraying (IRS) for malaria control

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Summary

OBJECTIVE (i) To develop a temperature- and rainfall-driven model of malaria transmission capable of prediction. (ii) To use the model to examine the relationship between the intervention timing and transmission intensity on the effectiveness of indoor residual spraying (IRS).

METHODS A dynamic model of malaria transmission was developed from existing models of malaria transmission dynamics. The model was used to retrospectively predict actual malaria cases from Hwange district in Zimbabwe using actual meteorological and IRS timing and coverage data. Simulations of alternative intervention scenarios (timing and coverage) examined the effectiveness of earlier and later interventions, at higher and lower coverage levels in epidemic and non-epidemic years.

FINDINGS The model was able to predict actual malaria cases in Hwange over a four-and-a-half-year period with a lead time of 4 months (e.g. January rainfall and temperature predicts April malaria) and a correlation coefficient of 0.825 ($r^2 = 0.6814$). The IRS simulations show that the marginal benefits of increasing IRS coverage are higher in high-transmission (HT) years relative to lower transmission years. This implies that over a period of years, maximum impact could be achieved with a given quantity of insecticide by increasing coverage in HT years. However, the model also shows that earlier spraying is more effective in all years, especially so in epidemic years, and that IRS has limited impact if it is carried out too late in relation to peak transmission.

CONCLUSION Temperature- and rainfall-driven models of malaria transmission have the potential to predict malaria epidemics. Early intervention based on prior knowledge of the magnitude of the malaria season can be more effective and efficient than carrying out routine activities every year. Malaria control planners need improved access to the technology that would allow them to better predict malaria epidemics and develop Malaria Early Warning Systems (MEWS). MEWS can then be linked to intervention planning to reduce the devastating impact of malaria epidemics on populations.

keywords malaria, model, timing, indoor residual spraying, Zimbabwe, epidemics

Introduction

Many studies have sought to examine the effectiveness or impact of indoor residual spraying (IRS) as a vector control measure against malaria (Curtis & Mnzava 2000; Charlwood *et al.* 2001; Romi *et al.* 2002; Sharp *et al.* 2002). There is a growing body of literature demonstrating that IRS is a cost-effective intervention against malaria (Goodman *et al.* 1999, 2001; Guyatt *et al.* 2002; Conteh *et al.* 2004). However, in an operational setting, effectiveness of IRS can be compromised by insecticide under-dosing (Masendu *et al.* 2002) or replastering of walls after spraying (Mnzava *et al.* 1998). Additional factors, so far not investigated, which may affect the effectiveness and cost-effectiveness of IRS are differences in the timing of intervention and the local transmission intensity. These questions warrant investigation as IRS is considered an appropriate intervention in epidemic-prone areas (Roll Back Malaria 2005) where, by definition, transmission intensity exhibits a high degree of inter-annual variability and where timeliness of interventions is critical in preventing or mitigating epidemics. Moreover, the development of

malaria early warning systems (MEWS) may enable epidemics to be predicted with sufficient lead time that intervention efforts can be targeted in space and time to achieve maximum impact. This paper examines the relationship between the timing of the intervention (in relation to the epidemic), inter-annual transmission intensity and the impact of residual spraying using a dynamic weather-driven model of malaria transmission to simulate effectiveness and thus identify optimal intervention scenarios.

Methods

Model development and overview

A dynamic model of malaria transmission, driven by temperature and rainfall was developed from existing models of the relationship between temperature and entomological variables such as gonotrophic and sporogonic cycle length (Detinova 1962; Lindsay & Birley 1996) and malaria transmission (Macdonald 1952; Saul *et al.* 1990). Model development was carried out using meteorological and epidemiological data from the Western highlands of Kenya where malaria is unstable and prone to epidemics. The meteorological data are a time series of dekadal (collected every 10 days) minimum and maximum temperature (used to calculate arithmetic mean) and daily rainfall in mm. The malaria cases are daily inpatient malaria cases recorded at Kapsabet hospital in the Nandi District.[1] A basic spreadsheet model structure was developed according to existing information on malaria transmission dynamics (e.g. published models and parameter values) and driven by the Kenyan meteorological data. The output of this model (malaria cases) was compared with the epidemiological data and altered iteratively to remove bugs and improve correlation between model output (predicted cases) and actual cases (epidemiological data). Once a satisfactory model had been developed using the Kenyan data,[2] the same model was re-run using meteorological data from Zimbabwe, to simulate malaria case data from Hwange district in Zimbabwe.

The Zimbabwe meteorological data was only available on a monthly as opposed to dekadal basis and so the model was adjusted accordingly. This was done by reducing the number of model calculations in each year to account for the fewer data points. Most interim stages of the model (submodels – see below) were not affected by this as they utilize variables which are either assumed to change only on a monthly basis or are governed by processes that vary with temperature. Monthly temperature and rainfall data from Hwange Meteorological Station from January 1993 to December 1997, 1 year before malaria case data were available, were fed into the model. A small number of initial infections was assumed so that the model reached a stable state by 1994. Initial values of model variables were set on the basis of available data from the study area and the literature. Where this was not available, reasonable initial values were chosen and then varied one at a time to fit and scale the model with the case data. Uncertainty analysis was carried out on unknown variables. The model was run and its ability to predict malaria cases from Hwange District in Zimbabwe was tested by cross correlation. A sensitivity analysis was carried out on the 'best-fit' model and simulations of different IRS coverage levels and timing were produced.

Description of study area

Matabeleland North Province is in the north-west of Zimbabwe, bordering with Zambia to the north and Botswana to the west. It has an area of 75 025 km^2, and an estimated population (for the analysis period) of 735 000 people of which 124 803 are under 5 years of age (Health Information Unit 1995). Malaria in Matabeleland North is seasonal, normally beginning in December and continuing until May with peak transmission occurring during March/April, following peak rainfall.

Hwange district has one of the highest incidences of malaria in Matabeleland North, although all districts in the province are affected by malaria. Average monthly minimum and maximum temperatures in Hwange district were 13.6 and 29.4 °C during the period of analysis and mean annual rainfall was 482 mm. Malaria transmission in this district is highly seasonal and inter-annual variability in reported case numbers is high.

Overview of the model

The model uses mean monthly maximum temperature and the cumulative monthly sum of rainfall to calculate values for key parameters. These are then combined to give the number of new infections, super infections and people recovering which are then used to calculate the number of humans infected with malaria each month. The model is designed for use in areas where brief seasonal transmission and occasional epidemics do not enable acquired immunity. The population are therefore considered to be non-immune. The model is described as six submodels briefly outlined below. Mathematical details of the model specification are provided in Appendix 1.

[1]Data collected and used by permission of Dr David Sang, Ministry of Health, Kenya.

[2]Further details on the Kenyan model available on request from the corresponding author.

Submodel 1 describes the number of (female) mosquitoes as a function of rainfall.

Submodel 2 describes the relationship between temperature and the length of the gonotrophic or feeding cycle. The gonotrophic cycle length is the period of time between successive egg laying. Although the length of the gonotrophic cycle is known to be related to humidity the relationship has not been defined and was therefore not explicitly included in the model.

Submodel 3 describes the relationship between temperature and the sporogonic cycle. The sporogonic cycle is the time taken for the parasite to undergo necessary development in the vector, enabling it to transmit malaria.

Submodels 2 and 3 are based on the work of Detinova (1962).

Submodel 4 describes vector survivorship in terms of survival probability per gonotrophic cycle and per day (Lindsay & Birley 1996). Combined with submodel 3, this allows the calculation of the probability of the vector surviving long enough for sporogonic development to be completed. Submodel 4 is also used to simulate the effects of a residual spray programme, which is considered in terms of its impact upon the probability of vector survival per gonotrophic cycle.

Submodel 5 describes the determination of the sporozoite rate. The sporozoite rate is the proportion of vectors with infectious pathogens in their salivary glands. The sporozoite rate sub-model used was developed by Saul *et al.* (1990).

Submodel 6 is the human infection model which calculates the number of new infections, superinfections and recoveries.

Model assumptions

The model is based on the following assumptions:

- Vector and host populations are homogenous.
- The probability of an individual vector surviving from one gonotrophic cycle to the next is constant and therefore independent of the age of that individual.
- Vectors which become infectious remain infectious.
- Feeding of an already infected vector on an infectious host has no effect on the course of the infection in the vector.
- Vectors bite randomly.
- Infected individuals bitten again by an infected vector will be superinfected. This is not counted as a new infection but will mean that the individual is not able to recover until the following month where recovery will then be governed by the probability of recovery.
- The proportion of multiple or mixed blood meals because of interrupted feeding may be a significant factor in transmission. However, it is not included in the model and all blood meals are assumed to be carried out in full on a single host.

Model inputs

The population estimates for Hwange district were obtained for the years 1994–1997 (National Heath Information and Surveillance Unit) and 1999 (Hwange District Health Service) where no data were available (1993 and 1998) the linear trend of the series was used to estimate population size.

Residual spraying was carried out annually in the district during the period of analysis; however, data on the coverage achieved by the spray programme were not available for all years. Limited information was available regarding coverage in more recent years and this was used to provide an estimate of the likely coverage achieved by the programme in previous years. The lack of data was further complicated by the ambiguous use of the term 'coverage' in source information, which does not refer to coverage of the total district but actually refers to coverage of the target area delineated for the spay programme. Reported coverage percentages were therefore converted to actual district coverage.

The probability of vectors surviving each feeding cycle (α) is considered to be fixed throughout the model, it is reduced (by a factor, β) when spraying is carried out. The reduction in survivorship caused by spraying is assumed to occur as soon as the spray programme is completed to its defined level of coverage, for example, if the spray programme is completed during January its effectiveness will start and be at a maximum in January. The residual action of the insecticide used is assumed to last for 6 months with a linear decline in effectiveness such that after six full months the insecticide is ineffective.

Survivorship is critical to malaria transmission and the probability of vectors surviving each feeding cycle is usually in the range of 0.4–0.6 (Charlwood *et al.* 1985; Mutero & Birley 1987; Graves *et al.* 1990; Hii *et al.* 1990). Data were obtained from the literature to further inform the choice of values for α and β. Magesa *et al.* (1991) found that the mean ovarian age grade of An. gambiae in traditional Tanzanian villages before and after DDT house spraying was 1.229 and 0.400 respectively. The ovarian age grade is determined by the dissection of the ovaries to count the number of dilatations left in the ovariole stalks subsequent to each ovulation and

Table 1 Value of variables achieving the highest correlation with case data

Variable description	Variable name	Value yielding highest correlation coefficient
Number of people initially infected	I	500
Constant in the rainfall to mosquito sub model	μ	992 123
Proportion of human blood-fed mosquitoes	h	0.38
Difference between indoor and outdoor temperature	l	1
Percentage coverage achieved by spray programme	c	0.24*
Percentage of vectors surviving each feeding cycle in unsprayed population	α	$e^{-1/1.229}$*
Percentage of vectors surviving each feeding cycle in sprayed population	$\alpha\beta$	$e^{-1/0.4}$*
Probability of vector becoming infected per infectious meal	k	1
Probability of pathogen becoming infectious in the vector	v	0.4
Length of phase 1 and 3 of gonotrophic cycle	v	1.26
Probability of recovery	r	0.182
Lag		4 months
Proportion of cases reporting at health facility	λ	0.54

*The variable was not altered using the solver function as the variable value chosen was based on *a priori* information rather than by fitting.

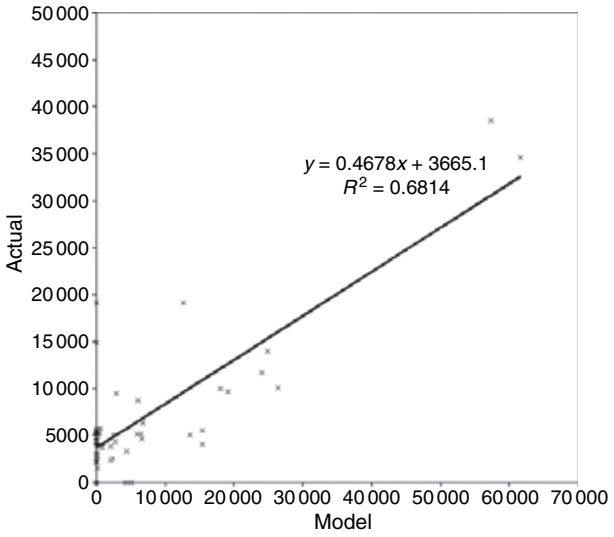

Figure 1 Scatter plot of model results for 'cases reporting by month' (model output) against reported malaria for Hwange district.

oviposition which corresponds to the number of gonotrophic cycles undergone (Gilles & Warrell 1993). These data were rearranged (see Appendix 2) to yield estimates of α and $\alpha\beta$ shown in Table 1. The selection of values for other model inputs is described below.

Fitting and testing the model

The ability of the model to predict the relative changes in malaria cases reported in the Hwange district during the period from January 1994 to June 1998 (source: National Heath Information and Surveillance Unit, Ministry of Health and Child Welfare) was measured by cross correlating the model results for the sum of all infections [new infections (F) and super infections (Z)] with the number of cases recorded at government health facilities. This was used because it is assumed that the case data will reflect not only new infections, but also individuals who are carrying parasites but are no longer clinically ill who receive another infected bite and are therefore sick again. The time-series data used include a range of transmission levels found in the area ranging from serious epidemic years to post-drought low transmission (see Figure 2).

The value of unknown variables were altered one at a time manually until the value of each variable that yielded the highest correlation coefficient was identified (see Table 2 for range tested for each variable). The 'solver' function[3] in Excel (Microsoft 1993) was then used to

[3]The solver function determines the maximum or minimum value of one cell by changing other cells and in this case was used to maximize the correlation between modelled and actual cases by varying unknown model inputs.

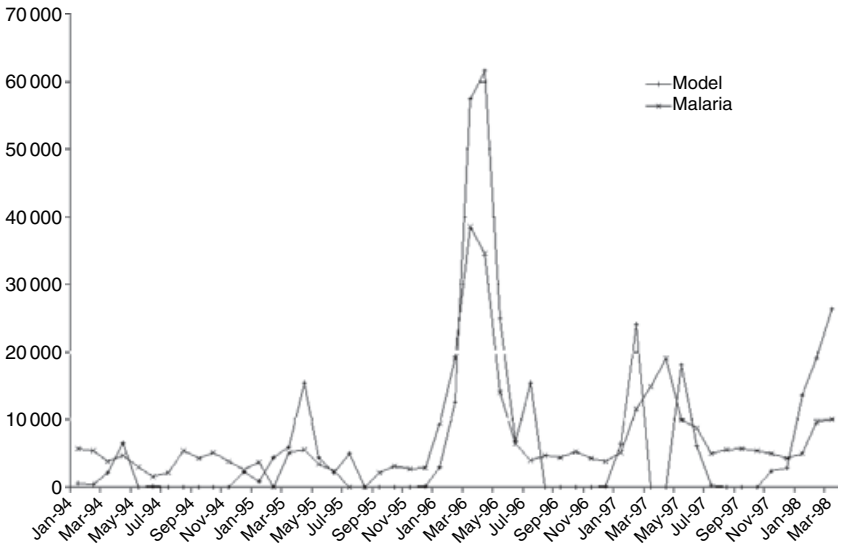

Figure 2 Modelled and actual reported malaria cases (adjusted for lag time).

Table 2 Variables included in uncertainty analysis

Variable	Range	Justification	Results
Rainfall to mosquito constant (μ)	250 000–1 500 000	No data – arbitrary	Linear scaling factor
Proportion of human blood-fed mosquitoes (h)	0.1–1	True value ranges between 0 and 1	Highly sensitive therefore included in SA
Temperature adjustment factor (l)	1–10 °C	No data – arbitrary	Linear scaling factor
Probability of vector becoming infected per infectious meal (k)	0–1	True value ranges between 0 and 1	Linear scaling factor
Probability of pathogen becoming infectious in the vector (v)	0–1	True value ranges between 0 and 1	Linear scaling factor
Length of phase 1 and 3 of gonotrophic cycle (v)	0.5–4	No data – arbitrary reasonable range	Included in SA as sensitivity depends on IRS coverage level
Probability of recovery (per month) (r)	0–0.9	80 days duration infectivity = 0.375 per month (Macdonald 1957)	Highly sensitive therefore include in SA

further improve the correlation between the model results and the case data for Zimbabwe.

The model output represents all infections occurring; however, not all malarial infections will present and be recorded at the health centre. A constant representing the proportion of cases in the community reporting at the government run health facilities (λ) was therefore introduced to fit the model output to the case data. The 'solver' function was used to obtain the value of λ which minimized the square of the difference between the sum of cases predicted by the model and the sum of actual cases. The resulting data were defined as 'cases reporting by month'.

Further analysis regarding the ability of the model to predict the magnitude or severity of malaria seasons was carried out by comparing the deviation from the mean value for each month for modelled and actual cases.

Uncertainty analysis

Uncertainty analysis was used to assess the effect on predicted cases resulting from uncertainty in input parameters. Variables identified as important were included in the subsequent sensitivity analysis. Table 2 provides a list of the variables and ranges examined in the uncertainty analysis.

Sensitivity analysis

Variables that were identified as important in the uncertainty analysis, and others of specific interest were subject to a one-way sensitivity analysis. Each variable was varied ±10% from the value which achieved the best fit. The number of cases predicted for a low-transmission (LT) year (1994) and a high-transmission (HT) year (1996) was recorded for each value and the percentage change in cases resulting from a 10% change in each variable was calculated. Sensitivity analysis was carried out on the proportion of human blood-fed mosquitoes (h), the proportion of vectors surviving the feeding cycle in the unsprayed (α) and sprayed ($\alpha\beta$) populations and the probability of recovery (r).

Alternative intervention scenarios examined

A range of IRS intervention scenarios was examined using the model based on variations of the actual IRS strategy. The IRS carried out in Hwange district during the period studied was completed by the end of December (early January at the latest) with a coverage rate of approximately 24% of the entire district (selective spraying of wards within the district). The first scenario simulated was a 'do-nothing' alternative where the model was used to simulate the number of cases if no IRS was carried out. Alternative IRS coverage levels of 24% (actual coverage), 50%, 75% and 100% with effectiveness on-set time (spray completion date) set to 1 January each year were then simulated. Simulations were then carried out applying 24% (baseline) IRS coverage with effectiveness on-set times of 1 August, 1 September, etc. to 1 March. For each scenario modelled, the total number of cases reporting each year was recorded. The number of cases prevented compared with the 'do-nothing' alternative, was then calculated for each scenario.

Results

Model results

Values of variables achieving best fit with data. Table 1 shows the value of each variable which achieved the highest correlation coefficient between the modelled and actual cases. Combining these variables with the population and climate data predicted the actual case data with a lag of 4 months and a correlation coefficient of 0.825 ($r^2 = 0.6814$). Figure 1 shows a scatter plot of actual cases against modelled cases and a fitted trend line, illustrating that the model tends to over-predict case numbers (even after adjusting for cases reporting). Figure 2 illustrates the modelled and actual reported malaria cases. The model clearly picks out the seasonality (timing) of transmission and also the magnitude of each malaria season.

Comparison of the deviation from the mean value for each month for modelled and actual cases revealed that deviations from the mean in the actual cases are positively related to deviations from the mean in the modelled cases with $r^2 = 0.8806$. In other words, the model predicts well the magnitude of malaria each month.

The values of the variables 'proportion of vectors surviving feeding cycle in unsprayed population' (α), 'proportion of vectors surviving feeding cycle in sprayed population' ($\alpha\beta$) and 'percentage coverage achieved by spray programme' (C) were not varied using the solver function as part of the model fitting as the critical relationship between these variables and the model output required that they should be based on actual data rather than varied to improve the fit of the model. However, manual varying of parameters showed that a C-value of 50% improved the correlation coefficient very slightly to 0.828 ($r^2 = 0.6854$) and increased the value of the proportion of cases reporting (λ) necessary to set predicted cases equal to recorded cases from 0.54 to 0.78. During the sensitivity analysis other values of α were tested while all other parameters were held constant. This analysis revealed that, *ceteris paribus* the highest correlation coefficient was obtained with $\alpha = 0.44$. Other values of $\alpha\beta$ were also tested in the sensitivity analysis revealing that a higher correlation coefficient (0.830, $r^2 = 0.6893$) could be obtained with $\alpha\beta$ equal to 0, in which case λ (the proportion of case that report) would increase to 0.59. However, to maintain the relationship between the value of α and $\alpha\beta$ obtained from Magesa *et al.* (1991) and in view of the relatively small increase correlation achieved by altering the value of $\alpha\beta$, the original value was maintained.

Uncertainty analysis results

The uncertainty analysis revealed that the model is relatively more sensitive to the rainfall to mosquito constant (μ) (which is positively related to transmission) in drier years. The temperature adjustment factor (l) is negatively related to transmission but the model is fairly robust to changes within the range examined. The probability of vector becoming infected per infectious meal (k) and probability of pathogen becoming infectious in the vector (v) are positively related to transmission and the model is robust to changes between 0.4 and 1; however, reducing the value of either of these variables below 0.2 (with the other set to 1) reduces transmission dramatically. The length of phase 1 and 3 of the gonotrophic cycle (v) is

positively related to transmission and the model is fairly robust to changes in this variable; however, if it drops below 0.5 transmission is reduced dramatically. The model is highly sensitive to changes in the proportion of human blood-fed mosquitoes (h) which was further investigated in the sensitivity analysis. In higher transmission years, the model is less sensitive to changes in the probability of recovery (per month) (r); however, in lower transmission years, altering r from 0.18 to 0.1 can have a dramatic impact on transmission; this was investigated further in the sensitivity analysis.

Sensitivity analysis results

The results of the sensitivity analysis are shown in Table 3. Reducing the proportion of human blood-fed mosquitoes (h) below the best-fit value (0.38) reduced cases by 48% and 41% in LT and HT years respectively. Plotting other years and other values for h (not shown here) confirms a threshold-type effect with transmission being reduced dramatically in all years for values of 0.3 or less. Increasing h has a greater impact in 1994 (LT) than 1996 (HT) probably because the model nears saturation point in 1996. As expected very high levels of h lead to the model predicting high case numbers every year.

Changes in the proportion of mosquitoes surviving the feeding cycle (α) impact in a similar way to changes in h, but the magnitude of the effect is greater. The model is relatively insensitive to changes in the proportion of mosquitoes surviving the feeding cycle in the sprayed population ($\alpha\beta$); however, this is likely to be partly because of the fact that the sensitivity analysis was carried out with a coverage equal to 24%; therefore, $\alpha\beta$ is acting only on a quarter of the vector population. Moreover, the value of this variable will begin to increase as the insecticide loses efficacy; therefore, its value at particular points during the epidemic curve will also be important, this is investigated in the scenarios below. The recovery rate (r) is inversely related to transmission and the magnitude of the effect is larger in LT compared with HT years.

Intervention scenario results

Table 4 shows the total number of cases occurring under each coverage and timing scenario, and Table 5 shows the number of cases prevented, compared with the 'do nothing' alternative for each coverage and timing scenario. Figure 3 shows the number of reported cases prevented with alternative levels of IRS coverage and fixed timing compared with a 'do-nothing' alternative. As expected, the number of cases prevented increases with increased coverage in all years. And, the marginal benefit (additional cases prevented for each incremental increase in IRS coverage) declines as coverage levels increase. The marginal benefits of increased coverage are greater and decline at a slower rate in higher transmission years when compared with lower transmission years.

Figure 4 shows the number of cases prevented (compared with a 'do nothing' alternative) with alternative timings of IRS and coverage fixed at 24%. In LT years (1993 and 1994), the timing has little impact on the number of cases prevented as long as IRS is completed between September and December. However, in medium transmission years (1995, 1997 and 1998), effectiveness (cases prevented) begins to decline if IRS is completed later than September or October. In 1996 (HT/epidemic year), the timing of IRS has a dramatic effect on the number of cases prevented. For example, if IRS is completed by

Table 3 Sensitivity analysis results

		Low-transmission (LT) year (1994)		High-transmission (HT) year (1996)	
Variable	Value tested	Number of cases	% change in cases	Number of cases	% change in cases
h (10% lower than best fit)	0.342	6247	−48	107 375	−41
h (best fit)	0.38	12 106	n/a	181 743	n/a
h (10% higher than best fit)	0.418	24 892	106	228 930	26
α (10% lower than best fit)	0.396	2960	−76	29 108	−84
α (best fit)	0.44	12 106	n/a	181 743	n/a
α (10% higher than best fit)	0.484	40 658	236	249 714	37
$\alpha\beta$ (10% lower than best fit)	0.072	12 445	2.8	180 236	0.83
$\alpha\beta$ (best fit)	0.08	12 106	n/a	181 743	n/a
$\alpha\beta$ (10% higher than best fit)	0.088	12 198	0.8	182 631	0.5
r (10% lower than best fit)	0.1638	14 748	22	197 807	8.8
r (best fit)	0.182	12 106	n/a	181 743	n/a
r (10% higher than best fit)	0.2002	9931	−18	161 536	−11

Table 4 Total number of cases occurring under varying scenarios

	Scenario												
		IRS coverage (effective from 1 January)				IRS (coverage 24%) effective from							
Year	'Do nothing' alternative	24%	50%	75%	100%	August	September	October	November	December	January	February	March
1993	559	237	88	33	16	483	N/A	N/A	N/A	N/A	237	470	540
1994	20 671	12 106	8114	6624	6155	5125	4120	5604	5990	8289	12 106	17 467	18 949
1995	81 202	38 153	22 505	17 010	15 261	10 103	8247	9231	11 995	19 674	38 153	55 989	59 961
1996	273 457	181 743	132 277	105 821	95 254	101 987	72 184	67 302	85 159	136 578	181 743	211 573	219 234
1997	123 551	60 168	37 872	28 317	25 018	54 179	40 350	39 010	57 809	61 390	60 168	81 104	89 581
1998	104 481	59 079	43 191	34 257	30 842	29 499	21 893	28 733	45 809	60 329	59 079	69 210	71 342

Table 5 Total number of cases prevented under varying scenarios compared with 'do nothing' alternative

	Scenario											
	IRS coverage (effective from January)				IRS effective from (coverage 24%)							
Year	24%	50%	75%	100%	August	September	October	November	December	January	February	March
1993	322	471	526	542	N/A	N/A	N/A	N/A	N/A	322	89	19
1994	8565	12 557	14 048	14 516	15 546	16 551	15 068	14 681	12 382	8565	3205	1722
1995	43 049	58 697	64 191	65 941	71 098	72 955	71 970	69 206	61 528	43 049	25 212	21 241
1996	91 714	141 181	167 636	178 204	171 471	201 273	206 156	188 298	136 879	91 714	61 884	54 224
1997	63 383	85 679	95 234	98 533	69 372	83 201	84 541	65 742	62 161	63 383	42 448	33 971
1998	45 402	61 290	70 224	73 638	74 982	82 588	75 748	58 672	44 152	45 402	35 271	33 139

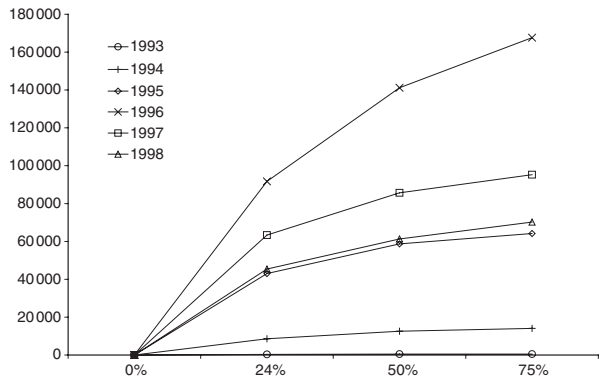

Figure 3 Total number of cases prevented under different IRS coverage scenarios (timing January).

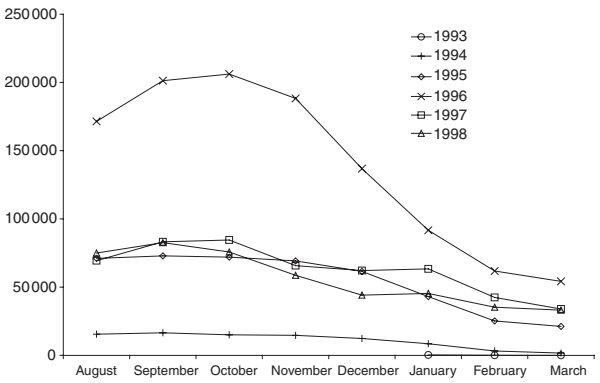

Figure 4 Total number of cases prevented under different IRS timing scenarios (coverage 24%).

October (with 24% coverage) around 67 300 cases occur; this rises to around 181 700 cases if IRS is not completed until January (see Table 4); so according to the model simulations, spraying earlier could reduce cases by an additional 114 400. In other years, the additional cases prevented by bringing IRS forward to September or October range between 8000 (1994) and 37 000 (1998). Spraying late (e.g. in February) prevents between 2 and 4.7 times fewer cases than spraying in October each year when compared with a 'do nothing' alternative.

In 1996, increasing coverage from 24% to 50% leads to a fall in cases of around 58 000, but spraying earlier with the 24% coverage level would reduce cases by 114 000 without incurring any additional insecticide costs. In fact,

according to the simulations, changing the timing of IRS completion from October to January would lead to a greater reduction in cases than increasing coverage levels to 100%.

Discussion

The model presented in this paper uses observed temperature to model gonotrophic and sporogonic cycle lengths and rainfall to drive mosquito numbers. These inputs are combined with models of daily vector survival and the sporozoite rate to produce monthly estimates of reported malaria cases for Hwange District, Zimbabwe. Having validated the predicted cases against actual cases using the known coverage and timing of the IRS, the model was used to simulate alternative IRS intervention scenarios.

The simulations show that the marginal benefits of increasing IRS coverage are higher in HT years relative to lower transmission years. This implies that over a period of years, maximum impact could be achieved with a given quantity of insecticide by increasing coverage in HT years and reducing it in LT years. However, the model also shows that earlier spraying is more effective in all years, especially so in epidemic years, and that IRS has limited impact if it is carried out too late in relation to peak transmission. This finding illustrates the problem described by Najera *et al.* (1998) and Connor *et al.* (1999) where vector control measures are implemented when transmission has already been naturally interrupted thus wasting scarce resources.

The model does not incorporate potential reductions in the effectiveness of IRS caused by replastering of walls after spraying, and this may cause the simulations to overestimate the benefits of earlier spraying. However, the model also makes a conservative assumption of the residual impact of the insecticide effectiveness duration of 6 months which means that, especially for the earlier interventions scenarios, the efficacy of the insecticide may actually continue beyond what has been modelled and therefore the model may underestimate the benefits of early spraying (for estimates of residual effects of insecticides in IRS, see Najera *et al.*, 1998).

Unfortunately, data on the impact on vector survivorship in sprayed and unsprayed populations were only available from a single study using DDT. Estimates of these variables for other insecticides and in other settings would be useful to validate the findings of this study and to examine the impact on transmission of different insecticides.

Another limitation of the study is that the model is validated using clinically diagnosed malaria cases which are subject to under-reporting and misdiagnosis. However, the skill of the model in predicting these data is good, particularly if we consider its ability to predict the epidemic year (1996). It would lend further weight for the model if it were to be tested using data sets from other locations. The potential for using the relationships used in this model as part of efforts to develop MEWS should also be considered.

Our results show that spraying is most effective when completed earlier (in September or October rather than December or January) every year. However, decisions on the coverage levels for each year should also be informed by the level of transmission that year. Unfortunately, this decision would have to be made before actual rainfall data are available to make predictions – although the model predicts cases with a 4-month lag, the whole of a month's rainfall would be needed to make a forecast, making the effective lead time 3 months. A practical alternative could be to spray certain areas early annually, and use forecasted information to carry out additional spraying in at-risk areas. The use of seasonal climate forecasts (Thomson *et al.* 2006) could therefore be used to inform coverage decisions; however, the benefits of this would have to be weighed against the reduced reliability of predictions based on a forecast rather than actual rainfall.

The model simulations have also revealed a potential benefit of MEWS in improving resource allocations in time. A subsequent study by the same authors will examine this using cost-effectiveness analysis. If accurate malaria forecasts are available, prevention and mitigation activities can be implemented in a timely manner to maximise the cases prevented and possibly even avert epidemics occurring altogether. However, this will be dependent upon the capacity (technical and economic) and willingness of malaria control programmes to act on forecasted and therefore uncertain information and on the forecasts being issued with adequate lead time for a response to be coordinated (Roll Back Malaria 2001). With IRS the lead time required may be relatively long; however, other interventions such as checking and replenishing drug stocks and warning communities and health staff of the impending epidemic can be done with shorter lead times. Evidence on the effectiveness of such interventions is currently lacking.

Conclusions

Although studies have previously investigated the effectiveness (and cost-effectiveness) of IRS, none have examined changes in effectiveness resulting from inter-annual variation in transmission levels. This is particularly relevant in epidemic or seasonal transmission areas where IRS is commonly used. In addition, the mode of action of IRS confers public rather than personal protection (vectors are generally killed whilst resting following a blood meal and

are therefore unable to transmit malaria). The timing of the application of IRS in relation to the timing and intensity of transmission season is therefore an important determinant of the transmission-reducing effects of IRS. This study has taken existing understanding of the effectiveness of IRS a step further by identifying and quantifying how the timing of the intervention affects its effectiveness. In addition, it has highlighted the potential efficiency gains that could be made by altering the coverage levels and the timing of IRS activities to reflect the diverse transmission levels which may occur in the same locations in different years. An accurate and timely MEWS and response capacity could help to improve efficiency of resource use and reduce the burden of malaria in areas of seasonal or epidemic-prone transmission.

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Appendix 1: Mathematical description of the model

Submodel 1: mosquito population

The number of female mosquitoes emerging each month is assumed to be directly proportional to monthly rainfall (R)

$$q = \mu R \tag{1}$$

Studies providing data on the number of bites per person per night by month in locations across Africa (E. Savage and M. Thomson, unpublished data) were identified, geo-referenced and then the climatic rainfall data for the relevant month and location were extracted from a climate surface data set (Hutchinson *et al.* 1995).

The relationship between rainfall and the number of bites per person per night for each location was found to be approximately linear and this relationship was therefore assumed in the model as reflected in Eqn 1 above.

Submodel 2: gonotrophic cycle length

The gonotrophic cycle (U) can be split into three phases (Detinova 1962):

(i) the search for the host and the bite;
(ii) the digestion of the blood meal (u);
(iii) the maturation of the ovaries, and the search for a suitable water body and oviposition (egg laying).

Phase one and three are assumed to be constant in length and together have duration (v).

The duration of phase two of the cycle (u) is known to be directly related to temperature and humidity and can be calculated as follows (from Detinova 1962):

$$u = \frac{f_U}{T_U - g_U} \tag{2}$$

where T_U is the indoor temperature which can be calculated from the outdoor ambient temperature (T) using an adjustment factor (l). f_U is the degree days (a measure of the total amount of heat required, between the lower and upper thresholds, for an organism to develop from one point to another in its life cycle) the minimum temperature required for digestion of blood.

The total gonotrophic cycle length is therefore:

$$U = v + \left(\frac{f_U}{(T + l) - g_U}\right) \tag{3}$$

Submodel 3: sporogonic cycle length

The length of the sporogonic cycle is the time from the female mosquito taking an infected blood meal to the appearance of sporozoites in its salivary glands. This process is dependent on temperature and is expressed thus (from Detinova 1962):

$$N = \frac{f_N}{(T_N - g_N)} \tag{4}$$

where f_N represents the number of degree days needed to complete the parasite development (111 °C days for *P. falciparum*) and g_N represents the threshold below which development ceases, (18 °C) (Detinova 1962).

Temperature (T_N) is again adjusted to account for differences between indoor and outdoor resting temperatures, using a weighting system, based on the period of time the vector spends indoors as a proportion of gonotrophic cycle length.
Hence:

$$N = \frac{f_N}{\left(T + \frac{lu}{U}\right) - g_N} \tag{5}$$

Submodel 4: vector survivorship

The model works on a daily time period. However, as spraying has an impact on survivorship per gonotrophic cycle, we first examined survivorship per gonotropic cycle and then rearranged this to give daily survival. For this reason, the model switches between daily survival and survival per gonotropic cycle.

The probability of a vector surviving each gonotrophic cycle is α which is assumed to be constant and independent of the length of the gonotrophic cycle (Hii *et al.* 1990). After Lindsay and Birley (1996), the daily probability of survival is therefore:

$$P = \alpha^{1/U} \tag{6}$$

This assumes that a mosquito's probability of daily survival decreases as the feeding cycle gets shorter (as temperature increases).

The model defines two populations of mosquitoes, those covered (C) and not covered ($1 - C$) by the spray programme where C is the percentage coverage achieved by the spray programme. The percentage of vectors surviving each gonotrophic cycle is expressed as α in the population not covered by the spray programme.

This is reduced by β in the population covered by the spray programme immediately after spraying, gradually increasing back towards α at a rate of $\beta/6$ per month over the effective residual life of the insecticide (assumed to be 6 months).

The mean probability of daily survival (P) for the whole population is

$$[\alpha(1 - C) + \alpha\beta C]^{1/U} \tag{7}$$

The probability of the vector surviving sporogony is a critical variable in the transmission of malaria. This is expressed as

$$P^N \tag{8}$$

Submodel 5: sporozoite rate

The sporozoite rate (S) is the proportion of vectors with infectious pathogens and was derived from summing infinite series as described by Saul *et al.* (1990). For notational convenience the formula shown uses the probability of surviving the gonotrophic cycle for an unsprayed population (α), in a sprayed situation this is substituted for $\alpha(1 - C) + \alpha\beta C$.

$$S = \frac{xhkvP^N}{(1 - \alpha + xhkv\alpha)} \tag{9}$$

where h is the proportion of human blood-fed mosquitoes, i.e. those feeding on humans rather than other species, e.g. cattle, x the proportion of humans that are infectious, k the probability of the vector becoming infected per infectious meal, v the probability (of the pathogen) becoming infectious in the vector, and the probability of the vector *not* becoming infectious as a result of a single feed is:

$$1 - xhkv$$

Submodel 6: human infection

The number of infectious mosquitoes biting humans is the product of the sporozoite rate (S), the number of mosquitoes (q) and the person biting habit (a).

The person biting habit represents the *frequency* at which mosquitoes feed on humans as opposed to other vertebrates:

$$a = \frac{h}{U} \tag{10}$$

where h is the proportion of human blood-fed mosquitoes (as described above) and U the gonotrophic cycle length.

When the total human population is equal to (d), the probability of a human receiving an infectious bite (R) is:

$$R = 1 - \left(1 - \frac{1}{d}\right)^{sqa} \tag{11}$$

An infectious bite received by a human is classified as a new infection if it is on an uninfected human and a superinfection if it is on an already infected human. The number of infected humans is I and so the number of new infections (F) is $R(d - I)$ and the number of superinfections (Z) is RI.

New infected humans recover after time t with a fixed probability r; hence, the number of people recovering at time t (c) is:

$$c = (I - Z)r \tag{12}$$

Dynamic model

The number of infected humans at time t (I_t) is the number of infected humans at time t–1 (I_{t-1}), minus the number of people recovering at time t (c_t), plus the number of people newly infected at time t (F_t):

$$I_t = I_{t-1} - c_t + F_t \tag{13}$$

Appendix 2

Magesa *et al.* (1991) found that the mean ovarian age grade of An. gambiae in traditional Tanzanian villages before and after DDT house spraying was 1.229 and 0.400 respectively. The ovarian age grade is determined by dissection of the ovaries to count the number of dilatations left in the ovariole stalks subsequent to each ovulation and oviposition which corresponds to the number of gonotrophic cycles undergone (Gilles & Warrell 1993). These values were used to calculate the value of α and $\alpha\beta$ as follows.

If the probability of vectors surviving sporogeny before spraying is α, the mean ovarian age grade of the population at any given time $\bar{t}$ is given by:

$$\bar{t} = \frac{\int_0^\infty t(\alpha)^t \mathrm{d}t}{\int_0^\infty t\alpha^t \mathrm{d}t} = -\frac{1}{\ln \alpha} \quad (14)$$

With spraying the probability of surviving the feeding cycle is given by $\alpha\beta$, similarly the mean ovarian age grade of the population at any given time after spraying is:

$$\bar{t} = \frac{-1}{\ln \alpha\beta} \quad (15)$$

Hence before intervention substituting data from Magesa *et al.* (1991) into Eqn 15 gives:

$$\frac{-1}{\ln \alpha} = 1.229$$

Rearranging gives:

$$\alpha = e^{-1/1.229}$$

After intervention substituting values from Magasa et al. into Eqn 16 and rearranging gives:

$$\frac{-1}{\ln \alpha\beta} = 0.4$$

$$\alpha\beta = e^{-1/0.4}$$

In addition to the value of α shown above, other values ranging between 0 and 1 were tested. For $\alpha\beta$ values between 0 and α were tested.

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Un modèle pour simuler l'impact de la synchronisation, de la couverture et de l'intensité de transmission sur l'efficacité de la pulvérisation de résidus d'intérieur pour le contrôle de la malaria

OBJECTIFS (i) Développer un modèle de prédiction de la transmission de la malaria basé sur la température et les précipitations. (ii) Utiliser le modèle pour examiner le rapport entre la synchronisation de l'intervention et l'intensité de transmission sur l'efficacité de la pulvérisation de résidus d'intérieur (PRI).

MÉTHODES Un modèle dynamique de la transmission de malaria a été développé à partir de modèles existants de dynamique de transmission de malaria. Le modèle a ensuite été utilisé pour prévoir rétrospectivement des cas réels de malaria dans le district de Hwange au Zimbabwe en utilisant les données sur la météorologie, la synchronisation de la PRI et la couverture. Les simulations de scénarios alternatifs d'intervention (synchronisation et couverture) ont été utilisées pour examiner l'efficacité des interventions appliquées plus tôt ou plus tard sur des étendues plus élevées et plus basses de la couverture durant les années épidémiques et non épidémiques.

RÉSULTATS Le modèle a permis de prévoir des cas réels de malaria à Hwange sur une période de quatre ans et demi avec un délai de quatre mois (par exemple: les précipitations et la température de janvier prévoyaient la malaria d'avril) et un coefficient de corrélation de 0,825 ($r^2 = 0{,}6814$). Les simulations de PRI démontrent que les avantages marginaux de l'augmentation de la couverture de PRI sont plus élevés pour les années de transmission élevée que pour celles de transmission faible. Ceci implique que durant un certain nombre d'années, un impact maximum pourrait être atteint avec une quantité donnée d'insecticide, en augmentant la couverture dans les années de transmission élevée. Le modèle démontre également que la pulvérisation très tôt est plus efficace pour toutes les années, spécialement pour les années épidémiques, et que la PRI a un impact limité lorsqu'elle est effectuée trop tard par rapport au pic de transmission.

CONCLUSION les modèles de transmission de malaria, basés sur la température et les précipitations, sont capables de prévoir des épidémies de malaria. L'intervention très tôt, basée sur la connaissance préalable de l'importance de la saison de malaria, peut être plus effective et plus efficace que le fait de mener des activités de contrôle en routine chaque année.

mots clés malaria, modèle, synchronization, pulvérisation de résidus d'intérieur, Zimbabwe, épidémies

Modelo para simular el impacto la cobertura, la intensidad de transmisión y del momento de realización de la intervención sobre la efectividad del rociamiento intradomiciliario con insecticidas de acción residual para el control de la malaria

OBJETIVOS (i) Desarrollar un modelo de transmisión de malaria, capaz de predecir a partir de datos de temperatura y precipitación (ii) Utilizar el modelo para examinar la relación entre el momento de la intervención y la intensidad de transmisión sobre el efecto del rociamiento intradomiciliario con insecticidas de acción residual (RIR)

MÉTODOS Se desarrolló un modelo dinámico para la transmisión de malaria a partir de otros modelos dinámicos para la transmisión de malaria ya existentes. El modelo se utilizó para predecir de forma retrospectiva los casos actuales de malaria del distrito de Hwange, en Zimbabwe, utilizando datos metereológicos reales, y de cobertura y del momento de realización el RIR. Mediante simulaciones de escenarios alternativos (en cuanto al momento de realizar la intervención y su cobertura), se examinó la efectividad de intervenciones más tempranas o más tardías, con mayor y menor nivel de cobertura, en años epidémicos y sin epidemia.

RESULTADOS El modelo fue capaz de predecir los casos de malaria reales en Hwange durante un periodo de cuatro años y medio, con un tiempo de antelación de cuatro meses (por ejemplo con datos de lluvias de Enero, se predice la malaria en Abril) y un coeficiente de correlación de 0.825 ($r^2 = 0.6814$). Las simulaciones del RIR demuestran que el beneficio marginal de aumentar la cobertura de RIR es mayor en años de alta transmisión que en aquellos de menor transmisión. Esto implica que durante un periodo de unos cuantos años se podría alcanzar un impacto máximo, con una cantidad dada de insecticida, aumentando la cobertura en años de alta transmisión. El modelo también muestra que el rociamiento temprano es siempre más efectivo, y en especial en los años epidémicos, y que el RIR tiene un impacto limitado si se realiza demasiado tarde con relación al pico de transmisión.

CONCLUSIÓN Los modelos de trasmisión de malaria basados en la temperatura y la precipitación, tienen el potencial de predecir las epidemias de malaria. Una intervención temprana, basada en un conocimiento previo de la magnitud de la estación de malaria, puede ser más efectiva y eficiente que llevar a cabo actividades de control rutinarias cada año.

palabras clave malaria, modelo, momento de la intervención, rociamiento intradomiciliario, insecticidas acción residual, Zimbabwe, epidemias