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# Mathematical analysis to prioritise strategies for malaria elimination

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ABSTRACT

Malaria and some other tropical diseases are currently targeted for elimination and eventually eradication. Since resources are limited, prioritisation of countries or areas for elimination is often necessary. However, this prioritisation is frequently conducted in an *ad hoc* manner. Lower transmission areas are usually targeted for elimination first, but for some areas this necessitates long and potentially expensive surveillance programs while transmission is eliminated from neighbouring higher transmission areas. We use a mathematical model to compare the implications of prioritisation choices in reducing overall burden and costs. We show that when the duration of the elimination program is independent of the transmission potential, burden is always reduced most by targeting high transmission areas first, but to reduce costs the optimal ordering depends on the actual transmission levels. In general, when overall transmission potential is low and the surveillance cost per secondary case compared to the cost per imported case is low, targeting the higher transmission area for elimination first is favoured.



## 1. Introduction

The *Global Technical Strategy for Malaria 2016–2030*, released by the World Health Organization (WHO) (World Health Organization, 2015), sets the current global goals for malaria control and elimination by 2030 as: (i) reducing the number of malaria cases and deaths globally by 90% as compared to 2015; and (ii) eliminating and preventing re-establishment of transmission in at least 35 countries where malaria transmission was ongoing in 2015. The main strategies towards achieving these goals are (i) “control through universal access to malaria prevention, diagnosis and treatment”; (ii) intensifying efforts towards elimination and prevention of re-introduction; and (iii) “transforming malaria surveillance into a core intervention” of both control and elimination strategies (World Health Organization, 2015; 2017).

Malaria control activities are recommended in all locations where transmission persists (although it is sometimes not deployed in locations where financial and/or operational resources are insufficient). However, efforts to eliminate malaria are mainly focused on the fringes of its geographical range, for example in the Asia-Pacific region (Gosling et al., 2012) and in Southern Africa (Southern African Development Community, 2013).

There is a global health priority in eliminating foci of drug resistance in the Greater Mekong subregion (Gueye et al., 2014), and spatially progressive elimination may be rational where the risk of re-establishment of transmission is low (Lines et al., 2008; Smith et al., 2013), or where a small focus of transmission has a disproportionate economic importance. Targeting isolated islands and other areas with low transmission potential for malaria elimination may also have value as tests of new technologies or systems; but in general it is unclear whether targeting low transmission areas is a better strategy than focusing those resources on eliminating malaria from higher transmission areas, especially when these lower transmission areas face risks of malaria importation from neighbouring higher transmission areas.

The strategy of progressive elimination from the fringes has been criticised because of the implicit inequity of prioritising low burden areas (Shah, 2010). This strategy also ignores the important lesson from those programs that have been successful in eradicating a disease (smallpox (Henderson, 2009), or that have approached eradication (polio (Aylward et al., 2003) and dracunculiasis (Ruiz-Tiben and Hopkins, 2006), that eradication programs need to focus early in challenging areas which are likely to remain a threat after the disease is gone elsewhere. More generally, it seems likely that any eradication or elimination program

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will be more efficient if core areas that export the infection are targeted at the start. This concurs with the experience of countries that have eliminated or approached elimination. Iran is now on its second attempt at national malaria elimination. Each time, interventions were rolled out nationally, burden reduction in the high transmission south east has been key to near-elimination in the north and west (Hemami et al., 2013).

An effective surveillance system is a key constituent intervention of intensified control efforts to eliminate malaria; and remains essential after malaria has been eliminated to prevent re-establishment of transmission (Kelly et al., 2012; World Health Organization, 2015). It must include a reactive component that is effective in detecting imported cases and preventing onward transmission from them. The surveillance system will need to be maintained as long as there is a risk of reintroduction, that is, until malaria has been eradicated. This can be operationally and financially challenging in tropical areas with high vectorial capacity (malaria transmission potential) (Roberts, 2010; Schapira and Zamani, 2012; Smith et al., 2011; World Health Organization, Global Malaria Programme and University of California, San Francisco, 2012).

There is therefore a need for decisions concerning elimination to be based on criteria that consider costs, overall disease burden and the risks associated with different options. This paper aims to provide a mathematical formulation to guide strategic thinking about how zones with different levels of disease burden should be targeted for elimination, on the assumptions that (i) malaria control is maintained in all areas; (ii) elimination is technically possible in all the areas being considered; (iii) but resources to intensify control programs to achieve elimination are limited to targeting one area at a time. The results are expressed in terms of general principles that may be applicable at different spatial scales across the whole range of malaria transmission intensities. To derive these principles, we only consider a simple economic model of two areas of equal population here, but some of this analysis may be extended to multiple areas. Although many studies, modelling and otherwise, have investigated the feasibility of malaria elimination (Moonen et al., 2010), and the persistence of elimination (Chiyaka et al., 2013; Smith et al., 2013), none have considered such mathematical economic models for ordering areas for intensified control efforts to achieve elimination.

We consider a simple system consisting of two connected geographical areas with similar populations but different initial levels of transmission, and equal (symmetric) movement of in both directions through the short term movement of people and possibly mosquito vectors. Symmetrical movement is a reasonable assumption here because imported malaria cases are usually not due to immigration but due to the short term movement of visitors from areas with higher transmission or returning residents. Therefore we assume that the importation of infection in either direction depends only on the prevalence in the source population.

Both areas are initially under control, with current tools, such as long lasting insecticidal nets and indoor residual spraying, maintaining the annual disease burden in each area at a relatively constant level. Although there are likely to be seasonal variations within each area, we do not explicitly consider them here because we are more interested in the general principles of the relationship between importation and elimination (which do not depend on seasonality), and not in the details of planning such elimination strategies (which depend on seasonality).

We assume that the technologies for time-limited elimination throughout the system are available (technical feasibility) with additional tools such as reactive case detection and reactive vector control (Moonen et al., 2010; World Health Organization, 2017). However, the human and/or financial resources to apply these additional intervention measures in both areas simultaneously are not available, so that overall elimination can only be achieved by intensified control measures in one area at a time, in each case until local transmission is interrupted.

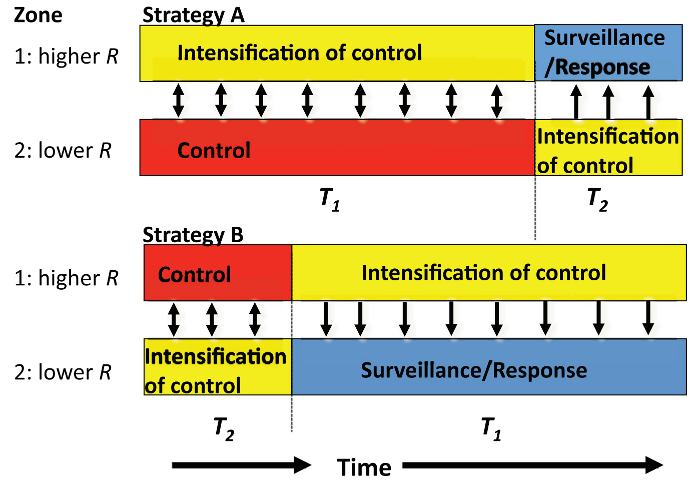


**Fig. 1.** Strategies being compared. The black arrows indicate the direction of the export/import of infected cases. Here, $R$ denotes the transmission potential and $T_i$ denotes the duration of intensified measures needed to achieve elimination (Table 1).

We label the higher transmission site as $i = 1$, with transmission potential (measured by the reproduction number) $R_1$ (see Table 1). We label the lower transmission site as $i = 2$ with transmission potential $R_2$ where $R_2 < R_1$. Both sites are additionally characterised by malaria prevalence at equilibrium, $p_i$, annual disease burden, $B_i$, vulnerability, $V_i$, and required duration of intensified control to eliminate transmission, $T_i$. More detailed descriptions of these and all other parameters are provided in Table 1. We define elimination here as the lack of sustained local transmission (that is, imported cases may lead to a few secondary cases but each chain of infection dies out and malaria cannot reestablish itself in the population). We use the WHO definition of elimination as the "interruption of local transmission (reduction to zero incidence of indigenous cases)" (World Health Organization, 2016). WHO malaria terminology distinguishes between introduced cases ("first generation local transmission" from an imported case) and indigenous cases ("contracted locally with no evidence of importation and no direct link to transmission from an imported case") (World Health Organization, 2016). Re-establishment of transmission is defined as the "renewed presence of a measurable incidence of locally acquired malaria infection due to repeated cycles of mosquito-borne infections in an area in which transmission had been interrupted" (World Health Organization, 2016). Therefore in a state of elimination, local transmission is possible so secondary (introduced) cases may arise from an imported case, but these should not lead to sustained (re-established) transmission.

There are two possible strategies for elimination across both sites: $J = \mathrm{A}$, intensification of control in the higher transmission site ($i = 1$) first, with continued control in lower burden area; and $J = \mathrm{B}$, intensification in the lower transmission site ($i = 2$) first, with continued routine control in the higher burden area. These two strategies are illustrated in Fig. 1.

We note that the intensification program must include an effective surveillance response system. After the intensification program has eliminated malaria in the first area and has moved to the second area, the surveillance response system must continue to operate in the first area to prevent reintroduction (re-establishment of transmission), but other control interventions may be withdrawn. We therefore assume that after malaria elimination in the first transmission zone, the transmission potential for secondary cases remains at pre-intervention levels, but there is an effective surveil-