Available online at www.sciencedirect.com
SCIENCE DIRECT®
Acta Tropica 94 (2005) 218–229
ACTA TROPICA
www.elsevier.com/locate/actatropica

Intensity of malaria transmission and the evolution of drug resistance

Ian M. Hastings [a,*], William M. Watkins [b]

[a] *Liverpool School of Tropical Medicine, Pembroke Place, Liverpool L3 5QA, UK*
[b] *Department of Pharmacology and Therapuetics, University of Liverpool, Liverpool L3 5QA, UK*

Available online 19 April 2005

Abstract

The intensity of malaria transmission varies both naturally and as a consequence of human public health intervention. The relationship between transmission intensity and the rate at which antimalarial drug resistance evolves affects the design of surveillance programmes, and the likely impact of malaria control programmes. Several theoretical studies have investigated this relationship and their key results are summarised and interpreted. The most important result is that transmission intensity does not directly affect the evolution of resistance. It exerts its influence through three clinical/epidemiological "mediators" (clonal multiplicity, the threat of infection, level of human immunity) which ultimately determine the dynamics of resistance via five "effector" variables: sexual recombination, intrahost dynamics, community drug use, proportion of malaria infections treated, and the number of parasites per host. We argue that the evolution of resistance is likely to be a two-stage process: mutations encoding drug tolerance preceding those encoding resistance. The evolution of drug tolerance is determined solely by the level of drug use in the community which is likely to have an extremely weak relationship with transmission intensity. The evolution of resistance is more complex and affected by all five effectors. The most likely scenarios are that resistance evolves faster in areas of high transmission if encoded by a single gene but if encoded by two or more genes it evolves fastest in areas of high or low transmission, with a minimum at intermediate levels of transmission.

Keywords: Drug resistance; Malaria; Epidemiology; Intensity of transmission

1. Introduction

In the absence of an effective vaccine, malaria as a disease is controlled primarily by drugs. The evolution of drug resistant malaria is therefore a vital concern for the long-term health of a large minority of the world's population, especially in Africa, where most of the world's malarial sickness and death occurs. Several recent papers have attempted to identify the factors that determine the rate at which resistance evolves. These make frequent recourse to mathematical detail but the question of importance to most researchers is a simple one, "will resistance evolve more rapidly in areas of high, or of low, transmission?" There are three main

* Corresponding author. Tel.: +44 151 705 3183; fax: +44 151 708 8733.
E-mail address: hastings@liverpool.ac.uk (I.M. Hastings).

0001-706X/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.actatropica.2005.04.003

reasons why this question is so important. Firstly, resistance to antimalarial drugs seems to have initially emerged in areas of predominantly low transmission in S America and SE Asia (Wongsrichanalai et al., 2002), so it is natural to ask whether drug deployment in Africa, where transmission may be much higher, will result in slower evolution of resistance. Secondly, it appears inevitable that resistance will eventually arise. The cost implications for changing a first line antimalarial are enormous (Shretta et al., 2000) and the design of an effective sentinel system to maximise the time available for the choice and deployment of alternative therapy is a vital public health tool; so should the sentinel sites be predominantly in areas of high or low transmission? The third reason lies in trying to asses the impact of control strategies on drug resistance: if control systems such as residual insecticide spraying and/or bednets reduce transmission rates, will this reap additional benefits by delaying the evolution of resistance or, conversely, will the benefit be partially offset by increased levels of drug resistance? We address this issue by reviewing past investigations into the nature of this relationship. This allows us to omit mathematical details of their derivation, focus on their different underlying assumptions, and to identify and present their key results. The assumptions, and likely parameter values, are then discussed in the light of available field and laboratory data. This manuscript, and the studies on which it rests, considers the evolution of drug resistance in *P. falciparum*. Many of the arguments and results are relevant to other Plasmodium species, but their epidemiology, genetic basis of resistance and drug treatment regimens differ from that of *P. falciparum*, so space precludes an explicit extension of the results to other species.

Several theoretical investigations have been made into the dynamics of how antimalarial resistance evolves, for example, Cross and Singer (1991), Curtis and Otoo (1986), Dye and Williams (1997), Hastings (1997), Hastings et al. (2002b), White (1999), reviewed in Hastings and D'Alessandro (2000). Two of these studies did not explicitly consider the effect of transmission intensity, i.e. Cross and Singer (1991) and Curtis and Otoo (1986) but the others all discussed this aspect to varying degrees.[1] The results of these investigations are remarkably consistent as will be described below, the intensity of transmission per se does not directly affect the rate at which resistance evolves, but affects three main epidemiological factors (or Mediators) which in turn determine the dynamics via five "effector" variables. It is these five "effectors" that enter the equations and directly determine the dynamics of resistance. These mediators and effectors are illustrated in Fig. 1 and are sexual recombination, intrahost dynamics, the level of drug use in the population, the proportion of malaria infections treated, and the number of parasites in a human host (the "biomass"). Any discussion about the role of intensity of transmission in promoting or hindering the evolution of antimalarial drug resistance must therefore rest on an understanding of the relationship between transmission intensity and its mediators and effectors. This is the aim of this current review.

It is important to note that 'resistance' is defined operationally in the models cited above as meaning that the parasites are completely unaffected by the drug. This assumption is primarily made for mathematical convenience and is widely used in population genetics to investigate other types of resistance such as occurs to antibiotics, pesticides, and herbicides. However, drug resistance in malaria does not usually arise through a single mutational step, but more commonly arises as the end of a longer process during which parasites accumulate mutations and become ever more tolerant of the drug. Increased drug tolerance allows these parasites to survive in humans containing residual levels of a drug taken sometime previously. The frequent use of antimalarial drugs in endemic areas means that many people harbour sub-therapeutic levels of the drug, which constitutes a potent selection pressure driving tolerant mutations through the parasite population (Watkins and Mosobo, 1993). A key operational point is that they remain susceptible to therapeutic doses of the drug so are not clinically 'resistant' and are not detected by standard measurements of drug efficacy. This is most easily observed in the process by which *P. falciparum* acquires resistance to the antimalarial drug sulphadoxine/pyrimethamine (SP) through the sequential accumulation of mutations in the *dhfr* gene (Plowe et al., 1997; Sibley et al., 2001). Characterisation of these mu-

[1] Only two studies claimed that intensity of transmission had an unambiguous effect on the rate of evolution of drug resistance. Interestingly they came to opposite conclusions but can be reconciled by an understanding of their underlying assumptions (Appendix A).