CURRENT OPINION

Drugs 2000 Apr; 59 (4): 719-743
0012-6667/00/0004-0719/$25.00/0

Resurgent Malaria at the Millennium
Control Strategies in Crisis

J. Kevin Baird

Parasitic Diseases Program, US Naval Medical Research Unit No. 2, Jakarta, Indonesia

Abstract

Completion of the Panama Canal in 1914 marked the beginning of an era of vector control that achieved conspicuous success against malaria. In 1955 the World Health Organization (WHO) adopted the controversial Global Eradication Campaign emphasising DDT (dichlorodiphenyltrichloroethane) spraying in homes. The incidence of malaria fell sharply where the programme was implemented, but the strategy was not applied in holoendemic Africa. This, along with the failure to achieve eradication in larger tropical regions, contributed to disillusionment with the policy. The World Health Assembly abandoned the eradication strategy in 1969. A resurgence of malaria began at about that time and today reaches into areas where eradication or control had been achieved. A global malaria crisis looms. In 1993 the WHO adopted a Global Malaria Control Strategy that placed priority in control of disease rather than infection. This formalises a policy that emphasises diagnosis and treatment in a primary healthcare setting, while de-emphasising spraying of residual insecticides. The new policy explicitly stresses malaria in Africa, but expresses the intent to bring control programmes around the world into line with the strategy.

This review raises the argument that a global control strategy conceived to address the extraordinary malaria situation in Africa may not be suitable elsewhere. The basis of argument lies in the accomplishments of the Global Eradication Campaign viewed in an historical and geographical context. Resurgent malaria accompanying declining vector control activities in Asia and the Americas suggests that the abandonment of residual spraying may be premature given the tools now at hand. The inadequacy of vector control as the primary instrument of malaria control in holoendemic Africa does not preclude its utility in Asia and the Americas.

In 1955 the eradication of malaria seemed within reach.[1] Less than 50 years later malaria is resurgent, causing an increasing number of infections across an expanded geographic range (fig. 1).[2,3] Spreading resistance to available antimalarials has rendered effective treatment increasingly difficult for most people exposed to infection. In some areas, the possibility of untreatable multidrug-resistant malaria looms and economic realities in many areas leave malaria essentially incurable with the affordable antimalarials at hand. Parasite survival in the face of chemotherapeutic intervention is more likely than ever. In many areas, the ability to perform a microscopic diagnosis of malaria has been lost with the retirement of a generation of health workers trained during the heyday of the Global Eradication Campaign. Likewise, the deterioration of vector control programmes and

mounting social pressure against using pesticides like DDT (dichlorodiphenyltrichloroethane) favour vector survival and disease transmission. Finally, three urgently needed weapons against malaria have yet to materialise: a vaccine for prevention; an affordable, well tolerated and effective alternative to chloroquine for the treatment of uncomplicated malaria; and a practical alternative to DDT for vector control. The rule in endemic areas is high risk of infection, inadequate diagnosis, ineffective treatment and a derelict prevention infrastructure. Not since before World War II have tropical public health officers faced so serious a menace with such inadequate tools to fight it. The situation holds the potential for an explosive increase in the risk of malaria and there is general disagreement surrounding strategies to avert such a disaster.

Malaria control activities in the developing world have historically been guided by strategies put forth by the World Health Organization (WHO). The World Health Assembly has delivered landmark policies in malaria control in 1955, 1969 and, most recently, 1993. The last contribution, 'World Declaration on the Control of Malaria and Global Malaria Control Strategy',[4] represents a radical departure from past policies. The strategy embraces the philosophy of controlling disease rather than infection *per se*. Apart from insecticide-treated bed nets, vector control measures have been deemphasised. The declaration does not advocate complete abandonment of vector control, but endorses its application under stringent criteria that virtually preclude use in developing nations. The new policy focuses attention and resources upon diagnosis and treatment of infected individuals in a primary healthcare setting, rather than preventing infection in communities. This strategy represents a sensible approach to attacking malaria in holoendemic Africa, where about 90% of the 300 to 500 million new cases of malaria and 1.5 to 2.7 million

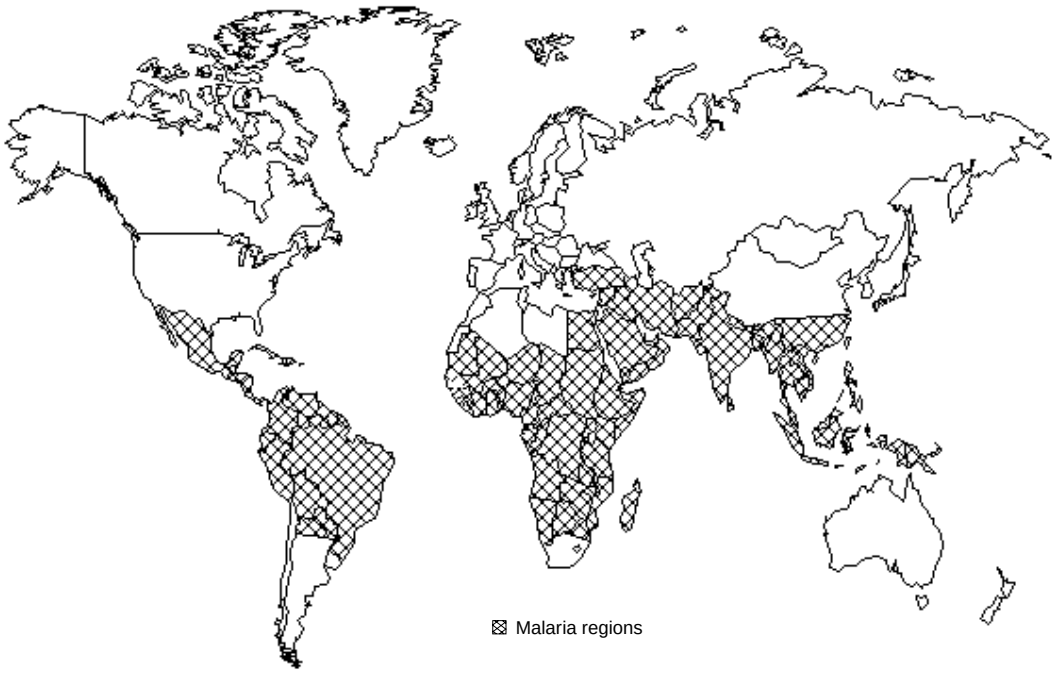

Fig. 1. Geographic range of malaria in 1994.

deaths occur each year.[5] However, the suitability of this explicitly African strategy for the rest of the world has not been established. This is a critical issue because the resurgence of malaria most threatens endemic regions outside Africa.

The debate over clinical- versus vector-based approaches to malaria control began soon after Ronald Ross identified anopheline mosquitoes as vectors in 1897. Ross's vigorous advocacy of malaria control through attack on the mosquito sparked controversy.[6] Completion of the Panama Canal in 1914, made possible by controlling the vectors of malaria and yellow fever, vindicated Ross. Vector control came to dominate malaria control strategies, infrastructure and practice for the next 50 years. The most recent WHO policy represents a formal departure from that approach, essentially instituting the clinical approach to the control of malaria. However, no compelling body of work demonstrates the utility of clinical management as the primary instrument of a broadly applied malaria control programme. The public health advantage gained through a focus on clinical management in lieu of vector control remains hypothetical. What explains the broad advocacy of this approach? The history of malaria and its control in the 20th century offers insights.

This review examines the retreat and resurgence of malaria in the 20th century. What has been done to control malaria? What is being done? What should be done? Discordant answers to the last question in the community of malaria workers reveal disagreement on strategies intended to bring malaria under control. Clinical- versus vector-based control strategies form broad lines of division at the foundation of strategic thinking. This review explores the basis of that division by examining the global resurgence of malaria in an historical and geographical context. The WHO's 1993 Global Malaria Control Strategy emerged from the perceived failure of its predecessor, the 1955 policy that aimed for eradication. The earlier policy was neither applied to nor relevant to holoendemic malaria in sub-Saharan Africa. The new policy maps out strategies that carry a distinctly African point of view with respect to malaria as a public health issue. Therein lies the basis of discord: a control strategy conceived in an African context may not be globally applicable. Control of disease rather than infection is sensible in holoendemic sub-Saharan Africa, where, by virtue of naturally acquired immunity, each infection carries a relatively low risk of disease or death. Resources may be focused on the minority at risk (infants, small children and pregnant women). In Asia and the Americas, however, each infection carries a relatively high risk of disease or death. Thus, late intervention in the clinical setting carries avoidable risks, especially against a backdrop of the currently poor instruments of diagnosis and treatment. Control of risk of infection by attacking the vector is a sensible and, as the retreat of malaria earlier in the century demonstrated, practical approach.

1. Malaria in Retreat: 1904 to 1969

1.1 Malaria Revealed

An obscure French Army surgeon, Alphonse Laveran, ascertained the protozoan cause of malaria in 1880.[7] Leading malariologists of the day initially dismissed Laveran's finding, instead clinging to the fashionable concept of a bacterial cause of malaria. Clinicians and scientists with access to malaria patients and having ability with the microscope gradually affirmed Laveran. He received the Nobel Prize in 1907. In 1897 Ronald Ross, then a British Indian Army medical officer, described the infection of anopheline mosquitoes fed on parasitaemic birds.[8] The prominent Italian malariologists led by Grassi confirmed the findings of Ross in humans in 1899.[9] Ross received the Nobel Prize in 1902. At the beginning of the 20th century the specific cause of malaria and its route of transmission was known with certainty.

Ross advocated mosquito sanitation as the primary means of controlling malaria. During the 1900s his theories were tested in Senegal, Ghana and Burma,[6] with either limited success or none at all. Ross persisted in his advocacy of attacking the vector and sparked acrimonious criticism from those

advocating an approach focused on clinical treatment with quinine as a means of malaria control. Former colleagues in the Indian Medical Service, such as SP James, criticised mosquito control, citing results obtained in Mian Mir (Pakistan). James[10] (as cited by Nye and Gibson[6]) stated publicly in the presence of Ross, 'I will only say that anti-malarial measures and mosquito-destruction measures are not, and have never been synonymous terms ... success in such operations has often been reported on evidence that will not bear criticism and is often ridiculous'. This point of view was justifiable at the time. There had been no compelling demonstration of the utility of vector sanitation to control malaria. The Panama Canal changed all of that. It firmly established vector control as a sound basis for disease control.

1.2 The Panama Canal

The construction of the Panama Canal by the US represented more than a triumph of engineering genius, tenacity and national will. The historian McCullough[11] wrote, '[i]n the history of finance capitalism, in the history of medicine, it was an event of signal consequence'. The importance of the accomplishment to medicine may be best appreciated by understanding the failure that preceded it. In 1881 France began an effort to construct a canal across the Isthmus of Panama. France invested $287 million and the country's national prestige. The project seized the attention of the world. Ferdinand de Lesseps, the national hero of France and builder of the Suez Canal, headed the effort.

In 1881 Pasteur's germ theory of disease had gained broad acceptance among educated people. Laveran's description of plasmodia as the cause of malaria, reported in 1880, was still 10 years from similar acceptance. Proof of mosquitoes as vectors of malaria and yellow fever would wait another 15 years. Through the 8 years of intense French effort in Panama, McCullough[11] writes, '[c]ompany doctors advised staying out of the hot sun and to avoid getting wet. ... New arrivals were warned against the night air and were told not to eat fruit'. Most people earnestly believed that virtuous living protected against diseases like malaria and yellow fever. Medical science had little to offer the builders of the canal and catastrophe ensued.

McCullough[11] wrote of the chief engineer in Panama, 'Bunau-Varilla estimated that of every one hundred new arrivals at least twenty died, and of those who survived, only twenty were physically strong enough to do any real work; "and many of that number had lost the best of their intellectual value." Others calculated that of every four people who came out of France at least two, often three, died of fever'. A cemetery at Gold Hill near the Culebra Cut holds the graves of nearly a thousand French men, women and children from that era. Many more thousands of lives were lost, mostly labourers imported from Jamaica and other French colonies. Among a peak workforce of just under 20 000, approximately 200 died each month. Even those receiving the best possible food, housing and medical care were vulnerable. The senior French engineer in Panama, Dingler, in late 1883 brought his wife, son, daughter and the daughter's fiancé to Panama, and all but Dingler were dead of yellow fever by the end of 1884.

In 1889 the effort in Panama collapsed under the weight of sickness and death. Investor confidence crumbled when reliable reports of the catastrophe reached France. The failure precipitated a national scandal that ultimately toppled the government and disgraced national figures of the time: de Lesseps, Alexandre Gustave Eiffel and Georges Clemenceau. Tropical vector-borne diseases defeated the most determined effort of one of the most scientifically and economically accomplished nations of the day.

On 15 August 1914 the ocean steamer *Ancon* transited the Panama Canal, 10 years after the Americans began construction. Perhaps the single most important difference between the French and American efforts was the certain knowledge in 1904 that specific mosquitoes transmitted malaria and yellow fever. Colonel William Crawford Gorgas had been with Walter Reed in Cuba and supervised the attack on mosquitoes in Havana that eradicated yellow fever and virtually eliminated malaria from what had been a city of very high risk. Gorgas arrived in

Panama at the outset of the effort in 1904, personally tasked by President Theodore Roosevelt with repeating the Havana accomplishment in Panama City, Colon and the Canal Zone.[11] The success of vector control during construction at Panama, unambiguously measured in the health and accomplishment of a peak workforce of 45 000, proved that a rational and methodical approach to mosquito sanitation prevented otherwise crippling tropical fevers. An important point from this history is the success enjoyed without benefit of modern insecticides or antimalarials. Attacking the specific breeding sites of known vectors using crude implements and the disciplined application of a workforce of just 4000 men, as well as minimising human contact with mosquitoes by use of nets and screens, permitted construction of a canal across 60 miles of deadly jungle. The success of Gorgas in Panama, made possible by the research accomplishments of Ross[8] and Reed et al.,[12] marked the beginning of the retreat of malaria in the 20th century and it showed the way. The stage had been set for the struggle against the vectors of malaria.

1.3 The Global Eradication Campaign

The three decades following the opening of the Panama Canal brought powerful new weapons against malaria. The aniline dye industry in Germany had produced families of compounds that cured malaria and a wide variety of chemicals that killed or repelled mosquitoes. An important success using modern larvicides and household spraying before the advent of DDT was the complete eradication of *Anopheles gambiae* from Brazil. That mosquito is the extraordinarily efficient vector of malaria in most of Africa. This work in Brazil was sponsored by the Rockefeller Foundation and directed by Fred Soper. According to Packard,[13] 'Soper's apparent achievements revalidated an approach to disease control that relied on narrowly defined technical interventions directed solely at activities of the mosquito'. The significance of this achievement may be appreciated by imagining the intense malaria transmission of sub-Saharan Africa occurring through tropical South America. Soper's vector eradication activities over 60 years ago spared millions of lives and perhaps the economic vitality of the continent.

The strategic urgencies of World War II spurred a determined effort to refine and field the new chemical weapons against malaria. The unpublished record of the Board for Coordination of Malaria Studies (5 bound volumes, Washington, DC, 1943-1946) begins with, '[w]hen the supply of quinine was suddenly cut off by the Japanese invasion of Pearl Harbor in December of 1941, our Army, Navy, and Marines faced a deadly serious problem. A long war in the most malaria-infested areas of the world lay before them and they were deprived of their only reliable therapeutic weapon, quinine'. The experiences of military forces in the European, African and Pacific theatres of action justified these concerns.[14] The strategic importance of malaria as a serious threat to military forces, reinforced by American experiences in Korea and Vietnam,[14] continues to influence malaria research across a broad front.

Chloroquine and DDT were used by the US military by 1944, and within just a few years were in use around the globe. These chemicals were inexpensive, effective and well tolerated with a good safety profile. Chloroquine cured with relatively few doses and without the sometimes severe adverse effects of drugs like quinine or atebrine. Perhaps more importantly, the history of the development of chloroquine in Nazi Germany and its wartime seizure by the US precluded commercialisation.[15] The drug was broadly affordable at the peak of its efficacy. For DDT, a single application to the interior of a home provided protection against feeding anophelines through a transmission season. The stability of DDT allowed maximum coverage of households at minimal cost. The agricultural application of DDT came later, and poisoned the land and public opinion against it.

The new weapons against malaria spawned exuberant optimism. The title of the book written by one of the pre-eminent malariologists of the middle of the century, Paul Russel,[16] 'Man's Mastery of Malaria', epitomises this spirit. The eradication of

malaria seemed feasible and the leading scientists of the day anticipated it. An uninterrupted string of extraordinary successes justified the optimism of that time. Malaria had been fully eradicated from places where it had always been endemic. For example, the eradication of malaria from the US had been accomplished, where in 1914 an estimated 600 000 cases of malaria had occurred.[17] Faust and Debakey[18] wrote in 1941, '[i]t is true that reported malaria deaths for 1940 were the lowest on record, totaling 1346 for the entire South, or a rate of 3.02 per 100,000 population'. Just 59 years later even this ebbing incidence of death, appearing 'low' at the time, seems almost inconceivable. Such a rate in the US southern states today would yield more than 5000 deaths annually. The memory of malaria as a major cause of morbidity and mortality in the US has vanished, but the eradication of malaria in the 1950s justified confidence in the weapons that accomplished the feat.

In May 1955 the World Health Assembly adopted the Global Malaria Eradication Campaign. The strategy rested on the concept of interruption of transmission by vector control followed by an emphasis on case detection and treatment. MacDonald[19] had demonstrated mathematically the feasibility of this approach to eradication. The United States Agency for International Development (USAID) played a major supporting role around the globe in terms of fiscal resources and technical guidance.[20] The accomplishment of reduced or eliminated risk of infection, virtually everywhere except holoendemic Africa, was astonishing (fig. 2). Malaria disappeared from the US, Japan, Korea, Taiwan, Spain, Italy, the Balkans, Greece and northern Africa, regions that had been seasonally malarious through history. Successes even occurred in the tropics. Malaria was eradicated across vast stretches of the South Pacific, including the tropical northern tier of Australia. Malaria disappeared from the Greater and Lesser Antilles archipelagos, with the exception of the island of Hispaniola (Haiti and Dominica). The significance of this accomplishment may be appreciated by British military statistics from the Caribbean region for the period 1895 to

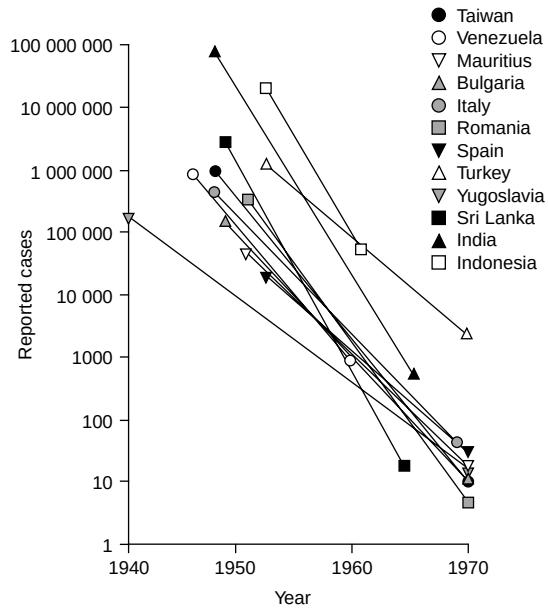

Fig. 2. The retreat of malaria between 1937 and 1969 (adapted from data reported by Jukes,[21] Sharma[22] and Atmosoedjono[23]).

1904; 104.2 malaria admissions to hospital with 1.42 deaths per 1000 European troops per year, and 120 admissions and 2.5 deaths per 1000 West Indian troops per year.[24]

Success was not limited to eradication *per se*. Malaria was brought under control across vast tropical zones where meso-, hyper- and holoendemic malaria had always prevailed. On Java, an island over 600 miles in length and home to almost 100 million people, widespread hyper- and holoendemic malaria was rolled back to a few hypoendemic foci and occasional outbreaks at scattered locations.[23] The US International Cooperation Administration (the predecessor of USAID) in collaboration with WHO and the fledgling Republic of Indonesia began DDT spraying campaigns in Java and elsewhere in 1951. In Central Java the slide positive rate fell from 24% to less than 1% between 1953 and 1959.[23] Today malaria transmission rarely occurs in East and West Java, and fewer than a dozen hypoendemic foci persist in Central Java.[25] DDT spraying campaigns in Madagascar during the 1950s

pushed malaria transmission to vanishingly low levels on the vast central highland plateau.[3,26] In Sri Lanka, the number of cases fell from over 2 million in 1946 to less than 100 in 1963.[21] In Guyana, George Giglioli supervised a DDT spraying campaign between 1947 and 1951 that eliminated malaria transmission from the heavily populated coastal area.[27] Figure 2 illustrates data reported by Jukes[21] and other sources revealing the sharp decline in reported malaria between 1937 and 1969.

Perhaps the most compelling successes of the Global Eradication Campaign, by virtue of the daunting scale of geography and human population, were Brazil and India. Brazil during the 1950s had 5 million cases each year and by 1960 the number of cases fell to just 50 000.[28] In India before 1945 an estimated 75 million new cases occurred each year, with 800 000 deaths.[22] Out of a total population of 466 million people in 1965, 373 million had been freed of risk of malaria.[29] Eradication had been achieved in 56% of the population by 1968 and only 10% remained in the DDT attack phase. In 1964 the annual parasite index (number of cases per 1000 population) was 0.00098, or roughly 1 case of malaria among 1 million people.[22] The breathtaking success of the India story is recorded in the fact that no deaths caused by malaria were recorded in 1968. The lives of nearly a million people each year had been spared and DDT spraying largely accounted for the accomplishment.

In a retrospective view that includes the current resurgence of malaria, the gain made against malaria during the period 1945 to 1965 stands out as an astonishing success by almost any measure. The degree of success appears all the more remarkable in view of the fact that few international agencies took the campaign seriously enough to offer substantial support. According to Packard,[30] '[m]any health authorities, both within and outside the Assembly, [WHO] viewed eradication as at best fool hardy, and at worst, potentially disastrous'. The USAID embraced the strategy and contributed $1.2 billion between 1950 and 1972.[20] In contrast, the WHO put up $20.3 million between 1956 and 1963, and $17.5 million of that was contributed by the US. Only $2.8 million was donated for the effort by all other nations combined.[29] The Global Eradication Campaign was, in a fiscal sense, a unilateral initiative of the US. Other leading developed nations largely rejected the campaign. France and the UK, with general accord among governments in Africa, stand out as examples.[29] The primary 'failure' of the Global Eradication Campaign may have been political rather than operational or technical. If one retrospectively supplants the unrealistic goal of eradication with one of control, the campaign appears brilliantly successful. Unfortunately, the value of the campaign has been measured in large part by its failure to actually eradicate malaria in much of the tropics, or to affect malaria in holoendemic Africa, where it was never applied.

1.4 Legacy of the Global Eradication Campaign

Unabated intense transmission in holoendemic Africa contributed substantially to disillusionment with the Global Eradication Campaign. Ironically, the abatement of malaria almost everywhere else rendered the lack of progress in Africa especially conspicuous. Today, in the long shadow of the 'failure' of eradication, global policy makers have focused upon holoendemic Africa. Authoritative strategic thinking in malaria control carries a distinctly African frame of reference. The emphasis on Africa in the World Declaration on the Control of Malaria and Global Malaria Control Strategy is explicit. According to Trigg and Kondrachine,[29] the document has been 'confirmed by the World Health Assembly in 1993, and by both the Forty-ninth Session of the United Nations General Assembly and the Thirty-third Ordinary Session of the Assembly of Heads of State and Government of the Organisation of African Unity in 1994 and 1997, respectively'. Trigg and Kondrachine[29] summarise by writing, '[t]he strategy calls for disease- rather than parasite-oriented control programmes. ... The strategy is firmly rooted in the primary healthcare approach ...'. This global strategy aims to diminish disease caused by malaria through developing effective diagnosis and treatment through

a primary healthcare instrument. The details of approach and the emphasis on Africa following this strategy may be found in the Multilateral Initiative against Malaria in Africa and the Roll Back Malaria campaign. The WHO has emphasised the application of this strategy with priority given to the creation of national malaria control programmes in sub-Saharan Africa, and the 'reorienting' of existing programmes in the rest of the world, 'in line with the principles of the global strategy'.[29]

The rationale for the new WHO policy lies in the epidemiology of disease and death caused by malaria in holoendemic Africa. The risk of severe anaemia and cerebral malaria in infants, very young children and pregnant women, especially primigravidae, is extraordinarily high in holoendemic Africa. In contrast, older children and adults have little or no risk of disease despite virtually everyone being infected at least several times per year. Thus, abatement of severe anaemia and cerebral malaria among infants, young children and pregnant women lies at the core of strategic thinking in the Global Malaria Control Strategy. Improved clinical management of disease and protection measures directed at this narrow segment of the population constitute the basis of measures intended to reduce the burden of death and disease caused by malaria.

The distinct epidemiology of disease and death caused by malaria outside Africa bears consideration in formulating and accepting control strategies. In Asia and the Americas the risk of infection is relatively low, but the risk of disease or death with infection is relatively high. This represents the converse of the African scenario. Should intervention against low risk of infection and high risk of disease or death be deferred to the point of disease? Moreover, risk of disease and death is not focused upon a narrow segment of the population. The bearing of resources intended to intervene against disease and death may thus be expected to be correspondingly diffused and less efficacious. Finally, the focus on malaria control in holoendemic Africa, driven by the fact that most malaria now occurs there, defers engagement of the threat of resurgent malaria. Malaria in other regions, largely the entire length of southern Asia and Central and South America, accounts almost entirely for the 'global' resurgence of malaria. In contrast, malaria in most of sub-Saharan Africa is hyper- to holoendemic and has been that way through history. Although increasing resistance to antimalarials threatens higher risk of severe disease and death (in infants, young children and pregnant women),[31] the absolute number of infections and the geographic range of malaria in holoendemic Africa remain stable. Addressing the spreading geographic range and increasing incidence of malaria outside Africa may require the development of intervention strategies aimed at reducing risk of infection rather than disease with infection.

2. Malaria in Resurgence: 1970 to Today

The resurgence of malaria that has occurred since the late 1960s is generally acknowledged. According to Campbell,[32] '... there has been a dramatic, worldwide increase in malaria-related illness and death over the past two decades'. According to Kondrachine and Trigg,[33] '[a]n increasing number of malaria epidemics has been documented throughout the world'. According to the Institute of Medicine of the National Academy of Sciences,[34] '[m]alaria which had been eliminated or effectively suppressed in many parts of the world, is undergoing a resurgence'. Incidence of clinical disease caused by malaria has increased in endemic areas, and malaria has encroached into areas considered free of risk for several decades.

Even in the US, recent outbreaks of malaria have occurred in California, Texas, New Jersey, New York, Michigan, Virginia and Florida[17] (unpublished data). Competent anopheline vectors are seasonally abundant in North America, and repatriated travellers to or migrants from endemic areas carrying gametocytes may infect these mosquito populations. However, imported malaria accounts for the vast majority of reported cases in the US. During the 1960s and 1970s fewer than 50 cases of malaria were reported in US civilians. This number has climbed steadily to over 500 per year at present,

and the number of actual cases is estimated to be 2 to 3 times higher.[35]

Increasingly frequent travel to and from the tropics partly explains such statistics, but these trends nonetheless reflect an overall greater risk of infection. An enduring cycle of transmission in the US or Europe leading to endemic malaria is highly unlikely because the level of healthcare available to almost all people virtually precludes the possibility of permanent infectious pools of carriers. Nevertheless, migration from endemic zones into subtropical and temperate areas lacking the highest standards of medical care indeed threatens the reintroduction of endemic malaria. Once re-established, the control or eradication of endemic malaria may prove monumentally difficult in the absence of instruments of control like chloroquine and DDT.

Clear evidence of the global resurgence of malaria emerges piecemeal from many sources, mostly WHO surveillance statistics. Although some countries still report relatively stable or declining malaria (e.g. Colombia, Ecuador, Mexico, Nepal, Bhutan, Thailand, Oman and Saudi Arabia[36,37]), encroachment and resurgence appears to be the rule. Malaria had been eradicated from Armenia, Azerbaijan and Tadjikistan in the 1960s, and only about 200 annual cases were recorded in the years before 1994, when suddenly over 3000 cases were reported.[37] Falciparum malaria has reappeared in Tadjikistan for the first time in 35 years.[37] An estimated 2 to 3 million annual cases of malaria now occur in Afghanistan.[36] There were 8700 cases of vivax malaria in Turkey in 1990, and 84 345 cases in 1994.[37] In Iraq 3400 cases were reported in 1989 compared with 98 222 cases in 1994.[36] Syria has had increasing numbers of vivax malaria cases since the 1980s.[36]

South Korea has seen a logarithmic increase in vivax malaria since it reappeared in 1993 (see fig. 3).[38] In Bangladesh 33 000 cases of malaria were reported in 1988 and 166 564 in 1994.[37] The number of infections in Bhutan has increased by about a third between 1992 and 1994.[37] In Sri Lanka the number of cases in 1982 was 38 500, and in 1987 peaked at 676 000; in 1994 273 000 cases occurred.[37] The great strides made against malaria in India during the 1950s began to deteriorate in the late 1960s. In the mid 1960s the number of reported malaria cases was always less than 200 000 per annum. In just 10 years, by 1976, the number of cases surged to 6.45 million.[22] Since that time up to the mid 1990s, the number stabilised at around 2 million cases annually. Malaria in Indonesia appears to be decreasing,[37] but this may be the result of exceptional reporting on the heavily populated islands of Java and Bali, where aggressive surveillance and vector control continue to flourish. Change in the malaria status on the outer islands of Indonesia, like most remote areas in the tropics, is largely unknown. The widespread practice of self-treatment leaves many millions of cases unreported.

In Brazil, over 700 000 cases occurred in 1991, up more than 10-fold from the number of annual cases in the early 1960s.[36] The Pan American Health Organization (PAHO) statistics reported by Roberts et al.[39] show the proportion of malaria positive blood film examinations in Brazil to have increased from less than 5% in the 1970s to >15% in the early 1990s and rising to above 20% in the mid 1990s. Similar statistics are described for Guyana and Peru.[39] Peru reported 32 000 cases in 1988 and 127 000 in 1994, and falciparum malaria has

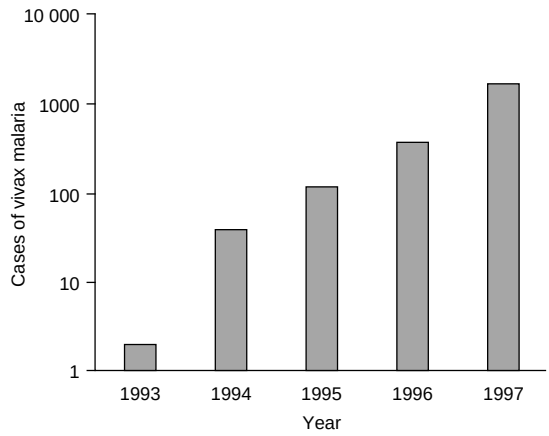

Fig. 3. Logarithmically increasing scale of transmission of *Plasmodium vivax* in South Korea near the Demilitarized Zone.[38]

re-emerged.[37] Reported malaria cases in Belize increased 3-fold between 1991 and 1994 (to 9957 cases).[37]

During the early 1970s the number of reported malaria cases in South Africa totalled less than 2000, whereas in 1993 and 1994 over 13 000 and 10 000 cases, respectively, were reported.[40] In Madagascar, malaria suddenly reappeared in epidemic fashion in 1987, quickly re-established hyperendemicity and remains so today.[41] Highland areas of Kenya have recently experienced an increasing number of epidemics of malaria.[42] Djibouti and Somalia have also experienced sharp increases in malaria rates in the wake of the disruption of social services by war.[36]

In the patchwork of data collected from many sources and by as many means, an unmistakable trend toward deterioration of the malaria situation emerges. Most of the available global data are at least 5 years old and there is little reason to expect that newer data will reveal anything but further deterioration. Malaria is spreading at an alarming rate, with more sharply rising numbers of cases in endemic areas, and encroachment into areas where it had been nearly or completely eradicated. The resurgence does not extend to the holoendemic areas of Africa for the simple reasons that its measure in incidence normally resides at ceiling values and its geographic range has never retreated.

3. What Explains the Resurgence of Malaria?

Many factors account for the global resurgence of malaria. The hierarchy of importance for these factors varies across a wide array of conditions. Political, social and economic forces may be especially difficult to sort out and often profoundly influence the risk of infection. The social upheaval of war in the tropics often provokes epidemic malaria. Likewise, region-specific physical and meteorological factors create isolated outbreaks, e.g. unusually heavy monsoons causing epidemic malaria in Rajasthan during 1994,[43] and epidemic malaria in the highlands of Irian Jaya, Indonesia during the El Nino weather anomalies (MJ Bangs and Ministry of Health, Republic of Indonesia, personal communications). Credible evidence suggests that global warming may be responsible for outbreaks of malaria at higher elevations.[44] The availability of healthcare and its quality also influence risk, as does the capacity to conduct sustainable vector control activities.

This review does not attempt a universal scope of factors that may have contributed to the resurgence of malaria. Instead, the analysis presented here accepts the premise that the increased risk of malaria relates to changes in key factors that brought about the global retreat of malaria. In that context chloroquine treatment and DDT spraying stand prominently as signposts to a broader explanation. These two substances played dominant roles against malaria between 1945 and 1965. The emergence of resistance to chloroquine and the deterioration of the national programmes that applied DDT have been coincident with the resurgence of malaria. A broad basis of evidence at least supports the view that these factors may be linked in a cause and effect relationship. In any event, examination of these factors is useful because treatment and prevention dominate aspects of public health policies for the control of malaria. Thus, examining the loss of chloroquine to resistance and the sharp decline in DDT spraying may help the development of a rationale for alternative strategies.

3.1 Resistance to Chloroquine

The emergence of resistance to chloroquine probably represents the single most important factor contributing to the global resurgence of malaria. Chloroquine now fails to cure most infections acquired in most endemic areas. The current importance of chloroquine for the treatment of malaria may be difficult to grasp given its inferior therapeutic properties compared with other standard antimalarials. The generally sustained efficacy of quinine and the availability of antimalarials such as mefloquine and halofantrine seem to offer suitable alternatives to chloroquine. The key to understanding why that is not true for almost all of the people exposed to malaria may be found in the so-

cial and economic setting of the impoverished rural tropics.

Chloroquine remains widely used in the tropics despite its inability to achieve cure (chloroquine sensitivity persists only in Central America, the Caribbean and parts of the Middle East). People living in rural areas with severely limited financial resources represent the vast majority of new malaria infections each year. In these areas chloroquine is sold over the counter at low cost. Most people in the rural tropics do not have routine access to a healthcare provider and treat themselves without benefit of medical evaluation and counsel. In this context the relatively infrequent use of quinine or other effective antimalarials may be understood. Most people taking quinine experience a range of mildly to severely unpleasant adverse effects such as tinnitus, vertigo and nausea lasting through the 5 to 10 days of several daily doses. These adverse effects often obscure the recovery from malaria. The punishing treatment costs about $5.00 (about 1 day of wages) for the 20 to 30 tablets, and few manage the good compliance necessary for cure. In contrast, a regimen of chloroquine usually costs much less than $1.00 for the 5 to 10 tablets (often about $US0.20), and the patient almost always feels better within 24 hours, with nearly complete clinical recovery after 72 hours. In Indonesia, virtually all patients experienced clinical recovery, even where the risk of RIII resistance was relatively high.[45] This was also true in Guyana, South America (JK Baird & T Tiwari, unpublished data). The high risk of recurrent parasitaemia with chloroquine therapy must be weighed against that with inadequate compliance to quinine and the likelihood of reinfection within the month or two following treatment. The self-treating poor of the rural tropics will opt for more rapid recovery at lower cost, even if incomplete and with a high risk of recurrence. Most chloroquine users fail to appreciate that inadequate treatment contributes to the risk of infection among their family members and neighbours.

In addition to poor therapeutic performance, other characteristics of chloroquine account for the heightened risk to the community in the face of resistance. Chloroquine lingers in the bloodstream long after treatment. One month after a peak concentration of about 1200 μg/L on day 2 of standard therapy, concentrations averaging about 100 μg/L whole blood remain.[46] Chloroquine treatment has no inhibitory effect on the infectivity of *Plasmodium falciparum* gametocytes to anopheline mosquitoes. Chloroquine actually enhanced infectivity to anophelines relative to treatment with pyrimethamine/sulfadoxine in humans.[47] A person treating a chloroquine-resistant infection with chloroquine will (1) feel better quickly at relatively low cost, (2) maintain an asymptomatic parasitaemia for several weeks or more, (3) cull out chloroquine-sensitive parasites, leaving resistant trophozoites to differentiate to gametocytes, and (4) remain infectious to anopheline mosquitoes. Chloroquine creates the potential for large pools of asymptomatic carriers of drug-resistant strains that readily infect mosquitoes.

Chloroquine use in the face of resistance promotes transmission. Effectively communicating this problem to lay chloroquine users may be very difficult. Solving these problems may require supplanting chloroquine with a safely self-administered drug that costs less and works better. The technical and economic difficulty of doing so has proven onerous. There is no drug now available that approaches the utility of chloroquine at the zenith of its efficacy, nor is one foreseen. The failure to develop an alternative to chloroquine for people living in the rural tropics virtually assures the longevity of the use of this drug and the problems it engenders.

Resistance to chloroquine by *Plasmodium vivax* was first confirmed in 1989 from Papua New Guinea.[48] It has since been documented in Indonesia, Myanmar, India and Guyana.[49-53] On the northern coast of Irian Jaya (Indonesian New Guinea), half of the dozens of patients evaluated were again parasitaemic 14 days after receiving supervised chloroquine therapy.[50,54] Most patients seeking treatment for confirmed vivax malaria at clinic in the same area already had ordinarily curative concentrations of chloroquine in their blood.[55]

In that region, one of the few adequately studied, resistance to chloroquine accounts for most clinical vivax malaria. This problem poses a very serious threat to public health wherever vivax malaria occurs. The potential loss of chloroquine to resistance by *P. vivax* in Asia and the Americas would almost certainly exacerbate the resurgence of malaria already occurring in those regions.

3.2 Repudiation of DDT and the Deterioration of Vector Control Programmes

In the public consciousness, DDT represents an icon of the capacity of technology to do harm. This pesticide conjures the spectre of environmental destruction and damaged health. This view fails to make the key conceptual separation of crop pest control from the spraying of interior walls in homes to control vectors of human disease.

DDT applied to the interior of homes differs radically in terms of quantities and environmental consequence from DDT applied to large tracts of arable, well drained land. In 1971, the year before the US banned the agricultural application of DDT, 71 million kilograms were sprayed in the US alone. This dusting of an appreciable portion of the US occurred every year for more than 20 years. The relative stability of DDT in the environment and its high affinity for fatty tissues established a marked bioaccumulation, notably in several raptor bird species, including the American bald eagle.[21] The most serious adverse effect to human health was reported in a study suggesting a link between DDT concentrations in human adipose tissue and risk of breast cancer,[56] but definitive studies invalidated that association.[57-59] According to the 1991 Institute of Medicine report on malaria,[60] DDT 'remains one of the most effective insecticides for malaria control efforts in endemic countries. Compared with other available insecticides, it is inexpensive and, importantly, is nontoxic to humans'. The report continues, 'the use of DDT as a residual indoor spray does not introduce DDT into the environment in amounts sufficient to enter the food chain, and thus this usage does not have adverse ecological consequences'. It is difficult to reconcile the almost complete retraction of DDT from strategic thinking on malaria control with the sentiment expressed in that report.

Social pressure not to apply DDT, sometimes extreme, comes from international aid agencies and from non-governmental environmental groups that equate synthetic insecticide use with destruction of the environment. According to Sharp and le Sueur,[40] '[s]ocial attitudes against the use of DDT have increased to the degree that certain international research funding agencies will no longer fund research in any way associated with DDT'. Cursory inspection of funding opportunities from a wide variety of agencies engaged in malaria research bears out that sentiment. In the context of mainstream scientific endeavour in the interest of public health in the tropics, DDT appears to have been eliminated as a topic, except for exploration of harmful effects. Most informed people agree that DDT creates risks to health and habitat, but debate surrounds estimation of the risk-to-benefit ratio that weighs the burden of vector-borne infectious diseases.

The general repudiation of DDT spraying, together with the shift in policy away from spraying strategies, has contributed substantially to the deterioration of vector control programmes in the developing world. Trigg and Kondrachine[29] attributed the resurgence in malaria during the 1980s and 1990s in part to the reluctance of governments to move away from 'practices used during the eradication era', including the spraying of residual insecticides such as DDT. The authors stressed inappropriate application of DDT in this context, but the assertion emphasises the extent to which authoritative agencies have turned away from vector control as a viable instrument of controlling infection. The WHO has recently launched two important initiatives representing concrete steps toward implementing the 1993 declaration of a new global malaria control strategy. The Roll Back Malaria campaign (WHO, UNICEF, UNDP and the World Bank) lists objectives that do not include vector control activities beyond insecticide-treated bed nets.[61] The Multilateral Initiative for Malaria also

fails to address vector control issues outside Africa. Diminishing reliance on insecticide spraying campaigns as an instrument of control has been described in the context of 'progress' in control by the WHO.[62] The WHO does not stand alone in this position. Many other leading agencies have actively and passively discouraged national malaria control policies that focus on the spraying of insecticides, especially DDT. The decline to collapse of vector control programmes, which has already occurred in many tropical nations, should be anticipated in this social and political milieu.

Apart from social pressures and the characterisation of the spraying campaigns of the 1950s and 1960s as a failure, what accounts for the reluctance to sustain a commitment to residual spraying programmes as an instrument of control? Some authorities obviously believe the clinical approach will better control disease in the community, or that resistance to DDT has rendered it ineffective as an instrument of control. Many authorities argue that vector control has not proven sustainable in developing nations. Compelling evidence to support these views is lacking. The best available evidence indicates that declining vector control, along with inadequate treatment and diagnosis, may be driving the resurgence of malaria outside holoendemic Africa.

3.3 Vector Control Activity and Malaria Attack Rates

A causal link between the deterioration of vector control programmes and the global resurgence of malaria is difficult to establish, but supporting evidence is widely available. In the review of the resurgence of malaria on Madagascar, Fontinille et al.[63] blamed the situation on the collapse of vector control activities, as did Mouchet et al..[3] Figure 4 illustrates data from Sri Lanka reported by Jukes[21] that is typical of that surrounding the cessation of DDT spraying. A resurgence of malaria occurs after DDT spraying programmes are terminated or allowed to deteriorate. Sharma[22] provides a detailed account of the success and subsequent col-

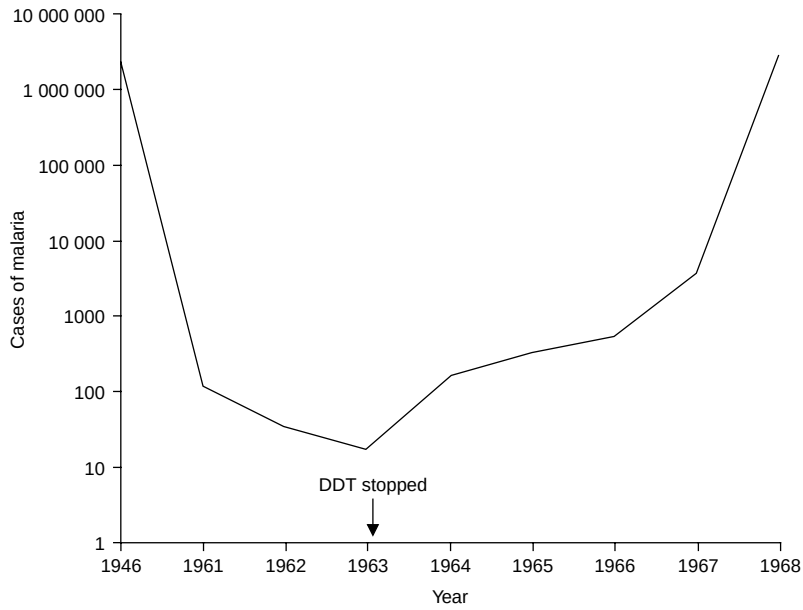

Fig. 4. Malaria in Sri Lanka before and after cessation of dichlorodiphenyltrichloroethane (DDT) spraying in 1963 (adapted from data reported by Jukes[21]).

lapse of malaria control in India during the 1960s and 1970s. This extraordinary history provides a glimpse at the complexities and operational difficulties of a large national malaria control programme. Sharma listed shortages of DDT and other operational setbacks among the major factors behind the resurgence of malaria in India. He conceded that vector resistance to DDT may have contributed, but pointed out that most important vectors in India failed to develop resistance to DDT, and malaria carried by those species also resurged, 'with equal vengeance'. Sharma noted sharp reductions in spraying activities as a permanent feature of control activities during 1992 to 1994, that '... produced a rapid deterioration in the malaria situation'.

An analysis by Roberts et al.[39] described an inverse relationship between declining DDT house spray rates and rising standardised annual parasite index, using data from nations in the Americas between 1959 and 1995 reported by PAHO. Increasing infection rates accompanied proportionately diminishing house spray rates. Correlation does not prove causality, but the analysis begs an explanation. Likewise, the view that shifting malaria control activities to diagnosis and treatment improves the malaria situation also demands proof. Unlike the launch of vector control with the accomplishments of Gorgas in Panama and Soper in Brazil, there has been no compelling demonstration of the effectiveness of the strategy for control in the primary healthcare setting. Available data offer little as a basis for confidence. For example, during a 5-year study at Antioquia, Colombia, the annual blood examination rate (ABER) increased from 17% to 82% (reflecting a shift in emphasis), while the annual parasite index (API, cases per 1000 people at risk) increased from 38 to 87.[64] This may be an artifact of more aggressive case detection, but the approach demands vindication in data demonstrating diminished risk of infection in communities where it is applied. PAHO recently attributed a 63% reduction in the *P. falciparum* crude mortality rate (from 8.3 deaths/100 000 exposed in 1994 to 3.0 in 1998) in the Americas to 'Implementation of the GMCS [Global Malaria Control Strategy] in the Region ...', i.e. case detection and treatment.[65] However, the 307 deaths reported in 1998 were based on preliminary data, and the accuracy of such statistics may vary to such an extent as to render such comparisons unreliable. Advocates of control based on clinical interventions in lieu of vector control should execute and publish the results of studies designed to test the hypotheses relevant to this issue. Such work may serve as a basis for meaningful deliberation of the issue in the scientific literature.

3.4 Vector Resistance to DDT and Resurgent Malaria

Resistance to DDT by anopheline vectors has been widely cited as an important factor contributing to the global resurgence of malaria. However, the available data fail to support that view. No study has unequivocally linked DDT resistance to an increase in malaria attack rates. Brogdon and McAllister[66] write, 'careful scrutiny of current information about vector resistance shows that the full effect of resistance on control efforts is not known'. The lack of evidence on this question raises the possibility that DDT resistance has little effect on control activities. Indeed, one hypothesis suggests that physiological resistance is of little or no consequence to control, and that so-called 'behavioral resistance' may actually enhance the performance of DDT as an instrument of prevention.

This concept was explained by Roberts and Andre.[67] Physiological or biochemical resistance is gauged by mortality, whereas behavioural resistance is a function of excito-repellency. Mosquitoes may develop resistance to insecticides either by adapting behaviours that remove them from contact or by becoming repelled at the scent. The protective effects of DDT may rely upon repellency rather than mortality, i.e. simply reducing the likelihood of contact between humans and mosquitoes without necessarily killing mosquitoes. Where this is true, the importance of behavioural resistance supersedes that of resistance to killing (as measured in standardised tests for insecticide resistance), and may promote protection conferred by

DDT spraying in homes. This was the finding in the exhaustive studies reported by Bangs.[68] It is remarkable that more than 50 years after the launch of DDT spraying on a massive scale, little is known of how the insecticide actually works. This reflects one of the true failures of the Global Eradication Campaign; its neglect of research as a necessary complement to operations left important questions unanswered.

3.5 Social Momentum for the Elimination of DDT

A global ban on DDT production is being pursued by a number of organisations dedicated to protecting the environment from human activities. The World Wildlife Fund has announced a strategic plan for accomplishing the global ban on DDT by the year 2007.[69] The United Nations Environmental Programme (UNEP) appears to be the most likely instrument of such a ban. The argument presented in this review is that DDT has been an extraordinarily useful tool against malaria. The best available data suggest that DDT indoor spraying remains effective and does not harm the environment or human health, and authoritative sources have supported this view.[60] On the other hand, leading international agencies actively discourage DDT spraying campaigns. This contradiction largely captures the schism that exists in the community of malaria workers. Residual DDT spraying as a method of controlling malaria has been repudiated by those believing a better approach is possible. Others perceive the failure to apply DDT in the face of a global malaria crisis as irresponsible in the absence of proven or practical alternatives.

Social pressure against DDT is immense. Many communities in the tropics would almost certainly reject its use in their homes. It seems likely, however, that the decision would hinge upon the severity of malaria in the community. The suddenness and cross-sectional attack of epidemic malaria terrifies. Stricken communities may embrace almost any measure of protection in the face of such a serious and immediate threat. The resurgence of malaria around the globe allows a reasonable forecast of more and more epidemics. Many millions of people with severely limited resources face a rapidly growing risk of epidemic malaria. What tools will be brought to bear on the problem? If a global ban on DDT production is realised, that tool vanishes. Tacit approval of the ban on DDT by the community of science, and the encouragement to dismantle the infrastructure of residual insecticide spraying programmes, comes with a very heavy burden of responsibility to the people facing resurgent malaria.

4. Regaining Control of Malaria

The global resurgence in malaria followed a general breakdown in malaria control programmes. The basis of failure has been attributed to the reluctance to reorient away from vector control and toward diagnosis and treatment,[29] whereas others attribute it to deteriorating vector control activities.[39] These opposing views may be reconciled through conceptual separation of malaria in Africa from the rest of the world. Controlling malaria morbidity and mortality through emphasis on diagnosis and treatment in a primary healthcare setting is a sensible approach in holoendemic Africa but not necessarily elsewhere. In Asia and the Americas, where malaria is resurgent, the best available evidence argues for control activities focused on the vector, using residual repellent insecticides in dwellings. There should be fundamentally distinct strategies for Africa versus elsewhere, but in both settings poor people treating their infections need affordable drugs that work well and safely without medical supervision. Chloroquine needs to be abolished where it no longer cures, but nothing less than a drug that works better at lower cost could accomplish that.

4.1 Conceptual Separation of Malaria in Africa from Elsewhere

Malaria in holoendemic Africa is singular in its intensity and intransigence. The global resurgence of malaria does not include holoendemic Africa because no substantial gains against risk of infection have been made (outside urban areas) on most of

the continent. North Africa, subtropical southern Africa and the region of the Horn are exceptions. Malaria control activities based largely on DDT spraying brought about a retreat of malaria in those regions, and a resurgence has followed the deterioration of those programmes.[3] Although the geographical range and number of infections in holoendemic Africa cannot be considered resurgent, the rising tide of resistance to available antimalarials threatens the effectiveness of treatment regimens. The threat of increasing risk of severe disease and death caused by drug resistance looms across holoendemic Africa, but only for those at risk, i.e. infants, small children and pregnant women.

The risk of severe disease among very young African children and primigravid women is relatively high even in the absence of drug resistance. Almost everyone else in holoendemic Africa has a very low risk of severe disease by virtue of naturally acquired immunity. The risk of severe disease among older children and adults is vanishingly low despite very high risk of infection (approximately >500% per year). Thus, control of disease in young children and pregnant women, rather than limiting risk of infection among everyone, constitutes the focus and hope for malaria control in Africa. However, the suitability of this approach for the rest of the world seems doubtful. The basis of doubt may be found in comparing the dynamics of malaria transmission and disease in Africa with that elsewhere (table I).

The most important distinguishing feature of African malaria is the risk of infection. The incidence of new infection in sub-Saharan Africa is much higher than any place else. Measured rates typically reach 8 infections per person-year.[70] The north coast of the island of New Guinea has the highest measured attack rates outside the Sahel, ranging from 1 to 5 infections per person-year.[71] In most other places the risk of infection is relatively low. The incidence of malaria in the rural Amazon of Brazil, for example, appears to be about 0.1 infections per person-year.[72] Setting aside healthcare considerations, risk of infection by *P. falciparum* generally equates with risk of death in most of the tropics. The risk of death without acquired immune or chemotherapeutic intervention is not known, but anywhere between 5% and 50% seems probable. In contrast, risk of death is a small fraction of the risk of infection in the Sahel. This distinction has far-reaching implications with regard to strategies intended to diminish morbidity and mortality caused by malaria.

A hypothetical analysis illustrates this point. An attack rate of 0.2 infections per person-year in a region of 100 000 people would yield an annual average of 20 000 cases of malaria, or each person being infected about once every 5 years. Control strategies that reduce the risk of infection by 50% would prevent 10 000 cases, each case carrying a much higher risk of death or debilitating disease relative to one in holoendemic Africa. In contrast, an attack rate of 5 infections per person-year in a region of 100 000 people would yield 500 000 infections, or each person being infected 5 times an-

Table I. Distinctions between malaria in Asia and America, versus Africa

	Endemic Asia and America	Holoendemic Africa
Risk of infection	Very low	Very high
Risk of death with infection	Very high	Very low
Population at risk of death	All ages	Infants, small children and primigravid women
Acquired immunity	No	Yes
Reduction in people infected with 50% effective control	50%	0%
Risk of control	None	Diminished naturally acquired immunity
History of vector control	Effective	Not applied
History of effective control	Yes	No
History of eradication	Yes	No

nually. Reducing the risk of infection by 50% in this instance would result in 2.5 infections per person per year. Thus, despite reducing the attack rate 2-fold, the annual risk of infection would remain in excess of 100% for all residents. The efficacy of control measures with regard to preventing infection among individuals depends upon the attack rate. Effective control measures in an area like Sumatra may have little utility in, for example, Burkina Faso. Likewise, control of malaria by focusing control resources on attacking clinical disease in Sumatra may allow otherwise preventable exposure to risk of infection with attendant high risk of severe disease and death.

An important variable in these considerations is naturally acquired immunity. The plot shown in figure 5 illustrates a hypothetical change in risk of disease in relation to exposure to infection. Up to a point where natural immunity begins to diminish risk of disease, that risk rises proportionate to the risk of infection (segment A). Natural immunity consolidates with increasing exposure to infection (segment B). Adults in holoendemic Africa rarely suffer severe disease caused by malaria (segment C). This protection is the product of poorly understood immune factors related to age and recent exposure to infection.[73] The threshold of infection (the frequency of exposure) required to maintain acquired immune protection remains unknown. One series of studies suggests that 2 to 6 infections per year may suffice.[74] If this is true, reducing risk of infection may increase risk of disease. An analysis of risk of disease under various endemic settings in Africa by Snow et al.[75] suggested such a scenario. Assuming a protective threshold of 3 infections per year, reducing the risk of infection from 5 to 1 infection per year would hypothetically render the majority of people more susceptible to disease (i.e. moving from segment C to segment B of fig. 5). On the other hand, very high incidence density of infection correlates with risk of severe malarial anaemia[76] and reducing that burden may save lives while preventing infection in relatively few (i.e. moving from segment D to segment C). Many studies of insecticide-treated bed nets demonstrate protection from death in holoendemic Africa and seem consistent with this view. The complex and poorly understood nuances of naturally acquired immunity and high risk of multiple infections each year should not confound control strategies outside Africa (New Guinea is an exception). For almost everyone outside holoendemic Africa, only segment A of figure 5 is relevant, i.e. risk of severe disease increases proportionately with risk of exposure.

The best approach to reducing risk of disease constitutes the core question for strategies for the control of malaria. The African approach may not be suitable for Asia and the Americas. Its emphasis lies on improving treatment of and diminishing exposure to infection among infants and primigravidae because the burden of severe disease lies in that relatively small segment of the population. Rela-

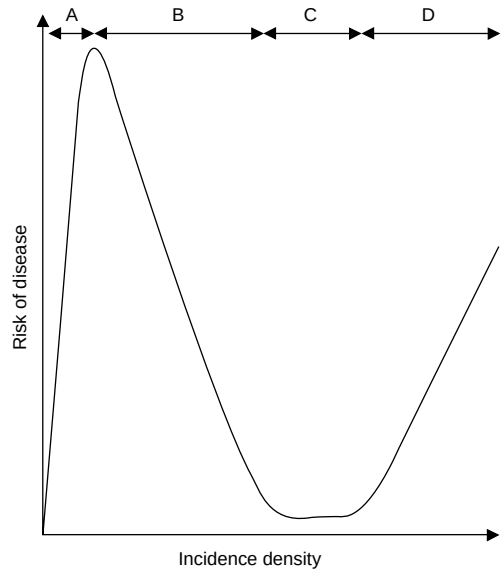

Fig. 5. Hypothetical relationship between risk of disease caused by malaria and the incidence density of exposure to infection. Where malaria is incidental, epidemic or hypoendemic (segment A), risk of disease generally equates with risk of exposure. Where malaria is meso- to holoendemic (segment B), naturally acquired immunity consolidates with increasing exposure. Where malaria is hyper- to holoendemic disease rarely occurs (segment C), except among the young, where transmission is especially intense (segment D).

tively expensive insecticide-treated bed net programmes, as well as chemoprophylactic or chemotherapeutic interventions, may be economically focused upon those most at risk. Given the intensity of exposure in holoendemic Africa, the likelihood of appreciably diminishing the number of people infected may be considered remote by conventional vector control means. In contrast, in endemic areas outside holoendemic Africa, the entire population is at relatively low risk of infection but high risk of severe disease with infection. In this setting reducing risk of severe disease through minimising risk of exposure to infection *per se*, i.e. vector control, may be tenable. As sketched in this review, vector control has a proven record of effectiveness in a non-African setting. The economic and technical difficulties of accomplishing effective diagnosis and treatment in the rural tropics, given the tools now at hand, should further encourage activities directed against the vectors of malaria.

4.2 Diagnosis and Treatment

The utility of reliable diagnosis and treatment varies with the risk of malaria among patients with fever. Where the risk is high, most people treat themselves without the involvement of a medical professional. Under these circumstances improved diagnostic capability may have little effect on the control of malaria. Even where adequately staffed clinics are available, a presumptive clinical diagnosis of malaria is often the rule. This practice poses no particular danger to patients actually infected with plasmodia, but it exposes people with other illnesses to unnecessary treatment and may delay or preclude appropriate therapy.

Reliable malaria diagnostic capability requires an investment in a trained microscopist, microscope, staining supplies and reagents, and a commitment to exercise quality assurance. Given the presumptive treatment of malaria in the absence of diagnostic services where the risk of malaria among febrile patients is high, it is difficult to see how definitive diagnosis would substantially improve the control of malaria (table II). On the other hand, effective diagnosis where the risk of malaria among febrile patients is low may be an effective instrument of control. The minimal effort (assuming the number of febrile patients would be low compared with that in a highly endemic area) nets a relatively large benefit with respect to control. Assuming the availability of effective treatment, the effort would systematically diminish the small number of disease carriers in the community and minimise transmission. Moreover, diagnostic capability enables active case detection and survey, i.e. identifying and treating asymptomatic carriers. The clinical and public health importance of a definitive diagnosis of malaria is relatively high where the risk of malaria and presumptive therapy for it among febrile patients is low. Whether used in a clinical or survey setting, the public health utility of a definitive diagnosis of malaria wilts without effective therapy.

Effective treatment for malaria is the exception in the rural tropics. The encroachment of resistance to chloroquine or pyrimethamine/sulfadoxine largely explains this problem. The eroding efficacy of

Table II. Presumptive versus definitive diagnosis of malaria as an instrument of control

	Malaria risk among febrile patients	
	low	high
Febrile cases/unit time	Few	Many
Clinical diagnosis of malaria	Infrequent	Frequent
Usual misdiagnosis	False negative	False positive
Benefit of definitive diagnosis	Appropriate treatment	Avoid unnecessary treatment
Beneficiary	Few with malaria	Few without malaria
Cost/beneficiary	High	High
Effort/beneficiary	Small	Large
Control value of definitive diagnosis	High	Low

these drugs has contributed substantially to the resurgence of malaria over the past 30 years. Although new antimalarials have appeared in the marketplace during this time, none has yet supplanted chloroquine. The characteristics of their cost, safety, tolerability and efficacy have not matched those of chloroquine. The prohibitive cost of most new antimalarials precludes immediate clinical relevance to the vast majority of people exposed to infection. Although the expiry of patent protection of these drugs may eventually see them more universally available, drugs such as mefloquine or halofantrine are less well tolerated than chloroquine.[77] There are no drugs on the market at any cost or in advanced development that appear to be as well tolerated as chloroquine. Hope for such a product in the foreseeable future appears dim.

Combining blood schizonticidal antimalarials represents an important or even imperative measure to address the important problem of resistance to available therapies. Combinations of existing antimalarials, especially those now available in rural clinics and marketplaces, hold great potential for effective, self-administered therapies for uncomplicated malaria. For example, combining chloroquine or pyrimethamine/sulfadoxine with an artemisinin derivative may rescue an otherwise ineffective therapy while simultaneously guarding against the emergence of resistance to artemisinin. This approach, as explained by White and others,[78,79] deserves vigorous investigation. Applying combined therapies to the problem should demand a high standard of proof of safety and efficacy in randomised, double-blind, placebo-controlled (i.e. monotherapy + placebo) trials. Among the many challenges to the use of combined therapies for malaria is development of the research capability needed to generate proven formulations and administration regimens. Current work on the artemisinin derivatives in combination with standard therapies such as mefloquine[80-83] lays the foundation for clinical research strategies for such endeavours in developing nations.

The availability of demonstrably well tolerated and effective combined therapies constitutes the first half of the journey to bringing the malaria problem under control. Such products should move through meaningful licensing in order to realise the full measure of impact against malaria. Licensing accomplishes essential guarantees of safety, efficacy and good manufacture, thereby protecting the product and the people receiving it. Licensing therapies requires special expertise and a commitment to meet challenging regulatory requirements.

Regulatory obstacles in the commercial development of drugs in the developed nations add tremendously to the cost of drugs in the free marketplace. Combined therapies using drugs that lack patent protection, and the intrinsic difficulties in having industry competitors share Investigational New Drug licences, largely cripple the commercial pharmaceutical industry in this arena. These industries should not be looked to for progress in developing and fielding combined antimalarial therapies. Noncommercial organisations must seize the initiative of developing licensed combinations of antimalarials. Seeing development of antimalarials through to distribution at costs that undercut the demand for inappropriately used drugs may radically improve treatment of uncomplicated malaria in remote areas of the tropics. The key is providing access to inexpensive and well tolerated therapy that can be administered with minimal medical supervision, if any at all.

4.3 Vector Control

The industry that creates insecticides uses a development paradigm that largely ignores applications against insect vectors of human disease. It is highly commercial and driven by agricultural market forces. Medically important insecticides such as malathion and various pyrethroids have been incidental products developed for agricultural applications. The licensing of insecticides for agricultural use demands minimal effect on the environment, i.e. rapid lethal activity and quick degradation. Low toxicity to plants and short residual action drive the design of agricultural pesticides, while human toxicity and noxiousness apply largely to degradation products. The active product may be

both, provided its degradation yields safe and well tolerated derivatives. Malathion typifies such products: it is mildly toxic and appreciably noxious to human beings but it rapidly degrades to innocuous products. These characteristics make it an ideal agricultural pesticide. The criteria that bring successful agricultural pesticides to the marketplace are not necessarily favourable for the control of medically important arthropods. The fact that DDT was developed as a medical insecticide and then applied agriculturally suggests that the converse may also be true. Medical insecticides should be developed independently of agricultural pesticides.

The properties of DDT, with the effective performance evident in its extraordinary accomplishments, should serve as the 'gold standard' for development criteria. The ideal pesticide for the control of vector-borne diseases would be stable in the interior environment, unstable outdoors, have a low capacity for bioaccumulation (e.g. partition poorly into vertebrate tissue) and be powerfully repellent to human blood meal-seeking insects. The safety of such a pesticide to plants would be almost irrelevant, while mammalian toxicity and tolerance would be critically important. Likewise, the disposition of the compound on surfaces in the home, rather than on crops, would appropriately narrow the search. This development equation differs radically from that for products for agricultural use. Important insecticides for the control of malaria should not be expected from the agricultural sector. Thus, it may be essential to commit to the de novo design and development of pesticides intended specifically for the control of vector-borne diseases.

The resurgence of malaria that now threatens public health through the tropics into subtropical zones demands immediate measures. New insecticides, if the challenge to develop them were taken up, would enter into long range plans for turning back malaria. The development, licensing, manufacture and distribution of a new pesticide would take at least 5 years under the best of circumstances. In the meantime, consideration should be given to the use of DDT itself. Although authoritative sources cite vector resistance to DDT as an important contributing factor in the global resurgence of malaria,[29,33,34,65] evidence supporting that contention is broadly lacking. Likewise, the propensity for DDT to accumulate in human and animal tissues is beyond doubt, but there has been no unequivocal demonstration of serious adverse effects on human health. Finally, the medical application of DDT has not been shown to cause significant harm to the environment. If DDT remains a well tolerated and effective means of preventing human morbidity and mortality caused by malaria, policy makers should offer compelling arguments for its exclusion from the practice of control.

Proponents of the ban on DDT point to its pirating from intended medical uses into the agricultural sector. This practice undoubtedly occurs, but its effect must be minimal given the relatively small quantities of DDT needed for medical versus agricultural applications. Some farmers may cheat with pirated DDT, but short of the near total capture of medical DDT for illicit agricultural use, the contamination of the environment may be reasonably forecast as minimal. Formulating 'medical DDT' with a herbicide or any other substance that farmers find intolerable on crops would largely solve this problem. The difficulty lies in securing the expertise and political will to formulate, license and manufacture medical DDT.

The rising tide of malaria may ultimately force the application of residual pesticides. Meaningful deliberation of the risks and benefits of DDT as a tool to be applied against malaria should take place. Also, a commitment to development of medical insecticides would represent an important step forward in the long term. The social pressure for outlawing DDT may be irresponsible with regard to protecting human health against diseases that kill millions, but no less so than the failure of the community of science to develop socially and environmentally acceptable pesticides specifically suited for use against medically important arthropods. It is a stunning realisation that we almost completely lack such capability in the face of the vector-borne diseases that threaten public health everywhere.

5. Conclusions

The retreat of vector control as the primary instrument of limiting morbidity and mortality caused by malaria outside holoendemic Africa is being driven by loosely conceived concepts of its failure. These are listed below.

- *Vector control is unsustainable in developing nations.* This view largely ignores the extraordinary achievements realised relatively quickly and with little or no political and fiscal support from anywhere in the developed world outside the US. The sustainability of vector control with a broader commitment to support it seems likely. The maintenance of extremely low levels of malaria on the islands of Java and Bali in Indonesia for a period of over 30 years demonstrates that committed developing nations sustain such programmes and reap their benefits.
- *DDT harms human health and the environment.* There is no direct evidence to support this concept, and much of the indirect evidence derives from the impact of the agricultural application of DDT. Despite the many millions of tons of DDT applied liberally to crops for more than 20 years (a practice that ceased in the US almost 30 years ago), exposure to DDT in the environment does not increase the risk of any human disease. Thus, it seems likely that the medical application of DDT in homes rather than dusted onto crops represents a lesser risk to both human and wildlife health. Claims of subtle health effects of DDT pale in comparison to the unambiguous and lethal threat of malaria.
- *Vector resistance to DDT has rendered it ineffective.* This concept appears repeatedly in the medical literature without substantiation. Reports of diminished susceptibility to the lethal effects of DDT by anopheline mosquitoes may not be relevant in the practice of malaria control. Excito-repellency apparently represents the basis of preventing malaria, i.e. diminishing vector contact with humans without killing mosquitoes. Credible reviews of the available evidence do not show resistance to influence DDT effectiveness in controlling malaria.
- *DDT is socially unacceptable.* This concept is largely true, but the tendency to leverage this liability against vector control in general should be resisted. The medical application of DDT is socially unacceptable in the same manner that most Americans find the metric system intolerable; the prevailing view is not necessarily correct, nor does it disqualify efforts to address it. More importantly, misconceptions about DDT do not relieve the community of science from the duty to field a better product. Reliance upon agricultural industry to develop and supply insecticides of medical importance is unacceptable.
- *DDT spraying programmes do not work.* This concept captures elements of all of the above, but also includes the failure to eradicate malaria during the Global Eradication Campaign, or to have an impact on malaria in holoendemic Africa. Even strident advocates of DDT do not argue for a return to the eradication strategy, nor would most recommend such an objective for holoendemic Africa. Nonetheless, the campaign showed that control through spraying a stable residual insecticide that repels mosquitoes achieves control. In the face of an increasingly volatile malaria situation in Asia and the Americas, this history bears recall.

The momentum to control malaria through clinical management outside holoendemic Africa carries important risks. Gauging these is difficult because the strategy represents venturing into largely uncharted territory. Diagnosis and treatment has not been the primary instrument of control across vast endemic regions, except in Africa. The important risks are summarised below.

- *Malaria is poised to spiral out of control.* A global malaria crisis may not be the time to explore untried strategies of dealing with the problem. The consequences of failure may be too great.
- *Diagnostic performance is poor in most endemic areas.* Although new dipstick technologies promise some day to improve the reliability

of the diagnosis of malaria, today these tests are relatively insensitive (sensitivity is uniformly superior only above 100 parasites/μl). In endemic areas where the author has worked, more than three-quarters of parasitaemias fall below this threshold. Expense of the dipstick assays is also a problem. Even at the cut-rate cost of $US1.00 per test, this is too expensive for most people exposed to malaria. Today, in the face of crisis, diagnostic capabilities in many endemic areas are either poor or nonexistent. Reliance upon diagnosis as a foundation of control is risky under these circumstances.

- *Treatment is inadequate in most endemic areas.* The benefit of prompt and reliable diagnosis vanishes with inadequate treatment. Chloroquine and pyrimethamine/sulfadoxine overwhelmingly dominate the antimalarial pharmacies of healthcare providers and merchants in the impoverished rural tropics. These drugs fail to achieve cure more often than not. Promising new therapies and therapeutic strategies are on the horizon, but none is broadly fielded where the malaria crisis looms. Reliance upon treatment as a foundation of control is risky under these circumstances.
- *Asians and Americans exposed to malaria are not immune.* Compared with the risk to Africans living in holoendemic areas (except possibly infants, small children and pregnant women) the risk of severe disease and death with infection in any Asian or American is very much higher. Thus, an infection in Sumatra carries a much higher probability of morbidity or mortality than one in Burkina Faso. A control strategy that does not intervene until clinical illness manifests in the patient from Sumatra seems unnecessarily risky. Moreover, the reluctance to abate risk of exposure for fear of diminishing naturally acquired immunity is irrelevant in Sumatra.

Turning back resurgent malaria requires acknowledgement that the problem lies predominantly outside holoendemic Africa. The severe and worsening malaria situation in most of that region revolves around evidence of deteriorating efficacy of chemotherapeutic agents. Malaria in holoendemic Africa remains stable but appears to be increasingly difficult to manage in the clinic or through appropriate treatment at home. The best route to addressing this problem has been set forth by the WHO 1993 policy on control strategies. In contrast, the worsening malaria situation in Asia and the Americas revolves around an alarming increase in the number and geographic range of reported infections. The two most important factors contributing to this resurgence may be clinical resistance to available chemotherapeutic agents, and a general degradation in the will and ability to conduct sustainable vector control activities. The latter problem may worsen with applying an African solution to an American and Asian problem. Separating policies for holoendemic Africa from those suitable in the Americas and Asia may help solve both problems. A focused policy with greatly intensified effort to reduce childhood morbidity and mortality in Africa has been accomplished under the leadership of the WHO. However, the resurgence in numbers of malaria cases and the encroachment of the disease into areas where it had been virtually eradicated outside holoendemic Africa may continue unabated without a parallel policy focused on that unique problem.

The best available evidence suggests that vector control programmes applying DDT or other residual insecticides offer the best hope for turning back resurgent malaria in Asia and the Americas. If the use of DDT is socially impractical, an effort should be made to develop more suitable medical pesticides through a rational process driven by medical rather than agricultural entomology needs. The criteria that drive the development of agricultural pesticides conflict with those needed for the creation of medically important products. The historical and continuing reliance upon the agricultural pesticide industry for medical applications offers no bright prospects. The lack of will to attack this problem by seizing the medical insecticide development initiative from agricultural interests may be the greatest impediment to achieving great strides against

resurgent malaria and, incidentally or intentionally, other vector-borne disease as well.

A well tolerated and affordable treatment for malaria with a high likelihood of compliance is equally important to bringing resurgent malaria under control. The heart of the problem has important parallels with the insecticides. Reliance on the pharmaceutical industry to provide such antimalarials is unrealistic. Even the US Department of Defense, which produced chloroquine and primaquine, rationally turns over hugely expensive development costs to pharmaceutical partners that subsequently market relatively expensive products, e.g. mefloquine or halofantrine. The initiative to develop well tolerated and affordable antimalarials should be seized by the governments of nations struggling with malaria and the international agencies that support their efforts in public health. Combining available antimalarials and evaluating these in rigorous clinical trials may be the best approach to accomplishing a useful product in the shortest time.

Malaria affects the poor. Solutions that poor people can afford and independently manage at the village level offer the brightest hope. This may be one of the few characteristics that solutions for Africa, the Americas and Asia share. Otherwise, these regions face fundamentally distinct problems. The poor rely upon the community of science for guidance on relieving themselves from the onerous burden of malaria. The challenge for national governments and international agencies is to offer guidance that proves practical across a spectrum of environmental, social and economic conditions. Current conditions in the rural tropics such as poor diagnosis, inadequate treatment, and an enfeebled vector control infrastructure underpin the forecast of an increasingly serious problem. Averting the onslaught of malaria thus expected in the first decade of the new millennium defines a monumental challenge.

Acknowledgements

The author is grateful to Stephen L. Hoffman, Donald J. Roberts, James R. Campbell and Michael J. Bangs for their thoughtful reviews of this manuscript. The views of the author are his own and are not to be construed as representing those of the US Department of Defence or of the US Navy.

References

1. Harrison G. Mosquitoes, malaria and man: a history of the hostilities since 1880. London: John Murray, 1978: 314
2. Krogstad DJ. Malaria as a reemerging disease. Epidemiol Rev 1996; 18: 77-89
3. Mouchet J, Manguin S, Sircoulon J, et al. Evolution of malaria in Africa for the past 40 years: impact of climatic and human factors. J Am Mosquito Control Assoc 1998; 14: 121-30
4. World Health Organization. Implementation of the global malaria control strategy. WHO Technical Report Series no. 839. Geneva: WHO, 1993
5. World Health Organization. Malaria fact sheet no.94. Geneva: WHO, 1998
6. Nye ER, Gibson ME. Ronald Ross: malariologist and polymath. London: Macmillan Press, 1996: 316
7. Boyd MF. Historical review, In: Boyd MF, editor. Malariology. Philadelphia: WB Saunders, 1949: 3-25
8. Ross R. On some peculiar pigmented cells found in two mosquitoes fed on malarial blood. BMJ 1897; ii: 1786-8
9. Grassi B, Bignami A, Bastianelli G. Ulteriori ricerche sul ciclo dei parassiti malarici umani nel corpo del zanarone. Atti Reale Accademia dei Lincei 1899 S.5; 8: 21
10. James SP. Malaria in Mian Mir. In: Jennings WE, editor. Transactions of the Bombay Medical Conference, 1909. Bombay: Bennett, Coleman, 1909: 84-9
11. McCullough D. The path between the seas: the creation of the Panama Canal, 1870-1914. New York: Simon & Schuster, 1978: 698
12. Reed W, Carroll J, Agramonte A. Experimental yellow fever. Trans Assoc Am Physicians 1901; 16: 45-70
13. Packard RM. Malaria dreams: postwar visions of health and development in the third world. Med Anthropol 1997; 17: 279-96
14. Beadle C, Hoffman SL. History of malaria in the United States naval forces at war: World War I through the Vietnam conflict. Clin Infect Dis 1993; 16: 320-9
15. Coatney GR. Pitfalls in a discovery: the chronicle of chloroquine. Am J Trop Med Hyg 1963; 12: 121-8
16. Russel PF. Man's mastery of malaria. London: Oxford University Press, 1955
17. Zucker JR. Changing patterns of autochthonous malaria transmission in the United States: a review of recent outbreaks. Emerg Infect Dis 1996; 2; 37-43
18. Faust EC, Debakey L. Malaria mortality in the Southern United States for the year 1940, with supplementary data on malaria in other states. J Natl Malaria Soc 1942; 1: 125-31
19. MacDonald G. The epidemiology and control of malaria. London: Oxford University Press, 1957
20. United States Agency for International Development. Malaria: meeting the global challenge. AID science & technology in development series. Boston: Oelgeschlager, Gunn, & Hain Publishers, 1985
21. Jukes TH. Insecticides in health, agriculture and the environment. Naturwissenschaften 1974; 61: 6-16
22. Sharma VP. Re-emergence of malaria in India. Indian J Med Res 1996; 103; 26-45
23. Atmosoedjono S. Malaria control in Indonesia since World War II. Wageningen Agricultural University Papers 1990; 90-7: 141-54

24. Curtin PD. Malarial immunities in Nineteenth Century West Africa and the Caribbean. Parassitologia 1994; 36: 69-82
25. Baird JK, Sismadi P, Masbar S, et al. A focus of endemic malaria in Central Java. Am J Trop Med Hyg 1996; 54: 98-104
26. Lepers JP, Fontinille D, Rason MD, et al. Transmission and epidemiology of newly transmitted falciparum malaria in the central highland plateau of Madagascar. Ann Trop Med Parasitol 1991; 85: 297-304
27. Reynolds DJ. The Demerara doctor. Perspectives in Health 1996; 1 (2) [online]. Available from: URL: http://www.paho.org/english/DPImag/Number2/dpi2pdemerara.html [Accessed 2000 Feb 29]
28. Cruz MA. Human migration and the spread of malaria in Brazil. Parasitol Today 1987; 3: 166-70
29. Trigg PI, Kondrachine AV. Commentary: malaria control in the 1990s. Bull WHO 1998; 76: 11-6
30. Packard RM. 'No other logical choice': global malaria eradication and the politics of international health in the post-war era. Parassitologia 1998; 40: 217-29
31. Butler D, Maurice J, O'Brien C. Time to put malaria control on the global agenda. Nature 1997; 386: 535-6
32. Campbell CC. Malaria: an emerging and re-emerging global plague. FEMS Immunol Med Microbiol 1997; 18: 325-31
33. Kondrachine AV, Trigg PI. Global overview of malaria. Indian J Med Res 1997; 106: 39-52
34. National Academy of Sciences (US). Vaccines Against malaria: hope in a gathering storm. Washington: National Academy Press, 1996
35. Greenberg AE, Lobel HO. Mortality from plasmodium falciparum malaria in travelers from the United States, 1959 to 1987. Ann Intern Med 1990; 113: 326-7
36. World Health Organization. World malaria situation in 1994: Part II, the Americas. Wkly Epidemiol Rec 1997; 72: 277-84
37. World Health Organization. World malaria situation in 1994: Part III. Wkly Epidemiol Rec WHO 1997; 72: 285-90
38. Feighner BH, Pak SI, Novakoski WL, et al. Reemergence of *Plasmodium vivax* malaria in the Republic of Korea. Emerg Infect Dis 1998; 4: 295-7
39. Roberts DR, Laughlin LL, Hsheih P. DDT, global strategies, and a malaria control crisis. Emerg Infect Dis 1997; 3: 295-302
40. Sharp BL, le Sueur D. Malaria in South Africa: the past, the present and selected implications for the future. S Afr Med J 1996; 86: 83-9
41. Lepers JP, Deloron P, Andriamagatiana-Rason MD, et al. Newly transmitted plasmodium falciparum malaria in the central highland plateaux of Madagascar: assessment of clinical impact in a rural community. Bull WHO 1990; 68: 217-22
42. Malakooti MA, Biomndo K, Shanks GD. Reemergence of epidemic malaria in the highlands of western Kenya. Emerg Infect Dis 1998; 4: 671-6
43. Shukla RP, Pandey AC, Mathur A. Investigation of malaria outbreak in Rajasthan. Indian J Malariol 1995; 32: 119-28
44. Martens WJ, Niessen LW, Rotmans J. Potential impact of global climate change on malaria risk. Environ Health Perspect 1995; 103: 458-64
45. Baird JK, Basri H, Jones TR, et al. Resistance to antimalarials in northeastern Irian Jaya, Indonesia. Am J Trop Med Hyg 1991; 44: 640-4
46. Baird JK, Leksana B, Masbar S, et al. Diagnosis of resistance to chloroquine by *Plasmodium vivax*: timing of recurrence and whole blood chloroquine levels. Am J Trop Med Hyg 1997; 56: 621-6
47. Hogh B, Gamage-Mendis A, Butcher GA, et al. The differing impact of chloroquine and pyrimethamine/sulfadoxine upon the infectivity of malaria species to the mosquito vector. Am J Trop Med Hyg 1998; 58: 176-82
48. Rieckmann KH, Davis DR, Halton DC. Plasmodium vivax resistance to chloroquine? Lancet 1989; II: 1183-4
49. Schwartz IK, Lackritz EM, Patchen LC. Chloroquine-resistant Plasmodium vivax from Indonesia. N Engl J Med 1991; 324: 927
50. Baird JK, Basri H, Subianto B, et al. Treatment of chloroquine resistant *Plasmodium vivax* with chloroquine and primaquine or halofantrine. J Infect Dis 1995; 171: 1678-82
51. Than M, Kyaw MP, Soe AY, et al. Development of resistance to chloroquine by Plasmodium vivax in Myanmar. Trans R Soc Trop Med Hyg 1995; 89: 307-8
52. Garg M, Gopinathan N, Bodhe P, et al. Vivax malaria resistant to chloroquine: case reports from Bombay. Trans R Soc Trop Med Hyg 1995; 89: 656-7
53. Phillips EJ, Keystone JS, Kain KC. Failure of combined chloroquine and high-dose primaquine therapy for Plasmodium vivax acquired in Guyana, South America. Clin Infect Dis 1996; 23: 1171-3
54. Baird JK, Wiady I, Fryauff DJ, et al. In vivo resistance to chloroquine by *Plasmodium vivax* and *Plasmodium falciparum* at Nabire, Irian Jaya, Indonesia. Am J Trop Med Hyg 1997; 56: 627-31
55. Baird JK, Leksana B, Masbar S, et al. Whole blood chloroquine concentrations with *Plasmodium vivax* in Irian Jaya, Indonesia. Am J Trop Med Hyg 1997; 56: 618-20
56. Wolff MS, Toniolo PG, Lee EW, et al. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 1993; 85: 648-52
57. Krieger N, Wolff MS, Hiatt RA, et al. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst 1994; 86: 589-99
58. Hunter DJ, Hankinson SE, Laden F, et al. Plasma organochlorine levels and risk of breast cancer. N Engl J Med 1997; 337: 1253-8
59. Longnecker MP, Rogan WJ, Lucier G. The health effects of DDT and PCBS and an overview of organochlorines in public health. Ann Rev Public Health 1997; 18: 211-44
60. Institute of Medicine. Malaria: obstacles & opportunities. In: Oaks Jr SC, Mitchell VS, Pearson GW, et al, editors. Washington DC: National Academy Press, 1991
61. World Health Organization. Four international organizations unite to roll back malaria, World Health Organization Press Release WHO/77 of 30 October 1998. Accessed at http://www.who.ch/
62. World Health Organization. Multilateral perspective on malaria begins to take shape: tropical diseases newsletter no. 55, February 1998. Geneva: WHO, 1998
63. Fontinille D, Lepers JP, Campbell GH, et al. Malaria transmission and vector biology in Manarintsoa, high plateau of Madagascar. Am J Trop Med Hyg 1990; 43: 107-15
64. Pan American Health Organization. Status of malaria programs in the Americas. XLII Report. Washington, DC: Pan American Health Organization, 1994
65. Pan American Health Organization. Report on the status of malaria programs in the Americas. HCP/HCT/149/99, August 1999
66. Brogdon WG, McAllister JC. Insecticide resistance and vector control. Emerg Infect Dis 1998; 4: 605-14
67. Roberts DR, Andre RG. Insecticide resistance issues in vector-borne disease control. Am J Trop Med Hyg 1994; 50 Suppl.: 21-34
68. Bangs MJ. Doctoral dissertation. Bethesda (MD): Uniformed Services University of the Health Sciences, 1998

69. World Wildlife Fund News. WWF urges World Health Assembly delegates to phase out deadly DDT pesticide (May 21 1999) [online]. Available from: URL: http://www.worldwildlife.org/toxics/whatsnew [Accessed 2000 Mar 3]
70. Beadle C, McElroy PD, Oster CN, et al. Impact of transmission intensity and age on Plasmodium falciparum density and associated fever: implications for malaria vaccine trial design. J Infect Dis 1995; 172: 1047-54
71. Jones TR, Baird JK, Bangs MJ, et al. Malaria vaccine study site in Irian Jaya, Indonesia: plasmodium falciparum incidence measurements, epidemiologic considerations in sample size estimation. Am J Trop Med Hyg 1994; 50: 210-8
72. Pan American Health Organization. Status of malaria programs in the Americas. XLV Report. Washington DC: Pan American Health Organization, 1997
73. Baird JK. Age-dependent characteristics of protection vs. susceptibility to Plasmodium falciparum. Ann Trop Med Parasitol 1998; 92: 367-90
74. Baird JK. Host age as a determinant of naturally acquired immunity to Plasmodium falciparum. Parasitol Today 1995; 11: 105-11
75. Snow RW, Omumbo JA, Lowe B, et al. Relation between severe malaria morbidity in children and level of *Plasmodium falciparum* transmission in Africa. Lancet 1997; 349: 1650-4
76. McElroy PD, Beier JC, Oster CN, et al. Dose- and time-dependent relations between infective Anopheles inoculation and outcomes of Plasmodium falciparum parasitemia among children in Western Kenya. Am J Epidemiol 1997; 145: 945-56
77. Baird JK, Hoffman SL. Prevention of malaria in travelers. Med Clin North Am 1999; 83: 923-44
78. White NJ, Nosten F, Looareesuwan S, et al. Averting a malaria disaster. Lancet 1999; 353: 1965-7
79. White N. Antimalarial drug resistance and combination chemotherapy. Phil Trans R Soc Lond B Biol Sci 1999; 354: 739-49
80. Price R, van Vugt M, Phaipun L, et al. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. Am J Trop Med Hyg 1999; 60: 547-55
81. Nosten F, Hien TT, White NJ. Use of artemisinin derivatives for the control of malaria. Med Trop (Mars) 1998; 58 Suppl. 3: 45-9
82. Price RN, Nosten F, Luxemberger C, et al. Artesunate/mefloquine treatment of multi-drug resistant falciparum malaria. Trans R Soc Trop Med Hyg 1997; 91: 574-7
83. Van Vugt M, Brockman A, Gemperli B, et al. Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multi-drug resistant falciparum malaria. Antimicrob Agents Chemother 1998; 42: 135-9

Correspondence and offprints: Dr *J. Kevin Baird*, Parasitic Diseases Program, US Naval Medical Research Unit No.2, American Embassy, Jakarta, FPO AP 96520-8132, USA.