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Prospects for Eradication and Elimination of Malaria: a technical briefing for DFID

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ACRONYMS

ACT	Artemisinin Combination Therapy
AMF-m	Affordable Medicine Facility-malaria
BCG	Boston Consulting Group
BMGF	Bill and Melinda Gates Foundation
CMH	Commission for Macro-economics and Health
CHWs	Community Health Workers
DALY	Disability Adjusted Life Years
DCPP	Disease Control Priorities Project
DDT	Dichloro-Diphenyl-Trichloroethane
DFID	Department for International Development
EIR	Entomological Inoculation Rate
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GIS	Geographical Information System
IPT	Intermittent Preventive Treatment
IRS	Indoor Residual Spraying
ITNs	Insecticide Treated Nets
IVCC	Innovative Vector Control Consortium
LLINs	Long Lasting Insecticidal Nets
MMV	Medicines for Malaria Venture
RDT	Rapid Diagnostic Tests
R&D	Research and Development
RBM	Roll Back Malaria
SSA	Social Security Agency
STI	Swiss Tropical Institute
UNICEF	United Nations Children's Fund
WHO	World Health Organisation

1.   EXECUTIVE SUMMARY

The goal of eradicating malaria was announced by the Bill & Melinda Gates Foundation in October 2007, and endorsed by Dr. Chan, Director-General of the WHO at the same meeting. Both accept these are long-term aspirations, and will need new tools. The boldness of this new position is very welcome, and helps to focus attention on a long-term task of developing the methods that will make eradication possible. This briefing, however, concentrates on what is achievable with current tools and contemporary epidemiology. New tools are likely to become available over time now that eradication is back on the agenda, backed by significant resources, but there are none which are likely to make global eradication possible currently near deployment.

Regional malaria elimination campaigns began in the late 1940s; the global eradication campaign began a few years later and continued until 1969. These succeeded in eliminating malaria from Europe, North America, and pushing it back a long way in parts of Asia and South-Central America. However, most of the mortality due to malaria occurs in sub-Saharan Africa north of Zimbabwe, and in this region eradication efforts were limited to relatively small-scale pilot projects. Some of these demonstration projects (such as the Garki project in Nigeria) were technically well done, and produced substantial reductions in malaria and major health gains, but did not completely interrupt transmission. The scientific conclusion was that eradication in Africa was not feasible, not because interventions were badly executed or due to insufficient commitment, but for technical reasons.

Using *current* tools there is a broad consensus that elimination of falciparum malaria (the potentially fatal species) should be technically achievable in much of mainland Asia and South America, and in many islands. It would be difficult both technically and politically, would require substantial strengthening of the basic health services, and would take many decades on a background of social and political stability. Set against these difficulties, however, are benefits this could have for other areas, including Africa. In particular the risks of drug resistance emerging from Southeast Asia, which has been the source of most drug resistance to date, mean elimination here is an attractive target. There are three phases of eradication or elimination campaigns- an initial attack phase which reduces transmission, a consolidation phase and a long tail of mopping up pockets of continuing transmission. Each has different technical challenges. All require a substantial level of resources to be committed, with only the first phase showing the rapid change in incidence that makes it relatively easy to maintain political and financial support. The last phase is likely to be the most difficult to sustain political commitment for.

Using current tools almost all technical opinion agrees that eradicating falciparum malaria in Africa is not possible, and eradicating vivax malaria (non-fatal, but common) in Asia is unlikely to be possible, and would certainly take much longer than the elimination of falciparum malaria. Shrinking the map of malaria in Africa is possible, but is likely to be difficult to sustain. If it is attempted it must not be at the expense of malaria control in those areas where most malaria deaths occur.

Recommendations to DFID, taking account of its poverty reduction priorities

For *eradication* a DFID policy which supported eradication as a long-term goal, without implying it is possible with current tools would be bold but reasonable. It is not impossible that global eradication can be achieved, only that it is not possible with current methods. Setting this aim changes the framework in which debate can occur about how we could do it, without distorting current priorities.

DFID could consider supporting local *elimination* in some areas. The significant investment needed to attempt elimination is only likely to be attractive in areas where malaria transmission is marginal making it technically feasible, the chances of reinvasion are low, and ideally where secondary gains to other areas justify the diversion of resources to this goal. These conditions may be met in parts of Asia, at least for falciparum malaria. Southeast Asia in particular is a potentially useful target to reduce risks of drug resistance emerging. In Africa it may be technically possible in the Horn of Africa region. Elimination has political risks; by definition areas where malaria can be eliminated with current tools are areas where there is already relatively little malaria, so it can look like throwing resources at a problem of low local importance. This is an issue faced by all eradication attempts during the long and costly end-game, and the length of time this would take should not be underestimated.

Any new targets of elimination and eradication should not divert attention or resources away from maximising our efforts in intensified *control,* which for practical purposes are similar to the first two phases of elimination*.* This is especially true in hyperendemic Africa where most of the deaths occur and where eradication and elimination are not currently realisable as goals. *A major attack on malaria short of elimination* is technically feasible now across many countries in Africa, and would lead to a substantial (and potentially spectacular) reduction in mortality and morbidity from malaria, especially in the areas with highest transmission, provided it could be sustained. The long-term costs of sustaining this should however not be underestimated. The ease with which control is achieved in a country would probably give a better estimate, from real data, of whether malaria elimination in that area was possible than current data.

A serious attempt at maximising control would mean significant scaling up of anti-vector methods including ITNs and indoor and controlled exterior residual spraying, and better use of, and targeting of, effective drugs. This, in turn, requires investment in the public health infrastructure, and where the private sector predominates, as it does among the poorest in many areas, considering measures such as the Affordable Medicine Facility- malaria (AMF-m). There has been far more emphasis placed historically on acquiring drugs and insecticides than supporting the systems which are needed to deploy them; system strengthening would be essential for both control and elimination efforts.

The two aims of "shrinking the map" and "reducing by 70% the malaria burden (especially child deaths)" are geographically distinct. The places where 80% of deaths occur are, by definition, the places where local elimination is impossible. There will always be tension between these two aims, and the potential for competition for funding. DFID policy will need to recognise that with a few important exceptions, the countries where 80% of deaths occur are among the poorest in the world, while those where shrinking the map is feasible are mostly less poor. Since both these aims are highly desirable, finding the right balance between them will be an important element of the consensus-building process, and any campaign.

The rest of this briefing outlines the reasons for these conclusions and provides the scientific background to the advice.

2.   ERADICATION IS BACK ON THE AGENDA

The global malaria eradication programme was formally ended in 1969 and collapsed in the 1970s, for reasons outlined below. This failure created such a deep sense of disillusion that eradication has seemed a taboo subject for malaria experts since that time. This has gone on far too long. In October 2007 Bill and Melinda Gates announced that nothing short of eradication was acceptable. This was endorsed by the Director-General of the WHO. Both the Bill & Melinda Gates Foundation and the WHO were careful to stress that this was a long-term aspiration, and that they were not arguing that eradication is possible with current tools. This announcement of an aim of eradication has two very positive implications. The first is to make it clear that developing tools to eradicate malaria is now back on the agenda, after a gap of many decades. This builds on considerable increase in investment in tools for control in the last decade, including by DFID, and the creation of agencies such as the Medicines for Malaria Venture (MMV) and the Global Fund, which have already proved successful. The second is to provide an impetus to a much bolder vision of malaria interventions than has been contemplated since almost all current technical experts in malaria started work. Both of these are welcome. The authors of this briefing are strongly supportive of this changed framework. In this document, we have tried to summarise its short-to-medium term implications: what the UK and its partners can hope to achieve within the next two decades, with current tools and those that are likely to be ready for deployment by 2020. Many of the new drugs, vector control methods, and other control tools (including possibly vaccines) that are now under development will by then be ready for deployment, but these were not originally designed with eradication in mind, and are unlikely to make a decisive difference to the feasibility of complete and final eradication in the most endemic areas of Africa.

Elimination, eradication and control - definitions

Exact definitions are given in Annexe 1.

Global Eradication has a precise definition in international health: the complete and permanent worldwide extinction of the infectious organism. For malaria this means the parasite no longer exists, can never come back, and all forms of control and treatment can be abandoned permanently.

This sense of "once and for all", of extra effort now to save greater effort in the long run, allows the promise of eradication justifiably to claim a much greater share of total health expenditure than would otherwise be regarded as cost-effective.   For example, in India in the 1960s, expenditure on malaria control amounted to 35% of the total health budget[1].   This was out of proportion to malaria's relative contribution to the burden of disease, and would never have been justified without the promise of eradication. If the aim of a permanent end to all expenditure on malaria control had been achieved, a few years of expenditure at this level would have been fully economically justified. If the risk of failure is ignored, eradication is normally highly attractive in economic terms[2]. Any analyses of the costs of malaria eradication in Europe in the 1940s would consider it an excellent investment. It is therefore well worth considering where it is possible.

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[1] Gramiccia G and Beales PF (1988) The recent history of malaria control and eradication pp1335-1378 in *Principles and Practice of Malariology*, eds. WH Wernsdorfer and Sir I MacGregor, Churchill Livingstone Edinburgh.
[2] Barrett S (2004) Eradication versus control: the economics of global infectious disease policies. Bulletin of the World Health Organization **82** 639-718.

Even if eradication cannot be achieved globally it may be worthwhile if it can be achieved in a landmass or island where reinvasion can realistically be prevented (as occurred in Europe and the USA). Malaria eradication does not eradicate the mosquito vector, but reduces the transmission of malaria to such a low level that the parasite dies out. However, this means that if the parasite should ever reinvade, the vectors will be there. This is the situation in Europe and the USA. Although environmental and socioeconomic changes have greatly reduced the potential for transmission in most areas, there are some locations where the vectors still exist in substantial numbers. For this reason, occasional cases of transmission within Europe and the USA do occur, but these are rapidly detected and eliminated. Without the health system that provides prompt detection and response, these isolated cases have the potential to initiate significant malaria outbreaks.

Strictly speaking, *elimination* means "local eradication", interruption and maintained absence of transmission in a given country. 'Elimination as a public health problem' is a looser concept which can be interpreted in different ways, but can be used to mean sustained malaria control leading to a reduction of malaria deaths to trivial levels. It is important to distinguish between these two forms of elimination.

Elimination does not claim absolute permanence or completeness, but it nevertheless promises that once elimination has been achieved, it will be relatively easy and cheap to maintain in a stable or semi-stable state. This is potentially a "killer assumption", because stability cannot be taken for granted in many settings. Thus it is always important to examine carefully what claims are being made about the stability of the post-elimination state. In the case of *elimination* meaning local interruption of transmission, the question is "how complete and robust are the barriers against re-invasion?" In most cases, natural geographic barriers (such as the ocean) and health system barriers will both be necessary. The first prevents mosquito movement and limits the number of infected human travellers to manageable numbers, the second ensures that outbreaks started by infected travellers are detected and eliminated when they are still manageably small. On the other hand, if *elimination* is intended to achieve a state of suppression short of local eradication, so that a local reservoir of infection (however small) will still exist, then the question is whether this suppressed state is expected to be stable, and if so why? One answer is that the control measures which achieve elimination are to be sustained with the same intensity indefinitely. If, however, relaxing the very costly intensity of control efforts once elimination has been achieved is anticipated, there must be some other reason to expect the situation to be stable. Like other infections, malaria is governed by the balance between their natural propensity to increase and the limitations imposed by finite resources and human immunity. This balance is a stable equilibrium: if it is disturbed, for example by a campaign that suppresses but fails to eradicate, our default expectation has to be that the disease will tend to return to its previous equilibrium as soon as these measures are relaxed, unless the underlying environment has changed substantially.

There are some vector-borne diseases with good biological reasons to hope that elimination will be reasonably stable and sustainable in the medium term. Two good examples are lymphatic filariasis and Chagas' disease[3]. In the case of malaria, however, there are no reasons to expect a state of suppression short of eradication to be stable once control measures are relaxed, except in cases where socio-economic and environmental development have occurred in the intervening period which make malaria transmission less likely. In other words, elimination must mean only two things: either local eradication or sustained suppression by indefinitely-prolonged control efforts.

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[3] In the former, *elimination* short of eradication should be moderately stable because the worms that cause the disease have a long life cycle: the parasite population will rebound but only very slowly. Chagas' disease is a zoonosis mainly transmitted between animals in the forest; eradication is therefore not possible, but we should be able to isolate people from this cycle and eliminate human-to-human transmission.

For malaria in Asia and southern America local elimination may be realistic. In much of Africa it is highly unlikely to be so, because the potential force of transmission is so great- over 100x that in Asia in many places. This is mainly due to the anopheles mosquito species which are different in Africa and other continents. The main malaria mosquito vectors in Africa are highly efficient at transmitting malaria, long-lived and hardy, take almost all of their blood meals from humans and have a wide range of sites to breed. It is the combination of these factors, and in particular these species' long lifespan, that leads to this massively higher transmission. The key concept here is the "basic case reproduction rate" of the infection, R_0, which in malaria is a function of the vector's capacity to transmit (vectorial capacity, also VC) [4]. If $R_0 = 2$, then one person with malaria passes it on to 2 others, 2 pass on to 4, etc, and in n rounds of transmission there will in theory be 2^n cases arising from a single index case. As long as $R_0 > 1$, the infection will increase until its growth is constrained by some limiting factor (such as human immunity). Conversely, if $R_0 < 1$, the disease will decline; maintaining $R_0 < 1$ is a prerequisite for eradication. A fuller discussion of the mathematical model of malaria transmission and control (the Macdonald-Ross model) is given in the annexes.

In the case of smallpox (the only disease currently eradicated, and a relatively easy target), estimates of R_0 prior to eradication vary from 3.5 to 6. The R_0 of malaria in most of Asia varies around 1, increasing in the monsoon, decreasing in the dry seasons. Malaria in lowland rural equatorial Africa is in quite a different league, with estimates of R_0 mostly in the range 100 to 1000.[5] This means that to achieve an $R_0 < 1$, which is essential for eradication, transmission has to be reduced over 100x, and this reduced transmission sustained over many decades. Current tools, even perfectly applied in combination, do not realistically allow this. True eradication is therefore mathematically almost impossible using current tools. It should be stressed that Africa is not homogeneous; in some areas almost no transmission occurs at all, including some highland areas, cities, deserts and most of South Africa, but these are next to areas where high transmission can occur and R_0 is high.

R_0 represents the potential case reproduction rate in the absence of immunity; in practice, the actual case reproduction rate is constrained by human immunity. Nevertheless, very high R_0 of malaria in Africa has implications for elimination/eradication. It means that the parasite population is capable of re-expanding very rapidly if transmission control measures are imposed and then relaxed. If this were to happen after only a short period of control, the damage caused by this re-expansion would be limited, as it would essentially be a rapid return to business as normal. If, however, it occurred after several years there would be serious risks. Currently what limits malaria deaths in much of Africa is immunity; crudely children, who catch malaria several times a year, either die of it or become semi-immune by the age of 5 years. They can acquire malaria after this, but do not die from it. In these "hyperendemic" conditions, most people are infected much of the time, but episodes of serious illness are relatively rare because of this immunity. If malaria were nearly removed from such an area by intensive control efforts over several years, the young population born in the period of control and, eventually, the whole population would become susceptible, as they would have had no malaria to boost their immunity. If the control measures were then relaxed, the disease would return very rapidly with massive transmission, in the form of devastating epidemics causing much loss of life. The longer the period of elimination, the bigger the crisis if malaria is reintroduced as the larger the non-immune population will be. It is therefore not a trivial risk: devastating epidemics of this kind have been seen in the past in Sri Lanka and even very recently in the Madagascan highlands. This

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[4] Vectorial capacity or Ro is roughly proportional to ma^2p^n where m=density of mosquitoes, a=man biting rate, p=probability of surviving a full day and n=the number of days in the extrinsic (mosquito) cycle, generally 9-10 depending on temperature, see Annex 4 for a fuller description of this model.
[5] Smith, D.L., McKenzie, F.E., Snow, R.W. & Hay, S.I. (2007). Revisiting the basic reproductive number for malaria and its implications for malaria control. Public Library of Science Biology, 5(3): e42.

potential problem has implications for the alternative strategy of sustained intensive suppression in areas of high transmission.

It is often assumed that malaria vaccines could reproduce this immunity, and so mitigate this risk. Theoretically this is a real hope for the future, but for technical reasons which are outlined briefly in the annexes, the vaccines currently in clinical trials are unlikely achieve this even if they work very well as they are aiming for a different sort of immunity.

Control is attempting to minimise the disease in a sustainable way. This is the current policy with malaria using a combination of anti-vector methods (e.g. insecticide-treated bednets (ITN) and indoor residual spraying with DDT and other insecticides (IRS), and early treatment with effective drugs such as artemisinin combination therapy (ACT).

In the African context, it is useful to distinguish between "transmission control" and "disease control". For *transmission control* (the "sustained intensive suppression" described above) the focus is on infection, and the aim to prevent people from becoming infected with malaria parasites by minimising transmission, mainly by means of vector control. This will always be a prerequisite of elimination or eradication. For *disease control*, the main focus is on detecting, diagnosing and treating the illness when infection turns to disease. Preventing the infection in the first place is given lower priority, although the realisation that insecticide-treated nets can reduce childhood mortality has seen a resurgence of interest in preventive interventions in Africa. It is theoretically possible to achieve complete disease control (in the sense nobody dies from malaria) whilst significant transmission still occurs; very few children who have malaria need die since malaria diagnosed early and treated with available effective drugs is an easily curable disease. This distinction between eliminating infection and eliminating clinical disease is therefore important, because it is in this area that there is likely to be the most room for debate about the meaning of "elimination of malaria as a public health problem in Africa".

3.   HISTORY OF MALARIA ERADICATION

The Global Malaria Eradication Campaign was a massive and remarkable effort. It was prompted by successful campaigns using DDT in the 1940s, formally initiated as a time-limited campaign by the World Health Assembly in 1955 and eventually down-graded by the same body in 1969[6].   It remains the single biggest global public health effort in history, employed substantial resources, and was well designed, well-led and in most places well-executed. It occurred during the post-war pre-independence period when centralised planning was both easier to achieve and more widely accepted than currently is the case. It failed in its ultimate goal primarily for technical reasons. Donor fatigue was a factor, but it was secondary to the technical problems, which are as challenging now as they were then.

Outside Africa, the global eradication campaign made remarkable progress in its first decade, but by the end of the 1960s major problems had emerged. The most important were resistance to insecticides (which was widespread and a major obstacle), and to drugs (which had appeared and was starting to spread, although substantially less of a problem than it is now). There were also operational problems: lack of access to remote and politically unstable areas, infrastructural weakness, and difficulty of maintaining technical standards in complex field operations. During the "consolidation" phase of the local eradication process, it proved difficult and unexpectedly expensive

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[6] It is worth noting that eradication remained the long-term goal: what was dropped was the short-term deadline that had been a key concept in the Campaign's creation.

to keep up the surveillance needed to detect persistent foci and local outbreaks of infection and stop them from spreading. In addition, this surveillance phase was turning out to be far more prolonged than had been expected. By the early 1970s, the struggle against malaria in many places outside Africa had reached, or at least seemed to be approaching, stalemate. In parts of Asia eradication came tantalisingly close -- Sri Lanka, for example, had only 18 cases of malaria in its final year of eradication compared to over 10,000 a year now. For reasons discussed below a sufficient amount has changed in Asia and the southern Americas it is worth reconsidering eradication or elimination there again. The changes have not however been in our technical capacity, but rather that increasing wealth and industrialisation have had a dramatic impact on malaria transmission; we would now be attacking a much weaker target with similar tools.

In Africa the story was different, and even more discouraging. There were some pilot eradication operations around the edges of the continent: in South Africa (where house-spraying techniques were first developed) and on islands like Zanzibar and Cap Verde. There was also effective spraying in defined areas of high population density and economic importance, such as the Copper Belt in Zambia, and the Gezira irrigation scheme in Sudan. The most informative experience, however, came from a series of spraying trials, carried out in order to measure (a) whether malaria transmission could be interrupted, i.e. brought to absolute zero at least locally, and (b) the health benefits of removing malaria as a public health problem. A series of trials were conducted in hyper-endemic areas in West and East Africa (Burkina Faso, Tanzania, Kenya, etc), culminating in an intensive and famous study by the WHO, in Garki, Nigeria. Despite the wide range of conditions and operational approaches, the conclusions from these trials were consistent[7]. In all cases, a substantial degree of malaria control was achieved: in the longer trials, the prevalence of infection in the general population dropped to a few percent, and malaria was indeed more or less removed as a public health problem. The health benefits of this were unexpectedly large: for example all-cause infant mortality was reduced by about half in all the trials where it was measured. But transmission was never reduced to zero, it persisted in at least parts of the sprayed area, and thus R_0 was never reduced low enough for long enough. Because of this, and because we were so fixed upon eradication, these trials were regarded as failures, despite the impressive health benefits.

In the early 1970s, in Garki, the experiment was repeated one last time, with no expense spared. The most powerful available insecticide was sprayed, with care to ensure the highest standards of operational quality and completeness of coverage, reinforced by mass drug administration giving an anti-malaria drug treatment to everyone. WHO experts concluded, in a very careful and influential report, that it was not feasible to interrupt malaria transmission in West Africa and sustainably achieve $R_0 < 1$, even using the best available control tools deployed in combination and in ideal circumstances because the force of transmission was simply too high and overwhelmed all current tools. Viewed in isolation the Garki project was excellently conducted but had some limitations and should not be over-interpreted. Coming on top of the previous series of trials, however, where the conclusions had been uniformly similar, the implications were considered inescapable: if eradication was not feasible in West Africa, then it was not feasible as a global goal. By that time, the global eradication campaign had already lost its "time-limited" element, mainly because of the stalemate situations that had been reached in several other parts of the world. This new evidence from Africa was the final nail in its coffin.

What has changed since then? Our weapons of attack – the insecticides and drugs – are perhaps a little better now, but the difference is probably not great. More important are the environmental and

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[7] Bradley DJ. Morbidity and mortality at Pare-Taveta, Kenya and Tanzania, 1954-66: the effects of a period of malaria control. In: Feachem RG, Jamison DT, eds. Disease and mortality in sub-Saharan Africa. World Bank, Oxford University Press, 1991: 248–263.

socio-economic changes that may have rendered background transmission levels somewhat lower than before. However, these factors are certainly not sufficient to justify any confidence that a repeat of the Garki trial would achieve complete success. Moreover, in many parts of Africa, other important factors – notably levels of civil security and infrastructure – are arguably less conducive to a technically complex sustained intensive campaign now than in the 1970s. Thus, until we have convincing new evidence to the contrary, the assumption has to be that in parts of Africa transmission cannot be interrupted with the tools we have. This is certainly the current consensus among malaria scientists.

In retrospect we must ask why, as the health benefits observed in these trials were so spectacular, did we not simply switch to a goal of sustained very intensive control? We had shown that malaria could indeed be reduced to a very low level as a public health problem in Africa, even though we couldn't drive it to extinction. A large part of the answer is that we now knew, through the experience of these trials, that the degree of suppression necessary in Africa could only be achieved with massive, intensive and unrelenting application of insecticides. Having now done this, we had good reason to doubt that efforts of this intensity could be scaled up to the necessary degree, and then maintained in the long run, throughout the vast, poor and remote parts of Africa. Doubts about operational sustainability were therefore important. Technical sustainability was, however, even more decisive. By that time, we knew from experience that our insecticides and drugs were vulnerable to the problem of resistance. We knew that the strength of selection for resistance depended on how intensively the drugs and insecticides were used, and we knew that elimination in Africa required highly intense application of insecticide without a break. We knew from large-scale experience in India, and from the more limited spraying in Africa, that in these circumstances, the capacity of vector populations to evolve resistance to successive classes of insecticide was greater and more rapid than our capacity to discover and develop new ones, and this has remained true to date. In other words, although our tools were capable of suppressing malaria to a low level when they were new, parasite and vector populations could adapt to them quite quickly. A sustained attack using such tools would instigate an arms race, in which our industrial research capacity to invent new chemical tools would be matched against the biological capacity of mosquitoes and parasites to evolve resistance. We had no reason to be confident we could win such a race, in fact, we already had experience of running out of effective insecticides in trying to control several important vectors (*Anopheles culicifacies* in India for example)[8]. All this raised the serious risk that attempts to sustain a massive level of deployment of insecticides and drugs would render our best chemicals useless.

Financial and political sustainability was an additional factor, especially towards the end of the eradication effort in the late 1960s. This revolved around the nature of the decay curve of malaria eradication. If malaria reduces by 1/3rd in the first year, 1/3rd of that in the second year etc, early gains are spectacular, and political support is easy to maintain. 20 years later the same amount of money has to be spent, but by now malaria is a small problem, and the incremental improvements, whilst still 33% year on year, are hard to demonstrate. The end-game is actually even more expensive than the early gains, because in addition to maintaining excellent control (attack) measures (which still cost the same as in the heady first few years) a robust surveillance system (never cheap) has to be introduced to identify the pockets where malaria is still being transmitted. These often occur in marginalised areas of deprivation, where lack of funds to seek treatment, lowered immunity and poor housing combine, and these are difficult to access either for control or surveillance. The final tail of eradication of any disease is always therefore much longer (in decades for malaria) than enthusiasts expect. Measles, polio, filariasis and leprosy provide four recent examples of this. Maintaining political support for a massively expensive campaign which now affects only a small and marginalised

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[8] This in not specific to insecticides. The use of chloroquinised salt in areas where vectors were difficult to target including Cambodia and the Amazon may have contributed to drug resistance emerging.

proportion of the population has proved challenging. The first malaria eradication campaign encountered these problems in multiple sites, and this was one of the main problems that contributed to the decision to end the campaign. As one delegate to the World Health Assembly put it: "It (malaria eradication) is rather like climbing a mountain: when it seems that the next crest ahead really *must* be the summit, but when you get to it you find a new prospect or continuing climb stretching away into the distance".[9]

4.   WHAT HAS CHANGED SINCE THE GLOBAL ERADICATION ATTEMPT?

New tools

Whilst there have been multiple adaptations of old tools, such as insecticide treated nets, all of which are advances and are important for malaria control and to minimise mortality from malaria, there have been few which are likely to be relevant to eradication. There are no convincing scientific reasons to believe that had the current new tools been available in the 1940s-1960s eradication would have been achieved. In the annexes there is a fuller review of some options, but some of the existing new tools are:

- *Insecticide treated nets (ITNs)*. ITNs, especially in their recent long-lasting design, are a major control tool, but certainly no more effective in most settings than IRS in the 1970s. ITNs have not reduced the prevalence of malaria infection in Africa to the degree observed in the spray trials of the 1960s, although low levels of coverage with ITNs is often an issue. ITNs are more vulnerable to being overwhelmed by emerging resistance because they are so constrained in the choice of insecticide due to toxicity concerns. At the moment, only pyrethroids are considered safe enough for use on nets in such close proximity to humans. At least two major forms of pyrethroid resistance are already spreading; one is already widespread in West and Central Africa. There is currently some talk about combining IRS with ITNs. It possible that this might indeed be slightly more powerful than IRS alone, but not sufficient to provide the substantial (10-100-fold) reduction in transmission that would be needed to improve on previous eradication efforts. It is important in this and other tools to acknowledge that the efficacy seen in early well controlled trials of any intervention is often different from the effectiveness of interventions when used in real-life settings. Effectiveness can sometimes be greater, but more commonly is less than that seen under experimental conditions.

- *Vaccines*. Malaria vaccines - at least those that currently have a good prospect of reaching an advanced stage of development - are designed mainly to protect against infection, but not to prevent development of disease if infected, or to reduce transmission. Therefore whilst they may have an important impact on health, they will have relatively little impact on malaria eradication in hyperendemic areas except at the terminal stages, where an effective vaccine might be a useful adjunct. In low transmission settings their impact will be greater, but here current tools are likely to be sufficient. Different sorts of vaccines might work, but they are not currently being developed. This technical point is expanded on in the annexe.

- *Artemisinin combination drugs* (ACTs). These are highly effective, but no more so than chloroquine in the 1960s. ACTs, do however kill not only the multiplicative blood stages of the parasite, but also the gametocytes that the parasite makes in order to infect mosquitoes. This is useful in settings where transmission is low, so a relatively high proportion of people

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[9] Litsios S (1996) The Tomorrow of Malaria   181pp Pacific Press, New Zealand

who are infectious to mosquitoes are symptomatic and therefore seek treatment (eg Thailand, South Africa). In most of Africa the reservoir of infection is in adults and older children who have no symptoms, so seek no treatment[10]; the impact of the drugs on transmission is therefore limited. Even among children less than 40% with probable malaria are treated with any antimalarial currently, let alone an ACT (UNICEF/RBM). The possible use of ACTs and long-lasting drugs in mass treatment is expanded on in Annexe 1.

- *Rapid diagnostic tests* (RDTs). These may well become important in the final stages of eradication (see below), and they have considerable potential importance in targeting limited resources and reducing mortality from non-malarial causes. Their importance for eradication in high-transmission settings is however very limited as they do not impact directly on transmission except in very low transmission settings. They do not help tip the balance in areas where eradication is currently difficult or impossible.

5.   CHANGED EPIDEMIOLOGY

In some areas of the world malaria has gone though a massive reduction in incidence since the eradication attempt. This does favour the possibility of elimination being considered in these areas. In some areas transmission is probably lower than assumed by current estimates, which are based on historical data.

Malaria used to be the leading case of childhood mortality in much of South and Southeast Asia. In many of these countries it is now only seen in fringe areas; for example in Thailand and Vietnam, only border areas have any significant malaria risks. The same is true in much of South America. This has occurred only in part because of malaria control efforts; rather it is a welcome by-product of increasingly wealthy and industrialising societies. The reasons socio-economic development has this effect are complex, and vary by country. They include changes in mosquito habitat (such as deforestation), better housing which is less mosquito-friendly, changes in human behaviour (e.g. people not sleeping in forests at night), pollution, better health services, better resourced malaria control and the general propensity for healthy people not to die from infections diseases of any sort. The combined effect of these can be substantial. In many areas malaria has essentially literally been built out of the equation, because the places where humans and anopheles mosquitoes come into contact are now very few. If the malaria eradication attempt of the 1947-1979 era had been made in these areas starting from the current base it might well have succeeded in elimination.

There is evidence that in certain parts of Africa malaria incidence is dropping. Current estimates of incidence are almost certainly overestimates in some areas. Transmission is however still many times above that seen in most parts of Asia when eradication was tried, and failed.   It remains the case that more than 80% of the world's malaria deaths occur in Africa.   Malaria in Africa could certainly be pushed down significantly further, with undoubted major health benefits, and all those involved in public health there would welcome a serious attempt to achieve this - but this is a long way short of saying elimination or eradication is feasible.

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[10] Drakeley CJ, Akim NI, Sauerwein RW, Greenwood BM, Targett GA. Estimates of the infectious reservoir of Plasmodium falciparum malaria in The Gambia and in Tanzania. *Trans R Soc Trop Med Hyg.* 2000;94:472-6.

6.   WHERE CAN WE TARGET ELIMINATION?

Elimination (meaning local eradication) is technically possible in many places near to the edge of malaria's current distribution, so 'shrinking the map' of malaria distribution. Exactly where are the best possibilities must be considered in geographical detail, since it depends both on the details of the local epidemiology and on the idiosyncrasies of local infrastructure. More comprehensive geographical detail is presented in Annexe 2. Some principles and initial ideas are nevertheless worth mentioning here.

First, it is important to re-state the points explained above: in hyperendemic areas of Africa, where more than 80% of malaria deaths occur, elimination is not possible using existing tools– or at least it cannot be sustained for technical (as opposed to financial) reasons. There is a wide consensus around this point. This does not mean it would not be possible with tools which have not been developed, but they would have to be a substantial advance on current tools. Malaria in these areas can be reduced to low levels, but only for as long as very expensive elimination efforts are maintained; as soon as they were relaxed, malaria would come back at its previous rate (and morbidity and mortality might well be higher, due to reduced immunity).   There is a real risk that this would be achieved at the cost of losing the usefulness of our best drugs and insecticides because they would have to be deployed on a massive scale, making resistance relatively more likely. Financial sustainability is also a concern, but a secondary one; if eradication is not possible technically, the financial barriers are relatively less important.

Africa is of course a large and epidemiologically diverse continent, and there are parts of it where elimination is possible. Examples include South Africa and its borders, some countries in the Horn of Africa, and the central highlands of Madagascar.   In all these areas, near the edge of malaria's distribution, transmission has always been relatively less intense and more unstable; in fact these areas would probably have achieved elimination long ago if they were not next door to much larger areas of hyperendemic transmission, which act as a massive reservoir of re-invading parasites and vectors.

Parts of Asia, however, have an even stronger case for elimination.   China is already reduced the incidence of infection to very low levels throughout the central lowlands, and is now discussing the possibility of nationwide elimination of *Plasmodium falciparum.*   In Southeast Asia, an elimination campaign could not succeed without finding a way to operate in Myanmar. However, elimination in Southeast Asia could have substantial external benefits on a global scale. We have discovered in the last few years that Southeast Asia has been a major global source of the genes which make the parasite resistant to drugs: in particular, much of the drug resistance in Africa is attributable to genes imported from the Mekong subregion. We don't know why these "hotspots" are important in this way, but we do know that resistance to artemisinin drugs, which is a global threat of frightening magnitude, has already been reported from the same area near to the Thai-Cambodia border.   Eliminating malaria in these areas would therefore potentially provide substantial benefits for other areas.

The primary target of elimination campaigns would (or should) be *P. falciparum* malaria.   The other common species in Asia and Latin America, *P. vivax*, is both much less important as a cause of death and much more difficult as a target.   It is also much harder to eradicate: it can remain dormant in the liver of the human host for years, eventually emerging to initiate a full-blown bloodstream infection up to 8 years later. Thus, the surveillance that is needed to detect and deal with such cases must be extended for a much longer period with this species. Eradication of vivax malaria is only likely to be possible when drugs or vaccines which kill the dormant liver phase, and are safe for mass deployment, are available; at present none are on the horizon.

Turning to individual countries, which are considered in greater detail in the annexe, they can broadly be grouped into four challenges, although every country is clearly different, and a single country can have many epidemiological settings.

1) Countries which are hyperendemic for falciparum malaria, with R_0 well over 50, and often in the 100s. In these areas elimination is very unlikely to be achieved and sustained with current tools, but the health benefits of a major control effort would be greatest. Most of these countries are in tropical sub-Saharan Africa.
2) Countries which have much lower rates of transmission of falciparum malaria, where elimination is a technically feasible option. Some counties in Asia (eg Thailand, Yemen) and Africa fall into this group -- the question about sustainability depends on whether reinvasion from neighbouring countries is likely.
3) Countries which have some falciparum malaria, but where vivax malaria is the predominant species. Eliminating falciparum malaria, but not vivax malaria, may be possible in these countries using current tools.
4) Countries which have levels of transmission which are not especially high, but where specific technical challenges greatly hinder the application or effectiveness of current tools. Examples include countries where much of the malaria transmission occurs outside or early in the evening (exophilic mosquitoes), with nomadic populations, with vectors already resistant to existing insecticides, or with difficult terrain and social structures for malaria control.

7.   THE PHASES OF MALARIA ERADICATION AND CONTROL

For highly endemic countries three distinct phases can be anticipated. The first two phases are the same for both substantial reduction in malaria transmission (which can be achieved with current tools, and would save many lives) and elimination/eradication. The third phase is specific to elimination; it is the longest and the most costly phase, and requires innovative thinking. A technical and operational plan for each of these phases needs to be thought through before elimination attempts are undertaken, as each has different technical challenges.

Phase 1- Attack phase, aiming rapidly to reduce malaria transmission. This requires proper mapping of risk, followed by highly effective application of a combination of all methods which have a substantial impact on transmission. It is likely to require some combination of IRS and other anti-vector methods with mass drug administration (see annexe on new tools). The technical lessons learned during the global eradication campaign will help to guide this. Maintaining political and financial support in this phase is generally relatively easy since early gains are often spectacular, and it can confidently be predicted that there will be a significant reduction in morbidity and, in settings where many children die from malaria, mortality. In some settings it may be possible to achieve an R_0 of less than 1 in this phase, in some settings with current control tools this is not likely to be possible; this depends mainly on the prexisting R_0, as well as the technical challenges which vary by country. In some countries (for example those with mosquitoes which bite outside, or those with very difficult terrain or nomadic populations) new methods would be needed.

Phase 2 - Initial consolidation. The anti-vector measures need to continue to be applied at the same intensity. Even if elimination is not the goal some form of surveillance needs to be instituted, both to identify hotspots where transmission has not been brought down, and because the high selection pressure due to massive anti-vector and anti-parasite measures will accelerate resistance, which must be identified early. In addition the health services of highly endemic countries need a massive change of emphasis, from a model where the default position is that all febrile illness in children is treated as malaria unless it obviously is not (the current situation) to one where only those with

parasites are targeted with antimalarials. As time goes on an increase in the number of adults with severe malaria (currently a relatively small problem) can be anticipated. The scale of culture change this will require should not be underestimated, but if it is not achieved the attempt will be unsustainable. Maintaining political support is more difficult in this phase; the incremental gains are difficult to see.

Phase 3 - The end-game. This is the most difficult phase, and the one where the greatest degree of innovation is required. If elimination is the aim the planning for this phase is needed at the outset. It is only realistic to consider if R_0 has been brought below 1 in a country or region as a whole. On the positive side at this stage adding interventions which have even a limited impact on transmission is helpful -- drugs with anti-gametocidal activity, vaccines and other interventions which have a relatively modest impact are all likely to be useful as any further reduction will speed the time to elimination. On the negative side, experience from all the eradication campaigns (malaria, smallpox, polio, guinea worm, leprosy, filariasis) shows that this stage is always significantly longer, more technically challenging, more expensive and more difficult to sustain politically than those who embark on elimination or eradication anticipate. It places the greatest demands on the health system as it requires surveillance and response. All the anti-transmission measures and changes in health services need to be maintained. A robust surveillance system which covers the whole population, especially the hardest to reach areas where outbreaks are most likely is needed, along with a rapid response plan. In practice in this phase it is likely that transmission is very low (below $R_0=1$) in the general population, but that there are pockets of transmission which is well above this, and until all of these are identified and dealt with elimination cannot occur. Initially these may be large easily-identified areas, but as time goes on they become smaller and more fragmented, making detection more difficult. Maintaining support for this phase, which for malaria is likely to cost more than the other phases at a time when malaria is not seen as a major threat by the general population, proved challenging in the global eradication effort and is unlikely to be easier now. How long it would have to go on for depends partly on the technical excellence of the programme, but much more on the pre-existing force of transmission. It would be rash to plan for this phase to take less than decades in areas where the natural malaria transmission in the absence of enhanced control measures has an R_0 of greater than 50 (in practice many parts of Africa).

It is worth stressing that the first two phases of elimination are worth doing whether or not the last phase is attempted. Phase 1 and 2 of malaria elimination and maximising control look much the same. They would achieve a considerable degree of control, and save millions of lives, if well done, and they are certainly achievable with current tools. For practical purposes this would in many settings achieve elimination of malaria as a public health problem. Phase 3, which is the one over which most technical doubt hangs in high-transmission areas, should be seen as a separate challenge requiring a new approach. The difference between elimination (where it is technically possible) and control often comes often down to the question: given competing health priorities how much are we prepared to spend to achieve the final 10%?

8.   HEALTH SYSTEM AND DELIVERY STRENGTHENING

A prerequisite for any attempt at malaria elimination would have to be strengthening of health systems. At the same time, control of malaria in hyperendemic areas could have a very positive impact on the healthcare systems for all. The initial phase of attack can be delivered through vertical structures, although there are arguments for and against this. The second two phases would in many settings, especially in Africa, require substantial strengthening of medical and diagnostic services.

The primary reason for this is the need to detect and suppress outbreaks in order to prevent them from spreading. This involves far more than treating cases that turn up at the clinic (passive

detection), but rather an elaborate and extended follow-up system: tracing the case to its origin, checking everyone in the house (and often neighbouring houses) for current infection, and then an extended period of active surveillance to detect further cases that may be already incubating in the rest of the community. Focal spraying is often included in this response. If these activities are not prompt and thorough, a small outbreak can become an incipient epidemic. All this is best done as an extension of the existing health system; the disadvantages (e.g. cost) of setting up parallel malaria-specific systems were amply illustrated in the first Global Eradication Campaign.

In addition, there are good practical reasons for considering a strong health service to be a pre-requisite, including:

a) The further malaria elimination progresses, the smaller the proportion of people protected by immunity, so the greater the proportion likely to develop life-threatening disease when infected.
b) The further malaria elimination progresses, the greater the proportional burden non-malarial causes of fever will represent: it will no longer be acceptable to treat all fevers as malaria because of the financial cost of over-treatment and the health cost of mis-management of other infections
c) Stock-outs of drugs and other materials, currently a common occurrence, could have a substantial and dangerous impact on elimination efforts in areas of potential high transmission. Securing supply lines and substantial improvements in forecasting of drug needs is essential whether or not elimination is undertaken. This is more important with the ACT class of drugs, which have a relatively short shelf-life compared to other antimalarials.
d) In Phase 3 of any eradication attempt the only realistic method of providing passive case detection of upswings in malaria is the formal healthcare system. This is because this phase has to be assumed to go on for many years in high-transmission settings (very possibly decades), at a point where malaria would by definition be a small problem, so maintaining a large parallel system would become politically hard to sustain against competing priorities. Currently few health systems in sub-Saharan Africa except that in South Africa could realistically achieve this.

Phases 2 and 3 of elimination therefore require health systems which are able to provide appropriately trained and motivated staff and the drugs and other supplies needed to diagnose and treat this illness.

It might be tempting to achieve "quick wins" by creating disease-specific delivery structures. The very weak state of health services in much of Africa is well recognised. There are however two good reasons to consider seriously how new resources for malaria control can be deployed in support of health system strengthening. First, there is the opportunity to use new resources for malaria control to strengthen the systems, such as supply and logistics systems and health information systems, required to deliver a range of health interventions. For example, addressing supply chain problems to ensure regular availability of ACTs in health facilities could also improve the availability of essential commodities for other conditions, e.g. antibiotics for treatment of bacterial infections. Second, the activities involved in the shift to Phase 3 (passive case detection and timely response) would necessarily require a health system response: it is simply not efficient to mount an independent and duplicative system for monitoring and rapid response to malaria outbreaks, particularly when the timeframe involved is considerable (decades) and when new malaria cases would be a declining, and eventually very small, share of total utilization. Lessons from the previous eradication campaign point to the critical importance of ensuring that the surveillance phase receives adequate technical attention and funding over an extended time period.

Effective malaria elimination/eradication would require addressing key weaknesses in all of the core health system elements: service delivery, information systems, systems for distributing commodities and supplies, health workforce, health care financing and governance. Challenges of service

delivery were alluded to above: responding to these requires bringing together the elements of appropriately trained, remunerated, motivated and equipped health workers, a reliable system for distributing effective antimalarial drugs and other commodities to health facilities, and information systems which are able to provide timely information and feedback. In addition, there is a need to address concerns about resource availability and governance. In a world of expanded funding for malaria, narrow cash constraints are not expected to bind. However, the ability to spend this cash may be constrained by weaknesses in systems for planning and execution: these need to be addressed through strengthened planning and management systems. Furthermore, user fees in their various guises (formal fees or informal responses to insufficient health worker salaries) are known to create barriers to timely care seeking. Adopting health financing mechanisms which do not impede access, especially by the poorest, is a priority.

A final issue directly relevant to elimination relates to health system governance, particularly relating to the private sector which, in the case of malaria, is the source of treatment for around 50% (range 10 to 80%) of patients with fever. This is mostly not in the formal private healthcare system, but rather small shops and other retail outlets for antimalarials which are the current source of most antimalarial drugs consumed, especially by the poorest. Ensuring that these providers are informed about correct treatment and have access to affordable and effective antimalarial drugs is critical. In addition, both control and eradication strategies rely on effective health sector governance. This might include regulation of the types of antimalarial drugs available (in particular, measures to reduce the use of artemisinin monotherapy); and other complementary and voluntary measures such as training, accreditation, social marketing, etc. to ensure that the actions of private providers contribute to, rather than undermine, the public's health.

The health-service improvements may well be self-sustaining, and certainly would have a beneficial effect on healthcare for other diseases. A reduction of the burden on the health services, especially formal paediatric services, would accompany any serious reduction in incidence of malaria as malaria constitutes a substantial proportion of current outpatient and inpatient work. This has the opportunity to create a virtuous circle, where reducing incidence reduces strains on the service, which improves service levels overall, which in the later stages of elimination might lead to further reductions.

9.   WHAT MIGHT ERADICATION COST?

Three main categories of cost can be identified which are relevant to the question of the resource requirements and cost-effectiveness of eradication: the costs of the attack phase (Phase 1); the costs of consolidation/maintenance (Phases 2 and 3); and the costs associated with the risk of development of resistance to existing malaria control tools when deployed for eradication.

Attack phase: It is possible to attach an indicative cost to the attack phase of an elimination/eradication effort. This requires identification of the following: a list of specific countries, the size of the population at risk, the scale and intensity of existing control efforts, specification of the eradication strategy (which interventions, how deployed (frequency, targeting approaches), delivery systems), and information about the intensity of malaria transmission. With these data it is possible to apply unit costs of interventions to estimate the incremental costs of new initiatives. More information is now available about the costs of vector control strategies in a variety of settings (IRS in Zanzibar, Angola, Uganda, Equatorial Guinea, South Africa and Mozambique[11]; and ITNs distributed through a

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[11] Yukich et al., Schwabe et al., Worrall et al. Presentations at the American Society of Tropical Medicine and Hygiene, November 2007

range of delivery mechanisms in 5 countries (Malawi, Tanzania, Togo, Senegal and Eritrea[12]). Less information is available about the costs of vector control interventions outside of SSA, and almost nothing about the costs and cost-effectiveness of other measures such as environmental control methods. The costs of scaling up access to ACTs have been estimated for the IOM and adapted for the AMF-m, though little is known about the costs of delivering ACTs outside conventional channels. Non-linearities in marginal costs would also need to be considered, though available data do not permit this analysis.

It is also necessary to consider what health system strengthening is required to enable the delivery of interventions. Very few empirical data are available about these costs. In the case of the costs of the essential service package estimated for Commission for Macroeconomics and Health, intervention costs were inflated by 15% to reflect the costs of needed systems strengthening. The addition of these costs (increased salaries, higher levels of management, adequately funding existing services) had the effect of doubling the district-level costs.

Consolidation/maintenance phase: A robust surveillance and response system is a critical component of any elimination effort. As outlined above, this was found to be both expensive and difficult to sustain in the earlier eradication campaign. Estimating the cost of this component is even more difficult than costing the attack phase because it will also be highly dependent on the capacity of the health system and will also be required over a longer time frame. The interventions required and their associated costs will be highly context specific.

Costs of resistance: Alongside the costs of delivering interventions and sustaining a surveillance system there are the costs associated with the risk of development of resistance to existing and new tools. As noted above, there are reasons to be concerned that selection for resistance is more likely with the intense application of interventions that would be required under an eradication strategy. The potential costs are those related to the need to develop, test and apply new, potentially more expensive, tools (new insecticides, new drugs, etc), and the potential human costs associated with malaria rebound among a population that has lost its acquired immunity.

Cost and cost-effectiveness considerations: Any economic evaluation of eradication needs to take into account the benefits as well as the costs. These will include health benefits (cases averted, effects of prolonged use of effective drugs if elimination can be achieved in Asia where drug resistance is emerging) and broader economic benefits if elimination/eradication results in increased investment, tourism, etc. Changing the way that drugs are deployed (e.g. active case screening and detection, greater use of diagnostics) could also have the effect of reducing the speed of development of resistance compared with, e.g. widespread presumptive treatment. Dynamic transmission models are needed to examine the complex interactions between the ways that malaria control tools are applied and the development of resistance. The inclusion of non-health outcomes will require a cost-benefit rather than a cost-effectiveness approach to economic evaluation. In addition, there will be important issues around what time horizon to use, since the main outcome is the (discounted) net social benefit over time.

Existing data on cost and cost-effectiveness of interventions have primarily been generated with an eye to personal protection, and estimates are largely derived from static rather than dynamic models, the latter including the effects of intervention on transmission. Using these static models, DCPP estimates of the mean cost/DALY averted in a high-transmission, low income African setting are $11-

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[12] Yukich et al. 2007. Operations, cost and cost-effectiveness of five insecticide-treated net programmes (Eritrea, Malawi, Tanzania, Togo and Senegal) and two indoor residual spraying programmes (Kwa Zulu Natal and Mozambique). Swiss Tropical Institute.

17 for ITNs, $9-12 for IRS (one round / year) and $17-24 for IRS (2 rounds per year). A widely used threshold is that interventions costing less than $150 per DALY averted are considered to be "cost-effective". However, new analyses would be needed to model cost-effectiveness under an eradication scenario because of the need to consider a range of potential resistance trajectories, and to explicitly include effects on transmission among the outcomes. A number of transmission models are now in progress or available and could be adapted to model the cost-effectiveness of different eradication strategies.

Costs of expanding coverage of malaria control: The cost of expanded malaria control efforts has been estimated by BCG for the Gates Foundation and WHO has also produced a costing model for sustained malaria control in 81 most-affected malaria endemic countries[13]. The WHO estimate includes the costs of scaling up vector control (LLINs), IPT in pregnant women, use of RDTs and ACTs for case management, management of severe and complicated malaria, and epidemic prevention and response. The incremental costs of these interventions (excluding the costs of running the health system) were included. Estimates of the cost of health infrastructure strengthening were made using the classification developed in the CMH costing. These measures included training for staff and CHWs, communication/health information, and monitoring and evaluation. The cost of scaling up to full coverage was estimated to be US$3.8 to 4.5 billion per year. The BCG estimate is around $7 billion per year. Both figures probably underestimate the costs of health system strengthening. This type of costing exercise is primarily useful for assessing global resource availability and benchmarking against needs, and more detailed country-level analyses would be needed to refine these estimates to be useful for country level programming.

There is one critical point that must be accepted at the outset of any eradication or elimination campaign: when eradication or elimination is the goal, the costs are likely to remain high throughout the course of campaign, even when the goal is near and the disease is rare. Generally costs actually increase at the end of an eradication campaign because of the cost of intensive surveillance. Eventually, the marginal cost per (observed) case will be exceptionally high. So it is important we do not embark on this course unless we are confident we have the determination to carry on to the end. A related point pertains to the issue of political commitment: the decision to continue eradication will have to be made by different people from those who make the decision to begin it; elimination even in Asia, would take many decades. This political problem was very apparent in the global eradication attempt.

10. WHAT ARE THE RISKS OF PROMISING AND FAILING IN ERADICATION?

Five types of risk can be identified:

1) Political: After the first eradication campaign succeeded in raising great hopes, the realisation that it was not possible after all brought an equal measure of despair among those responsible politically and financially for malaria control. There followed two decades of neglect of malaria and gross underfunding. Existing cost-effective control measures were simply not deployed. There was also a strong reaction against vertical disease-specific approaches of all kinds: Primary Health Care became the dominant paradigm for tropical public health. During that time, malaria was neglected not because its importance in Africa was not realised, but because of disbelief that anything worthwhile could be done, beyond prompt treatment of cases. It is only in the last decade that malaria control has again been seriously resourced.

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[13] Kisewski et al. 2007. Estimated global resources needed to attain international malaria control goals. Bulletin of the WHO 85(8): 623-630.

2) Accelerated resistance to insecticides and loss of our best drugs: Any attempt at eradication or elimination will involve intense application of insecticides and drugs: the more intense and prolonged the campaign, the stronger the selection for resistance.   The aim, of course, is to achieve eradication before resistance comes and to produce new tools at the necessary rates to replace failing ones, but this rests on optimistic assumptions.

3) Epidemics: When intensive control is applied effectively in an area of very high transmission intensity, malaria can return very quickly if the forces that suppress it are ever withdrawn. The effects of this will be all the worse if the suppression has been sustained for a few years, so that the human population has lost most of its immunity.   Devastating epidemics have occurred in these circumstances.

4) Diversion of resources: Eradication or elimination is much more costly and labour-intensive than high-level control (meaning the best available control not aiming at elimination). If it is assumed that at least some of this extra expenditure (the gap between high-level control and elimination) is money which would otherwise have been spent on other important health priorities (HIV, sanitation, malnutrition etc) the choice to eliminate eradicate could divert both financial and human resources in a way which has an overall negative impact on public health.

5) Geographic diversion: There is a risk that to maintain an appearance of progress resources will be allocated to those areas where dramatic shrinking of the map is most realistic- which by definition are those areas where the burden of disease is smallest.

11.   ARE THERE ANY GROUPS OR REPORTS PROPOSING OR LOBBYING FOR ERADICATION, AND COMMENTS ON THESE?

Yes. These fall into several broad groups.

1) Those who take a long view of eradication. They accept that current tools are insufficient to bring about eradication now, but that if eradication is back on the agenda, and properly resourced, the current technical and operational barriers to eradication can be overcome by a combination of research into new tools and learning-by-doing. They accept this is a very long-term goal. This seems a realistic approach. It gets around one serious barrier to eradication in the future -- that nobody has been developing tools specifically with eradication in mind. The Bill & Melinda Gates Foundation and, arguably, the DG of the WHO are in this group. BMGF have considerable resources to back it up.

2) Those who believe that the barriers to eradication are mainly political, rather than technical, and that we could eradicate using current tools if we just resourced it better and tried harder. This is not the view of the great majority of malaria technical experts (including these authors).

3) Some endemic countries are very enthusiastic about malaria eradication, which understandably plays well politically in highly malaria-endemic countries. Generally there is an inverse relationship between enthusiasm for eradication and technical feasibility; elimination is most difficult in those countries where it is most a problem, but these are the countries where the idea of eradication is inevitably most politically appealing. A few countries which themselves have low levels of malaria are enthusiastic for elimination in their neighbours, as this would provide a cordon sanitaire for them.

4) Those who propose elimination in particular geographical areas. This makes some sense where there is some additional knock-on gain (e.g. elimination in Southeast Asia may slow the emergence of drug resistance) and the areas are not contiguous with highly endemic areas from which reinvasion of malaria will inevitably occur. Where it is proposed in countries which border highly endemic areas the logic is less easy to follow.

There are also groups who feel (as others did in the 1950s) that our "helplessness" in the face of intense malaria in Africa should not prevent us from doing what can be done elsewhere. There is some force to this argument. We are not "helpless" in Africa: there is much to be done, and hundreds of thousands of deaths which could be prevented using tools we have, which are not properly resourced or deployed. The fact that eradication is not currently possible in parts of Africa does not in itself mean that elimination or eradication should not be considered elsewhere, provided it would be sustainable in these areas.

12.   ADVICE TO DFID ON ITS POSITION ON MALARIA ERADICATION, ELIMINATION AND CONTROL

It is easy to forget that the failure of the first eradication campaign was primarily technical, and only secondarily political. We have some new tools, and have lost some old tools, but there has been no technical breakthrough which makes malaria eradication now significantly more realistic than it was in the global eradication era. What has changed is that malaria transmission in much of Asia starts at a far lower base now than it did when the eradication attempt began. What unfortunately has not changed is that malaria transmission in parts of Africa is over 100x that of areas where eradication was achieved. Even perfectly applied for many decades (a considerable assumption), current tools are not sufficient to overwhelm this force of transmission.

For *eradication* a DFID policy which supported it as a long-term goal, whilst accepting it is not possible with current tools, would be a bold move but a reasonable one. It is not unthinkable that global eradication can be achieved, but it is not possible with current methods. Opening up the possibility changes the framework in which debate can occur about how we could do it, without distorting current priorities. It would however be long (even with excellent tools more than the lifetime of these authors), costly, and potentially politically difficult to sustain towards the end when the visibility of malaria as a public health problem had diminished.

For *elimination* DFID could reasonably consider whether this is worth supporting, but the significant investment needed to attempt this is only likely to bring adequate rewards in areas where malaria is marginal (it needs a final push over the cliff) making it technically feasible, the chances of reinvasion are low, and ideally where secondary gains to other areas justify the diversion of resources to this goal. These conditions may be met in parts of Asia, at least for falciparum malaria. Within Africa it may be true of the Horn of Africa region, at least technically (but possibly not politically; elimination requires sufficient political stability over some decades to maintain a major systematic campaign). Southeast Asia in particular is a potentially useful target to reduce risks of drug resistance emerging. Elimination using this logic has some political risks; by definition areas where malaria is realistic to eliminate are areas where there is already not much malaria, so it can look like throwing resources at a problem which is of low local importance. This is similar to the problem which is faced in all eradication attempts during the long and costly end-game.

A major attack on malaria short of elimination is technically feasible now, and would lead to a substantial reduction in mortality and morbidity form malaria, especially in the areas with highest transmission, provided it could be sustained. The first two phases of elimination outlined above would

be the same; the difference would be that the end-game phase, which is the most costly and difficult, and the most uncertain, would not be attempted except in areas where this had a realistic chance of success. To some extent the ease with which the first two phases are achieved in any given setting would give a far better estimate, from real data, of whether malaria elimination in that area was possible than current data.

The targets of elimination and eradication should however not divert attention or resources away from the fact that we are a very long way from maximising our possible efforts in intensified *control,* which for practical purposes are similar to Phases 1 and 2 of elimination*.* This is especially true in the area with the core of the problem, hyperendemic Africa, where eradication and elimination are not really relevant as goals for the moment and most of the deaths occur. Greater investment in malaria control measures if properly applied can have a dramatic impact on mortality; this was demonstrated in the eradication era, and has been demonstrated more recently in countries such as Zambia which have had major investment in malaria control. This means using anti-vector methods including ITNs and indoor residual spraying, and better use of, and targeting of, effective drugs. This, in turn, requires a substantial investment in the public health infrastructure, and where the private sector predominates, as it does among the poorest in many areas, considering measures such as the Affordable Medicine Facility- malaria (AMF-m). There has been far more emphasis placed historically on acquiring drugs and insecticides than supporting the systems which are needed to deploy them. DFID has taken a leading role in redressing this balance, but healthcare system strengthening would be essential if elimination, or even intensive control, is contemplated. Investing in malaria control and healthcare systems have been accepted as some of the most cost-effective current interventions in global health.

It should be recognised that the two aims of "shrinking the map" and "reducing by 70% the malaria burden (especially child deaths)" are geographically quite distinct. The places where 80% of deaths occur are, by definition, the places where local eradication is impossible. There will always be tension between these two aims, and the potential for competition for funding. When DFID considers this issue, it will want to bear in mind that with a few important exceptions, the countries where 80% of deaths occur are by and large among the poorest in the world, while those where shrinking the map is feasible are mostly not so poor. Given the strong poverty-elimination focus of DFID policy, those making decisions on this within DFID need to be aware of the risk that the demands of "shrinking the map" might distract political attention, and/or financial resources, away from the task of "reducing the malaria burden". Since both these aims are highly desirable, finding the right balance between them will be an important and prolonged element of the consensus-building process, and any campaign.

ACKNOWLEDGEMENTS

Attachments

Annexe 1. Definitions of elimination, eradication.
Annexe 2. A more detailed geographical analysis of potential for elimination.
Annexe 3. Potential new tools- including insecticides, vaccines and drugs.
Annexe 4. The Macdonald-Ross mathematical model and measures of transmission.

It was initially intended to have an annexe on cost-effectiveness. After examining the existing literature however it is insufficient to produce an informative summary of cost-effectiveness of interventions when being applied in an eradication context. The data cited in the text are from static models with data from high-transmission, low-income Africa. While there are a small number of studies from low transmission settings these do not use comparable outcomes and also are primarily derived from static models. Further analytical work in this area is strongly recommended.

ANNEXE 1. DEFINITIONS

With an increasing number of global elimination initiatives in the 1990s and on the background of the experiences with malaria and smallpox came the need for more precise definitions. The following[14] are now generally accepted as the basis for conceptualizing such initiatives:

Control: Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction.
Elimination of disease: Reduction to zero of the incidence of a specified disease in a defined geographic area as a result of deliberate efforts; continued intervention measures are required.
Elimination of infection: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent re-establishment are required.
Eradication: Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed.
Extinction: The specific infectious agent no longer exists in nature or the laboratory.

For malaria, a recent WHO consultation defined malaria elimination for national certification purposes as "the interruption of local transmission by mosquitoes"[15]

In some countries like China, the term "Basic elimination" has been used for malaria to designate a situation, where elimination of infection appears to have been achieved, but small controllable outbreaks, mainly as a result of importation of cases may occur.[16]

"Elimination as a (major) public health problem" is a term that has frequently been applied as the goal of control programmes. It is then implicitly accepted that there is no clear fully generalisable definition of what constitutes a public health problem, so that this depends on the context, and an elastic notion of "locally acceptable level". When this term has been used in international initiatives and campaigns, it has generally proved more useful when it has been pre-defined rather than being defined post-hoc when the elimination attempt had not succeeded as well as was initially anticipated. It can very useful as a concept in particular geographical regions or countries. It can very useful as a concept in particular geographical regions or countries, when it is clearly defined what it means. For malaria for example this could mean preventing all deaths from malaria- a great goal, but very different from elimination.

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[14] Ottesen et al. How is eradication to be defined and what are the biological criteria. In: Dowdle WR & Hopkins DR eds The Eradication of Infectious Diseases, Dahlem Workshop Report. John Wiley & Sons. Chichester, 1997
[15] WHO. Informal consultation on malaria elimination: setting up the WHO agenda. Tunis, 25-26 February 2006. Geneva, WHO, 2006.
[16] Kidson, C., Indaratna, K. Ecology, economics and political will: the vicissitudes of malaria strategies in Asia. *Parassitologia*,, **40** 39-46, 1998

ANNEXE 2. OPPORTUNITIES, OBSTACLES AND RISKS FOR ELIMINATION OF *PLASMODIUM FALCIPARUM* MALARIA IN DIFFERENT COUNTRIES AND REGIONS OF THE WORLD WITH CURRENTLY EXISTING TOOLS

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Contents
Introduction

Introduction

The following text is meant to present an overview of the kinds of problems faced by efforts to eliminate falciparum malaria in today's world. It is recognised that in rapidly industrialising countries overall risks of malaria may in certain circumstances drop rapidly due to changes in habitat and human behaviour which make human-anopheles interactions less likely. The political environment, which has to be sufficiently stable to maintain control efforts in all parts of a country over many years obviously may also change, for better or worse, unpredictably. Some remarks made about individual countries may not in all cases reflect the current situation when considering the dynamics of this disease, and additionally the progress that has certainly been made in recent years in many places thanks to support from GFATM and other sources. Given this unpredictability this annexe is therefore meant to be neither prescriptive nor predictive, but illustrative of the factors that need to be taken into consideration. The opinion of the authors of this briefing is that a realistic view of the difficulties likely to be encountered in any setting is essential at the outset if political commitment is to be sustained in any elimination attempt. Optimistic claims have historically been instrumental in mobilising political support for elimination attempts of malaria and other diseases, but subsequently it has sometimes been so much more difficult to maintain the commitment due to this over-optimism, when the true difficulties and costs were encountered.

When considering possibilities for elimination, it is worth recalling two concepts, which were established during the global eradication campaign:
Receptivity: which corresponds to vectorial capacity (or R_0) in the absence of continued insecticide-based vector control measures, and *Vulnerability*: which corresponds to the risk of importation of parasite carriers and the spread of parasites from these, related to migrations from endemic areas and the performance of health services at border crossings and/or in receptive areas.

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[17] Contributions from Drs José Najera, Christopher Whitty and Jo Lines are gratefully acknowledged.

Clearly, in areas, where both vulnerability and receptivity are high, elimination is extremely difficult and is likely to demand high long-term investments. When both are low, the opposite is the case.

In the below, certain areas and countries, where malaria elimination is deemed to be *technically feasible*, have been identified. The main issue then becomes *operational feasibility*. In some of these areas, where transmission is of low intensity and health services well developed, implementation may not pose huge problems. It should however, be considered that for most such areas, it will be necessary
   a)   to apply either IRS or LLINs or both with high coverage possibly supplemented with locally appropriate larval control, over a period of several years
   b)   that the determination of the best mix of vector control methods and the best insecticide and timing of operations would require a local assessment, district- or at least province-wise
   c)   that DDT resistance is widespread in many of these areas, making it necessary[18] to use insecticides with shorter duration that would need to be applied 3-4 times a year or more, depending on seasonality and
   d)   that it is necessary to obtain full, sincere and durable political commitment and local community participation in areas, where malaria may no longer be a major public health problem and IRS may be perceived as a nuisance more than an activity to improve health.
   e)   There must also be sufficient political stability *over the time needed* to complete elimination, and the higher the initial transmission rate the longer this will, generally, take.

As long as it is not possible to set a time limit for eradication, any local or national elimination must be accompanied and followed by rigorous surveillance, which would be more difficult than in the past in areas which previously had centralised health services where private health services are now dominant. On the other hand, it should be said that health services in rural areas are often much better developed than they were 50 years ago, and that, in general, knowledge on the requirements for strengthening them is also better.

This report concentrates particularly on those countries where elimination is technically feasible, or might be technically feasible. Less emphasis is given to those countries where almost all technical opinion would be that elimination is not feasible with current tools, although clearly those countries are also those with the greatest malaria burden.

For more details on the experience of the past, reference is made to Gramiccia & Beales, 1988.

1.   Oceania

Malaria occurs in New Guinea (island), Vanuatu and Solomon Islands. Malaria vectors are absent in other Pacific Islands. It is not known whether the ecology interdicts their establishment there, but these islands are obviously well justified in maintaining strict controls on air- and sea-craft.

Papua New Guinea, West Papua (Indonesia) and Torres Strait Islands (Australia)

Transmission is intense in lowland areas with gradual decreases in higher altitudes. In the midlands, economic development has been associated with increased mosquito breeding sites. The health

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[18] As often pointed out by some entomologists, DDT can be effective despite resistance because of its repellent effect. However, while this repellency may be satisfactory for malaria control, especially in areas, where the vectors are not very efficient, it will rarely drive down the longevity of the vectors sufficiently to allow elimination in intense transmission conditions.

services are better than in many other countries; technically a combination of intensive vector control and case management could, despite intense transmission, probably interrupt transmission in most of the country. However, a significant proportion of the population lives in areas where the development and maintenance of basic health services as well as provision of vector control is constrained by extremely difficult geographical access. This has historically been compounded by chronic, low level civil unrest.

Epidemiologically, the situation is similar in West Papua (the Western part of New Guinea Island); the health services there are somewhat better developed, the political situation is more controlled and the current malaria burden somewhat lower, but malaria elimination is currently unlikely to be possible because of the access problems.

It is worth noting that although Australia officially achieved "malaria eradication" in 1981, the disease still occurs in the Torres Strait Islands.

Vanuatu

The country presents an epidemiological gradient from north to south, with unstable malaria in the southernmost islands. Malaria was eliminated from Aneityum, one of the southernmost islands, in the 1990s. Elimination should be easy in Tafea Province, which is comprised of several small islands. From there it would probably be possible to advance northwards, but in the larger northern islands, the costs of establishing and maintaining curative and preventive services in remote communities would be very high. Vanuatu would have the advantage of low vulnerability: The islands are probably rarely reached by parasite carriers from other countries, but this would need to be examined more closely.

Solomon Islands

This country has a history of repeated elimination attempts followed by resurgences. The fact that it is comprised of isolated islands, that malaria is a major public health problem and perhaps that it played a significant role in WWII has attracted both well-designed and more capricious elimination schemes. The geographical isolation is a factor in favour of elimination, but it needs to be recalled that in the past, when malaria had reached a low level it was reintroduced from Papua New Guinea. From a technical viewpoint is possible that a multi-pronged attack could lead to elimination. It would have to be well synchronized over many of the islands because of the high internal population mobility. It should be noted that one of the reasons previous attempts have failed is that major civil strife has erupted repeatedly leading to destruction of health facilities including those of the malaria control programme.

2. East and South-east Asia

In many areas including irrigated rice cultivation plains with huge populations, elimination has been achieved or could be achieved. The core problem, which threatens sustainability in adjacent areas is forest and forest fringe malaria. Forest malaria refers to the situation of communities living permanently in forests, often migrating from place to place. The vectors are often partially exophilic and exophagic; despite this, IRS and ITNs usually have some effect, the former of course only if there are sprayable walls, which is not always the case due to the very hot and humid climate. This effect is relative: there are no examples of lasting malaria elimination in South-east Asian forest village areas. Forest fringe malaria occurs in populations usually living in areas at some distance from forests, where the vectorial capacity is very low. For various reasons, mainly agriculture, these people enter forests, get infected and bring the parasites to their home villages, where they may cause outbreaks

or maintain low level transmission – which can usually be controlled well with IRS or ITNs. Some people entering forests for gem-mining, smuggling, guerilla warfare etc. come from far away, have low immunity, frequently use antimalarial drugs and are liable to carry the disease (sometimes with highly resistant parasites) to other countries. The great difficulty is in protecting people staying at temporary habitats in the forest. IRS is of course non feasible. Hammock nets have been tried, but the results have been variable. Improved control of forest and forest-fringe malaria would be possible by tailoring strategies and not least communication to each individual group, trying out and applying different vector control measures including repellents, and innovative methods for case-finding and management. In this, it should be considered that malaria is usually not the only problem affecting these communities. Curative services addressing only malaria tend over time to be supplanted by private services, often combining poor quality with high cost, on a background of poor education of both consumers and in many cases suppliers.

China

Falciparum malaria persists in China in Yunnan Province, which borders on Laos and Myanmar and in Hainan Island. It disappeared (at least as far as reported cases are concerned) from Guangxi Province, which borders on Vietnam, in the 1990s. The disappearance occurred as Vietnam succeeded in bringing its malaria problem under control, especially in the north. Interruption of transmission in Yunnan would be possible with appropriate investments, but would be under continued threat from importation across the long southern and western border. In this, it should be considered that from an international perspective, malaria in Laos and Myanmar is a problem for Yunnan, not vice versa. In contrast, elimination in Hainan Island is overdue. It would mean getting rid of a relatively small local health problem, with some benefit for tourism, but with no bearing on global malaria. China has over the years eliminated falciparum malaria from a number of provinces, with little fanfare.

Philippines

As a result, in large part to deforestation, malaria has been eliminated from or disappeared from most of the Philippine Islands. Subject to a proper analysis of population migration patterns, an effort at elimination, island by island would be rational. However, in the areas that are still endemic, the population is scattered in small communities and investments in basic health care have been declining. This has been compounded by chronic civil unrest in Mindanao and the Sulu Islands in the far south. Forest malaria persists in Palawan with scattered communities with rudimentary health care. It is impossible to say, whether elimination would be technically possible in this environment.

Vietnam and Thailand

Like in China, falciparum malaria has to a large extent become a border problem, meaning not that transmission has been interrupted, but that transmission probably could be interrupted in most areas, if importation of cases would cease. This is not likely to occur soon, and it has never been possible to control migration across the long borders. One technical issue is that Viet Nam and surrounding countries still have small isolated deep-forest communities who are migrants and/or live in houses without sprayable walls.

Laos

In most of the country, the intensity of transmission is moderate and elimination would be technically feasible. This would benefit also the China and Viet Nam (there is no malaria on the border to Thailand, which is largely the Mekong River, and the malaria situation on the other sides of the

Cambodian and Myanmar borders is not better than in Laos). With increasing social stability in recent years, the main obstacle has become infrastructure. The populations in malaria endemic areas are extremely dispersed and extremely poor. Provision of both preventive and curative care to these remote communities is costly and labour-intensive.

Cambodia

Malaria in Cambodia has the characteristics of forest and forest fringe malaria. In the 1950s and 1960s, as it was realized that transmission could not be controlled with IRS, chloroquinized salt was introduced in western Cambodia and in all probability this is what led to chloroquine resistance, which later spread to the rest of the world. Today, western Cambodia is the epifocus of resistance to certain ACTs (and possibly artemisinin per se), which has spread across the Thai border,[19] and, it is feared, to the Myanmar-Thai border. This problem constitutes an international health emergency, which should be addressed vigorously. In comparison with the situation half a century ago, the forest cover has greatly diminished and there are more options for vector control and personal protection. The strategy needs to be creative and multi-pronged and include measures to engage both the affected communities and political authorities across the countries. It should aim at elimination in a defined area. Even if elimination is not achieved, such a strategy could still have huge benefits for the world in delaying and reducing the spread of multi-drug resistant parasites.

Myanmar/Burma

Myanmar is the weakest link in the South-east Asian malaria epic. The forest malaria of the other countries is present on a much larger scale both in terms of areas and population size. All of this is compounded by well known political problems, which in 2005 led to the interruption of support from GFATM. Even if favourable political change should come about this will not necessarily translate into improvements in operational feasibility as the inter-ethnic conflicts which occur in many of the most affected areas may well take many years to be resolved.

Bangladesh and North-east India (from Assam and eastwards)

Most of the malaria is similar to that of Myanmar and Cambodia. Particularly in India, the technical problems have historically been compounded by governance problems and intermittent insurgency.

Malaysia, Indonesia west of West Papua and Timor-Leste

Malaysia has built up good basic health services over decades. The "domestic" malaria problem is now almost restricted to Sabah and the Orang Asli peoples living in forests in central peninsular Malaysia. It is possible that these two areas, having all the technical difficulties of forest malaria and none of the often accompanying political ones, would be useful testing grounds for innovative strategies. In other parts of Malaysia, transmission is now almost interrupted, but tends to flare up in small outbreaks due to importation, mainly from Indonesia. Most of the immigrants are poor clandestine labourers, and it has so far not been possible to control them. Thus, elimination in Malaysia, as much as it seems "around the corner" would be an uphill struggle as long as malaria is regularly imported from Indonesia.

In eastern Indonesia, malaria occurs as coastal malaria, which is technically controllable, but remains a major problem, because of difficult access. More cases are forest and forest fringe malaria with the same technical difficulties as elsewhere. After many years of absence, malaria returned to central

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[19] http://www.who.int/malaria/docs/drugresistance/ReportThaiCam.pdf

Java in the 1990s and has still not been eliminated from there. As in the Philippines, it is rational to consider elimination island by island, but again based on a thorough analysis of migratory patterns. In contrast to the Philippines, however, Indonesia has huge populations, for example in Kalimantan, Sulawesi, Flores, West Timor and other eastern islands, where malaria is a major public health problem, and where civil unrest is not currently a generalized constraint on the development of curative and basic health services. A detailed analysis of vulnerability would probably show that the risk of reintroduction in the "unstable malaria" foci in the central and western islands could be greatly reduced by reduction of the malaria burden and parasite reservoir in the east. Focusing first on elimination in the central islands (Java, Lombok and Bali) and the west may be politically popular, but not necessarily rational from an epidemiological or equity angle.

3.   South Asia

India west of Assam, Bhutan, Nepal and Sri Lanka

Eastern India (Orissa, Jharkhand,West Bengal, Bihar and Madhya Pradesh) has the world's largest internationally neglected malaria problem.   It is estimated that close to 50% of India's falciparum malaria cases and deaths occur in these areas in districts with a total population of 100 million. Data presented at a meeting arranged by WHO 21-23 November 2007 suggest that the number of deaths from malaria in India may be between 70,000 and 200,000 per year. In these states, most malaria is forest-related, but it seems that in general, the vectors and the human ecology makes the transmission more amenable to control, despite the fact that the entomological inoculation rate may reach 150 per year. After 50 years, IRS has grown unpopular and the quality of spraying is poor and sometimes associated with environmental and health hazards. It is now planned to introduce LLINs on a large scale and to establish basic curative services in villages to include RDTs and ACTs. These efforts, which constitute a major reform of the malaria control programme, are also in line with the Government's high-profile *National Rural Health Mission*, which foresees increased investment in rural health care, which has been neglected for years (except family planning). Considerable health gains can be expected, but some of the areas are affected by long-standing insurgency and governance problems, which have historically acted as barriers to effective malaria control.   In western India, malaria is generally unstable in rural areas and associated with irrigation and development activities, in the arid north-west also with rainfall. In many of these areas, malaria could technically be eliminated (though the negative impact of insecticide resistance should not be underestimated), but this would be much easier once the parasite reservoir in the east has been reduced, and is not an obvious national priority until other areas are controlled. India has an almost unique problem of urban malaria, transmitted by *An.stephensi* and to some extent *An.culicifacies*, being more serious than in adjacent rural areas and affecting most cities from Ahmedabad in the west to Kolkata in the east and from Delhi in the north to Chennai in the south. The vectors are mainly found in artificial containers, the parasites are often imported with a poor, unregulated work-force from the east and the transmission has been found to be extremely difficult to control. The problem will diminish, once malaria is better controlled in rural areas in the east, but it may well prove to be a technical obstacle to elimination in the Sub-continent. The possible spread of urban sub-species of *An.stephensi* to other countries is also a threat that should be taken seriously.

In Nepal and Bhutan there should be no major technical obstacles to elimination. The problems to be addressed are in access to health services and coverage of prevention. In Nepal, civil unrest is currently an obstacle. For both countries, the risk of importation from India needs to be considered.

In Sri Lanka, on the basis of past experience, elimination should be possible, if the civil war would come to an end. Some of the transmission occurs in areas of civil unrest. Sri Lanka may be among the few major nation-states, where malaria is currently an important public health problem, and where

elimination of *P*.falciparum would be a rational objective in the context of national public health planning. Elimination would have to be bolstered with a very good surveillance system and special measures to prevent introduction from across the sea.

4.   Central Asia

Falciparum malaria is widespread in Afghanistan, but unstable, and should be eliminable from a technical viewpoint, although nomadism and terrain are important constraints. Planning for it is unlikely to be useful unless the security situation improves significantly. In Tajikistan, falciparum malaria has returned because of Afghanistan and an internal deterioration of health services including malaria control. Despite the persistent transmission in Afghanistan, it is reasonable for Tadjikistan to aim at elimination, and progress is actually being made.

5.   West Asia and the Middle East

Pakistan

Elimination in Pakistan should not meet any insuperable technical problem, though insecticide resistance needs attention. The political situation, both in Pakistan and is neighbours has historically not been ideal for an elimination campaign, and that remains the case in many areas. The problems of the decentralised health sector would provide a major challenge to the later stages of elimination. Urban malaria occurs in Karachi, but seems not to be of the same magnitude as in India, though it is difficult to know, given the state of surveillance.

Iran

Iran would probably be able to eliminate falciparum malaria were it not for the current high risk of importation from Pakistan and Afghanistan.

Saudi Arabia and Yemen

The two countries have committed to a joint programme for elimination of malaria supported financially by other Gulf states. If border collaboration can be further developed and health services with good surveillance developed, this could well prove to be technically feasible, although Yemen provides some unique technical challenges. Although malaria in the Arabian peninsula is a rather isolated phenomenon, such an achievement would be of international interest, because the main vector is *An.gambiae s.l.*

Other countries in the Middle East

These are already almost free from falciparum malaria. United Arab Emirates is the most recent country to have eliminated malaria (also vivax), and its experiences will be of great interest to its neighbours. Parasite importation, especially with labourers, will be a continued threat necessitating strong surveillance.

6.   Islands in the Indian Ocean and around Africa

Mauritius

The long history of malaria control and elimination in Mauritius is highly instructive. Falciparum malaria has been eliminated from this island.

Comoros

This country has a situation, which could be considered somewhat comparable to that of the Solomon Islands, with the important difference that the political situation has historically been more stable. The possibility of elimination merits careful consideration, but given that the transmission is by Afro-tropical vectors, it should be anticipated that such an attempt would be both costly and long drawn out. It would therefore be important only to embark on elimination of there is true national political commitment as opposed to receiving a kind offer from a foreign agency.

Madagascar

Transmission can be interrupted in most of the highland areas with unstable malaria. However, it is debateable whether it is a better investment (for population health and economy) to further reduce the now quite low transmission in the highlands or to reduce the still high morbidity and mortality burden in the lowlands. An equity perspective would prioritise the latter. Given the large population and the intense transmission in the lowlands, it seems highly unlikely that nationwide elimination is currently technically feasible.

Zanzibar (U.R:Tanzania)

Surveillance data indicates that transmission has been greatly reduced in recent years. However, because of the proximity to the mainland, this receptive island is highly vulnerable, so it is unlikely currently to more cost-effective to aim for elimination with the ensuing high demands on surveillance when compared with continued progress in reducing the burden.

Sao Tome and Principe, Bioko (Equatorial Guinea) and Cape Verde

A study has indicated that from a receptivity viewpoint, malaria could be eliminated from Principe, but the vulnerability of this island, and that of the nation as a whole, has not been properly assessed. Malaria control has made excellent progress in recent years and will hopefully be allowed to continue doing so. In Bioko island, elimination is currently being attempted, and the outcomes will be of great interest to others. In Cape Verde, malaria persists only in one small focus, and at least from a receptivity viewpoint, it should be relatively easy to eliminate it.

7. North Africa

By and large, falciparum malaria has been eliminated (and the elimination of vivax malaria is making progress).

8. Southern Africa

South Africa, with little or no transmission in much of the country and a very well organized control programme, has neither interrupted transmission nor been able to control the influx of parasite carriers. Attempting to push the boundary of malaria transmission further north, for example to the north of Zimbabwe, Botswana and Namibia is being considered but would be costly and would have to be associated with systematic screening of migrants and almost constant fire-fighting to put down outbreaks. Malaria in these areas can be reduced to low levels, but not sustainably, and at the potential cost of losing the usefulness of the current best drugs and insecticides.

In the 1960s and early 1970s in colonial times, malaria was largely eliminated from the southernmost part of Mozambique, but when the line was pushed towards the agriculturally important Limpopo valley, progress became increasingly difficult, slow and costly. Migrant labour and excito-repellency to DDT made it increasingly difficult to sustain the gains. After independence in 1975, the government decided to give higher priority to the development of rural health care and universal access to immunization than to freeing the south of malaria.

In the Copper Belt of Zambia, a relatively arid area with moderate vectorial capacity, it was possible in the past and is now again in process, to establish a cycle of wealth and health, by using a mix of methods to suppress malaria to low levels. So far, the aim has been high-level control to minimise the public health impact of malaria but not elimination. That would imply very high investments in surveillance, which could arguably be better spent on malaria control elsewhere, in areas of the country, where strengthened health services and malaria control could be part of social and agricultural development.

9.   Horn of Africa

In Ethiopia, malaria control is making good progress again after serious setbacks in the 1990s culminating in an epidemic in 2003-4, which may have claimed around 70,000 – 200,000 malaria deaths in Ethiopia over a six month period in 2003-4 (Guintran: Technical support to malaria epidemics surveillance in Ethiopia December 2003 – April 2004, mission report. WHO, unpublished, 2004). Ethiopia includes large populations living in lowlands with hyper-endemic malaria, so national elimination is in no way technically feasible. Experience has shown that continued annual investments are necessary to prevent the potentially very dangerous epidemics. In contrast, elimination could be technically feasible in Djibouti, Eritrea and Somalia.

10.   East Africa

The situation could be considered similar to that of Ethiopia. There is every reason to invest heavily in aggressive malaria control in the unstable highland malaria areas, as this is the only way to avoid major epidemics. Pre-eradication projects achieved interruption of malaria in some areas of East Africa, but these were on a small scale and with an operational perfection in the application of IRS, which could hardly be replicated anywhere in the world. Elimination can therefore not be considered technically feasible in lowlands with stable malaria and intense transmission. Very good progress, which is being made in a city like Dar es Salaam through a combination of vector control methods deserves to be emulated in any other places across Africa. In highly urbanized city centres, it is perfectly feasible to reduce transmission to extremely low levels, but setting elimination as an objective in such areas would currently not be rational.

11.   Central Africa

Central Africa may be the region of the world with the most severe health care deficiencies and consequently highest malaria mortality. There is every reason to invest more in malaria control to save lives. For technical reasons outlined elsewhere in the report, elimination could not currently be envisaged.

12.   West Africa

In relation to elimination, the situation is similar to that of Central Africa, although greater seasonality provides both greater challenges and some opportunities for control. There are serious constraints to

malaria control, which now need to be better addressed, such as the risk of epidemics in the Sahel, the difficulties of providing basic health services for nomads, and the need to find alternative methods in areas, where the summer heat precludes the use of bednets.

13.   North and Central America

Falciparum malaria is slowly disappearing from most of the countries concerned, but it still seems to linger in Nicaragua and Honduras, especially in sparsely populated areas on the Atlantic coast of Nicaragua, where remote localities, extreme poverty, variety of ethnic groups and inadequate health services have for long been major obstacles. In other countries the main identified problems are labour migration, precarious dwellings and, in some areas, socio-political problems.   Achieving elimination would require a more concerted effort, including revitalization of properly conducted IRS campaigns and basic health services in the problem areas.   The effort would be costly and necessitate inter-country coordination, and deciding to prioritize this would require political commitment specifically to malaria elimination.

Haiti and Dominican Republic

Almost all cases in these two countries are *P.falciparum.* Those of Domenican Republic occur almost exclusively among Haitian workers, which led to strengthening of vigilance at roads and mountain paths with little success. The finding that transmission occurred in the labour camps of sugar cane plantations, led to some improvement. The obstacle to elimination of malaria in Hspaniola is political, not technical.

14.   South America

Forest and forest fringe malaria with similar characteristics to South-east Asia are found in the interior of Brazil, French Guiana, Guyana, Suriname, Venezuela, Colombia, Ecuador, Peru and Paraguay. Based on the experience of the past, intense surveillance of drug resistance is of international importance. Gold mining in in, the Amazon is mainly on the plain, and presents one of challenges. Mining is carried out by sizable groups of people. This would facilitate control among those particular groups, although they are often illegal and do not use public health services.   Elimination of falciparum malaria in South America depends on the feasibility in the Amazon. Despite vigorous efforts in the days of the global eradication campaign, this has not been demonstrated, although the challenge may now be somewhat reduced by economic development and deforestation.   Outside forest and forest-fringe areas, endemic falciparum malaria is now sporadic and could probably be eliminated, if the problem were first effectively addressed in forested areas. In Colombia and Peru the operational context is complicated by armed conflict and the drug trade.

ANNEXE 3. NEW TOOLS AND OTHER RESEARCH PRIORITIES IF ELIMINATION OR ERADICATION IS TO BE ATTEMPTED.

Elimination or eradication requires all the tools needed in conventional malaria control, none of which are rendered obsolete but rather more important by the decision to attempt elimination. Attempting elimination will put great selection pressure on both vectors and malaria parasites; the result will inevitably be a more rapid evolution of resistance mechanisms to the anti-vector and anti-parasite measures we deploy. An attempt at elimination therefore has to be accompanied by a pipeline of new insecticides, and new drugs, to deal with the inevitable spread of resistance. Additionally new tools will be needed; it is agreed by the great majority of those working in malaria that current tools are inadequate to eliminate malaria in the areas where malaria transmission is highest. In particular we need tools which can have a substantial impact on transmission; without R0 being sustainably less than 1, elimination will not occur. Improving on deployment is also essential- excellent tools used ineffectively have little impact, and current deployment methods are often very ineffective. It is not realistic to think a single intervention will eliminate malaria. Rather, as with survival from coronary artery in the industrialised North over the last 20 years, the incremental effect of multiple interventions, none of which in themselves are startling, can have a substantial effect when combined. If R0 is over 100, however, the cumulative effect will have to be considerable.

New insecticides.

As outlined in the main report, any serious attempt at elimination or eradication will exert extreme selection pressure on the malaria vectors, and is likely to speed up the development and spread of insecticide resistance. Our problem is not that we do not have effective and acceptably non-toxic insecticides for IRS and bednets now, but rather that the ability of the most heavily attacked vector populations to evolve resistance to insecticides in the face of strong selection pressure will be faster than our ability to produce new insecticides. Pyrethroid insecticides are ideal for use on nets: they are safe, biodegradable, and their mode of action is exceptionally rapid, which is necessary if the aim is to protect the net-user from biting as well as to kill mosquitoes. But pyrethroid resistance is spreading. What are the chances of finding another class of insecticides to replace them? The market in agricultural insecticides is more than ten times larger than the public health insecticide market. R&D investment in the search for new insecticides is similarly weighted. This is good and bad news for public health. On the one hand, it means that overall global research investment is very much larger than it would be if no agricultural market existed. On the other hand, this search is strongly biased towards the molecular characteristics needed for agricultural applications, which are not the same as those needed for public health applications either in characteristics or toxicity. Additionally the widespread use of insecticides in agriculture (inevitable if they are developed first for this use) can accelerate the appearance and spread of resistance in mosquitoes. Work supported by the Gates-funded IVCC is working with industry to redress this balance, by re-examining compounds that have been detected in previous industrial screening processes as having insecticidal activity of a kind unsuitable for further development for agricultural purposes, but potentially suitable for public health purposes. This idea may well yield one or a few compounds for further development, but at the moment, it seems unlikely that any of these will be as good as the pyrethroids for use on nets.

Insecticide resistance is therefore one of the greatest threats to any concerted and prolonged attempt at transmission control, whether the goal is elimination, eradication or sustained control. The prospects for a reliable supply of new insecticides as the campaign proceeds are currently highly uncertain. Further investment in the search for new molecules will be an essential part of any serious attempt at large scale elimination. Nevertheless, it must be recognised that even a substantial increase in research will reduce but not eliminate this uncertainty.

Antimalarial drugs

A constant pipeline of antimalarial medicines is essential. In elimination/eradication, they would have an important role, but are unlikely to be decisive. Drugs of various types already exist and are licensed for use. A decision to aim for elimination or eradication would put a different emphasis on which types need to be developed compared to current control.

a) *Drugs to treat clinical malaria*. Until eradication is achieved, people will acquire malaria and need to be treated. Drugs to treat clinical malaria target the asexual stages of the malaria life-cycle, inside red-blood cells. This stage is what kills people, but is not what transmits malaria. Most drugs which kill malaria asexual parasites have little impact on gametocytes at a population level. Drugs to treat clinical malaria therefore remain essential, but they have little role for transmission control in intense transmission conditions or in the attack phase of an eradication campaign, unless they have additional properties (see below).   On the other hand, in very low transmission settings, early detection and effective treatment of malaria with these drugs does have an important role (this is of the main measure to maintain malaria-free status in for example Europe and the USA). Ensuring that the detection is early and the treatment 100% effective is a critical condition for success in the long 'tail' (consolidation phase 3) of any elimination campaign.

Where early treatment with effective drugs does score very highly is when the aim is elimination of malaria as a pubic health problem (as opposed to complete local eradication of the parasite). Almost all people who acquire malaria can be prevented from developing severe malaria by reliable prompt treatment with an effective antimalarial.

b) *Drugs which kill gametocytes.* Some drugs can kill or reduce gametocytes, making the person treated less, or non-infectious to mosquitoes. The artemisinin derivatives have some anti-gametocyte effect, although this is probably limited to young gametocytes, and are not fully effective. Other existing drugs, like primaquine and its new congeners like, tafenoquine, kill all gametocytes more effectively. Unfortunately, these drugs carry a risk of haemolysis, depending on the prevalence of the genetic condition glucose-6-phosphate dehydrogenase deficiency, which is common in many populations living in malaria-endemic areas (10-20% is not atypical). This haemolysis can sometimes be dangerous, and this is a significant operational problem when the patient's G6PD status is unknown.

Anti-gametocyte drugs can theoretically be used in two ways: in routine treatment of patients with malaria, and as mass drug administration. Using anti-gametocyte drugs systematically in case management will have some effect on transmission, but this is likely only to be of public health significance in areas of very low transmission. Where transmission is intense, most people who have been infected do not come for treatment at all, as they do not feel sick, or they come only after having infected many mosquitoes because the force of transmission is so high. The majority of transmission in many of these settings comes from asymptomatic adults. Therefore anti-gametocidal drugs used in treatment, including the ACTs, are likely to have a useful effect in Phase 2 (consolidation) and 3 (maintenance) of any elimination attempt, and in any area where malaria transmission is already low, but will probably contribute only marginally in the high-transmission settings, and certainly not sufficiently to reduce R0s of over 100 to within sight of 1.

Some expects consider that mass drug administration with gametocidal drugs holds considerable promise and could contribute significantly to reducing transmission in higher transmission settings, although this is a theoretical advantage and has not been conclusively proved. It is likely to be most effective in areas where transmission is highly seasonal, used in the low season when

transmission is lowest. Since the most effective current anti-gametocyte drugs (tafenoquine and primaquine) are potentially hazardous where G6PD prevalence is high (especially in Asia, where the deficiency tends to be greater) either new drugs with the same properties but little effect on G6PD-deficient individuals need to be developed, or (operationally more difficult) rapid tests for G6PD deficiency would need to be deployed.

c) *Long-acting drugs with prophylactic effects.* These include ACTs with very long-acting partner drugs. In some settings mass drug administration with drugs which both treat and provide prophylactic effects to prevent reinfection for a period have proved effective at reducing transmission, both in the eradication era when chloroquine was an effective drug, and more recently. In some villages in Cambodia, several courses of mass treatment (of all members of the population) using ACTs with long-acting partner drugs have been able to rid those villages of falciparum malaria. In Aneityum, Vanuatu, a small island with low transmission, and in a number of places in the eradication era, mass treatment with an effective medicine can be instrumental in the endgame towards local elimination, once transmission had been reduced to near 0 by vector control. It is unlikely that mass drug administration for prophylaxis to the whole population could contribute much to Phase 1 (attack) of any eradication effort in high transmission settings (that was certainly the experience in the global eradication campaign). Moreover, mass drug administration, especially with long-acting drugs, probably imposes much stronger selection for drug resistance than more selective forms of treatment.

d) *Drugs which kill the hypnozoites of vivax malaria.* The hypnozoites of vivax malaria are the form which lies dormant, and then causes several relapses months or even years after a primary infection. It is this which makes eliminating vivax more challenging than falciparum malaria. The global eradication campaign made far less impact on vivax malaria than falciparum malaria where the diseases co-existed. A drug (or vaccine) which killed hypnozoites and was sufficiently safe for mass drug administration would be a major advance. Currently the two available drugs are primaquine and tafenoquine. Primaquine is only moderately effective and needs to be taken for prolonged periods (2 weeks), and has the problems with G6PD deficiency outlined above. Tafenoquine is possibly more effective, and certainly operationally easier to use as it does not require 2 weeks of treatment but limited data so far indicate that the dangers of haemolysis in the case of G6PD deficiency are similar to primaquine. The technical challenges of developing a safe drug to kill hypnozoites should however not be insurmountable, and a number of drugs in early development could have the potential to fill this niche.

Vaccines

There have been considerable developments in the malaria vaccine field, which may provide hope that malaria vaccines can play a major role in malaria control- this section does not discuss this area, but only their potential role in elimination and eradication. There is often an assumption that an effective vaccine would be an essential component of an eradication or elimination strategy. There is no scientific basis for this assumption. Whilst a long-acting and effective vaccine might have some part to play in several settings, it is unlikely that vaccination could make elimination possible in most areas where it currently is not possible. This is not an argument against supporting research and development for malaria vaccines, which potentially have a number of important roles, but against supporting them mainly in the expectation they can deliver eradication. Vaccines were the key to eradication of smallpox, and the near-elimination of polio, but these diseases are so different from malaria that drawing parallels is misleading. In particular in both diseases lifelong immunity can be acquired after a single natural infection, which vaccines are able to replicate, and there were no alternative tools. Vaccines may have an important role to play in malaria elimination, but they are not likely to be sufficient, and in many settings are not necessary. Much of what they can achieve to

support elimination depends on the maximum long-lived immunity that can be achieved- and this is currently guesswork.

There are a number of possible malaria vaccine types, and any one vaccine may have more than one effect (so they might have both infection and disease modifying effects- the current vaccine candidate RTS,S may for example), but for the purposes of elimination or eradication the key ones and their potential roles are:

a) *Vaccines which primarily act to prevent infection* (ie vaccinees are less likely to have parasites in their blood). Most current vaccines have this as their goal, including the currently best developed, RTS,S, and sporozoite vaccines which have some additional promise. A 100% effective, lifelong vaccine given to 100% of the population which required no boosting by natural infection subsequently would, obviously, achieve eradication, but this is a very long way from where we are now. A 50% effective vaccine given to all adults and children (a more realistic goal, still some way off) would reduce transmission because 50% fewer would produce parasites, and so produce gametocytes which infect mosquitoes. The effects of this are pretty well linear, and would lead to a reduction of around 50%[20]. The effect of this in an area where R_0 is 300 (as in parts of Africa) would still leave malaria at over 100x the force of transmission needed to maintain itself in the population. Even an 80% effective vaccine given to 100% of the population would only reduce transmission by about 80%, well above the R_0 of <1 needed for elimination or eradication. In high transmission settings, therefore, even a very effective vaccine would not have the decisive impact for elimination, although it could be useful as part of a wide variety of methods used in a combined way. On the other hand in areas of the world where R_0 is currently around 1, an effective vaccine could have a decisive impact, but in most of these areas elimination can be achieved using current tools. It is expected that some of the potential vaccines against malaria infection, including sporozoite vaccines, may be helped by repeated exposure to new infections boosting immunity, so prolonging the protective effect; as malaria transmission is reduced, this becomes less frequent, and the immunity following vaccination may wane, so that transmission would settle at an equilibrium level.

b) *Vaccines which reduce the chance that a patient who has an infection with malaria has severe disease*. This form of immunity is what protects most adults in Africa; they carry parasites, but are not affected by them (most of the time). Two things follow from this; such immunity can be induced, so a malaria vaccine of this type is theoretically possible; it is probably distinct from the immunity to infection. Immunity to disease seems to be relatively long-lived. A pure disease-modifying vaccine would not have an impact on transmission, as it would presumably not prevent gametocytes. It would however have an important role in reducing the risks associated with elimination efforts in high-transmission areas. In such settings, malaria elimination or near-elimination would lead to a loss of immunity, very quickly, in young children (who would never be exposed), and probably over several years, in adults. If malaria returns, for example as a result of relaxation of vector control during civil unrest, it could spread rapidly, with a large part or even the whole population vulnerable to dying from the disease. An "anti-disease vaccine" could substantially reduce the risks in such a scenario. Currently there is limited understanding of immunity to disease (as opposed to infection), and designing and testing such a vaccine is difficult, but this may be an important area to consider. Such a vaccine would obviously be useful also in control, by reducing the morbidity and mortality burden. A subset of this vaccine category, and one probably much closer to development than a general anti-

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[20] This is not entirely predicatable, and depends what is meant by effectiveness.. A vaccine which reduced the number of sporozoites reaching the liver or developing there by 50% in all vaccinated subjects would have little or no effect on transmission. A vaccine with 95% efficacy would as some people would probably not develop a blood stage infection, providing only 10 or so sporozoites are inoculated. In contrast a vaccine that gave 100% protection to 50% of the subjects who received it would have an effect on transmission.

disease vaccine are vaccines to protect pregnant women by reproducing natural immunity in pregnancy.

c) *Vaccines against gametocytes (transmission-blocking vaccines)*. Such vaccines aim to reduce the transmission by attacking the gametocytes. As with anti-infection vaccines their effect would be approximately linear: an 80% effective vaccine in 100% of the population would reduce transmission by around 80%. As with anti-infection vaccines a highly but not 100% effective vaccine with good coverage would therefore have a useful but not decisive impact in high transmission settings, and a much greater potential impact in areas where R_0 is close to 1.

d) *Vaccines against vivax malaria.* There has been very little research into such vaccines, and none anywhere near Phase III clinical testing. An effective vaccine against the hypnozoites of vivax malaria would be especially useful for reasons outlined elsewhere, and could make the elimination of vivax malaria in may settings realistic. Of all the possible vaccine types this is the one most likely to tip the balance in favour of elimination most decisively, and is not biologically unrealistic as the hypnozoites are present in low numbers for many months so provide a vulnerable target (but this is not currently a priority for vaccine development).

Genetically-engineered mosquitoes and sterile males

We have been developing strains of mosquito that are refractory to malaria infection since the 1970s, and they are eye-catching. The problem has never been that we cannot develop such mosquitoes, although doing so for all the important vector species would be challenging. Rather, the obstacle to development of a practical intervention has always been the means to spread the gene through wild population. Unless the mutation(s) provide a substantial survival advantage there is no reason why they should spread through the massive genetic pool, in Africa in particular. It is generally agreed that in order to introduce such a mechanism, the gene(s) for refractoriness will need to be attached to a genetic driving mechanism, such as a transposable element. We do not have any such driving mechanism now: there are candidates but they are not currently well-developed. There has been more progress in research on molecular basis of the refractoriness. Unfortunately, this research is consistent with the hypothesis that refractoriness genes are the product of a very long-standing evolutionary arms race between the parasite and the mosquito, with the mosquito repeatedly developing mechanisms to avoid infection, and the parasite consistently evolving to overcome these mechanisms and render them useless.   If so, then any refractoriness mechanism that we might introduce may well face a parasite population that already contains the genes to circumvent the introduced mechanism, or which can evolve to achieve this. Even if we were able to drive them through the population the effects of this therefore might well be relatively short-lived. The technology might have a role in specific situations with a single vector which is difficult to control using other measures (such as urban malaria in some cities in India), but in tackling the areas which provide the greatest challenge it is difficult to see them having the massive impact that would be needed on transmission within a realistic timeframe, even where there is a single vector species (which is exceptional), and where there is more than one this become even more problematic. Genetically modified mosquitoes should not therefore be dismissed, but may find only a relatively limited application, and are not likely to make elimination feasible where 80% of malaria deaths occur. Releasing large numbers of sterile male insects has been useful in controlling screwworm, and has been suggested as a method for malaria control, but there is no current evidence it would be effective.

New methods to deploy existing tools

One of the paradoxes of malaria control is that far more effort (and money) goes into developing new tools than into better ways to deploy them, despite overwhelming evidence that in many settings the

methods of deployment impose the greater brake on what can be achieved. So for example there may be passionate arguments about whether a 97% efficacious drug should be substituted for a 93% efficacious drug when only 20% of those who need an antimalarial get one, or about the merits of different forms of net in settings where only 15% of the population sleep under them. One of the reasons for the success of the first eradication campaign was that there was a concentration of effort on how to deploy the existing tools, and how to adapt them best to local circumstances for maximal effect. The imperfections of current methods of deployment would be a far greater problem in elimination or eradication, as near-perfect deployment would certainly be needed to achieve elimination in high-transmission settings. Delivery methods cannot be packaged neatly into groups in the same way drugs, insecticides or vaccines can be, but some principles are clear.

a) With a few important exceptions almost all delivery methods, whether public or private, tend to achieve lowest coverage amongst the poorest and the most geographically remote - yet these are the groups which are likely to be the final reservoir of infection in an elimination attempt.
b) Debate around delivery is often based as much on ideology as on evidence. This is especially true around public v private distribution of drugs, and free distribution of nets.
c) It is rarely the case that one delivery channel can reach everyone all the time: multiple complementary approaches are needed to maximise coverage.
d) It is often said and written that in Asia and the Americas, "functioning health systems are in place" in contrast to in Africa. In many malaria-endemic areas this is untrue. This is sometimes a result of neglect and conflict, but the inherent difficulties of dispersion, terrain and nomadism need to be addressed through designs tailored to each situation and developed in collaboration with the community concerned.
e) The further an elimination campaign progresses the more small pockets of high transmission where conventional tools fail matter, as they threaten progress in the rest. Social and cultural research will be at least as important as developing new tools for these. The catastrophic effect of cultural beliefs among a small group in a small section of northern Nigerian society on the global polio eradication campaign is an object lesson in this.

New methods of mapping malaria

In the initial attack phase of malaria, and even more in the consolidation phase an accurate current map of malaria prevalence is essential. In the third phase accurate surveillance is critical. New serological methods of determining incidence of malaria at a population level, and current GIS methods combined with updated population databases are clear advances on what was available in the global eradication attempt. On the other hand the pool of expertise in field entomology, which will be very important through all phases, is far smaller than it was when the global eradication attempt started. Modern molecular methods may make some of this lost ground, but not enough.

Mathematical models

The first global eradication attempt was made possible by the insights of the Macdonald-Ross mathematical model, which accurately predicted that an intervention which shortened the life of mosquitoes would have an effect far greater than simply reducing mosquito numbers or numbers of infected humans. The fact it was to the power of 9 or 10 meant policy makers realised it is also significantly more effective than would be expected without modelling. As new tools emerge modelling their effects may (and may not) produce surprising insights. The starting position should however normally be the Macdonald-Ross model, because it has proved robust and effective at predicting the effects of interventions. Few mathematical models have been this useful for policy. Because of its importance a longer description of the model is outlines in Annexe 4.

ANNEXE 4. QUANTIFYING MALARIA TRANSMISSION AND THE MACDONALD-ROSS MODEL OF MALARIA CONTROL AND ERADICATION

For malaria eradication, the goal is to interrupt the transmission of infection from one person to another. Transmission is influenced by many factors and we need to understand which interventions will have the most powerful effects on transmission. The essential concept is the *basic case reproduction rate*, R_o.[21] This is defined as the number of secondary cases arising from a single primary case in one round of transmission, if the human population has no immunity. This is explained in the main document- in brief from a single primary case if $R_o = 2$, then there will be two new cases in the first round of transmission, 4 in the second, 8 in the third, etc. If $R_o = 10$, there will be 10 cases in the first round, 100 in the second, and 1000 in the third. If $R_o > 1$, then the number of cases will grow exponentially until growth of the parasite is constrained by human immunity, or the entire human population is infected. If $R_o = 1$, the situation will remain stable. If each case causes less than one new case $R_o < 1$; if this is consistently sustained then the number of cases will decline until the infection disappears which is essential for elimination or eradication. For malaria in parts of equatorial Africa, R_o is in the range 100 to 1000, so many times greater than other eradicated diseases. In these areas in the absence of immunity malaria has an epidemic potential that is explosive.

Sir Ronald Ross, and later George Macdonald, analysed the elements of R_o by identifying all the events that have to occur for the parasite to be transferred from one person to another. The result was a model (formula), for R_o, which in its simplest form is:

$$R_o = \frac{m.a^2.p^n}{-r.\log_e p}$$

m = the number of female mosquitoes per person
a = the frequency with which each mosquito bites man (so **ma** = bites per person per day)
p = survival rate in mosquitoes (proportion of females surviving one day to the next)
n = the maturation period of the parasite in the mosquito, in days
r = the recovery rate in man (proportion of infected people recovering daily)

If human malaria cases have an average recovery rate of **r** per day, the average case will last for 1/**r** days. During this period, the parasite must be taken up by a mosquito, which it does at the rate **ma** (bites per human per day). Once infected, the mosquito must then survive for **n** days before it becomes infective: a proportion p^n of infected mosquitoes will do so. Each infective mosquito will then go on biting people (with frequency **a** per day) for the rest of its expected lifespan of $1/(-\log_e p)$ days. R_o is then the product of these elements. The rate at which mosquitoes feed on humans, a, appears as a square term because two such meals needed in a transmission cycle: one to infect the mosquito and one to pass the infection back to a human. To allow for the fact that the transfer from host to host is imperfect, some versions of the formula also include the terms **h** (the probability that a mosquito will become infected by a bite on an infected person) and **b** (the probability that a bite from an infective mosquito will result in human infection).

The model implies that R_o should be most sensitive to changes in **p**, the daily rate of survival (because this is raised to the **n**th power) and also relatively sensitive to changes in **a** (because it is

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[21] The concept of R_0 is general for all infectious diseases. A closely related concept specifically for vector-borne diseases R_0 is *vectoral capacity*. It represents the daily rate of secondary cases arising from one primary case, and consists of all the entomological factors in Macdonald's formula with the human factors removed.

squared). This explains why the African vector *An. gambiae* is the most efficient malaria vector in the world: compared to other *Anopheles* species, *An gambiae* is not usually found in great abundance but it is relatively long-lived and it prefers to bite man, which is why 80% of the world's malaria is in Africa.

This mathematical model demonstrated that the most obvious factor (the number of mosquitoes) was far less important than the length of time they live. Reducing the number of mosquitoes **m** by 80%, is less effective than reducing the rate of daily survival **p** by half. The effect of the former is linear (an 80% reduction in transmission) while the effects of the latter are raised to the power of 9 or 10 (transmission reduced by 99.9%)[22]. The effects of reducing mosquito numbers are linear: half the number of mosquitoes, half the malaria. In the 1950s, this model helped to inspire the first eradication era. At the time, campaigns of spraying houses with residual insecticides (IRS, which affects **p** as well as **m**) were proving much more powerful than any previous method of control: far more so than attacks on the breeding sites and insecticidal fogging (which affect **m** only) and efforts to improve the promptness and effectiveness of treatment (which increase the recovery rate **r**). By offering a technical explanation, Macdonald's theory accurately encouraged the belief that these successes could be generalised, and helped to inspire hope in the goal of global eradication. The reason the eradication failed was not that the model was proved wrong (data from eradication supported it), but rather that the extremely high starting R_0 in many parts of Africa was not taken properly into account. The model has proved very robust in predicting the effects of different control measures in many settings. It offers a way to assess the degree to which new technical developments will help to make eradication feasible.   For example, vaccines will presumably act on transmission by reducing **h** and/or **b.** This will indeed reduce R_o, but unlike IRS, it will do so only in direct proportion to vaccine efficacy and coverage.   The model can incorporate new tools as they emerge.

Other measures of transmission of malaria

R_0 is not the only measure of transmission, and cannot easily be measured directly in malaria. Its importance is mainly that it is the measure which predicts how difficult elimination/eradication is likely to be. Other important measures in malaria control include:
a) The entomological inoculation rate, EIR. This is the number of infectious bites a human will receive in a year. It is calculated by the proportion of mosquitoes which are infected (measured by catching and dissecting them) multiplied by the number of bites from anopheles mosquitoes a human will get in a year.   In Africa, typical EIRs vary from around 1 infective bite per person per year (very low by African standards) to several hundred per year (more than one infective bite per person per night). Outside Africa, EIRs of more than 1 per year are considered exceptionally high, and often the EIR is too low to be measureable.
b) The parasite prevalence rate. This is the proportion of people who at a given point in time are carrying malaria parasites in their blood. Not all of these will exhibit symptoms- in many parts of Africa it would not be untypical for a quarter of the adult population to have malaria at any given time, but be asymptomatic as they are protected by immunity to disease.
c) The clinical attack rate. This is the average number of clinical attacks (i.e. with symptoms) a person will have in a year. This is limited by immunity.

All of these measures are useful where transmission is high, and the impact of control measures can be measured by reductions in EIR or parasite prevalence. The EIR can however be immeasurably small where R_0 is well above 1. Falls of EIR to zero therefore are excellent news for control, but do not necessarily indicate elimination is realistic.

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[22] If **p** is reduced by half, transmission will decline by a factor $\mathbf{p}^{10} = 0.5^{10} = 1/1024 = 0.001$, i.e. a reduction of 99.9%.