Foresight

Infectious Diseases: preparing for the future

OFFICE OF SCIENCE AND INNOVATION

T5.8: Malaria in Africa: sources, risks, drivers and disease burden 2005–2030

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Abstract:

Malaria is a disease caused by the parasite *Plasmodium*, and transmitted to humans by bites from mosquitoes of the genus Anopheles. Human infections caused by *Plasmodium falciparum* can be life-threatening, especially for young children. Immunity significantly modifies the risks of severe disease and death as individuals get older, with the exception of pregnancy where women loose some of their acquired immunity. The authors estimate that 343 million people would have experienced a clinical attack of *P. falciparum* malaria and approximately 1 million would have died in Africa in 2005. The future of Africa's malaria burden will depend largely on the scaling-up of interventions that prevent infection (e.g. insecticide-treated nets or indoor residual house-spraying) or disease progression (e.g. prompt access to effective Artemisinin-based combination medicines to treat disease).`

These tools are available but are not being deployed rapidly or widely enough. A malaria vaccine will complement these interventions but is unlikely to be available for wide-spread deployment for another 15 years. A range of extrinsic factors will increase the malaria burden independent of intervention measures over the next 25 years. These include the coincidental distribution of the HIV pandemic, economic and political instability, under-nutrition and co-infection with other parasitic diseases. The rapid extent of urbanisation will paradoxically reduce the risk of malaria. Climate change is unlikely to affect the distribution or health burden of malaria in Africa. Because malaria contributes to poverty and poverty perpetuates malaria, the future malaria burden will be intimately tied to efforts to reduce poverty in Africa.

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1 Introduction

Mosquitoes of the genus Anopheles are the vector for the four Plasmodia parasites that cause malaria in humans (Greenwood et al. 2005). All four species of Plasmodia are found in Africa, but only *Plasmodium falciparum* and, to a much lesser extent, *P. vivax* are of public health significance. Members of the *Anopheles gambiae* complex are the most efficient vectors for *P. falciparum* malaria in Africa. Female anophelines require vertebrate blood to support egg production and may become infected with plasmodia (gametocytes) during feeding. They become infective on further feeding after sporogony, the temperature-dependent interval it takes for the malaria parasite to complete the sexual stage of its lifecycle in the mosquito. Unlike some vector-borne diseases, there is no reservoir species for malaria that can act as an additional source of infection. Human infection risks are highly heterogeneous across Africa, and an individual may receive between 0.3 and 1,000 malaria-infected bites per year (Hay et al. 2000).

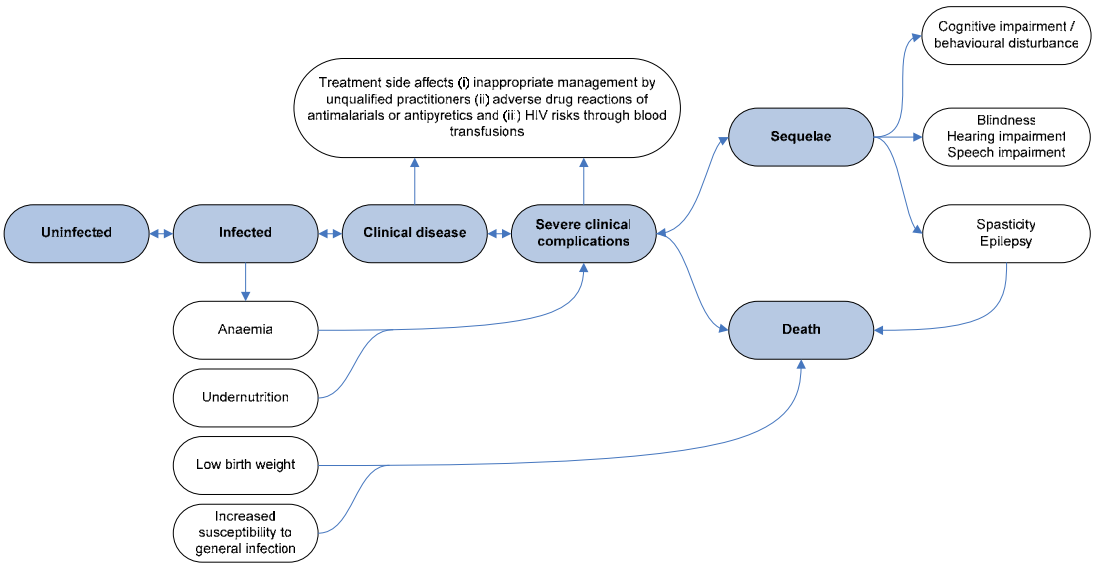
The relationships between *P. falciparum* infection, morbidity and disease outcome are complex. Individuals born into areas of stable *P. falciparum* transmission frequently move between periods of being infected with the parasite and states where they remain uninfected. Most individuals will, at some stage in their lives, develop a clinical response to infection, which often manifests itself as a febrile event. These clinical events may be self-limiting or may progress to a severe, life-threatening illness, in which case the patient survives through medical intervention or dies. There are additional morbid and fatal consequences associated with each step of the infection and disease process. Intervention trials have demonstrated that mortality in childhood is reduced beyond what would have been anticipated from a direct effect on malaria-specific deaths.

When malaria infection is viewed as a risk factor, increasing parasite exposure has been shown to account for over 60% of the variation in all-cause mortality in young African children (Snow et al. 2004). This probably operates through a series of mechanisms including: chronic sub-clinical infection leading to anaemia or other forms of malnutrition that independently increase susceptibility to severe clinical outcomes of future malaria infection; sub-clinical infections predisposing to the severity and outcome of other infectious diseases; or through asymptomatic infection of the placenta of a pregnant woman that significantly reduces birth weights and reduces children’s survival chances. A hidden burden is borne by patients who survive the severe consequences of infection and are left with debilitating sequelae, such as spasticity or epilepsy (Mung’ala et al. 2004), or more subtle consequences including behavioural disturbances or cognitive impairment (Holding and Kitsao-Wekelo 2004). The direct and indirect consequences of *P. falciparum* infection are summarised in Figure 1.

A characteristic of malaria in most parts of Africa is that infection with *P. falciparum* is common, and death from malaria, while numerically considerable at the population level, is relatively rare compared to the lifetime risks and frequency of infection. Most severe outcomes and death following

infection occur in children, indicating that the acquisition of immunity during childhood is an important survival mechanism for populations living under the conditions of stable, endemic malaria transmission common to Africa south of the Sahara. The cost, in terms of child deaths, is sufficiently high to have selected over many generations for several innate, genetic polymorphisms associated with red cell structure and function that confer protection against infection and disease (Weatherall and Clegg 2001).

Figure 1: The direct, indirect and consequential clinical consequences of *P. falciparum* infection (redrawn from Snow and Gilles, 2000)

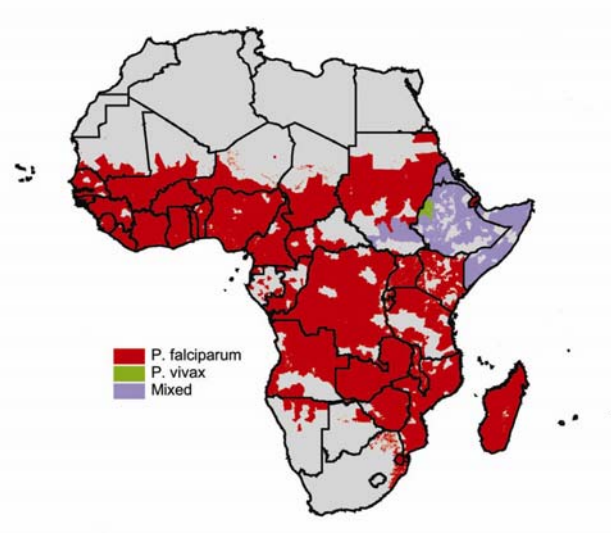


2 Measuring malaria risks and disease in Africa

Malaria distinguishes itself from other fatal, infectious pathogens in Africa, such as HIV and tuberculosis, in several important respects. First, *P. falciparum* infection is a universally common experience with almost all semi-immune individuals becoming sick at least once a year. Second, the febrile presentation of malaria is hard to distinguish from other common infectious diseases. Finally, the majority of fevers are managed at home without contact with formal health services. Those that do present to the formal health service (including those with diagnostic facilities such as microscopy) are often presumptively treated as malaria without detailed clinical and laboratory investigation.

The use of national disease registration systems (i.e. passive detection) to provide accurate estimates of disease burden rests on three assumptions: complete temporal coverage (every month is reported by a facility); complete spatial coverage (every health facility reports nationwide); and all disease events that present are reported accurately by health facilities. An example from the recently published *World Malaria Report* shows that nationally reported malaria cases in Kenya declined from 3.8 to 0.1 million cases over the period 1996–2002 (WHO 2005), whereas detailed estimates suggest that

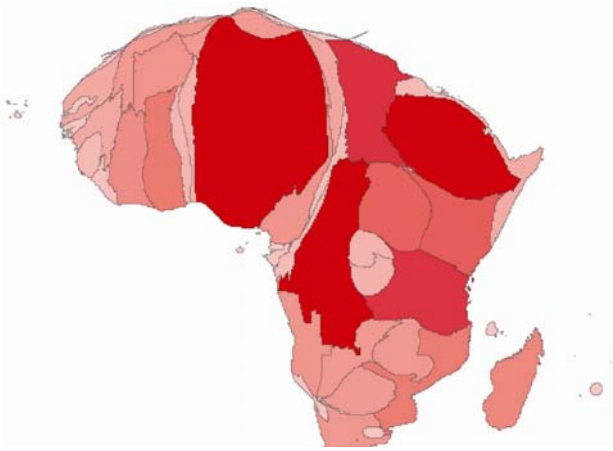
Figure 2a: Spatial extents of malaria risk in Africa



0.05 million cases would have been described in one of Kenya's 70 districts in 2002 (Mwangi et al. 2005). This highlights a common problem of malaria disease registration across the continent. It reflects more the vagaries of reporting than epidemiological reality (Azubuike and Ehiri 1999; Arudo et al. 2003). It is widely accepted that national disease reporting systems are woefully inadequate to define malaria burdens or to monitor trends in Africa.

Alternative approaches have been developed to estimate the risks of infection, illness and death due to *P. falciparum* across the continent. Recent advances in our understanding of disease epidemiology and the application of remotely sensed imagery from Earth-orbiting satellites have improved the precision with which risk and disease burdens can be estimated from limited, but high-quality, information. These models combine epidemiological research data on disease risk, ecological determinants of transmission and the demographics of populations on the continent. The 2005 biological limits of parasite transmission are shown in Figure 2a, representing 510 million and 23 million people at risk of *P. falciparum* and *P. vivax* infection respectively (Guerra et al. 2005; Note 1). Figure 2b highlights countries contributing the highest continental-level *P. falciparum* populations at risk (PAR).

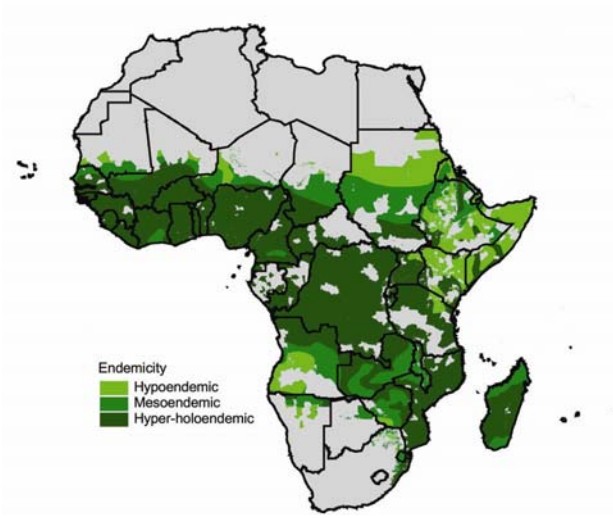
Figure 2b: Cartogram of population weighted *P. falciparum* risk in 2005. Red goes from darker to lighter according to higher or lower PAR. The size of the country area is the PAR weight of the areal unit (www.mapresso.com)



One consequence of living in a setting of high-intensity transmission is that children are exposed to malaria and develop immunity at a younger age than those in lower-transmission areas. Where the risks of infection are very low, the acquisition of immunity is slow, leaving all age groups at risk of both disease and death following parasite exposure. These risks will simply be a function of chance encounters with the parasite (Snow and Marsh 2002). The development of a contemporary, malaria-intensity risk map for *P. falciparum* in Africa is part of our

ongoing research efforts. This map will ultimately model the diversity of parasite exposure among communities across the continent, allowing for uncertainty and projected changes in various scenarios (Section 4.3). In the interim, historical spatial descriptions of malaria transmission intensity have been modified to accommodate changes in the extent of no risk, population growth and urbanisation (Figure 3: modified from Hay et al. 2004; 2005; Snow et al. 2005; Note 2).

Figure 3: Malaria-intensity adjusted population distribution risk map for Africa 2005 (see Note 2 for description of endemicity classes)



Immuno-epidemiological principles have been used to reconstruct prospective research survey data on the annualised risks of malaria disease and mortality from sites across Africa. These have been applied to PAR to develop a more informed understanding of the malaria burden on the continent, and they avoid the inadequacies of national disease reporting (modified using approaches described in Snow et al. 1999, 2003; Note 3).

Using these approaches, we estimate that, during 2005, 343.4 million clinical attacks of malaria are likely to have occurred in Africa; 209 million will be among children aged less than five years and over 86% will have occurred in areas of high malaria transmission. These estimates are five times higher than those generated by national disease reporting systems on the continent (total = 65 million, WHO 2005). The gross inadequacies in reporting disease events are amplified for deaths in that the majority of childhood deaths occur at home and go unregistered in any civil statistics. The WHO reported 93,404 malaria deaths from national statistics in their recent *World Malaria Report* (WHO 2005). Using similar modelled approaches to morbidity measurement, we estimate that, during 2005, Africa is likely to have witnessed 0.97 million deaths attributed directly to malaria, with 69% among children under five.

3 Drivers of changing malaria burdens in Africa between 2005, 2015 and 2030

The potential, natural distribution of malaria is progressively limited by environmental, population and social constraints or drivers. The environmental drivers are determined by the sensitivity of anopheline vectors and their plasmodium parasites to climate (temperature, rainfall and humidity and, thus, latitude and elevation). The population drivers reflect the requirement of the coincidental location of vector, parasite and humans, which further constrains the geographical extent of malaria. Many parts of Africa are uninhabited, for

example, while, in other parts, population density can be so high that malaria transmission is limited by urbanisation. Populations can also be independently affected by other conditions, such as immunosuppressive diseases like HIV/AIDS and malnutrition, that alter their susceptibility to malaria. The social determinants are anthropogenic activities including changes in land use (deforestation, agriculture etc.) and climate, but the most important determinant of the future limits, intensity and public health outcomes of *P. falciparum* in Africa in the next 15–20 years should be the scaling up of access to interventions. These will constrain the natural transmission limits and distributions of risk intensity across the continent, if implemented on a large scale.

3.1 Scaling up access to interventions

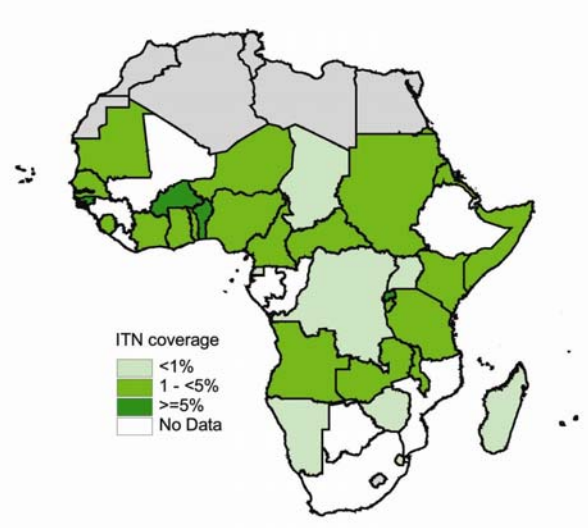
Without question, the most important driver of change to malaria risk and disease outcome in the next 10–20 years in Africa will be expansion in the use of interventions of proven efficacy.

Interventions can be divided broadly according to their effects on changing the risks of infection/transmission and on disease outcomes. During the last 20 years, an impressive body of evidence has been generated on the effects of preventing human-vector contact through the use of insecticide-treated nets (ITNs), the impact of failing and effective drugs on disease/transmission risks, novel uses of drugs through intermittent presumptive treatment and, to a lesser extent, the impact of direct insecticide targeting of vectors.

3.1.1 ITNs

The current combined evidence indicates that ITNs can reduce all-cause childhood mortality by 17%, resulting in 5.5 deaths averted for every 1,000 African children protected. Over 50% of clinical attacks can be prevented through the wide-scale use of ITNs, and infection prevalence can be reduced by 13% (Lengeler 2004). Health impacts are maximised when large sectors of a community are using ITNs, thereby providing a ‘public good’ by reducing local transmission (Curtis et al. 2005).

Figure 4: Countries in Africa with childhood ITN coverage (grey areas represent countries of no malaria risk)



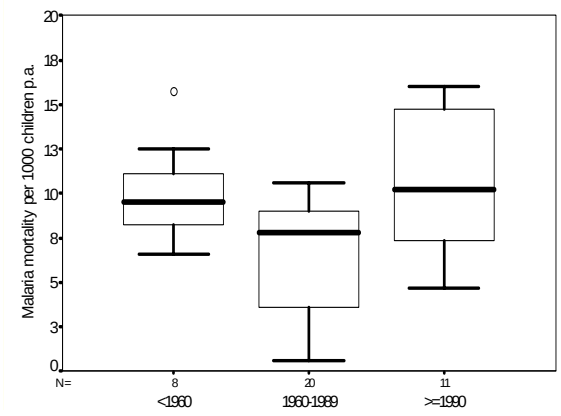
The first clinical trial of ITNs was undertaken over 20 years ago (Snow et al. 1988). According to national sample surveys in 33 African countries between 1999 and 2004, 1.9% of African children sleep under a net treated with insecticide. Only 7 of 33 countries have

achieved ITN coverage in excess of 5%. The only two countries to have reached a coverage ≥10%, the Gambia and Sao Tome and Principe, are among the smallest nations in Africa (Figure 4; Note 7). The Roll Back Malaria partnership has set a target of 60% of children sleeping under an ITN by 2010 (WHO 1999), which it recognises it will not meet if delivery approaches continue to be dependent upon poor people paying for the intervention (Curtis et al. 2003). There is now an effort to promote free nets as part of mass-vaccination campaigns, routine childhood immunisation and antenatal clinics (WHO, 2004). Re-treatment of nets has proved difficult to maintain in many African settings. However, the recent launch of two registered brands of permanently treated nets should circumvent this problem. These long-lasting insecticide-treated nets (LLITN: 50% of original anopheline knock-down efficacy remaining after two years) cost approximately US$4.80 each (RBM/WHO 2004).

3.1.2 Access to effective medicines

Cheap drugs such as chloroquine (CQ) and suplhadoxine-pyrimethamine (SP) have formed the bedrock of malaria management in Africa for the last 50 years. During the early 1990s, there was a rapid expansion of resistance to both drugs among the parasite populations (Talisuna et al. 2004; Roper et al. 2004). The result was a significant increase in malaria mortality in this period to levels comparable with those witnessed before Africa achieved universal independence from colonial rule. These rises took place despite a general decline in childhood deaths not attributed to malaria (Figure 5; Snow et al. 2003b).

Figure 5: Changes in malaria-specific mortality between 1912 and 1997 in Africa (Snow et al. 2003)



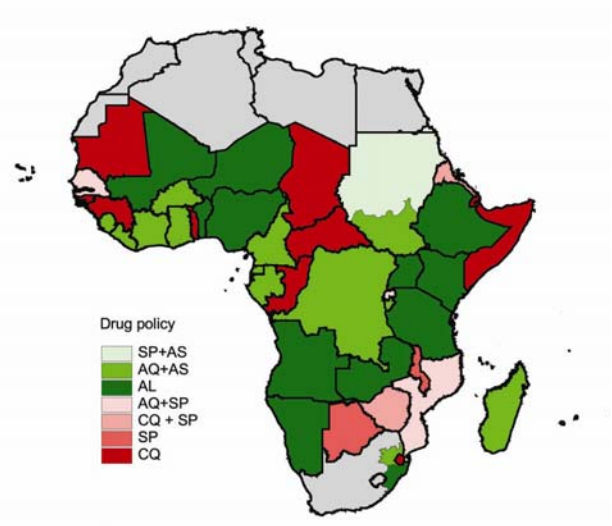
Currently favoured replacements for failing drugs in Africa are new compounds or existing drugs combined with artemisinin derivatives. These drugs have proved highly efficacious in areas of CQ and SP resistance (ISAG 2004) and offer real hope for the management of malaria in Africa. Empirical evidence of the benefits of introducing effective medicines comes from serial observations in the Kwa-Zulu Natal Province of South Africa, which demonstrated a dramatic decline in malaria morbidity following the introduction of artemether-lumefanthrine (AL) (Barnes and Folb 2004).

Artemisinin-based combination therapies (ACT) have additional benefits through the reduction in transmission, thereby serving as a public good in similar ways to wide-scale use of ITNs. The introduction of a combination of mefloquine and artesunate (AS) therapy among refugees along the Thai–

Burmese border was associated with an 18.5-fold reduction in gametocyte carriage rates, halving the *P. falciparum* transmission rates in the area (Nosten et al. 2000). Recent studies in the Gambia confirm that the use of AL can reduce sequestered immature gametocytes by as much as 6-fold compared to CQ/SP combinations (Sutherland et al. 2005).

Twenty-eight ministries of health have opted for ACT to replace failing monotherapeutics (Figure 6, Note 8). However, 15 of these, as of May 2005, were yet to have effectively implemented new drug policies.

Figure 6: Countries that have proposed national first-line treatment policy changes to ACT shown in green. Countries retaining CQ in dark red. Other combinations and use of SP shown as per legend (Note 8)



There are several potential, future threats to the likely success of wide-scale use of ACT in Africa by 2015. First, new ACT drugs cost 10 times more than current failing drugs, which puts them beyond the essential drugs budgets of most poor countries, which already require huge quantities of drugs to manage their fever burdens (Note 9). In response, the Global Fund for Tuberculosis, AIDS and Malaria (GFATM) has actively sought to encourage countries considering changing to ACT to solicit funding from them. This has been a successful route for funding. But it will only continue to be effective if there are guarantees of long-term sustainable financing. Alternative financing proposals, such as the centralised subsidisation of ACT production costs to levels similar to CQ or SP production, might prove easier options (IOM 2004). The second threat is that there is a dependence on the agricultural sector to produce sufficient quantities of the wormwood plant *Artemisia annua,* the source of artemisinins. Expansion of this agricultural subsector, diversification and improved financial regulation and insured/assured markets is critical. In the longer term, synthetic artemisinin compounds might eventually alleviate this sole dependence on natural products (Tang et al. 2004). Thirdly, even when CQ and SP were effective, appropriate use of these drugs at the point of clinical care was sub-optimal. Drugs must be given to the right patients, in the correct doses and with supportive care and counselling. Without equivalent investments in improving the standards of clinical care and diagnostics in Africa, effective medicines will not reach their maximum potential to reduce disease burdens and infection risks. Finally, access to medicines in much of Africa remains poor. In Kenya, less than 5% of children received an antimalarial within 24 hours of the onset of symptoms (Amin et al. 2003). Increasing accessibility to new ACTs for the most vulnerable groups, largely African children, will require innovative approaches to be developed and implemented at scale.

3.1.3 Indoor residual spraying (IRS)

IRS was instrumental in breaking malaria transmission in many parts of the world, including Sri Lanka and South America (WHO 1969). There is a paucity of community-wide, randomised controlled trials of IRS across Africa on which to make an informed choice about the likely benefits of this approach in reducing morbidity and mortality. Most studies have been undertaken in areas of low transmission, with results comparable to those of ITN use (Curtis and Mnzava 2000; Curtis et al. 1999; Goodman et al. 2001; Guyatt et al. 2002a). It is accepted, however, that interruption of transmission is harder to achieve under conditions of intense perennial transmission, while the logistical requirements and co-operation of the community to support effective IRS are thought to be harder to achieve in these remote areas of Africa.

There are 1.9 million people living at risk of hypoendemic malaria in southern Africa (Botswana, Zimbabwe, Swaziland, South Africa and Namibia), 0.67 million people living under hypoendemic conditions in rural, highland (≥1,500 million) communities in east Africa (Uganda, Tanzania, Kenya, Rwanda and Burundi) and 2.73 million people living in the peripheries of urban extents that experience hypoendemic malaria. Although these areas experience the lowest disease and mortality burdens (Note 3), it might be expected that a large impact on transmission might be achieved here, assuming that widespread and sustainable use of IRS were possible. These targeted areas are also the least poor communities and countries in Africa, so an average cost of US$1–2 per person protected might be affordable (Note 10).

3.1.4 Environmental management (EM)

The WHO defines EM as the implementation of activities related to the modification or manipulation of environmental factors to minimise vector propagation in order to reduce human–vector interaction. Three accepted strategies for EM are: (1) environmental modification (e.g. the removal or drainage of water); (2) environmental manipulation (e.g. polystyrene beads, filling with soil or the use of Bti toxin derived from the bacteria *Bacillus thuringiensis*); and (3) reducing human contact with infective vectors by zooprophylaxis, modification of human habitations, or purposely changing human behaviour. Recent reviews that promote the use of EM strategies (Killeen et al. 2000; Utzinger et al. 2001; Konradsen et al. 2004) have been unable to provide sufficient evidence that such approaches would be more cost-efficient per disease event averted than ITNs or IRS. While EM approaches might be low-cost and village-scale activities worthy of promotion, it seems extremely unlikely that they will form the basis of evidence-based, national disease prevention activities across Africa over the next 10–20 years.

3.1.5 Intermittent presumptive treatment (IPT) (pregnant women and infants)

It is estimated that, each year, over 30 million women become pregnant in malarious areas of Africa. In meso-holoendemic settings, pregnant women experience relatively little malaria-specific morbidity (e.g. fever) but have an increased risk of infection and higher-density parasitaemia leading to anaemia

and placental sequestration of the parasite (Guyatt and Snow 2001a; Steketee et al. 2001). Maternal anaemia is an important contributor to maternal mortality (elevated relative risks of 3.51 for severe anaemia), and it is estimated that 9% of the excess risk is directly attributed to *P. falciparum* infection (Brabin et al. 2001). Prematurity and low birth weight (<2,500 grams) associated with maternal malaria have been reported to indirectly contribute to between 3% and 8% of infant mortality (Steketee et al. 2001; Guyatt and Snow 2001b). If applied to the expected numbers of live births in meso-holoendemic areas of Africa, there may be as many as 100,000 infant deaths attributable to malaria in pregnancy (Guyatt and Snow 2004).

A therapeutic course of SP given on two or three occasions during the second or third trimesters of pregnancy (IPTp) is effective at preventing infection of the placenta, reduces the incidence of anaemia in pregnant mothers and increases the birth weights of newborn children (Schultz et al. 1994; Shulman et al. 1999, Rogerson et al. 2000; Van Eijk et al. 2004). However, the medium-term impact of IPTp is compromised for two reasons: (a) the efficacy of IPTp is reduced in HIV-positive women (Van Eijk et al. 2004); and (b) there are no safe alternatives for IPTp in areas where there is a rapid expansion of SP-resistant parasites.

The concept of IPT has recently been extended to target infants (IPTi) by providing therapeutic courses of antimalarials at the same time as vaccination. Two studies in Tanzania demonstrated that the provision of SP (Shellenberg et al. 2001) or amodiaquine (Massaga et al. 2003) reduced the incidence of malaria and severe anaemia during the first year of life by 59–64% and 50–67% respectively. The combined effects of IPTi and ITN are currently under investigation (Note 11).

3.1.6 Malaria vaccines

Historically, vaccines have been one of the most effective public health tools for controlling infectious diseases and, given the scale of the problem, effective vaccines against malaria could make a decisive difference. The complexity of the parasite's biology presents formidable problems for vaccine development such that optimism about the prospects for effective vaccination has waxed and waned over the last 20 years. Nevertheless, there is a major international effort to develop vaccines, and the WHO portfolio (www.who.int/vaccine_research/documents /en/malaria_table.pdf) lists 93 different vaccines under development in May 2005. Although many of these are variations on similar themes, there are a wide range of antigens and delivery systems targeted at all parts of the parasite lifecycle. Eleven different vaccines are currently at the stage of trials in endemic areas, either for safety and immunogenicity (7) or for efficacy (4). The most advanced candidate is RTS,S, a vaccine designed to prevent infection by targeting the pre-erythrocytic parasite. Trials in young children in Mozambique showed a protective efficacy of 30% against malaria disease and suggested that this may be higher against severe disease (Alonso et al. 2004). Phase-three trials in infants are likely to begin within the next two years, but even if these achieve convincing protection and regulatory and production scale-up issues are addressed rapidly, it is unlikely that a product for public health application

would be available before 2012. Other candidates are on a considerably longer timeline.

In summary, then, although the outlook for developing effective vaccines in the longer term is good, there is no prospect of a significant public health impact in the next 10 years. Indeed, a 20-year timeframe would probably be more realistic.

3.2 Demographic change

The UN Population Division (UNPD) predicts that Africa's population will grow from 0.906 billion in 2005 to 1.115 billion by 2015 and to 1.463 billion by 2030, assuming the medium variant fertility scenario (Note 4). All else being equal, the populations at risk of malaria will increase substantially over this time. With expanding populations, patterns and intensity of land use will change. The rate of population growth in urban areas is significantly higher than in rural regions, and so, some time before 2025, Africa will transition to a majority urban population. The growth of urban areas has important implications for malaria risk. Reviews of the influence of urbanisation on malaria transmission (Hay et al. 2000, 2005; Robert et al. 2003; Omumbo et al. 2005) indicate that a systematic reduction of *P. falciparum* risk occurs in urban areas due to reduced (i) anopheline species diversity; (ii) biting rates; (iii) mosquito infection rates; (iv) transmission; and thus (v) human malaria infections. Hay et al. (2005) estimate that urbanisation in Africa may reduce malaria mortality on the continent by 6.7%. Urbanisation might be expected to reduce the risks of parasite exposure in up to 53.5% of Africa's population by 2030, assuming UN definitions. Longer-term work investigating the interaction of these changes in urban settlement patterns and harmonising UN demographic descriptions of urban settlement with those most appropriate for vector-borne disease epidemiology is ongoing.

3.3 Land-use changes

The pressure on agricultural land as populations grow can lead to deforestation, increases in irrigation and dams, while poor land management can result in desertification. The influence of changes in land cover and land use on malaria are heavily dependent on the local contextual determinants of transmission, such that their impacts are rarely uniform. Deforestation rates in the 1990s in Africa (0.36% per annum) exceeded those in South America (0.33% per annum) and are projected to increase as human capacity to exploit forest habitat grows (Mayaux et al. 2005). The epidemiological impact of deforestation on malaria in Africa is unclear. Walsh et al. (1993) argue that deforestation will not radically alter the pattern of malaria, despite studies showing that deforestation favours the more efficient malaria vector *An. gambiae* over the forest vector *An. moucheti*, leading to higher transmission rates in deforested areas (Manga et al. 1995). Work is in progress to review systematically the relevant evidence.

In contrast, there has been a recent review of the global impact of irrigation and large dams on the malaria burden (Keiser et al. 2005). Africa has 9 million people exposed to enhanced malaria risk due to irrigated agriculture and large

dams. Of the 525 large and 45,594 small dams in Africa, most have been built since 1950, and these land-use patterns are set to increase in the next 10–20 years (Keiser et al. 2005). Some of the effects on malaria are vector-species specific. For example, the comeback of *An. funestus* in the Sahel after periods of extended drought and desertification has also been suggested to be due to irrigation (Konate et al. 2001), although reappearances elsewhere show this to be related to a return to a relatively wetter norm for the region (Labbo et al. 2004). Attempting to quantify some of these impacts will be the subject of future scenario modelling exercises.

3.4 Climate change

Malaria distribution, endemicity and seasonality are all linked fundamentally to climate (Rogers and Randolph 2000). It is also widely accepted that the Earth's climate is warming (IPCC 2001). It is a significant logical fallacy, however, to juxtapose these statements and thereby conclude that long-term changes in mean climate are already responsible for increases in malaria across Africa. There has been an absence of significant trends in time-series of meteorological variables extracted from synoptic climatologies at sites documenting malaria resurgences in east Africa (Hay et al. 2002a, 2002b). In addition, climate-derived indices of *P. falciparum* transmission (Craig et al. 1999) have also been shown to have been relatively insensitive to changes in temperature and rainfall during the entire 20th century (Small et al. 2003; Thomas 2004).

Modelling exercises using these same climate-derived indices of transmission (Craig et al. 1999), through various scenarios of climatic change, also warn that it would be unwise to assume a simple, unimodal response of malaria to future climate change (Thomas et al. 2004). Specifically, the climate scenario used was the medium–high, second-generation Hadley Centre global circulation model. This was deployed to generate synoptic climates for 30-year spans centred on the years 2025, 2055 and 2085. The results indicated that, in the next 30–40 years, the effects of climate change on stable *P. falciparum* malaria zones in Africa are complex and spatially heterogeneous, and that range contractions were more likely than expansions. Notably, there was no evidence that the highlands were particularly vulnerable to change in this period. It was only by the second half of this century that increases in the potential for stable transmission in the highlands were projected to be strong, though extremely heterogeneous. The authors conclude that climate change was unlikely to lead to widespread expansion in the distribution of stable malaria in Africa in the next few decades. Moreover, since the most recent and largest ever assemblage of climate predictions suggest little discernable climate change before 2030 (Stainforth et al. 2005), we expect, contrary to dogma, climate change to have a negligible effect on Africa's malaria burden by 2030.

3.5 Population movement and civil unrest

The massive expansion of global air travel has resulted in continued export of African *Anopheles gambiae* s.l. mosquitoes, giving rise to numerous cases of local malaria transmission in regions of the world declared 'malaria-free'.

African air traffic to European destinations represents a risk of *P.-falciparum*-infected *An. gambiae* invasion for just 2–4 months in an average year, when the European summer climate matches that of the principal west African malaria transmission season (Note 6; Tatem et al. 2005). Central America and the Caribbean are the regions most at risk of infected mosquito invasion, as their climates demonstrate the greatest similarity and annual synchrony with African malaria-transmission seasons.

The introduction of new air routes between Africa and these regions undoubtedly warrants extra vigilance. Current predictions are that air traveller volume will continue to increase dramatically over the next 15 years (Upham et al. 2003), and sea and land travel risks of malaria invasion will require future modelling and monitoring. Attempting to quantify some of these future trends will also be the subject of future scenario modelling exercises.

Regional conflicts result in massive population movements to avoid the ravages of war. The exodus of people traditionally unexposed to malaria from the hills and mountains of Burundi into endemic conditions in Tanzania resulted in a severe epidemic among these refugees in the mid-1990s. Displacement of non-immune populations to endemic settings, populations that become malnourished as refugees from their normal livelihoods, or exposing populations to newly created breeding sites all increase local transmission and disease risks. In Ethiopia, all these factors led to enormous morbidity and mortality when a relocation of famine-stricken populations from the relatively low endemicity highlands to the south-west took place (Woube 1997). This did not stop it being repeated in 2004. These migrations are very hard to predict and thus to project over time, but they are likely to remain a constant threat among many fragile political and economic systems in west and central Africa.

3.6 Risk modifiers

3.6.1 HIV

In sub-Saharan Africa, the HIV epidemic has been superimposed on the long-standing malaria pandemic. The wide geographical overlap and the concurrent high prevalence of both HIV and malaria mean that even modest interactions could lead to substantial public health impacts among populations exposed to both diseases. HIV-infected adults in malaria-endemic areas and HIV patients of all ages in areas of unstable malaria transmission have been shown to be at increased risk of malaria infection and death (French et al. 2001; Whitworth et al. 2000; Chandramohan and Greenwood 1998); an increased case–fatality rate of malaria is also apparent in HIV-infected children in endemic areas (Greenberg et al. 1991). Korenromp et al. (2005) have modelled the potential impact of the increasing HIV epidemic on malaria incidence in Africa, allowing for the stage of the HIV epidemic and malaria endemicity in any given setting. They estimate that HIV increased malaria incidence across 41 countries by 1.4% and malaria mortality by 6.1%. The impact of HIV on malaria was limited due to the different geographical distributions of HIV and malaria (urban and southern Africa versus rural and west Africa) and due to their different age patterns (peaks in adults and under-

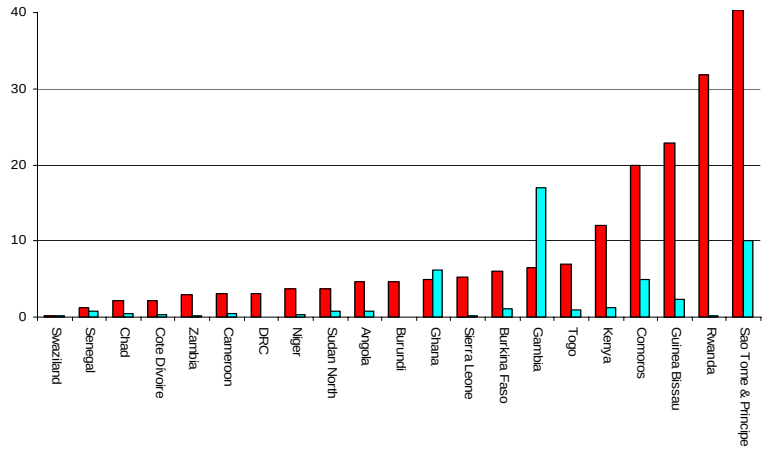
fives, respectively). In Botswana, Zimbabwe, Swaziland, South Africa and Namibia, however, malaria incidence and mortality increased by up to 29% and 119%, respectively, due to the co-existence of high HIV prevalence in rural areas of unstable malaria transmission.

Interactions between malaria and HIV are particularly important among pregnant women who, when co-infected, have a compounded higher risk of clinical attacks of malaria, anaemia and an increased risk of giving birth to a low birth-weight baby (Van Eijk et al. 2002). It is estimated that an additional 500,000 women will develop clinical malaria in Africa as a direct result of being HIV-infected (WHO 2004b). What remains unclear is whether malaria infection during pregnancy increases the vertical transmission of HIV.

3.6.2 Poverty and economic growth

Malaria and HIV/AIDS are diseases both borne of and contributing to poverty. The economic burden of malaria, estimated by means of cross-country regression analysis, shows that the disease is a significant factor in long-term economic growth, accounting for 0.25–1.3 percentage points. (Gallup and Sachs 2001). As such, it has been suggested that, over time, malaria alone may reduce per capita gross domestic product (GDP) in Africa by almost half. Conversely, Shepard et al. (1991) reviewed a series of cost-of-illness studies in Africa and proposed that, in 1987, a case of malaria cost US$9.84 (US$1.83 as the direct cost and US$8.01 as the indirect cost resulting from foregone income associated with malaria morbidity and mortality). They estimated the total cost as US$0.8 billion for Africa and that this represented 0.6–1.0% of the GDP of sub-Saharan-African economies. These disparities between the macroeconomic analysis of malaria's impact on per capita GDP and microeconomic studies of the composite costs to households highlight our poor understanding of the causal pathways between malaria and the compounded effects on household and national economies (Malaney et al. 2004).

Figure 7: Percentage ITN coverage in 21 countries in Africa expressed as coverage among the least-poor quintile (red) versus the poorest quintile (blue) (Note 12)



From a different perspective, poverty serves to limit access to interventions. There is now consistent evidence across Africa that the poorest quintiles of communities have the poorest access to and utilisation of preventative measures such as ITNs or antenatal services (Figure 7; Note 12) and the lowest use of

curative services for febrile illnesses (Armstrong-Schellenberg et al. 2003). Poverty therefore serves as a determinant of whether communities have the means to protect themselves from infection and access curative services when infections develop into a disease event.

While it is evident that malaria remains entrenched in the poorest regions of the world, this fact alone is insufficient to determine the future impact of malaria reduction on economic growth or the effects of maintaining communities in poverty and their increasing risks of malaria. Poor people, however, have considerably less access to interventions. The complex interaction between poverty, economic growth and household capacities to access interventions is an area that requires further research before effective future scenario projections can be made.

3.6.3 Malnutrition and worms

One striking feature of the global distribution of anthropometric markers of undernutrition and helminth infections is their congruence with the distribution of endemic malaria. Although *P. falciparum* malaria and malnutrition are both highly prevalent in sub-Saharan Africa, the existence of any precise clinical–epidemiological synergistic interaction has not been well established (Note 13). There is equally conflicting evidence surrounding the effects of worm burdens on *P. falciparum* infection prevalence and clinical incidence (Shapiro et al. 2005; Nacher 2004) and the role of micronutrients, particularly Vitamin A and Zinc (Nussenblatt and Semba 2002).

Evidence from ITN trials suggests improved growth among protected young children compared to unprotected children (D'Allessando et al. 1995; Snow et al. 1997b: Ter Kuile et al. 2003). Despite the biological plausibility of synergism, spatial congruence and some conflicting supportive evidence, the precise relationships between undernutrition, micronutrient deficiencies and helminth infections and the risks of clinical malaria require further investigation before empirical, projected, causal risk pathways can be quantified.

4 Summary views

4.1 Malaria risk and disease detection

Our only global and hence continental risk map of malaria transmission intensity was developed 40 years ago. New models of infection risk appropriate for understanding the epidemiology of the disease and its control today are needed urgently. The inadequacy of current malaria notification systems in Africa negates their use in defining current disease burdens or the likely impact of drivers of changing infection risk or disease outcome in the next two decades.

Preliminary models of infection risk and disease outcome have been developed that accommodate drivers of malaria transmission (climate and population settlement) and immunological drivers of age- and transmission-dependent disease risks. These now form the basis of UN approaches to

modelling malaria morbidity and mortality in Africa, led by the research community.

Future modelling of risk and disease will need to accommodate dynamic projections of changes in the most significant drivers, notably intervention access and coverage, population growth and settlement patterns, changes in land use, and changes in effect modifiers such as HIV, nutritional status and poverty.

4.2 Drivers of change and measuring uncertainty

The pressures of global change will undoubtedly cause the dynamics of malaria risk in Africa to evolve. It is unlikely, however, that the high basic reproduction rate of infection for *P. falciparum* will ever be reduced to the point of interrupting transmission across much of Africa. Subtle changes in climate and land use, while likely to influence vector-borne diseases outside Africa, are unlikely to impact greatly on malaria in this continent. Infection risks, disease and death from malaria will never be eliminated from Africa. But there is every reason to expect that scaling-up combinations of interventions that reduce human–vector contact, transmission and disease will, by 2015, substantially impact on the current estimated 350 million clinical attacks and 1 million deaths suffered by Africa's populations each year. Predictable demographic changes in population size, land use and the growing HIV epidemic will, however, create a moving target for the international community's malaria development goals in the next 10–25 years. Our confidence in the various drivers are summarised in the table shown in Note 14.

It is beyond the scope of the present document to quantify the composite risks and their projected spatial dynamics in the period 2005–2030 and is the subject of ongoing research (see below). However, a brief narrative summary is as follows:

Wide-scale use of LLITNs could reduce the clinical incidence of malaria across Africa by as much as 50%. Combined with other comparatively simple-to-deliver interventions such as IPTi, reductions in disease and infection incidence might exceed 60%. Given the saturation of incidence among young children (>1 clinical attack per year), effective medicines to manage disease events remain vital to the long-term success of changing the malaria burden on the continent. New ACT treatments should fill this niche and, additionally, curb the incidence of new infections by reducing the infectious reservoir. The combined effects of LLITN, IPTi and ACT will be non-linear and, importantly, this combination should cost less than US$20 per African child protected. Changes in urbanisation in the next 20 years will naturally alter the infection risk patterns on the continent and might decrease malaria mortality by approximately 6%. Conversely, the growing HIV epidemic, particularly in urban areas, might be expected to increase malaria mortality by approximately 6%. Poverty will serve as a natural barrier to achieving universal coverage of interventions, while malnutrition and polyparasitism will constrain the biological impact of interventions by further extents that require better quantification.

The external modifiers to the biological and population risk models remain as follows: (a) the ability of the international community to effectively create a long-term sustainable financing of commodities such as LLITNs and ACT; (b) the stability and governance of the continent's political structures to ensure a reduction in poverty, civil unrest and an increased performance of the health sector; and (c) linked to these broad development targets would be the reduction in the spread of HIV and reductions in malnutrition that affect disease progression in malaria. The certainty that interventions, if deployed on a broad scale, will have a huge impact is high. We are less certain how the threats to achieving this will impact on attaining universal intervention coverage.

4.3 Research requirements to improve malaria mapping on the continent

Current national and UN approaches to defining malaria risks, their public health impact and projected change are inadequate.

Not knowing where people live in relation to risk impairs the ability to effectively project the need for drugs and nets and therefore constrains the industrial sector's ability to meet demand.

Not knowing the relationships between risk and disease outcome limits the ability to target resources effectively to those most vulnerable and to areas likely to benefit most from selected intervention.

Not knowing the status of intervention coverage by risk and population results in an inability to articulate whether international targets for reducing disease burdens in Africa have been or are yet to be met. Building a credible malaria risk, disease and control atlas for Africa is an important research priority.

We know the likely impacts of ITNs, IPTi and effective drug use on disease outcomes from well-documented clinical trials. These can be modelled with degrees of certainty to estimate population-attributable impacts with combined intervention strategies. These impacts must be structured by different age-, endemicity-, poverty- and urban-specific target populations to create a framework that will make it possible to build credible biological and evidence-based scenarios related to projected variations in malaria risk and disease burden. Establishing the importance of the various drivers of malaria risk and disease is part of current efforts to define accurate global malaria cartography – the Malaria Atlas Project (MAP) that will be linked to broader development targets and causal pathways.

5 Notes

1: Geographical information systems (GIS) were used to triangulate and standardise international travel health guidelines (ITHG) from three independent sources to identify areas of 'no malaria' risk to the second-level administrative units within all African countries. These exclusion limits were further reduced using dominant-vector-species geographical data and climate-suitability criteria (based on temperature and rainfall thresholds (Craig et al. 1999; www.mara.org.za). The MARA model describes climatic conditions (or fuzzy climate suitability: FCS) that range from unsuitable (0) to completely suitable (1) for stable *P. falciparum* transmission. It was assumed that FCS values of zero are incompatible with malaria risk, supported by a recent analysis of parasite prevalence and FCS values in east Africa (Omumbo et al. 2004). The spatial resolution of the MARA model was too coarse to apply exclusions to the territories of Cape Verde, Comoros, Mauritius, Mayotte, and Sao Tome and Principe. For Comoros, the same altitudinal limit as that of Ethiopia (2,000m) was assumed, based on their similar dominant vectors. Altitude masks were unnecessary for the remaining low-lying island states as they have no areas above 1,810m, which is below the lowest altitude threshold reported elsewhere in Africa for the same dominant-vector-species compositions. The limits of transmission were then further constrained according to low population density (<1 person per km^2) and urban extents (>4,218 persons per km^2) using the digital 1 x 1 km interpolated population database created by the Global Rural–Urban Mapping Project (GRUMP) (CIESIN/IPFRI/CIAT, 2004). The iterative procedures were implemented to construct the contemporary African malaria transmission limits and populations were projected using the UN medium variants (see Note 4) to 2005 (Guerra et al. 2005). The following countries were regarded as not at risk of *P. falciparum* or *P. vivax* transmission: Tunisia, Libya, Western Sahara, Egypt and Lesotho. Areas of 'very limited risk' reported by ITHGs in Egypt were not captured by the climate mask and were therefore excluded, despite high malaria risk being documented in Fayoum governorate (Hassan et al. 2003).

2: Global information on 'the structure of worldwide malaria based on initial endemic levels' has been developed by revisiting the work of Lysenko (Lysenko and Semashko 1968; Lysenko and Beljaev 1969; Hay et al. 2004b; Snow et al. 2005), which remains the only global source of such data. Africa was largely regarded as supporting stable malaria transmission and was subdivided into endemicity classes based on a spleen rate classification later revised by Metselaar and Van Thiel (1959) and was thus defined by the parasite rate (PR) in the 2–10-year cohort (hypoendemic <0.1; mesoendemic 0.11–0.5; hyperendemic 0.51–0.75) save the holoendemic class (>0.75) where the PR refers to the one-year age group. These endemicity divisions were based on a major synthesis of historical records, documents and maps of a variety of malariometric indices (records of disease and vector presence and absence, altitude tolerances, spleen rates and parasite rates) used to record malaria endemicity until the mid-1960s. These division boundaries were then interpolated globally for malaria at the peak of its assumed

historical distribution, using a combination of expert opinion and maps of land-cover, land-use, elevation, as well as temperature and rainfall isohyets (Lysenko and Semashko 1968; Lysenko and Beljaev 1969; Hay et al. 2004b).

The Lysenko surfaces were scanned, geo-referenced and digitised from their original source at a scale of 1:3,000,000 using ERDAS Imagine 8.5 (Leica GIS and Mapping, Atlanta, USA) and ArcView (ESRI, Redlands, California, USA). Since the GRUMP HPD has a spatial resolution of 1 x 1 km resolution, overlaying the maps resulted in many GRUMP pixels for which no Lysenko endemicity class would map directly (Hay et al. 2004a). This was particularly apparent around areas with intricate coastlines and small islands. This was resolved pragmatically in ArcView 3.2 by, initially, gridding the scanned Lysenko surface to match the 1 x 1 km spatial resolution of the GRUMP HPD surface. The newly gridded Lysenko map was then expanded at coastlines to ensure every GRUMP HPD pixel had a Lysenko class assigned to it. The global extent of the GRUMP layer was then used to cut the expanded Lysenko surface, to eliminate any sea pixels given a Lysenko assignment in the expansion procedure. Isolated island groups left without an endemicity class in this process were assigned the endemicity of the nearest land mass. The 2005 limits of *P. falciparum* and *P. vivax* distribution were then overlaid on this distribution (Guerra et al. 2005). If any areas within these limits were not assigned a Lysenko endemicity class, it was interpolated with the mean value of its nearest neighbours with ERDAS Imagine 8.5 and manually corrected where necessary. Endemicity was assumed to be largely unchanged in Africa since 1900 and only regions of intense urbanisation (cites ≥1 million persons) and areas with population densities characteristic of the locations have been excluded in defining the transmission limits (Guerra et al. 2005).

3: Epidemiological research data on *P. falciparum* malaria mortality and morbidity have been compiled as part of the Burden of Malaria in Africa (BOMA) project funded by the Wellcome Trust, UK (Snow et al. 1999, 2003; Snow and Marsh 2002). For the purposes of the present analysis, data have been reconstructed to limit information to the period after 1985 and organised according to three malaria endemicity risk classifications (see Note 2): hypoendemic, mesoendemic and a combined class of hyper- and holoendemic. The latter class was merged in recognition that, under this range of malaria transmission, malaria-specific morbidity and mortality rates are likely to reach a plateau (Snow et al. 1997a; Trape and Rogier 1998; Snow and Marsh 2002). Annualised rates of malaria morbidity were obtained from prospective studies of weekly or fortnightly household fever surveillance studies in 22 communities across the continent experiencing the range of endemic conditions. Annualised risks for all ages were applied to total populations in each risk class during 2005 and adjusted for the proportional age-specific risks under different endemicity classifications, as described by Mwangi et al. (2005) and Diallo et al. (2002) and shown in the table below. For mortality, longitudinal demographic surveillance data that employed interview techniques with bereaved relatives were reorganised from previous disease burned estimations (Snow et al. 2003a) to adjust for the three malaria endemicity classes and by ages 0–4 years (27 studies) and 5–14 years (17 studies). Owing to the paucity of contemporary cause-specific, prospective

mortality data among adult populations in Africa, 15 studies dating back to the 1920s have been compiled to provide a single estimate of malaria mortality in this age group (Snow et al. 2003a), see table below. Age- and endemicity-specific annualised rates of malaria-specific mortality were then applied to the respective PAR during 2005.

	0–4 years	5–14 years	15+ years	Total
Hypoendemic				
PAR 2005	8,908,000	14,420,000	30,666,000	53,994,000
Median morbidity rate per person per annum (IQR)	–	–	–	0.043 (0.012, 0.043)
Morbid age-fraction	0.25	0.5	0.25	1
Morbid events (median)	580,436	1,160,871	580,436	2,321,742
Median mortality rate per 1,000 people per annum (IQR)	0.698 (0.382, 1.866)	0.495 (0.249, 0.742)	0.6 (0.37, 0.94)	
Fatal events (median)	6,218	7,138	18,400	13,356
Mesoendemic				
PAR 2005	11,098,000	18,475,000	39,267,000	68,840,000
Median morbidity rate per person per annum (IQR)	–	–	–	0.646 (0.286, 0.691)
Morbid age-fraction	0.48	0.48	0.04	1
Morbid events (median)	21,345,907	21,345,907	17,78,826	44,470,640
Median mortality rate per 1,000 people per annum (IQR)	4.65 (1.894, 7.496)	0.99 (0.443, 1.798)	0.6 (0.37, 0.94)	–
Fatal events (median)	51,606	18,290	23,560	93,456
Hyper/holoendemic				
PAR 2005	66,382,000	105,366,000	215,000,000	386,748,000
Median morbidity rate per person per annum (IQR)	–	–	–	0.767 (0.572. 1.529)
Morbid age-fraction	0.63	0.33	0.04	1
Morbid events (median)	186,880,501	97,889,786	11,865,429	296,635,716
Median mortality rate per 1,000 people per annum (IQR)	9.265 (7.891, 13.007)	1.172 (0.267, 2.363)	0.6 (0.37, 0.94)	
Fatal events (median)	615,029	123,489	129,000	867,518
Total for Africa 2005				
Morbid events	208,806,844	120,396,564	12,445,865	343,428,098
Fatal events	672,853	148,917	170,960	974,330

4: Scenario analyses of demographic trends are well developed (Alho 1997) and widely implemented using the United Nations Population Division's World Population Prospects (UNPD-WPP) database (http://esa.un.org/unpp/) (UN

2005). The UNPD-WPP population projection variants assume total fertility in all countries converges to 1.85 children per woman (cpw) and then held constant. Fertility declines at a rate established from all countries with declining fertility during 1950–2005. Under the high- and low-variant scenarios, fertility is projected to remain 0.5cpw above and below the fertility of the medium variant. Mortality is projected on the basis of models of change of life expectancy produced by the UNPD. For the 60 countries highly affected by the HIV/AIDS epidemic, estimates of the impact are made by modelling the course of the epidemic and by projecting the yearly incidence of HIV infection, revised where appropriate for the longer survival of persons receiving highly active antiretroviral therapy (ART). The future path of international migration is set on the basis of past estimates and an assessment of the policy stance of countries with regard to future international migration flows. Mortality and international migration assumptions are held consistent between these population variants or scenarios.

5: Modelling the effect of urbanization on malaria is more difficult than simply applying population projections as they need to be explicitly located on malaria risk surfaces. There is an opportunity, though, with global Landsat archive (www.glcf.umiacs.umd.edu/) to model change on land-use change patterns and trends at a 30 x 30 m spatial resolution globally. This public-domain record of global land-cover distribution provides snapshots of the Earth in 1980, 1990 and 2000. Such measurements have been used to train cellular automata models for future urban-growth scenarios using Landsat coverages. The land-use change (deforestation, agriculture, irrigation, urbanisation) scenario analyses can be quantified and projected using similar data, methods and models.

6: Using climatic similarity between the world's major airports combined with African malaria seasonality maps, monthly representations of the global air network in terms of malaria-infected *An. gambiae* invasion risk have recently been generated (Tatem et al. 2005). Confirmed cases of airport malaria were used to identify conservative thresholds of climatic similarity between airports sufficient for *An. gambiae* survival. Information on air-traffic volumes were then used to examine, month by month, those existing and future air routes at greatest risk of malaria importation and mosquito invasion, along with the importance of traffic volume. The location and timing of airport malaria cases is predictable, with strong correlations between incoming air-traffic volume from malaria-endemic African countries and numbers of airport malaria cases in Europe.

7: Data on net and ITN coverage from national sample surveys undertaken as part of Demographic and Health Surveys (DHS, www.measuredhs.com/publications) or Multiple Indicator Cluster Surveys (MICS, www.childinfo.org) were accessed on 5 May 2005. Either national reports were accessed via the web or, for countries for which data were not constructed in final reports, web-based databases were cross-referenced.

8: Data were obtained from Dr Peter Olumese of the RBM Department, WHO, on national drug policies and whether they had been implemented on 4 May 2005. Since 2003, 28 ministries of health (note: the United Republic of

Tanzania and Sudan have effectively two ministries and South Africa has initiated two different drug policies in the two major at risk provinces) have selected ACT as first-line recommended drugs for the management of uncomplicated malaria. Fourteen ministries of health in Africa have decided to implement the co-formulated AL as their first-line therapy (US$2.4 per adult treatment course: manufactured by Novartis Pharma AG) and 12 countries have opted for the blister-packed AQ + AS (US$1.8 per adult treatment course and principally manufactured by Sanofi Ltd). Northern Sudan has opted for SP + AS. Most countries that have selected AL as first-line recommended therapy for uncomplicated malaria have selected quinine (QN) as their second-line treatment for rescue treatment of first-line treatment failures. Twelve countries continue to recommend CQ (either as monotherapy or in combination with SP). Resistance data (clinical and parasitological failures by day 14) are available for 11 of these countries (www.who.int/malaria/resistance.htlm), six countries have median documented failure rates >20% and a further three have failure rates of >10%. These nine countries represent threats to effective case management among their sick populations (Central African Republic, Chad, Congo, Eritrea, Guinea, Mauritania, Somalia, Swaziland and Zimbabwe).

9: It has been estimated that there are approximately 2.84 billion self-reported fevers in Africa (Snow et al. 2003b). Not all fevers are malaria but fever often serves as a prompt to medicate with antimalarials. While this is appropriate for those at highest biological risk of developing severe complications possibly leading to death (young children), older children and adults are far less likely to require expensive antimalarial drugs as a presumptive management strategy for their fever. If 60% of paediatric fevers were presumptively managed with an ACT, US$0.4 billion to US$0.7 billion would be required to meet the commodity needs of Africa each year; this would range from US$1.8 billion to US$3.4 billion each year if 60% of all febrile patients were treated with ACT (Snow et al. 2003b). Countries such as Nigeria would require at least US$600 million per year to support its revised first-line drug (AL) if 60% of all fevers among all patient groups were managed as malaria.

10: In Africa, IRS has focused on selected ecological zones such as those experiencing unstable transmission (Sharp and le Sueur 1996), highlands (de Zulueta et al. 1964) and urban areas (Bang et al. 1993). There is also an increasing interest in the use of IRS for containment of epidemics in Africa (Mouchet et al. 1997; Brown et al. 1998; Etchegorry et al. 2001; Guyatt et al. 2002a). The costs per person protected are favourable compared to ITN. The cost of one cycle of IRS has been shown to vary from less than US$1 per person protected (Faye et al. 1992; Rowland 1999; Verle et al. 1999; Guyatt et al. 2002b) to US$2–3 (Curtis et al. 1998; Goodman et al. 2001).

11: Precisely how IPTi provides such a large clinical protection following comparatively few drug–infant contacts remains to be established. Additional studies of different drug regimens in Senegal and Mali have produced encouraging results and the added value of IPTi within an environment of wide-scale ITN use is also beginning to be established through field investigations (www.ipti-malaria.org/).

12: National survey data from 21 countries undertaken as part of MICS or DHS surveys (Note 7) presented ITN coverage among children aged under five by wealth quintiles. Wealth indices were established from household wealth assets questions asked during the household survey and constructed through principal components analysis to derive a quintile distribution. Figure 7 shows the comparison between the highest and lowest quintiles. Only two countries showed a higher coverage among the most economically vulnerable groups compared to the least vulnerable (Ghana and the Gambia); all other countries demonstrate a marked disparity in use of ITN by wealth index quintiles.

13: In the Gambia, susceptibility to mild malaria was not correlated with prior anthropometric status, serum albumin or markers of iron deficiency (Snow et al. 1991). Others have observed an outbreak in *P. falciparum* malaria in re-fed famine victims (Murray et al. 1987), a finding that supported the prevailing view that malnutrition may actually protect against clinical malaria (Edirisinghe 1986). However, recent studies conducted in Kenya (K Marsh, unpublished data) and the Gambia (Deen et al. 2002) show that signs of chronic malnourishment (stunting) is associated with increased parasite prevalence and higher parasitaemias and act as risk factors for the development of severe malaria (Kenya) and mild clinical attacks (the Gambia).

14: The key evidence relating to the future trends of these drivers is reviewed in the main document. Scenario testing will be undertaken for a number of key drivers of risk and disease change through to 2015 and 2030 as part of a separate preliminary exercise and forms the basis of a longer-term research initiative. Without empirical scenario modelling, we have constrained our terminology to the following qualitative grading system: very high confidence (>95% chance), high confidence (HC, 67–95% chance), medium confidence (MC, 33–67% chance), low confidence (LC, 5–33% chance) and very low confidence (VLC, <5% chance) (Moss and Schneider 2000) in the summary table below.

	2015		2030	
	Risk	**Disease**	**Risk**	**Disease**
Intervention				
ITN	HC	HC	HC	HC
ACT	MC	HC	HC	HC
IPT	MC	MC	MC	MC
IRS	MC	MC	MC	MC
EM	VLC	VLC	VLC	VLC
Vaccines	LC	LC	MC	HC
Combined control	HC	HC	HC	HC
Population growth	HC	MC	HC	MC
Urbanisation	MC	MC	MC	MC
Land-use changes				
Deforestation increases	LC	LC	LC	LC
Dams/irrigation increases	MC	LC	MC	LC
Desertification increases	VLC	VLC	VLC	VLC
International travel	VLC	VLC	VLC	VLC
Conflict/displaced persons	MC	MC	LC	LC
Climate change	VLC	VLC	VLC	VLC
HIV increases	MC	MC	MC	MC
Reducing poverty	LC	LC	MC	MC

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