Changes in the burden of malaria in sub-Saharan Africa

Wendy Prudhomme O'Meara, Judith Nekesa Mangeni, Rick Steketee, Brian Greenwood

The burden of malaria in countries in sub-Saharan Africa has declined with scaling up of prevention, diagnosis, and treatment. To assess the contribution of specific malaria interventions and other general factors in bringing about these changes, we reviewed studies that have reported recent changes in the incidence or prevalence of malaria in sub-Saharan Africa. Malaria control in southern Africa (South Africa, Mozambique, and Swaziland) began in the 1980s and has shown substantial, lasting declines linked to scale-up of specific interventions. In The Horn of Africa, Ethiopia and Eritrea have also experienced substantial decreases in the burden of malaria linked to the introduction of malaria control measures. Substantial increases in funding for malaria control and the procurement and distribution of effective means for prevention and treatment are associated with falls in malaria burden. In central Africa, little progress has been documented, possibly because of publication bias. In some countries a decline in malaria incidence began several years before scale-up of malaria control. In other countries, the change from a failing drug (chloroquine) to a more effective drug (sulphadoxine plus pyrimethamine or an artemisinin combination) led to immediate improvements; in others malaria reduction seemed to be associated with the scale-up of insecticide-treated bednets and indoor residual spraying.

Lancet Infect Dis 2010; 10: 545–55

Published Online July 15, 2010 DOI:10.1016/S1473-3099(10)70096-7

School of Public Health and Health Services, George Washington University, Washington, USA (W P O'Meara PhD); **Moi Teaching and Referral Hospital, Eldoret, Kenya** (J N Mangeni MPH); **Malaria Control and Evaluation Partnership in Africa (MACEPA), PATH, Ferney-Voltaire, France** (R Steketee MD); and **Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK** (Prof B Greenwood MD)

Correspondence to: Prof Brian Greenwood, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK **brian.greenwood@lshtm.ac.uk**

Introduction

After a period of neglect, the urgent need to control malaria has once again engaged the attention of the international health community. Control of malaria is now on the political agenda of several of the world's wealthiest countries and funds have become available from the Global Fund to Fight AIDS, Tuberculosis and Malaria, The US President's Malaria Initiative, the World Bank, and bilateral donors on a scale not seen since the first attempted malaria eradication campaign in the 1950s and 1960s. The global fight against malaria is now being coordinated by the Roll Back Malaria Partnership, and major donor foundations, such as the Bill and Melinda Gates Foundation, have greatly increased financial support for malaria research. When compared with the low coverage of malaria control measures in 1999–2001,[1] these investments have resulted in an increase in global production, procurement, distribution, and use of insecticide-treated bednets (ITNs). Global production more than tripled from 30 million in 2004 to 100 million in 2008. UNICEF procurement increased roughly 20-fold between 2000 and 2005 and has been stable since.[2,3] Ownership and use of ITNs within households, as measured by the number of children under 5 years of age reported to have used an ITN the previous night, increased by three to ten times between 2000 and 2008 in many African countries.[2] There has also been an increase of about 25 times in the global procurement of artemisinin combination therapies (ACTs) in the past 5 years.[2,3]

A renewed focus on elimination (cessation of local transmission of malaria within a defined geographical region) and eradication (global disappearance of one or more species of malaria parasite)[4] has spurred several new initiatives, such as the Malaria Elimination Group, focusing on practical components of malaria elimination and the Malaria Eradication Research Agenda group setting the research agenda needed to support elimination and eradication.

This drive towards elimination has been encouraged by reports from several malaria endemic areas of declines in incidence of clinical cases and deaths. These changes have coincided with scale-up of effective prevention with ITNs and the use of more effective treatments for malaria in endemic areas. In some areas, additional vector-control measures, including indoor residual spraying and larval control have been deployed. The situation in Africa as a whole and how specific interventions have contributed to success stories is unclear. Therefore, we reviewed the relation between reported changes in the incidence or prevalence of malaria and the introduction or scale-up of specific interventions in several countries in sub-Saharan Africa. In this Review, we aim to identify common patterns and investigate whether factors other than these specific interventions might have contributed to the changes in malaria burden that have been reported.

13 key papers, which describe recent changes in malaria morbidity in sub-Saharan Africa were identified by consultation with experts. These papers were used as a guideline for a search for similar or related published studies. For each article reported we noted the: country, region, study period, population size, local endemicity, control measures and other factors independent of the study that might have affected transmission, rainfall data (if available), the type of data (ie, outpatient numbers, inpatient numbers, malaria mortality, prevalence), whether cases were slide confirmed, and the percentage change and the years of change for each type of data reported. The total number of malaria outpatients or inpatients for each reported year and the total number of deaths were also noted, when the information was available.

For more on **the Roll Back Malaria Partnership** see http://www.rollbackmalaria.org

Changing malaria burden in sub-Saharan Africa

We identified studies that recorded trends in malaria indicators over time from countries in sub-Saharan Africa (figure 1, table). Most reports describe a recent decline in the incidence of malaria, the rest report little or no change.

For more on the **Malaria Elimination Group** see http://www.malariaeliminationgroup.org

For more on the **Malaria Eradication Research Agenda** see http://malera.tropika.net

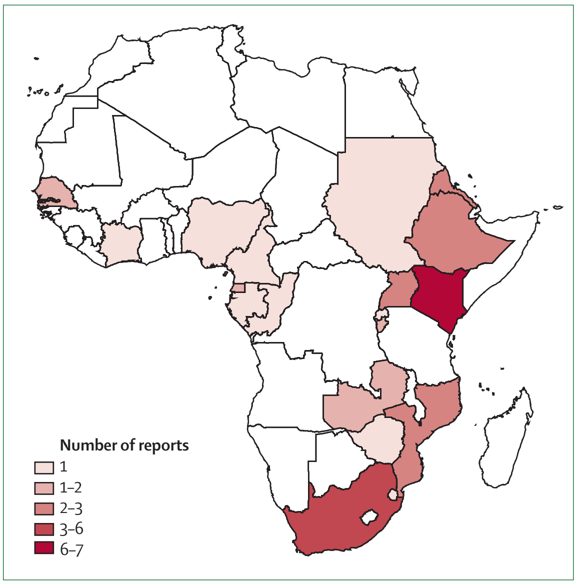

Figure 1: Distribution of reports included in the Review

The Horn of Africa

Reports from Ethiopia have documented declines in malaria morbidity across the country.[5,6] Surveillance from 2000–07 demonstrated a 70% reduction in both outpatients with slide-confirmed malaria and children less than 5 years old admitted to hospital for malaria. Outpatient malaria cases were already declining at the beginning of the surveillance period, before mass-distribution of ITNs and treatment with ACTs were introduced in late 2005. The decline in patients admitted to hospital with malaria was slower than the decline in outpatient malaria. The largest drop in morbidity occurred at the same time as in other parts of east Africa—2005–06.

The epidemiology of malaria in Ethiopia differs from that in most of sub-Saharan Africa. Transmission is heterogeneous and generally lower than in other countries, and *Plasmodium vivax* is endemic and causes up to 40% of clinical cases.[5] A small study showed a decline in the overall incidence of malaria accompanied by a shift from predominantly *P vivax* cases to 73% *Plasmodium falciparum* cases.[7]

Reports from Eritrea paint a similar picture. Between 1998 and 2004, substantial reductions in routinely reported clinical malaria cases were described following a scale-up of control measures.[8–10] There was a reduction in both the incidence of presumptive malaria in outpatient facilities (83% decline) and in the case fatality of malaria admissions (25% decline overall, but trend inconsistent over the time period). The largest decline in malaria cases was seen between 1998 and 2000. ITN ownership was 80% in 2004, but only 50% of households, when surveyed, reported anyone having slept under an ITN the night before. It is very likely that the massive scale-up of ITNs, indoor residual spraying, community-based management of fevers, and environmental management of mosquito breeding sites all contributed to these results. However, the incidence of malaria was already declining at the beginning of the surveillance period, before these interventions were introduced. Graves and colleagues[8] showed that malaria cases increased between 1996 and 1998 before beginning to decline in 1999; although the increase in cases could have been due to improved reporting practices. A time-series analysis by Nyarango and co-workers[10] showed that the scale-up of ITNs and indoor residual spraying was associated with a reduction in malaria cases but not with a decline in case fatality, whereas an expansion of community health-worker training was temporally associated with the decline in case fatality but not with the reduction in malaria cases.

East Africa

Many reports from east Africa have recorded substantial reductions in malaria transmission and morbidity in the region. In the coastal area of Kenya, paediatric malaria admissions declined by as much as 75% between 2003 and 2007.[11,12] Since the mid-1990s, parasite prevalence in the Kilifi district has declined progressively from 35% to less than 1%. Prevalence declined by 30% before any change in the incidence of malaria admissions was recorded. Although ITN use has increased concurrently with the decline in paediatric admissions,[12] the prevalence of malaria infection declined from 35% to 10% before ITN coverage reached 25%, and before the introduction of ACTs.[11]

In a district in central Kenya, the proportion of malaria outpatient visits declined from 40% in 2000 to 0% by the end of 2006, with the largest decline between 2003 and 2005.[13] Coverage with ITNs in the area is estimated to be 65%, substantially higher than that reported on the coast, and 35% of households reported use of some mosquito reduction method, such as environmental management or repellents. This study is one of the few in which entomological data were collected concurrently with longitudinal morbidity data. The entomological inoculation rate was estimated to be very low: 0–0·03 infectious bites per person per year in the hospital catchment area.

In western Kenya, malaria transmission in the lowland areas around Lake Victoria has historically been very high, with entomological inoculation rates estimated to be as high as 250 infectious bites per person per year.[14,15] Between 2003 and 2007, demographic surveillance revealed a 42% reduction in all-cause mortality among children less than 5 years of age.[16] A 16% decline in malaria-specific mortality was estimated using verbal autopsy methods.[16] Verbal autopsy methods have low specificity,[17] and malaria-specific mortality likely declined substantially more than was suggested by verbal autopsy.

Data compiled from paediatric inpatient records of 17 hospitals across Kenya (including hospitals on the coast and in western Kenya) showed different temporal trends in malaria admissions between 1999 and 2008.[18]

Only four hospitals had clear, substantial declines in malaria admissions. Six other sites had small or unstable declines. Only six of ten sites that reported reductions in malaria admissions also reported reductions in all-cause admissions, which would suggest a true decline in malaria admissions, rather than a re-classification because of changing diagnostic practices. In seven other sites, malaria admissions remained stable or increased. Across all sites together the number of paediatric malaria admissions decreased by 49%. However, this average masks the heterogeneity of the effect of nationwide malaria control.

In Rwanda, data from 20 facilities representing every district in the country showed a decline of more than 50% between 2005 and 2007 in both inpatient and outpatient slide-confirmed malaria cases.[6] Before 2005, the number of cases had been increasing annually, but began to decline shortly before or at the same time as mass distribution of long-lasting insecticidal bednets and the use of ACTs in 2006–07.

In neighbouring Burundi, routine health-facility reporting from the Karuzi province showed an epidemic peak of clinically diagnosed malaria in 2001, against a background of low but stable monthly incidence of

	Study period	Type of data recorded	Age range of cases	Slide-confirmed	Population*	Endemicity†	Change reported
Horn of Africa							
East Shoa, Ethiopia[5]	2002–06	Outpatient	All	Yes	Six malaria diagnosis and treatment centres	Low, unstable	Decrease
Ethiopia[6]	2001–07	Inpatient and outpatient	All	No	Country-wide	Low	70% (inpatient) and 81% (outpatient) decrease
Shashemane, Ethiopia[7]	1998–2003	Inpatient	All	Yes	One hospital	Low, unstable	58% decrease
Eritrea[8]	1996–2003	Inpatient and outpatient	All	No	Country-wide	Moderate	>75% decrease
Eritrea[9]	1998–2003	Inpatient, outpatient and community-based diagnosis	All	No	Country-wide	Moderate	>80% decrease
Eritrea[10]	1999–2004	Inpatient and outpatient	All	Yes	Country-wide	Moderate	83% decrease
East Africa							
Kilifi, Kenya[11]	1990–2007	Inpatient	<12 years	Yes	>200 000	Low to moderate	75% decrease
Coast Kenya[12]	1999–2007	Inpatient	<15 years	No	Three sentinel sites	Moderate	28–63% decrease
Mwea, Kenya[13]	2000–07	SPR inpatient and outpatient	All	Yes	160 000	Low to moderate	100% (40% SPR to 0) decrease
Kisumu, Kenya[14]	2003–07	Malaria mortality by verbal autopsy	..	No	Unknown	High	16% decrease
Kenya[15]	1999–2008	Inpatient	<14 years	No	17 hospitals	Varies	Variable: decreased in ten hospitals, increased in four and unchanged in three
Rwanda[6]	2001–07	Inpatient and outpatient	All	Yes	Country-wide	Varies	54% (inpatient) and 56% (outpatient) decrease
Karuzi, Burundi[16]	2002–05	Cross-sectional prevalence surveys	1–9 years	Yes	300 000	Low to moderate	38% decrease in prevalence in lowlands, no change in highlands
Karuzi, Burundi[17]	1997–2003	HMIS inpatient and outpatient	All	No	300 000	Low, unstable	No trend, one epidemic peak
Uganda[18]	1990–2001	Inpatient	<5 years	No	700 000	Two sites in study: one high and one low/unstable	54–275% increase
Kanungu, Uganda[19]	2006–08	Outpatient	All	Yes	One facility in one district	Moderate	25% decrease
Muheza, Tanzania[20]	1996–2003	Prevalence and outpatient	Prevalence in children >5 years; all outpatients	Prevalence yes; outpatient no	279 423	Moderate to high	No change
Korogwe, Tanzania[21]	2003–07	Prevalence	..	Yes	Two villages	Moderate to high	68–75% decrease
Southern Tanzania[22]	1986–2000	Inpatient and outpatient	All	No	Ten hospitals	Low to moderate	Variable: for inpatients, decrease in three hospitals, increased in four, and unchanged in three
Western highlands, Kenya[23]	1980–2000	Inpatient	All	No	Unknown	Low unstable	32–256% increase in paediatric admissions
Western highlands, Kenya[24]	2003–08	Outpatient	All	Yes	8000	Low unstable	100% (126 cases/1000 to 0) decrease
Uganda highlands[25]	2002–06	Outpatient	..	Yes	One hospital	Low, unstable	~ 50% increase

(Continued on next page)

cases.[19] Between 2002 and 2005, annual indoor residual spraying interventions in the province had only a small effect on parasite prevalence.[20] Prevalence in children less than 9 years old declined from 64% to 40%, but the latter figure was not always significantly different from the control group over the 3 years of intervention. No additive benefit of bednets could be detected, and indoor residual spraying in the lowland areas did not reduce prevalence of infection in adjacent highlands.[20]

In contrast to the largely encouraging reports from Kenya and Rwanda, data from a highland and a lowland area in western Uganda showed steadily increasing numbers of malaria cases and deaths in district hospitals from 1991 to 2000, with a two-fold to four-fold overall increase in the number of children admitted to hospital

	Study period	Type of data recorded	Age range of cases	Slide-confirmed	Population*	Endemicity†	Change reported
(Continued form previous page)							
Central Africa							
Brazzaville, Congo[26]	1989–2001	Inpatient	<5 years	No	One hospital	Moderate	No change
New Halfa, Eastern Sudan[27]	1986–2002	Outpatient	All	Yes	Eight referral laboratories	Moderate	No consistent trend
Molyko, Cameroon[28]	2000 and 2004	Parasite prevalence	4–15 years	Yes	12 500	Moderate	No change
Southern Africa							
Kwazulu Natal, South Africa (part 1 and 2)[29,30]	1970–2000	Inpatient and outpatient	All	Yes	285 000	Low	91% decrease
Kwazulu Natal, South Africa[31]	2000–03	Inpatient and outpatient	All	Yes	285 000	Low	99% decrease
South Africa[32]	1988–2003	Inpatient and outpatient	All	Yes	Three provinces	Low	75–93% decrease
South Africa, Mozambique, Swaziland[33]	1999–2005	Prevalence (Mozambique); inpatient and outpatient (South Africa and Swaziland)	All	Yes	~2 000 000	Low to moderate	78–96% decrease in cases, 53–94% decrease in prevalence
Maputo, Mozambique (part 1 and 2)[34,35]	2003–05	Inpatient and outpatient	<15 years	Yes	80 000	Moderate	No consistent trend
Limpopo, South Africa[36]	1998–2007	Inpatient and outpatient	All	Yes	5 000 000	Low	66% decrease
Zambia[37]	2006–08	Prevalence		Yes	Country-wide	Moderate	53% decrease
Chongwe, Zambia[38]	2003–08	SPR in outpatients	<5 years	Yes	171 000	..	98%
Zimbabwe[39]	2001–03	Weekly malaria surveillance data	All	No	Country-wide	..	50% increase
West Africa							
The Gambia[40]	2001–07 and 1999–2007	Inpatient and outpatient	All	Inpatient no; outpatient yes	Sentinel sites country-wide	Moderate	27–90% decrease
Libreville, Gabon[41]	2000–08	Outpatient and inpatient	0–11 years	Yes	530 000	..	80% decrease
M'lomp, Senegal[42]	1998–2002	Outpatient	All	Yes	8000	Moderate	No consistent trend, possible 18% decline in last years
Niakhar, Senegal[43]	1992–2004	Outpatient	All	No	30 000	..	No consistent trend
Ibadan, Nigeria[44]	2000–05	Inpatient (% of admissions)	<15 years	Yes	..	High	48% increase
Cote d'Ivoire[45]	2002–05	Outpatient and cross-sectional prevalence	Outpatient all; prevalence <15 years	Prevalence only	Two villages	High	No change
African Islands							
Zanzibar, Tanzania[46]	1999–2006	Parasite prevalence, inpatient and outpatient	Prevalence in <14 years; all outpatient and inpatient	Prevalence yes; inpatient and outpatient no	85 000	Low to moderate	77% decrease
Bioko Island, Equitorial Guineau[47]	2004–08	Parasite prevalence, all cause mortality	Prevalence: 2–5 years, mortality: <5 yrs	Yes	200 000	High	45% decrease in prevalence, 65% decrease in all-cause mortality
Sao Tome and Principe[48]	1995–2007	Inpatient and outpatient	All	Yes	150 000	Low to moderate	90% decrease
Sao Tome and Principe[49]	2004–06	Parasite prevalence	<9 years	Yes	Country–wide	Low to moderate	97% decrease

SPR=slide positivity rate. HMIS=health management information system. *Approximate population under surveillance or hospital catchment population. †As reported in the study.

Table: **Reports of changes in the pattern of malaria in sub-Saharan African 1999–2009.**

with the disease.[21] A slight decline in the proportion of positive blood films was seen in a single facility in an area of moderate transmission in Uganda after one round of indoor residual spraying in 2007.[22] 14 months after indoor residual spraying, the proportion of blood films that tested positive began to increase, suggesting that trends are easily reversed if control measures are not sustained.

In Muheza district, Tanzania, the number of malaria cases increased between 1994 and 2002,with prevalence among children remaining consistently above 80%.[23] However, the incidence of malaria has recently declined substantially in some parts of northeastern Tanzania. In the same district, the incidence of malaria in children fell rapidly during the early 2000s, reaching such a low level that a trial of intermittent preventive treatment in infants had to be stopped in 2005 as there were not enough cases.[24] In the neighbouring Korogwe district, the prevalence of malaria parasitaemia among febrile patients fell substantially between 2003 and 2006 from 78% to 24% in lowland areas and from 25% to 7% in highland areas.[25] These changes were detected by community health workers who treated fevers presumptively for malaria but collected blood films at the time of treatment. Improved access to effective treatment through the community programme probably contributed to the decline. At least four of eight hospitals included in a review of admission data in southwest Tanzania showed higher numbers of malaria admissions between 1995 and 2000 than in the preceding 10 years; the number of malaria admissions declined at only one of the hospitals.[26] The current situation in these areas has not been reported. Recent entomological data from the Kilombero Valley in Tanzania, an area with one of the highest rates of transmission in the world, reported a 60–70% lower entomological inoculation rate than previously recorded;[27] although the effect of that decline on clinical malaria is unknown.

In highland areas of east Africa, where malaria transmission is unstable and prone to epidemics, stable transmission has been reported in areas that have historically been thought to have only periodic epidemic transmission.[28] In these areas of stable transmission, adults have functional immunity to malaria and the age ratio of cases in children to adults is greater than one. The number of cases in three highland hospitals in western Kenya gradually increased up to the year 2000, although transmission remains strongly seasonal. More recent data from a few villages in highland Kenya show success of government efforts to control malaria. Malaria incidence declined from roughly 100 cases per 1000 people per year in 2003 to no cases at all in 2008.[29] Because ITN coverage was less than 25%, this success is probably attributable to sequential rounds of indoor residual spraying covering 70–95% of households. By contrast, data from two highland sites in Uganda show slight increases in slide-confirmed cases from 2002 to 2006.[30] Anecdotal evidence from Burundi suggests that malaria transmission is occurring at higher altitudes than ever before.[31]

Central Africa

Because of a lack of research initiatives and poor infrastructure to support routine case reporting data from central Africa are sparse. The limited data available show little change in the malaria burden from historical levels. In Brazzaville, Congo, the percentage of paediatric hospital admissions due to malaria (30%) did not change between 1989 and 2001.[32] Data from eight malaria reference laboratories in eastern Sudan showed a slight decline in the proportion of positive smears between 1998 and 2002, but this decline followed a period of increased malaria infection during several years of heavy rains[33] and brought the proportion back to the levels noted before the heavy rains. Two small cross-sectional studies in Cameroon in 2000 and 2004 showed a slight decline in parasite prevalence among asymptomatic children, but no change in prevalence among febrile children.[34]

Southern Africa

In South Africa, sustained malaria control over many decades has succeeded in stopping transmission throughout most of the country, with the exception of the northeastern border regions adjacent to Mozambique and Swaziland.[35] 30 years of passive and active detection of slide-confirmed malaria cases from the province of KwaZulu Natal give a comprehensive, long-term picture of the effect of changing control strategies, climatic factors, and other variables that have influenced the incidence of malaria over time. Parasites resistant to both chloroquine and sulphadoxine plus pyrimethamine, a rising prevalence of HIV, the emergence of mosquitoes resistant to pyrethroid insecticides used for indoor residual spraying, and increasing cases of imported malaria contributed to a five-fold increase in malaria cases in the province between the mid-1990s and 2001.[36] Climatic factors were shown to explain seasonality and short-term trends, but not long-term trends.[37] In 2001, DDT was reintroduced for indoor residual spraying and cases began to decline almost immediately. Data from sentinel facilities showed an 89% decline in malaria admissions and deaths and an 85% decline in outpatient malaria cases in the year after reintroduction of DDT. Replacement of failing sulphadoxine plus pyrimethamine with an ACT might also have contributed to the decline. By 2003, cases had declined by 99% from their peak in 2000.[38]

A related report from the bordering regions of Mozambique, Swaziland, and South Africa highlights the importance of coordinated regional control.[39] Although indoor residual spraying has been ongoing in Swaziland since 1981, malaria remained a significant public health problem. In 2001, when South Africa reintroduced DDT, Mozambique initiated indoor residual spraying programmes in the border regions. The prevalence of malaria declined substantially in regions of Mozambique that were part of the indoor residual spraying programmes, although it dropped below 20% in only one of five spray zones. Slide-confirmed inpatient and outpatient malaria cases at a district hospital in the indoor residual spraying areas showed no consistent trend between 2003 and 2005, indicating that the incidence of symptomatic cases might have stabilised.[40,41] The incidence of cases reported in the two bordering South African provinces declined by 80–95% in 4 years. Despite no changes in malaria control interventions, cases in Swaziland showed a similar decline of 95%, presumably as a result of activities in neighbouring regions.

On the western side of Swaziland, the province of Limpopo in South Africa also reported reductions in the incidence of malaria cases. Routine slide-confirmed case reporting data from 1998 to 2007 showed significant declines in cases from 2001 until the end of the reporting interval.[42] As in KwaZulu Natal, the main malaria control intervention in Limpopo is indoor residual spraying, with DDT being reintroduced in 2001. ACTs were deployed in 2004.

The Zambian National Malaria Control Programme has achieved substantial success in scaling up the use of ITNs, indoor residual spraying, and intermittent preventive treatment in pregnancy with sulphadoxine plus pyrimethamine. ITN ownership increased substantially from 22% in 2004, to 38% in 2006, and 62% in 2008.[43,44] Between 2006 and 2008, paediatric malaria parasite prevelance declined by 53% and moderate to severe anaemia by 69%.[44] A report from a single outpatient facility showed a remarkable decline in the proportion of febrile cases with malaria, from 40% in 2003 and 84% in 2004 to less than 1% in 2008.[45]

In Zimbabwe, data are less encouraging. Reductions in donor funding and national support are likely to account for the increasing morbidity and mortality from suspected malaria reported between 2001 and 2003.[46]

West Africa

Compelling evidence for a dramatic decline in malaria transmission comes from The Gambia where surveillance at five health facilities across the country showed a 50–85% decline in the prevalence of slide-confirmed malaria among outpatients and a 25–90% decline in malaria-related hospital admissions.[47] The trend persisted over 7 years with an apparent contribution from ITN coverage, which increased three-fold to 49% over the surveillance period. The observed reductions were before the introduction of ACTs. The number of outpatient cases declined before the number of inpatient cases did.

Apart from The Gambia, other evidence from west Africa comes from a handful of individual hospitals or villages. An urban hospital in Libreville, Gabon[48] reported an 80% decline in the number of children with positive blood smears in the inpatient and outpatient services. The decline began in 2003 and persisted until the end of the surveillance period in 2008. The decline pre-dated both the introduction of ACTs in 2006 and ITN distribution in 2005, the coverage of the latter reaching 50% in 2008. Data from one village in Senegal showed an increase in the incidence of slide-confirmed malaria between 1998 and 2001 followed by a slight decline of 20% in 2002, although the incidence in 2002 was still higher than in 1998.[49] In Niakhar, Senegal, presumptive malaria (facility surveillance) and malaria mortality (community-based verbal autopsy) fluctuated considerably between 1992 and 2004, but no consistent trends were observed.[50]

A study from a hospital in Nigeria reported severe malaria accounting for a steadily increasing proportion of hospital admissions between 2000 and 2005, with nearly 13% of patients admitted having either severe malarial anaemia or cerebral malaria by the end of the study.[51] Reports from Burkina Faso mention a three-fold increase in malaria cases at health facilities between 2000 and 2007 in at least one district, despite increasing bednet coverage.[52]

There was only one report that discussed the effect of agricultural practices on the risk of malaria infection.[53] Malaria indicators in two villages in Côte d'Ivoire with similar, intense transmission but different agriculture practices were compared. Both the number of malaria cases and the entomological inoculation rate temporarily declined in one village with irrigated rice farming when irrigation was interrupted for a season. During the same season, the village without irrigated rice farming had a very slight decline in presumptive malaria cases, despite an increase in entomological inoculation rate from 230 to 570 infective bite per person per year.

African islands

Some of the most remarkable successes have been reported from islands, including Bioko (part of Equatorial Guinea), Zanzibar, and Sao Tome and Principe. On Zanzibar, an 87% decline in parasite prevalence was mirrored by a 75% decline in clinically diagnosed malaria outpatient visits and hospital admissions.[54] Review of monthly clinical cases of malaria in children less than 5 years of age showed that the downward trend began about 1 year after the introduction of ACTs, and before the widespread distribution of ITNs. The number of cases dropped from more than 1500 per month to fewer than 100 per month before the initiation of ITN distribution campaigns. Changes in diagnostic practices might have had an effect on these figures. The timing of the decline (2005 to 2006) is similar to that of other reports from the region.

The Bioko Island Malaria Control Project was launched in 2003 and combined bi-annual indoor residual spraying programmes with the introduction of ACTs and scale-up of the use of intermittent preventive treatment in pregnancy.[55,56] Distribution of long-lasting insecticidal bednets started much later, in 2007. After 4 years of intensive vector control and improved case management, sporozoite rates were reduced by ten times, leading to a decline in cross-sectional prevalence of malaria parasitaemia in children from 42% to 18%, and a 50% reduction in the prevalence of fever. A remarkable 70% reduction in all-cause mortality in children age less than 5 years was reported in this intervention time interval.[57]

On Sao Tome, surveillance data between 1995 and 2007 showed malaria outpatient consultations and hospital admissions declined by 80–90% in both adults and children after introduction of indoor residual spraying, ACTs, and long-lasting insecticidal bednets in 2004.[58] Indoor residual spraying on Sao Tome resulted in a reduction of paediatric parasite prevalence from 30% to less than 1%, a greater reduction than indoor residual spraying programmes in Burundi, where prevalence fell from 50% to 40%, and in Mozambique, where prevalence fell from 65% to 20%.[59]

Discussion

The burden of malaria has declined substantially in several areas of sub-Saharan Africa, particularly in the past 3–5 years, coinciding with expanding coverage of malaria prevention and treatment in many countries (figure 2). Country-wide surveillance in Ethiopia and Eritrea reveals a 70% decline in malaria morbidity, with similar changes documented in parts of Kenya, The Gambia, Rwanda, and Zambia. Malaria control on islands has been remarkably successful, even though the approaches used have been diverse. However, other reports describe a static or deteriorating situation in some locations. Malaria transmission may be increasing in the highland areas of east Africa, perhaps as a result of environmental conditions that facilitate transmission. Several countries in west and central Africa have not yet had any significant reductions in malaria incidence. The situation in large parts of Africa is unknown.

The success stories include countries across the spectrum of transmission intensity. Progress may have been predominantly made in countries with low to moderate endemicity, but these countries might have started malaria control efforts at an early date. In southern Africa (South Africa, Swaziland, and parts of Mozambique), aggressive control started in the 1970s and 1980s and is ongoing. In this case, successful control was accelerated by adopting a regional strategy rather than individual country approaches. Although expanded control efforts began more recently in Eritrea and Ethiopia, they have seen early and durable declines. Unfortunately, data are not available for large parts of sub-Saharan Africa, including countries with high and often seasonally intense transmission.

Many reports attribute decreases in malaria morbidity to specific interventions, although the causal link between the decline and the intervention is more convincing in some cases than in others (figure 3). In several reports, the decline began before the specific intervention was deployed, or the decline was already underway at the beginning of the study period, suggesting that factors not investigated contributed to the decline. This is highlighted in the two reports from the coast of Kenya, one of which

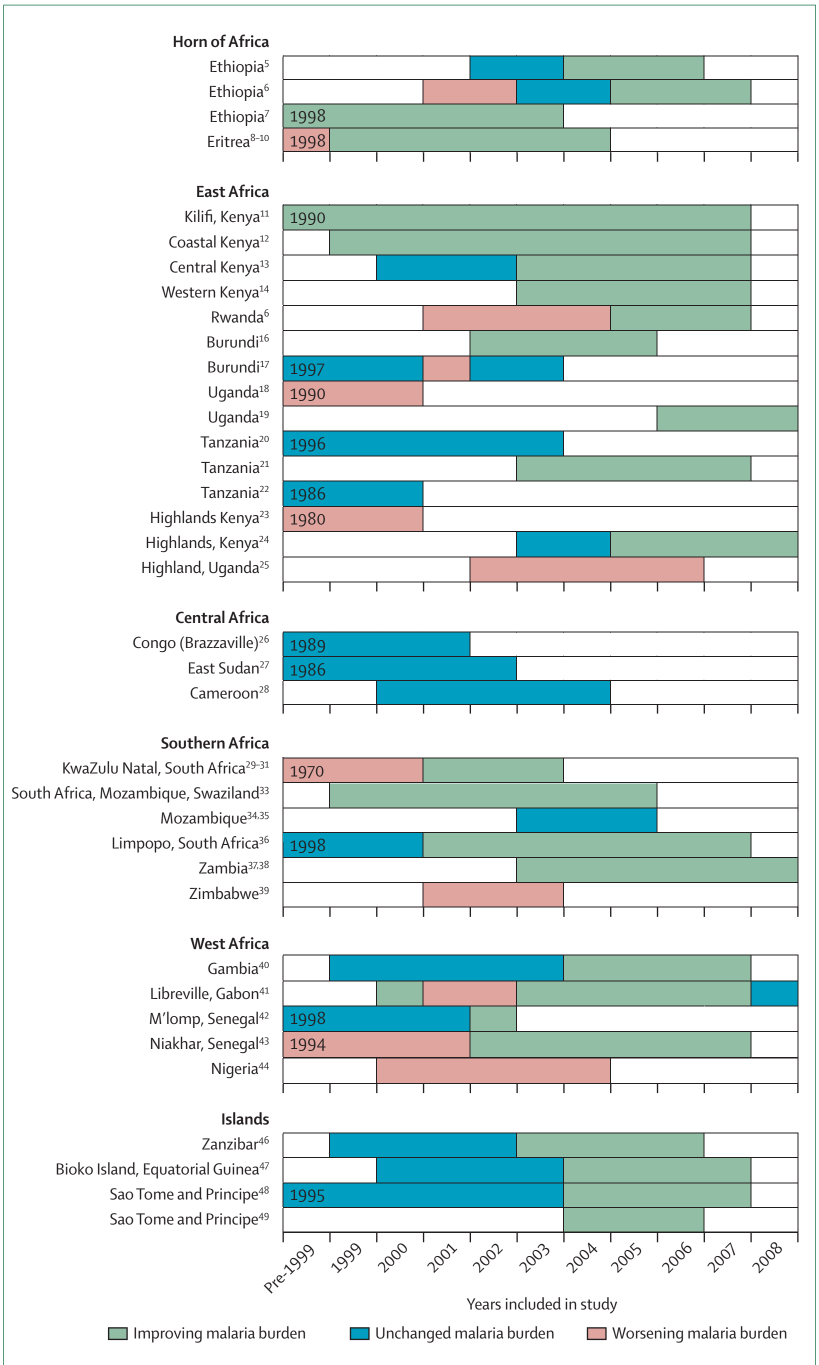

Figure 2: **Changes in the malaria burden in different regions of sub-Saharan Africa**
Malaria "burden" defined as worsening (red) if malaria indicators increased for 2 years consecutively, unchanged (blue) if malaria indicators decreased for at least 2 years consecutively, or improving (green) if they did not change in either direction during the study. Malaria indicators used were the incidence of inpatient or outpatient cases of malaria, deaths from malaria in children, or the prevalence of malaria infection.

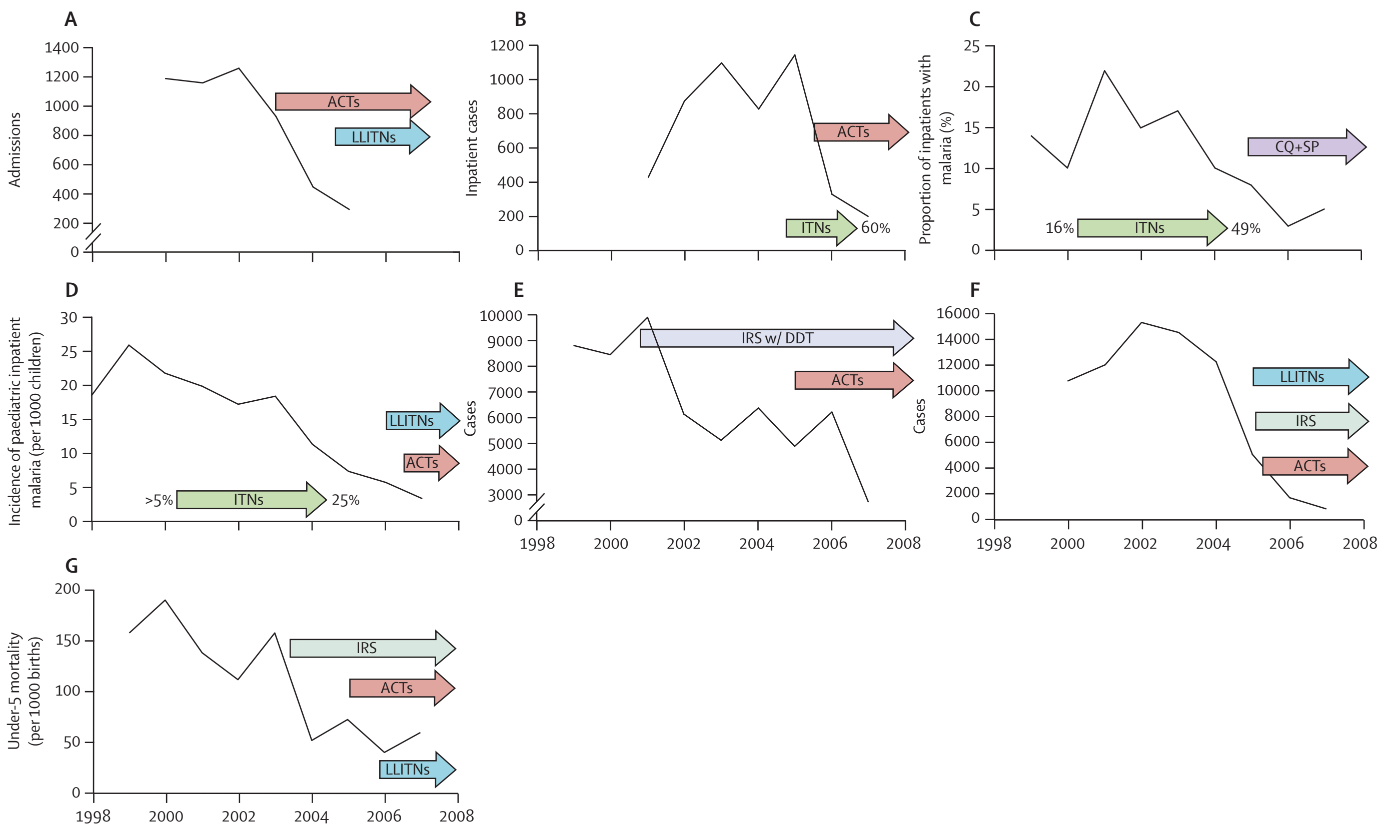

Figure 3: **Changes in malaria indicators over time relative to the introduction or scaling up of control measures in selected countries**
(A) Number of malaria hospital admissions in Zanzibar.[46] (B) Number of malaria hospital admissions in Ethiopia.[6] (C) Proportion of hospital admissions due to malaria in Fajara, The Gambia.[40] (D) Incidence of paediatric malaria hospital admissions (hospitalisations per 1000 children in the hospital catchment area) in Kilifi, Kenya.[11] (E) Number of malaria cases in Limpopo, South Africa.[36] (F) Number of malaria cases in Sao Tome and Principe.[48] (G) All cause mortality in children less than 5 years of age per 1000 births in Bioko Island, Equitorial Guinea.[47] ACT=artemisinin combination therapies. LLITNs=long-lasting insecticide-treated bednets. ITNs=insecticide-treated bednets. CQ+SP=chloroquine with sulfadoxine plus pyrimethamine. IRS=indoor residual spraying.

shows an association between ITN distribution and a decline in admissions of children with malaria to hospital whereas the other shows substantial changes in prevalence of malaria infection before the decline in admissions and the distribution of ITNs.[11,12] Similarly, in The Gambia and Zanzibar, the decline in malaria began before ITNs were rolled out. In Eritrea and Ethiopia, a substantial outbreak occurred from late 2002 to 2005,[60] thus declines in malaria incidence back to historical levels were already underway as interventions were introduced in 2005 and 2006. In other reports, the temporal association with the introduction of specific interventions is compelling, particularly in the data from the northern provinces of South Africa and Bioko Island.

Indoor residual spraying, ITNs, and ACTs reduce mortality and morbidity from malaria when deployed under controlled conditions. Indoor residual spraying probably had a key role in achieving successful malaria control in South Africa and on Bioko and Sao Tome islands but its effect seems to have been smaller in other places. There is strong evidence that ITNs can provide a substantial degree of protection against mortality and morbidity from malaria,[61] especially when used by a high proportion of the population. Widespread deployment of ACTs, which are partly gametocytocidal, would be expected to have an effect on transmission of malaria in communities where a high proportion of infected individuals have symptoms and seek treatment.[62,63] Thus, for example, introduction of ACTs might have contributed to the success of malaria control in South Africa.[38] ACTs would not be expected to have a major effect on malaria transmission in communities where only a small proportion of infected individuals are sick and seek treatment. In Zanzibar, the fall in malaria incidence before the introduction of ITNs or indoor residual spraying that followed the introduction of ACTs was, therefore, suprising.[54] This finding could be explained by the concurrent scale-up of malaria diagnostics which reduced the number of presumptive cases reported, or by the high incidence of chloroquine treatment failure at the time of the switch to ACTs. Similarly, in The Gambia and Kilifi district, Kenya, the fall in malaria incidence began at roughly the same time as first-line treatment with chloroquine was changed to treatment with sulphadoxine plus pyrimethamine or sulphadoxine plus pyrimethamine plus chloroquine .[11,47] This change replaced an ineffective drug (chloroquine) with an effective one (sulphadoxine plus pyrimethamine) and it provided a single-dose treatment (most likely improving cure rates) and a period of chemoprevention against new infections that persists for several weeks.[64] The chemopreventive effect of sulphadoxine-pyrimethamine might be especially important in areas such as The Gambia where malaria transmission is restricted to a few months of the year.

On the basis of current models of malaria transmission, we would not expect partial coverage with ITNs and the introduction of ACTs to result in the substantial changes in malaria incidence seen in areas with moderate transmission. Alternative explanations for these changes should be considered. Previous experience in Europe and North America has shown that malaria declines as social conditions and education improve. However, these changes (eg, improvements in house construction) are likely to be gradual and cannot account for the sudden changes seen during the past few years, although they might have contributed. Malaria transmission is strongly affected by climate. However, climate has been carefully monitored in several case studies, and although there have been fluctuations from year to year, no overall pattern emerges that can explain the remarkable reductions in malaria cases in some countries. A highly speculative explanation for the reductions is a change in the parasite or its mosquito vector that has reduced transmissibility of the infection. Both of these are biological possibilities, but such a change seems unlikely on the opposite sides of the continent at the same time. Finally, the transmissibility of *P falciparum* malaria might not be as high as has been previously thought, making it easier for any transmission blocking intervention directed at either the parasite (ACTs) or the vector (ITNs or indoor residual spraying) to reduce transmission.

We must bear in mind the limitations in using published scientific literature to assess the progress of ongoing malaria control programmes. Some of the reports in this Review might be biased towards presenting data that reflect well on the outcome of a control programme (to justify investments) or even presenting data that suggest the malaria burden is worsening (to encourage further investment into malaria control); maintenance of the status quo is unlikely to result in publication in the scientific literature. For example, three studies from Kenya show exciting reductions in the burden of malaria, but data from 17 hospitals reveal that there are many areas where malaria is not declining. Many of the reports we have reviewed are limited in time and geographic scope, and therefore might not accurately reflect nation-wide trends. Most of these reports rely on clinical diagnosis of malaria at a health facility. We cannot account for the effect of changes in access to care or use of health services on incidence measured at the facility. More importantly, changes in diagnostic practices or access to diagnostics over time can greatly affect observed trends. Despite these limitations, the overall picture that emerges when these studies are assembled is coherent and encouraging.

Search strategy and selection criteria

We searched the National Library of Medicine's Medline database with the Medical Subject Headings "Africa South of the Sahara", "Malaria/epidemiology", "Malaria/mortality", "Malaria/prevention and control", and "Malaria/transmission", omitting papers that contained the keywords "Malaria/immunology". The search was limited by restricting retrieval to articles published in the past 10 years. Our last search was done on March 29, 2010. The search identified 1528 publications. Articles were included if they reported at least 2 years of data on malaria-specific indicators (clinical or slide diagnosed case numbers, incidence, prevalence, or malaria-specific mortality) in a population of more than 1000 people. Cross-sectional studies reporting a single timepoint, those involving only pregnant women, intervention studies covering 1 year or less of follow-up, and entomological studies without any clinical or parasitological components were excluded. Also excluded were studies published in the selected time frame but which did not report data from the period 1999–2009. The titles for each citation were screened and 297 were selected for review of their abstracts. Screening of the abstracts yielded 82 publications for full review. After reviewing the full texts, 46 studies that fully met the inclusion criteria were identified.

Conclusions

Reports from several countries in sub-Saharan Africa show a substantial, recent decline in the burden of malaria. Similar changes might have occurred in some other countries, for example Senegal, but these have not been reported in peer-reviewed publications. In other countries, there has probably been little change in the malaria burden. Successful control seems to have been achieved in several different ways, but it has sometimes proved difficult to link the timing of an apparent decline in the incidence of malaria with the introduction of a specific intervention. Whether certain interventions are more likely to have an effect on different outcome measures cannot be determined, for example, whether scale-up of effective treatment has a greater effect on burden of clinical malaria than on prevalence. Although numbers of clinical cases have declined in many areas, this does not mean that transmission is being interrupted or that these areas are approaching elimination.

We have restricted our analysis to information presented in peer reviewed journals and presented at international scientific meetings, and we have focused on clinical malaria rather than on the prevalence of infection. Many other relevant datasets likely exist (eg, parasite prevalence data as presented in the Malaria Atlas Project), which would define the changing pattern of malaria in sub-Saharan Africa more clearly than we have been able to do in this Review. We hope that this initial attempt to review the changing pattern of malaria in sub-Saharan Africa and the possible causes will encourage more detailed work in this important area.

For more on the **Malaria Atlas Project** see http://www.map.ox.ac.uk

Contributors
WPO and BG conceived the paper. WPO and JMM developed the data search and extracted the data. All authors contributed to interpretation of the data, drafting the paper, and developing the figures.

Conflict of interests
We declare that we have no conflicts of interest.

Acknowledgments
We thank Geoffrey Targett and F Ellis McKenzie for their helpful comments on the paper.

References

1 Monasch R, Reinisch A, Steketee RW, Korenromp EL, Alnwick D, Bergevin Y. Child coverage with mosquito nets and malaria treatment from population-based surveys in african countries: a baseline for monitoring progress in roll back malaria. *Am J Trop Med Hyg* 2004; **71:** 232–38.
2 Malaria and children: progress in intervention coverage. Summary update. United Nations Children's Fund, New York.2009. http://www.unicef.org/health/files/WMD_optimized_reprint.pdf (accessed June 17, 2010).
3 Malaria and children: progress in intervention coverage. United Nations Children's Fund, New York. 2007. http://www.unicef.org/health/files/Malaria_Oct6_for_web%281%29.pdf (accessed June 17, 2010).
4 Roberts L, Enserink M. Malaria: did they really say...eradication? *Science* 2007; **318:** 1544–45.
5 Yeshiwondim AK, Gopal S, Hailemariam AT, Dengela DO, Patel HP. Spatial analysis of malaria incidence at the village level in areas with unstable transmission in Ethiopia. *Int J Health Geogr* 2009; **8:** 5.
6 Otten M, Aregawi M, Were W, et al. Initial evidence of reduction of malaria cases and deaths in Rwanda and Ethiopia due to rapid scale-up of malaria prevention and treatment. *Malar J* 2009; **8:** 14.
7 Manuel Ramos J, Reyes F, Tesfamariam A. Change in epidemiology of malaria infections in a rural area in Ethiopia. *J Travel Med* 2005; **12:** 155–56.
8 Graves PM, Osgood DE, Thomson MC, et al. Effectiveness of malaria control during changing climate conditions in Eritrea, 1998–2003. *Trop Med Int Health* 2008; **13:** 218–28.
9 Mufunda J, Nyarango P, Usman A, et al. Roll back malaria—an African success story in Eritrea. *S Afr Med J* 2007; **97:** 46–50.
10 Nyarango PM, Gebremeskel T, Mebrahtu G, et al. A steep decline of malaria morbidity and mortality trends in Eritrea between 2000 and 2004: the effect of combination of control methods. *Malar J* 2006; **5:** 33.
11 O'Meara WP, Bejon P, Mwangi TW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *Lancet* 2008; **372:** 1555–62.
12 Okiro EA, Hay SI, Gikandi PW, et al. The decline in paediatric malaria admissions on the coast of Kenya. *Malar J* 2007; **6:** 151.
13 Okech BA, Mwobobia IK, Kamau A, et al. Use of integrated malaria management reduces malaria in Kenya. *PLoS One* 2008; **3:** e4050.
14 Beier JC, Oster CN, Onyango FK, et al. *Plasmodium falciparum* incidence relative to entomological inoculation rates at a site proposed for testing malaria vaccines in Western Kenya. *Am J Trop Med Hyg* 1994; **50:** 529–36.
15 Beier JC, Perkins PV, Onyango FK, et al. Characterization of malaria transmission by Anopheles (Diptera: Culicidae) in western Kenya in preparation for malaria vaccine trials. *J Med Entomol* 1990; **27:** 570–77.
16 Adazu K, Hamel M, Feiken D, et al. Marked decline in childhood mortality in the Western Kenya DSS: evidence from longitudinal data 2003–2007. American Society of Tropical Medicine and Hygiene, 57th Annual Meeting; New Orleans, Louisiana, USA; Dec 7–11, 2008. Abstract #372.
17 Snow RW, Armstrong JRM, Forster D, et al. Childhood deaths in Africa: uses and limitations of verbal autopsies. *Lancet* 1992; **340:** 351–5.
18 Okiro EA, Alegana VA, Noor AM, Mutheu JJ, Juma E, Snow RW. Malaria paediatric hospitalization between 1999 and 2008 across Kenya. *BMC Med* 2009; **7:** 75.
19 Gomez-Elipe A, Otero A, van Herp M, Aguirre-Jaime A. Forecasting malaria incidence based on monthly case reports and environmental factors in Karuzi, Burundi, 1997–2003. *Malar J* 2007; **6:** 129.
20 Protopopoff N, Van Bortel W, Marcotty T, et al. Spatial targeted vector control is able to reduce malaria prevalence in the highlands of Burundi. *Am J Trop Med Hyg* 2008; **79:** 12–18.
21 Ndyomugyenyi R, Magnussen P. Trends in malaria-attributable morbidity and mortality among young children admitted to Ugandan hospitals, for the period 1990–2001. *Ann Trop Med Parasitol* 2004; **98:** 315–27.
22 Bukirwa H, Yau V, Kigozi R, et al. Assessing the impact of indoor residual spraying on malaria morbidity using a sentinel site surveillance system in Western Uganda. *Am J Trop Med Hyg* 2009; **81:** 611–14.
23 Alilio MS, Kitua A, Njunwa K, et al. Malaria control at the district level in Africa: the case of the muheza district in northeastern Tanzania. *Am J Trop Med Hyg* 2004; **71** (suppl 2): 205–13.
24 Gosling RD, Gesase S, Mosha JF, et al. Protective efficacy and safety of three antimalarial regimens for intermittent preventive treatment for malaria in infants: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; **374:** 1521–32.
25 Lusingu JP, Vestergaard L, Mmbando BP, et al. A declining burden of malaria in northeastern Tanzania. American Society of Tropical Medicine & Hygiene, 57th Annual Meeting; New Orleans, Louisiana, USA; Dec 7–11, 2008. Abstract #601.
26 Maegga BT, Cox J, Malley KD. Malaria in the southern highlands of Tanzania: a review of hospital records. *Tanzan Health Res Bull* 2005; **7:** 125–32.
27 Killeen GF, Tami A, Kihonda J, et al. Cost-sharing strategies combining targeted public subsidies with private-sector delivery achieve high bednet coverage and reduced malaria transmission in Kilombero Valley, southern Tanzania. *BMC Infect Dis* 2007; **7:** 121.
28 Hay SI, Noor AM, Simba M, et al. Clinical epidemiology of malaria in the highlands of western Kenya. *Emerg Infect Dis* 2002; **8:** 543–48.
29 John CC, Riedesel MA, Magak NG, et al. Possible interruption of malaria transmission, highland Kenya, 2007–2008. *Emerg Infect Dis* 2009; 15: 1917–24.
30 Kristan M, Abeku TA, Beard J, et al. Variations in entomological indices in relation to weather patterns and malaria incidence in East African highlands: implications for epidemic prevention and control. *Malar J* 2008; **7:** 231.
31 Bonora S, De Rosa FG, Boffito M, Di Perri G, Rossati A. Rising temperature and the malaria epidemic in Burundi. *Trends Parasitol* 2001; **17:** 572–73.
32 Mabiala-Babela JR, Samba-Louaka C, Mouko A, Senga P. Morbidity in a paediatric department (University Hospital of Brazzaville): 12 years later (1989–2001). *Arch Pediatr* 2003; **10:** 650–52.
33 Himeidan YE, Hamid EE, Thalib L, Elbashir MI, Adam I. Climatic variables and transmission of falciparum malaria in New Halfa, eastern Sudan. *East Mediterr Health J* 2007; **13:** 17–24.
34 Kimbi HK, Nformi D, Patchong AM, Ndamukong KJ. Influence of urbanisation on asymptomatic malaria in school children in Molyko, South West Cameroon. *East Afr Med J* 2006; **83:** 602–09.
35 Maharaj R, Mthembu DJ, Sharp BL. Impact of DDT re-introduction on malaria transmission in KwaZulu-Natal. *S Afr Med J* 2005; **95:** 871–74.
36 Craig MH, Kleinschmidt I, Le Sueur D, Sharp BL. Exploring 30 years of malaria case data in KwaZulu-Natal, South Africa: part II—the impact of non-climatic factors. *Trop Med Int Health* 2004; **9:** 1258–66.
37 Craig MH, Kleinschmidt I, Nawn JB, Le Sueur D, Sharp BL. Exploring 30 years of malaria case data in KwaZulu-Natal, South Africa: part I—the impact of climatic factors. *Trop Med Int Health* 2004; **9:** 1247–57.
38 Barnes KI, Durrheim DN, Little F, et al. Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal, South Africa. *PLoS Med* 2005; **2:** e330.
39 Sharp BL, Kleinschmidt I, Streat E, et al. Seven years of regional malaria control collaboration–Mozambique, South Africa, and Swaziland. *Am J Trop Med Hyg* 2007; **76:** 42–47.
40 Bassat Q, Guinovart C, Sigauque B, et al. Malaria in rural Mozambique–Part II: children admitted to hospital. *Malar J* 2008; **7:** 37.
41 Guinovart C, Bassat Q, Sigauque B, et al. Malaria in rural Mozambique–Part I: children attending the outpatient clinic. *Malar J* 2008; **7:** 36.

42 Gerritsen AA, Kruger P, van der Loeff MF, Grobusch MP. Malaria incidence in Limpopo Province, South Africa, 1998–2007. *Malar J* 2008; **7:** 162.

43 Steketee RW, Sipilanyambe N, Chimumbwa J, et al. National malaria control and scaling up for impact: the Zambia experience through 2006. *Am J Trop Med Hyg* 2008; **79:** 45–52.

44 Chizema-Kawesha E, Miller J, Steketee RW, Mukonka VM, Mukuka C. Scaling up malaria control in Zambia: progress and impact 2005–2008. *Am J Trop Med Hyg* (in press).

45 Chanda P, Hamainza B, Mulenga S, Chalwe V, Msiska C, Chizema-Kawesha E. Early results of integrated malaria control and implications for the management of fever in under-five children at a peripheral health facility: a case study of Chongwe rural health centre in Zambia. *Malar J* 2009; **8:** 49.

46 Weekly malaria surveillance in Zimbabwe. *Wkly Epidemiol Rec* 2003; **78:** 398–400.

47 Ceesay SJ, Casals-Pascual C, Erskine J, et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. *Lancet* 2008; **372:** 1545–54.

48 Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E, et al. Evidence of decline of malaria in the general hospital of Libreville, Gabon from 2000 to 2008. *Malar J* 2009; **8:** 300.

49 Sarrassat S, Senghor P, Le Hesran JY. Trends in malaria morbidity following the introduction of artesunate plus amodiaquine combination in M'lomp village dispensary, south-western Senegal. *Malar J* 2008; **7:** 215.

50 Munier A, Diallo A, Marra A, et al. Evolution of malaria mortality and morbidity after the emergence of chloroquine resistance in Niakhar, Senegal. *Malar J* 2009; **8:** 270.

51 Orimadegun AE, Fawole O, Okereke JO, Akinbami FO, Sodeinde O. Increasing burden of childhood severe malaria in a Nigerian tertiary hospital: implication for control. *J Trop Pediatr* 2007; **53:** 185–89.

52 Muller O, Ye M, Louis VR, Sie A. Malaria in sub-Saharan Africa. *Lancet* 2009; **373:** 122.

53 Koudou BG, Tano Y, Keiser J, et al. Effect of agricultural activities on prevalence rates, and clinical and presumptive malaria episodes in central Côte d'Ivoire. *Acta Trop* 2009; **111:** 268–74.

54 Bhattarai A, Ali AS, Kachur SP, et al. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. *PLoS Med* 2007; **4:** e309.

55 Kleinschmidt I, Sharp B, Benavente LE, et al. Reduction in infection with *Plasmodium falciparum* one year after the introduction of malaria control interventions on Bioko Island, Equatorial Guinea. *Am J Trop Med Hyg* 2006; **74:** 972–78.

56 Kleinschmidt I, Torrez M, Schwabe C, et al. Factors influencing the effectiveness of malaria control in Bioko Island, equatorial Guinea. *Am J Trop Med Hyg* 2007; **76:** 1027–32.

57 Kleinschmidt I, Schwabe C, Benavente L, et al. Marked increase in child survival after four years of intensive malaria control. *Am J Trop Med Hyg* 2009; **80:** 882–88.

58 Teklehaimanot HD, Teklehaimanot A, Kiszewski A, Rampao HS, Sachs JD. Malaria in Sao Tome and Principe: on the brink of elimination after three years of effective antimalarial measures. *Am J Trop Med Hyg* 2009; **80:** 133–40.

59 Tseng LF, Chang WC, Ferreira MC, Wu CH, Rampao HS, Lien JC. Rapid control of malaria by means of indoor residual spraying of alphacypermethrin in the Democratic Republic of Sao Tome and Principe. *Am J Trop Med Hyg* 2008; **78:** 248–50.

60 Negash K, Kebede A, Medhin A, et al. Malaria epidemics in the highlands of Ethiopia. *East Afr Med J* 2005; **82:** 186–92.

61 Lengeler C. Insecticide-treated bed nets for preventing malaria (Review). *Cochrane Database Syst Rev* 2004; **2:** CD000363.

62 Okell LC, Drakeley CJ, Bousema T, Whitty CJ, Ghani AC. Modelling the impact of artemisinin combination therapy and long-acting treatments on malaria transmission intensity. *PLoS Med* 2008; **5:** e226.

63 Price RN, Nosten F, Luxemburger C, et al. Effects of artemisinin derivatives on malaria transmissibility. *Lancet* 1996; **347:** 1654–58.

64 Cairns M, Carneiro I, Milligan P, et al. Duration of protection against malaria and anaemia provided by intermittent preventive treatment in infants in Navrongo, Ghana. *PLoS One* 2008; **3:** e2227.