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Malaria Surveillance Counts

Joel G. Breman* and Cherice N. Holloway
Fogarty International Center, National Institutes of Health, Bethesda, Maryland

Abstract. Clinical and epidemiologic surveillance of malaria cases and deaths is required to follow the progress of the reinvigorated malaria control programs nationally and internationally. Current recording, transmittal, analysis, feedback, and use of malaria surveillance information is delayed and imprecise: substantially < 10% of the malaria cases and deaths are being reported. Improvements are occurring, but more emphasis should be placed on prompt, accurate diagnosis, patient management, and recording of clinical manifestations at hospitals. Neurologic signs, severe anemia, metabolic changes, hyperparasitemia, and concurrent sepsis are medical emergencies and require proper clinical and laboratory detection; equipment, reagents, supervision, and certification of laboratorians and clinicians are necessary. Birth weight should also be a major measure of progress in malarial control and overall prenatal care. Although malaria is the most frequent diagnosis at outpatient clinics and hospitals in Africa, co-existing conditions also mandate improved diagnosis, treatment, and registration. Monthly transmittal of information from health units and collation, analysis and feedback through electronic reporting systems using modern information technologies are necessary for resource planning and staff motivation. Denominators to compute rates of illness and death require accurate censuses of communities from which patients come to health units: specialized disease and demographic household surveys designed and performed by nationals are needed to complement hospital-based numerator data. *Plasmodium falciparum* and *P. vivax* should be distinguished in the laboratory; the former causes the greatest mortality but the latter is increasingly recognized as a major peril. Because vector control is now a major component of all malaria control programs, there is an urgent need to monitor anopheline sensitivity to insecticides and entomologic inoculation rates. Where interrupting transmission is a goal, parasite rates in groups at greatest risk should be performed. Continual monitoring of plasmodial sensitivity to drugs is necessary using WHO protocols. Human, entomological, and parasitological surveillance must be performed at the same time in the same places and the information shared widely and used for improving control strategies and tactics. These surveillance priorities require training, provision of equipment, supervision, and commitment to sustainability by national authorities and international collaborators and donors.

INTRODUCTION

"When you cannot measure it, when you cannot express it in numbers, you have scarcely . . . advanced to the stage of Science, whatever the matter may be."
William Thomson, Lord Kelvin, 1824–1907.

The goal of all malaria research and control efforts is to increase understanding of and decrease illness, death, disability, and economic loss from this scourge. It really does matter if the "case count" is 1, 2, or 3 million deaths, and 500 million malaria illnesses or 5 billion clinical episodes resembling malaria in endemic areas.[1–5] Without an accurate count, one has difficulty setting and reaching objectives, ordering diagnostics and interventions, and attracting supporters who are result focused.[6] Would higher or lower numbers change the Millennium Development Goals or the World Health Organization (WHO) policies, strategies, and tactics based on the Abuja Declaration?[7–9] Probably not: those are political pronouncements and not based on epidemiologic reality. Data from the current indices designated for assessing the malaria burdens are overly delayed, incomplete, and imprecise; these measures do not help clinicians manage acutely ill patients. Such information does not optimally guide epidemiologists, public health workers, and decision makers to know how well they are doing in controlling and conquering malaria locally, nationally, and internationally.

There is greater need to focus on human illness first through clinical and epidemiologic surveillance: this is the main subject of this paper. As vector control is now one of the major malaria control strategies aimed toward reducing transmission, entomologic and parasitologic indicators need to be followed concurrently with human surveillance and the results reported promptly. Each area of surveillance—impact on human illness, entomologic and parasitologic status, and delivery of services (the process indicators currently emphasized)—requires special expertise.[10]

CURRENT GOALS, INDICATORS, AND DATA

The current goal of the Global Malaria Programme and the Roll Back Malaria Partnership (RBM) of the WHO is to "halve the malaria burden by 2010" by focusing on treatment, prevention, and epidemic response (Table 1). Recently, the RBM increased the target for correct treatment of patients, distribution and use of bed nets, and preventive treatment of pregnant women from 60% to 80% by 2010. A number of "core" malaria process indicators have been established for tracking the services delivered (http://www.rollbackmalarial.org/merg.html) (Table 2). The Millennium Development Goal (MDG) for malaria is to "halt and begin to reverse the incidence of malaria and other major diseases by the target date of 2015" (http://www.un.org/millenniumgoals/). The United Nations Millennium Project, stating that the MDG goal was difficult to interpret and measure, proposed to "(r)educe malaria morbidity and mortality by 75% by 2015 from the 2005 baseline level."[11] However, for virtually all countries and the world, there is no baseline level. As is widely known, countries in sub-Saharan Africa and the Indian subcontinent contribute the greatest burden.[2,3,5]

The country profiles from the African region of WHO (http://www.afro.who.int/malaria/country-profile/index.html) give the most up-to-date publicly available data on malaria; yet, the most recent information dates to 2002 and before

* Address correspondence to Joel G. Breman, 16 Center Drive, Fogarty International Center, Bethesda, MD 20892. E-mail: jbreman@nih.gov

TABLE 1
Malaria control goals, strategies, and targets—2000 goal: halve the burden by 2010 (Roll Back Malaria Partnership)

Strategy	Targets for 2010 (Abuja Malaria Summit, 2000, revised 2007)
• Prompt access to effective treatment	• 80% of patients having access to and using correct and affordable treatment within 24 hours of symptom onset
• Provision of insecticide-treated nets (ITNs)	• 80% of children < 5 years and pregnant women benefiting from personal and community protection, such as ITNs
• Prevention and control of malaria in pregnant women	• 80% of pregnant women at risk accessing intermittent preventive treatment*
• Epidemic and emergency response	• 60% of epidemics detected within 2 weeks of onset • 60% of epidemics responded to within 2 weeks of detection

* The original Abuja declaration recommended chemoprophylaxis; current WHO and Roll Back Malaria policy strongly recommends IPT.
Source: WHO 2003b, 2005.

(Table 3). Seventy-seven million cases of malaria and 94 thousand deaths are reported officially; between 20–60% of cases and the vast majority of deaths are in children < 5 years of age. These morbidity and mortality estimations are less than 10% of what occurs even though microscopy is not often used to confirm the diagnosis. Communications with the African regional office of WHO (E. Minkoulou, personal communication, 2007) give cases and deaths from 2001 to 2006 reported by Ministries of Health (Table 4). There are large discrepancies in numbers of cases reported, incidence, hospital admissions, and deaths. Tables 5 and 6 give the 2006 reports from the Eastern Mediterranean office of WHO (EMRO), divided into countries with no or limited transmission and those with widespread transmission (http://www.emro.who.int/rbm/Epidemiology-CurrentData.htm): over 80% of the 3.5 million malaria cases reported from EMRO are from Sudan; EMRO estimates that > 10 million cases occurred in the region. Malaria in Southeast Asian countries of WHO (SEARO) is shown for 2004 in Figure 1. (http://www.searo.who.int/EN/Section10/Section21/Section1370.htm). India reports 76% of the 2.5 million malaria cases; Myanmar reports 53% and India 25% of the 3.8 thousand deaths in SEARO. Table 7 shows the malaria reports from the Western Pacific Region of WHO (WPRO) for 2005 (http://www.wpro.who.int/sites/mvp/data/malaria/2005.htm). The Solomon Islands, Vanuatu, and Papua New Guinea have the highest incidence of confirmed malaria. Relatively little malaria occurs in the Americas (900 thousand laboratory confirmed cases in 2006), mostly reported from Brazil (65%), and other countries in the Amazon basin (Table 8, Figure 2; http://www.paho.org/english/ad/dpc/cd/malaria.htm). Southeast Europe is the area where malaria remains a peril, particularly in newly independent countries of the former Soviet Union and in southern Turkey (Figure 3; http://www.euro.who.int/malaria/ctryinfo/ctryinfotop). Globally all countries are at risk, as many of thousands of malaria cases are imported into malaria-free countries yearly from endemic sites. *Plasmodium falciparum* causes the major morbidity and mortality globally, but *P. vivax* is increasingly recognized as an important pathogen, especially in Southeast Asia and the Western Pacific.[12]

TABLE 2
Core malaria indicators advised by the Malaria Monitoring and Evaluation Reference Group, 2007: Essential activity indicators as proportions

- Households with at least one insecticide-treated net (ITN)
- Children with fever in last 2 weeks who received antimalarial treatment according to national policy within 24 hours of onset of fever
- Pregnant women who slept under an ITN the previous night
- Women who received intermittent preventive treatment (IPT) for malaria during their last pregnancy: IPT is two doses of sulfadoxine-pyrimethamine

Reference: Roll Back Malaria website: http://www.rollbackmalaria.org/merg.html. Accessed August 7, 2007.

CONUNDRUMS

How can these data collected in different ways in different places be used in current program planning? Apart from delays, the difficulty in diagnosing malaria correctly is the main reason for the imprecision in quantifying the burden.[13] This is because reliable and cheap microscopy or rapid diagnostic testing is not generally available or performed properly, microscopy particularly in sub-Saharan Africa. Even when available, the results are often inaccurate. There is a lack of specificity, sensitivity, and predictive values in clinical and laboratory diagnosis, especially when the frequency and density of parasitemias are low.[14,15] These confirmatory tests must be standardized and supervised, and those performing the tests should be certified if the quality of diagnosis and patient management are to improve.

A related conundrum is the challenge of diagnosing and managing co-existing conditions. Is febrile illness and plasmodial parasitemia in an endemic area enough to confirm malaria as the diagnosis? Yes, and it should be recorded as malaria. Is plasmodial parasitemia, acute or repeated, with another condition (e.g., chronic ankylostomiasis and iron deficiency), enough to confirm malaria as a diagnosis for anemia? Again, yes, but the intestinal helminthiasis is a coexisting cause of the anemia and should be recorded as a second condition.[16] Is maternal parasitemia during pregnancy or placental parasitemia at delivery enough to confirm malaria as the cause of a newborn with low birth weight? Again, yes, but HIV, syphilis, and other sexually transmitted infections may coexist and merit proper diagnosis and management.[17] Frequent existence of multiple pathologies underscores the necessity of improving clinical and laboratory diagnosis and the quality of medical care. When dual or multiple conditions exist, it is difficult if not impossible to parse the attributable fraction contribution of each pathogen or condition to the patient's clinical status or to the community's epidemiologic profile. The patient has multiple conditions for which multiple treatments are required, and surveillance data should reflect this. Hence, the concept of malaria as a "direct" or "indirect" cause of morbidity and mortality is not useful for diagnosing and managing patients or for counting cases.

TABLE 3
Malaria morbidity and mortality reported by country and priority groups: African region of WHO

Country (year)	Population ×10³	Cases reported			Hospital admissions		Deaths	
		No. (1000s)	Incidence/ 1000	Percent < 5 years of age (%)	No.	Percent < 5 years of age (%)	Total	Percent < 5 years of age (%)
Algeria (2002)	31,558	307	1	–	–	–	–	–
Angola (2002)	13,931	1,409	10	34	–	–	11,344	56
Benin (2001)	6,461	779	12	40	32,008	54	670	74
Botswana (2002)	1,566	28	2	–	–	–	14	–
Burkina Faso (1999)	11,257	880	8	45	34,431	50	3,479	68
Burundi (2002)	6,743	1,809	27	–	–	–	330	–
Cameroon (1998)	14,202	664	5	–	–	–	–	–
Cape Verde (1999)	417	29	7	–	–	–	–	–
Central African Republic (1999)	3,637	128	4	60	0	0	484	74
Chad (2001)	8,127	386	5	0	19,463	43	1,001	60
Comoros (2001)	728	3,718	511	37	820	32	16	31
Congo (1998)	2,841	171	6	–	–	–	–	–
Cote D'Ivoire (2001)	16,383	400	2	33	40,375	28	422	45
Democratic Republic of Congo (2002)	54,408	231	< 1	–	–	–	–	–
Equitorial Guinea (1990)	352	256	73	–	–	–	–	–
Eritrea (2001)	3,821	126	3	21	10,886	18	129	35
Ethiopia (2001)	64,424	151	< 1	23	12,786	23	0	0
Gabon (1998)	1,165	802	69	–	–	–	–	–
Gambia (1999)	1,260	128	10	58	–	–	–	–
Ghana (2002)	20,264	2,831	14	34	161,062	51	3,536	38
Guinea (2000)	8,154	899	11	33	14,933	41	441	56
Guinea–Bisseau (2002)	1,257	195	16	48	66,703	65	780	59
Kenya (2000)	30,669	742	2	40	9,452	34	683	30
Liberia (1998)	2,511	778	31	–	–	–	–	–
Madagascar (2002)	16,959	0	0	–	–	–	–	–
Malawi (2002)	11,848	1,362	11	0	57,649	45	57,649	3
Mali (2001)	11,681	87	1	34	1,056	57	182	66
Mauritania (2002)	2,825	167	6	19	7,312	13	100	31
Mauritus (2002)	1,182	22	2	–	–	–	–	–
Mozambique (2002)	19,035	1,902	10	0	0	0	1,910	0
Nambia (2002)	1,826	359	20	0	0	0	1,023	0
Niger (2002)	11,633	682	6	49	4,777	30	1,096	74
Nigeria (2000)	113,862	31,685	28	42	2,205	53	58	48
Rwanda (2000)	7,609	915	12	30	123,026	31	2,678	43
Sao Tome and Principe (1998)	141	36	26	33	8,160	23	154	94
Senegal (2000)	9,421	1,120	12	27	36,860	18	1,337	38
Seychelles (2002)	84	0	0	–	–	–	–	–
Sierra Leone (1999)	4,336	410	9	–	–	–	–	–
South Africa (2002)	44,127	15,619	35	0	0	0	96	0
Swaziland (1999)	905	30	3	0	3,259	0	148	0
Tanzania (2001)	36,032	673	2	–	–	–	–	–
Togo (2001)	4,652	432	9	36	12,904	54	791	0
Uganda (2002)	24,810	1,878	8	38	–	–	–	–
Zambia (2000)	10,421	1,139	11	61	157,898	–	3,268	53
Zimbabwe (2002)	13,142	599	5	–	–	–	626	–
Total	652,667	76,964	–	–	818,025	–	94,445	–

Source: http//www.afro.who.int/malaria/country-profile/index.html.
– or 0 = no data available.

WHAT SHOULD BE DONE?

Clinical measures. Start with patients. Those in rural and urban malarious areas are becoming severely ill and dying mainly from hematologic (anemia), metabolic (hypoglycemia, acidosis), and neurologic (cytoadherence of red blood cells and cerebral malaria) manifestations[4,18]; these events often occur together.[19] Associated conditions that often go undiagnosed are sepsis and enteritis.[20,21] Low birth weight is caused by or associated with maternal parasitemia and placental sequestration of parasites.[17] All of these potentially lethal conditions are measurable and treatable. Sequential measurements of how often these conditions occur, their outcomes, and trends will indicate how well we are doing in managing patients and controlling the disease in the community. WHO Expert Committees have met and defined severe malaria and its management.[22,23] Monitoring the frequency of severe clinical events associated with malaria is needed to assess the success of control programs. Of particular importance are severe anemia, metabolic complications, hyperparasitemia, and possible sepsis because immediate management is lifesaving (Table 9).[24] Birth weight assessment reflects effective prenatal protection from malaria and other causes of prematurity and intrauterine growth retardation, all of which decrease greatly a newborn's chances of survival.

These indices require laboratory diagnostics, and their assessment should start in public and private hospitals or other places where staff are trained and supervised; reagents and testing equipment must be present in adequate supply and properly refrigerated and conserved. Agreed on standards

TABLE 4
Malaria cases, deaths, and percent deaths, African region of The World Health Organization, 2000–2006

Country	2000			2001			2002			2003			2004			2005			2006		
	Cases	Deaths	Percent deaths	Cases	Deaths	Percent deaths	Cases	Deaths	Percent deaths	Cases	Deaths	Percent deaths	Cases	Deaths	Percent deaths	Cases	Deaths	Percent deaths	Cases	Deaths	Percent deaths
Algeria	–	–	–	156	0	0	196	0	0	86	0	0	55	0	0	–	–	–	–	–	–
Angola	1,635,884	–	–	1,124,557	9,255	0.8	409,294	3,488	0.9	–	–	–	1,880,679	18,800	1.0	2,282,461	12,433	0.5	–	–	–
Benin	708,444	740	0.1	779,041	670	0.1	782,818	707	0.1	819,256	560	0.1	853,034	944	0.1	803,462	323	0	45,503	62	0.1
Botswana	71,555	30	0	49,619	59	0.1	28,971	15	0.1	48,237	29	0.1	22,404	0	0	10,117	10	0.1	10,357	13	0.1
Burkina Faso	1,008,441	3,262	0.3	1,176,460	4,233	0.4	1,434,053	4,057	0.3	1,797,788	5,159	0.3	1,814,684	4,205	0.2	1,818,690	5,645	0.3	426,604	1,239	0.3
Burundi	3,057,239	–	–	2,855,868	579	0	1,808,588	1,289	0.1	1,861,354	1,341	0.1	1,304,085	1,071	0.1	568,958	467	0.1	674,103	568	0.1
Cameroon	–	–	–	–	–	–	–	–	–	41,348	305	0.7	76,192	152	0.2	277,413	836	0.3	–	–	–
Cape Verde	1	0	0	1	0	0	1	0	0	22	0	0	45	2	4.4	–	–	–	70	8	11.4
Central African Republic	89,614	539	0.6	140,742	541	0.4	–	–	–	95,644	417	0.4	152,364	859	0.6	–	–	–	–	–	–
Chad	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Comoros	9,619	41	0.4	3,718	8	0.2	–	–	–	–	–	–	37,843	0	0	29,148	2	0	–	–	–
Congo	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cote D'Ivoire	34,413	644	1.9	400,402	446	0.1	1,153,581	1,242	0.1	1,393,120	946	0.1	1,582,075	1,289	0.1	1,812,600	1,757	0.1	–	–	–
Democratic Republic of Congo	964,623	3,856	0.4	2,199,247	11,597	0.5	2,640,168	7,553	0.3	4,555,056	16,498	0.4	4,028,950	12,999	0.3	6,697,778	17,103	0.3	2,766,697	–	–
Eritria	119,155	94	0.1	125,746	129	0.1	68,783	85	0.1	55,193	98	0.2	23,665	16	0.1	26,665	38	0.1	11,135	29	0.3
Ethiopia	–	–	–	7,951,579	1,159	0	8,516,058	1,263	0	9,274,781	2,324	0	10,906,802	4,662	0	10,244,587	3,550	0	918,274	987	0.1
Gabon	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Gambia	–	–	–	77,584	137	0.2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ghana	–	–	–	–	–	–	–	–	–	294,998	190	0.1	651,661	380	0.1	228,242	162	0.1	–	–	–
Guinea	3,349,528	4,095	0.1	3,383,025	3,726	0.1	1,458,015	3,337	0.2	1,486,236	3,094	0.2	2,790,349	2,688	0.1	3,921,200	2,718	0.1	–	–	–
Guinea Equatorial	1,736,417	831	0	851,877	517	0.1	850,147	440	0.1	731,911	586	0.1	876,837	528	0.1	850,309	490	0.1	–	–	–
Guinea-Bissau	–	–	–	–	–	–	194,976	–	–	241,089	714	0.3	151,215	371	0.2	148,526	391	0.3	–	–	–
Kenya	186,659	683	0.4	133,784	–	–	87,914	–	–	2,149,322	–	–	2,002,824	–	–	–	–	–	60,372	–	–
Lesotho	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Liberia	–	–	–	–	–	–	–	–	–	83,869	–	–	208,088	–	–	62,415	40	0.1	–	–	–
Madagascar	1,383,239	591	0	1,429,491	742	0.1	1,598,919	757	0	2,198,197	1,000	0	1,358,408	866	0.1	–	–	–	–	–	–
Malawi	3,566,277	7,139	0.2	3,756,798	4,286	0.1	2,687,927	5,775	0.2	3,268,554	4,787	0.1	2,776,737	3,039	0.1	1,739,314	405	0	–	–	–
Mali	99,217	153	0.2	86,512	182	0.2	697	–	–	20,879	29	0.1	38,455	44	0.1	44,866	22	0	44,348	9	0
Mauritania	259,093	491	0.2	243,942	337	0.1	211,870	100	0	–	–	–	140,926	31	0	–	110	–	–	–	–
Mauritus	62	0	0	66	0	0	39	0	0	40	0	0	26	–	–	17	–	–	–	–	–
Mozambique	3,446,220	2,039	0.1	3,947,335	4,700	0.1	4,592,799	4,214	0.1	5,182,555	3,562	0.1	5,610,884	4,150	0.1	5,813,725	4,209	0.1	2,315,777	2,129	0.1
Namibia	494,867	1,031	0.2	538,512	1,728	0.3	445,803	1,504	0.3	468,259	1,106	0.2	610,799	1,185	0.2	348,385	1,325	0.4	–	–	–
Niger	1,203,294	2,439	0.2	723,950	4,018	0.6	681,709	2,433	0.4	817,071	4,287	0.5	822,694	3,181	0.4	732,059	3,083	0.4	621,707	1,150	0.2
Nigeria	2,508,298	5,725	0.2	2,253,519	4,317	0.2	2,710,407	4,122	0.2	3,740,803	5,926	0.2	3,109,166	5,119	0.2	2,610,730	3,417	0.1	–	–	–
Rwanda	475,106	1,923	0.4	989,925	2,589	0.3	1,061,367	1,858	0.2	1,190,516	1,434	0.1	1,271,674	1,076	0.1	991,612	629	0.1	–	–	–
Sao Tome & Principe*	174	181	–	1,948	172	8.8	367	181	–	44,520	145	0.3	36,870	124	0.3	21,633	70	0.3	–	–	–
Senegal	1,120,094	1,337	0.1	927,870	1,563	0.2	987,868	1,257	0.1	1,425,306	1,607	0.1	1,154,350	1,524	0.1	995,907	1,286	0.1	–	–	–
Seychelles	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sierra Leone	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	266,808	–	–
South Africa	64,622	459	0.7	26,506	119	0.4	15,649	96	0.6	13,459	142	1.1	13,290	89	0.7	7,141	60	0.8	8,580	61	0.7
Swaziland	45,581	60	0.1	19,799	13	0.1	14,863	8	0.1	12,670	17	0.1	6,952	12	0.2	7,099	51	0.7	838	–	–
Tanzania	205,429	495	0.2	336,683	838	0.2	266,519	441	0.2	9,754,381	14,842	0.2	9,288,457	19,550	0.2	5,955,716	7,736	0.1	1,964,303	2,597	0.1
Togo	457,425	1,209	0.3	472,505	1,356	0.3	557,648	1,663	0.3	490,256	1,130	0.2	516,942	1,183	0.2	–	–	–	–	–	–
Uganda	8,745	146	1.7	5,211,845	–	–	7,545,449	146	0	9,657,332	897	0	10,712,601	2,573	0	4,487,069	1,054	0	573,963	435	0.1
Zambia	3,602,564	8,952	0.2	4,150,096	9,391	0.2	4,101,169	9,023	0.2	4,642,774	9,178	0.2	4,329,668	8,289	0.2	4,339,028	7,697	0.2	–	–	
Zimbabwe	1,533,960	1,012	0.1	1,564,342	1,607	0.1	1,348,137	1,893	0.1	638,906	1,139	0.2	1,830,181	1,587	0.1	644,591	569	0.1	371,986	381	0.1
Total	33,445,859	50,197	0.2	47,935,050	71,014	0.1	48,262,769	58,947	0.1	68,495,788	83,489	0.1	72,992,931	102,588	0.1	58,521,463	77,688	0.1	11,081,425	9,668	0.1

Source: Ministries of Health and African Regional Office of WHO, January 4, 2007.
–, no report.
* Data from Sao Tome & Principe from 2000 through 2002 are incomplete compared to later years.

TABLE 5
Malaria morbidity and mortality for the Eastern Mediterranean region countries having interrupted or limited transmission, 2006

Countries	Population	Cases		Species transmitted locally
		Total	Autochthonous	
Bahrain	688,345	70	0	Nil
Egypt	78,887,007	29	0	Nil
Iran, Islamic Republic of*	65,400,000	15,909	13,127	*P. vivax* > *P. falciparum*
Iraq	27,499,638	24	23	*P. vivax*
Jordan	5,630,000	116	2‡	Nil
Kuwait	3,182,960	235	0	Nil
Lebanon	3,874,050	42	0	Nil
Libyan Arab Jamahiriya	6,036,914	10	0	Nil
Morocco	33,757,175	83	0	Nil
Oman	3,200,000	443	0	Nil
Palestine		2	0	Nil
Qatar	907,229	198	0	Nil
Saudi Arabia†	27,600,000	1,278	269	*P. falciparum* > *P. vivax*
Syrian Arab Republic	18,600,000	34	0	Nil
Tunisia	10,216,000	36	0	Nil
United Arab Emirates	4,400,000	1,663	0	Nil
Total	289,879,318	20,142	13,421	

* Endemic areas mainly in the southeast.
† Endemic areas mainly in the southwest.
‡ Introduced falciparum cases.
>, predominance of one species.

must be established for measurements, and laboratories and clinical services evaluated periodically and certified to assure that they are meeting these standards.

Integrated management of childhood illness. The WHO estimates that six disease syndromes account for 73% of the > 10 million deaths of those < 5 years of age; these are pneumonia (19%), diarrhea (18%), malaria (8%), neonatal pneumonia or sepsis (10%), preterm delivery (10%), and birth asphyxia (8%), with under-nutrition being an underlying cause in more than one half of deaths of those < 5 years of age.[25] Multiple studies and reports have shown that 25–40% of patients coming to dispensaries and hospitals in malarious areas of Africa are diagnosed with malaria, usually without laboratory confirmation[9]; fever or recent history of fever is used as the cardinal symptom. With the development of treatment algorithms, the Integrated Management of Childhood Illness (IMCI) program at WHO has greatly helped front-line health workers make accurate clinical judgments on many common clinical conditions including malaria.[26] This systematic evidence-based clinical approach is quite rational and facilitates administering and ordering medicines, educating the patient, and establishing criteria for referral. Problems with ICMI have been poor coverage because of a lack of resources, overburdening the peripheral health worker with too many tasks, and poor supervision.[27] For instance, in an area with a high level of malaria transmission and parasitemia in young children, a child with fever may receive an antimalarial drug, irrespective of other diagnoses. This would be fully justified where there is no confirmatory test but not if a properly done blood smear was negative for asexual parasites. In areas of Ethiopia and Kenya, researchers found that conjunctival and palmar "pallor" could help to diagnose anemia associated with malaria, but assessment of the hemoglobin (or hematocrit) and parasitemia status promptly would be the best medical practice (Figure 4).[28,29] Beyond malaria, all of the local clinical diagnoses should be entered into a computerized database for disease assessment, anticipation of future trends, and rational management of resources at the district level as has been done successfully in Tanzania.[30]

Access, use, and quality. For patients with severe malaria, prompt access, correct treatment, and referral is a matter of life and death. Children with severe anemia (hemoglobin < 5 g/dL) and respiratory distress survived more often if they received a transfusion within 1–2 days of admission to a district hospital compared with those who did not.[31] Pregnant women with obstetrical complications and anemia have a high risk of dying from hemorrhage during childbirth, particularly when they arrive late to a hospital.[32] Patients with severe neurologic and cerebral manifestations having a short duration of onset merit rapid detection and management because they suffer a high mortality rate.[33,34] A recent study showed that treating rural African and Bangladeshi children with acute severe malaria (inability to swallow) with artesunate given by rectal suppository in the village before referral decreased mortality by 25%: the delay before arrival to the local health unit where standard parenteral treatment could be given was about 4 hours in Africa and 1.5 hours in Bangladesh (M. Gomes, personal communication, 2007). Time intervals from illness onset to treatment must be assessed routinely in malaria control and other health programs and used as indicators for the success of control programs. The WHO recommendation is treatment within 24 hours and the frequency of how often this occurs is a process indicator.

TABLE 6
Malaria morbidity and mortality for the Eastern Mediterranean region countries with continuing widespread transmission, 2006

Countries	Population	Cases			Species transmitted
		Reported	Confirmed	Estimated	
Afghanistan	31,056,997	329,154	82,692	1,500,000	*P. vivax* > *P. falciparum*
Djibouti	650,000	7,708	1,796	60,000	*P. falciparum* > *P. vivax*
Pakistan	164,741,924	NA	124,000	1,600,000	*P. vivax* > *P. falciparum*
Somalia	8,800,000	49,256	16,430	1,300,000	*P. falciparum* > *P. vivax*
Sudan	40,200,000	2,888,943	589,138	5,000,000	*P. falciparum* > *P. vivax*
Yemen	19,800,000	217,270	55,000	900,000	*P. falciparum* > *P. vivax*
Total	265,248,921	3,492,331	569,056	10,360,000	

Since 2004 in heavily endemic conditions.
* Estimated figures in 2005.
NA, not available; >, predominance of one species.

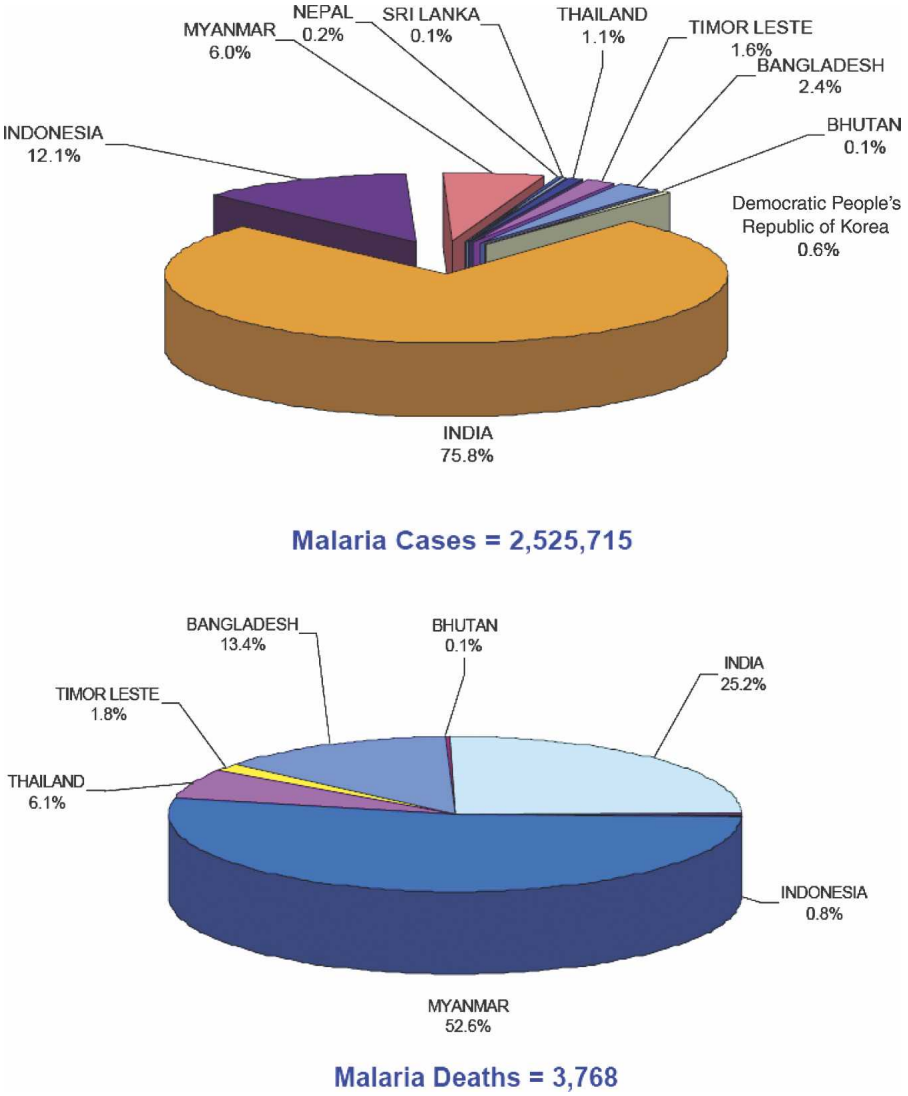

FIGURE 1. Malaria cases and death in South East Asia region of WHO, 2004.

MORBIDITY AND MORTALITY

The most important indicator for evaluating the overall impact of malaria control is overall and population-specific mortality rates, particularly those < 5 years of age in heavily endemic areas. Countries can measure this by routine vital statistics collection systems for numerating events that are tied to periodically updated demographic surveys that provide accurate denominators; special prospective disease and demography surveys following representative cohorts over

TABLE 7
Malaria morbidity and mortality for the Western Pacific Region of WHO, 2005

Country	Population (in thousands)	No. of confirmed malaria cases	Percent falciparum cases	No. of malaria deaths	Incidence (confirmed malaria cases per 1,000)	Mortality rate (per 100,000)
Cambodia	14,825	49,436	82	296	3.33	2.00
China	1,322,275	21,935	16	48	0.02	0
Lao People's Democratic Republic	5,918	13,602	96	77	2.3	1.30
Malaysia	23,325	5,569	40	33	0.22	0.13
Papua New Guinea	5,959	98,762	65	725	16.57	12.17
Philippines	82,809	46,485	63	145	0.56	0.18
Republic of Korea	48,182	1,323	0	0	0.03	0.00
Solomon Islands	504	76,762	71	38	152.31	7.54
Vanuatu	222	9,834	43	0	44.33	0.00
Vietnam	83,585	19,497	73	18	0.23	0.02
Total	1,589,602	343,205	549	1,380	0.00	0.09

WHO, Regional Office for the Western Pacific.

TABLE 8
Malaria morbidity trend in the Americas: 2000, 2005, 2010, and 2015 annual data (no. of cases)

Country	2000 (baseline)	2005	2006	2010 (RBM objectives: expected 50% reduction)	2015 (MDGs: expected 75% reduction)
Belize*	1,486	1,577	844	743.00	371.50
Mexico*	7,390	2,967	2,415	3,695.00	1,847.50
Costa Rica*	1,879	3,541	2,903	939.50	469.75
El Salvador	745	67	67	372.50	186.25
Guatemala	53,311	39,571	31,093	26,655.50	13,327.75
Honduras	35,125	16,121	11,459	17,562.50	8,781.25
Nicaragua*	23,878	6,617	2,988	11,939.00	5,969.50
Panama	1,036	3,667	1,663	518.00	259.00
Haiti	16,897	21,778	21,778	8,448.50	4,224.25
Dominican Republic	1,233	3,837	3,837	616.50	308.25
French Guiana	3,708	4,414	4,074	1,854.00	927.00
Guyana	24,018	38,984	21,064	12,009.00	6,004.50
Suriname*	13,132	9,014	4,000	6,566.00	3,283.00
Brazil	613,241	600,887	548,597	306,620.50	153,310.25
Bolivia	31,469	20,142	18,995	15,734.50	7,867.25
Colombia	107,616	118,163	116,872	53,808.00	26,904.00
Ecuador	104,528	16,487	7,318	52,264.00	26,132.00
Peru*	68,321	93,581	64,871	34,160.50	17,080.25
Venezuela*	29,736	45,049	37,062	14,868.00	7,434.00
Argentina	440	115	115	220.00	110.00
Paraguay	6,853	376	376	3,426.50	1,713.25
TOTAL	1,146,042	1,046,955	902,391	573,021.00	286,510.50

* The data are preliminary.
Source: http://www.paho.org/english/ad/dpc/cd/malaria.htm
Indicates preliminary country report.
Indicates country officially reported.

long periods of time; and specialized disease-specific transversal surveys. The INDEPTH network has 38 demographic surveillance sites covering 19 countries in Africa, Southeast Asia, and the Western Pacific (http://www.indepth-network.org/dss_site_profiles/sites.htm). This project provides the best examples of a community-based cohort survey.[35,36] Vital statistics and demographic censuses for health remain poorly developed in low-income countries. Innovative surrogate approaches have included assessing the ages of persons buried at cemeteries, reviewing notices of deaths in newspapers (especially for maternal deaths), and interrogations of families (verbal autopsies) for determining deaths and cause of death over time.

Although disease frequencies can be determined during epidemics, malaria-specific death rates are more difficult to define in areas with stable transmission and the presence of other infections causing fever. Strengthening of routine clinical and laboratory diagnosis—first at the state, province, and district level in hospitals and referral centers—will be the most useful if the information is sent and analyzed promptly. The goal of every country should be to assure that reporting includes facilities from the private sector, military, religious, and non-governmental organizations.[37]

Surveillance authorities should note that many public and private hospitals and university teaching facilities may report to the Ministries of Education, Science, or Defense and not to

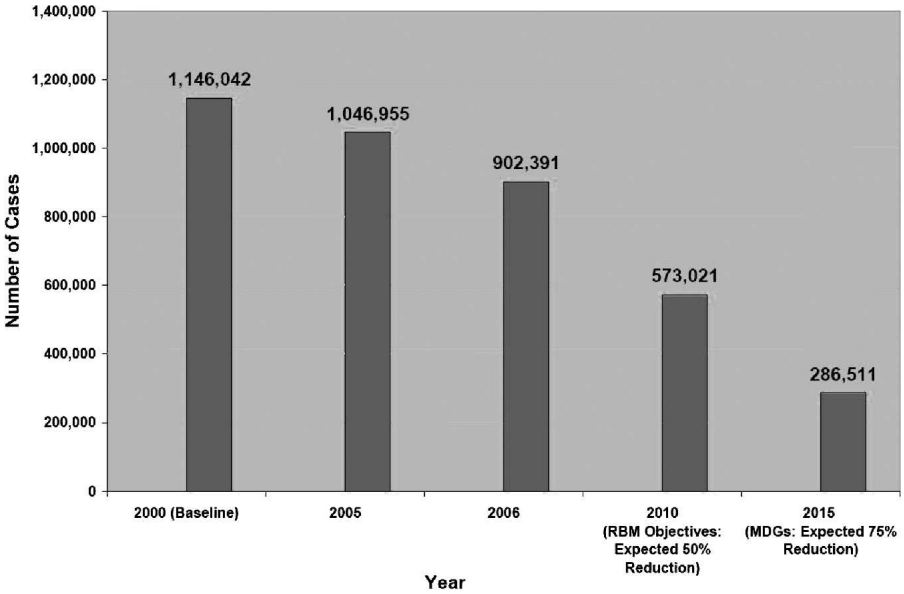

FIGURE 2. Regional malaria morbidity trend in the Americas: 2000, 2005, 2010, 2015.

FIGURE 3. Number of autochthonous cases of malaria in the European region of WHO, 2005.

the epidemiologic and statistical services at the Ministry of Health. Surveillance systems must be expanded to dispensaries when the hospitals are reporting satisfactorily. Monthly or more frequent electronic reporting with precoded diagnoses should be the goal of every country. Information technology and wireless satellite communications are well advanced and being increasingly used at modest cost.[38] Surveys performed by groups outside of the country, while independent and unbiased, are usually too delayed in sharing results and often neglect training nationals.

TRACKING MALARIA TRANSMISSION AND CONTROL

The major measures of malaria endemicity and intensity of transmission have been parasitologic (parasite rates by age), clinical/hematologic (spleen rates, anemia rates by age), and entomologic (entomologic inoculation rates (EIRs) by anopheline species). The parasitologic and spleen rates in children 2–9 years of age have been used to describe the classic endemic categories: hypoendemic (< 10%); mesoendemic (11–50%); hyperendemic (51–75%); and holoendemic (> 75%), but no sampling methods generalizable to populations have been advised for these measurements. Those categories are of limited use because the indices can change throughout a year; they are based on parasitologic diagnoses and surveys that are not performed routinely and are often of questionable reliability; the research teams that perform the surveys do not often report the results promptly to the control program. It is recommended that such surveys first be done on children < 5 years of age and pregnant women (or other high-risk groups) coming to outpatient clinics. Outpatient testing would be similar to periodic serologic testing of HIV in pregnant women and other high-risk groups to assess the success of prevention and control programs.[39] Anemia results from multiple causes, including repeated attacks of malaria, including episodes of parasitemia resistant to drugs.

Similarly, entomologic indices are not assessed routinely, except in some countries that rely greatly on classic vector control approaches (insecticide residual spray [IRS] of dwellings, larviciding, and other forms of environmental management) as in the Americas, Southeast Asia, and the Western Pacific.[9] Entomologic assessments, particularly EIRs, are frequently done by research institutions only and are often unlinked to prevention policies or actions. These measures are crucial for assessing progress in disease elimination and eradication and should now be used in control programs aiming to decrease transmission, especially in Africa. Entomologic studies require skill in collecting and identifying anopheline species and subspecies in larval and adult habitats using sound sampling methods before, during, and after intervention programs.[40,41] The EIRs vary considerably depending on temperature, rainfall, humidity, and other environmental and control parameters. As for all malariometric surveys, the quality of the data may vary, based on the rigor of the study, including acumen of the laboratorian. The Africa Network on Vector Resistance has published useful information on standardized testing of mosquito sensitivity to insecticides (http://www.who.int/tdr/topics/mol_entomology/files/anvr_news.pdf).

RESISTANCE OF PARASITES TO DRUGS AND MOSQUITOES TO INSECTICIDES

Every malaria control program should track the efficacy and effectiveness of the interventions. Parasite resistance to artemisinin-based combination therapies (ACTs) is not expected in the near future because of their mode of action and pharmacokinetics.[42] Regrettably, other drugs are commonly used, to which parasites are resistant. The best assessment of efficacy is the 28-day *in vivo* test of response in ill patients in priority groups (i.e., children < 5 years of age and pregnant women). If intermittent preventive treatment of infants (IPTi) is given, the drug used should be tested for efficacy in the youngest children. *In vitro* testing and the newer molecular tests to identify drug-resistant genes in parasites can identify early patterns of resistance but results of these tests do not consider the immune status of the patient.[43] Collaboration between control programs and research centers is required. This will assure that *in vivo*, *in vitro*, and molecular drug sensitivity surveillance and other important data (e.g., drug availability, use, and costs) are used in developing patient management guidelines, for ordering drugs, and for preparing and updating training and health education material for health staff and caregivers.

Where IRS is employed, bioassay assessment of the sensitivity of *Anopheles* to the insecticides used must be done periodically using WHO protocols.[40] Toxicity monitoring of spray personnel is also needed. Although long-duration treated nets should retain insecticide potency, the materials need to be inspected and assayed for confirmation of quality and amount of the chemical[44]; nets that require dipping every 6 months require chemical analysis periodically to assure potency. Sham or counterfeit drugs are now a major problem in Asia and Africa, and antimalarials are a target for the counterfeiters. A plan needs to be developed to survey the drugs, nets, insecticides, and other supplies to assure they meet national and international specifications.

CONCLUSION

Current surveillance for malaria is inadequate. The process indicators identified by control programs are important but will not indicate whether the burden of disease has changed

TABLE 9
Selected severe clinical malaria conditions requiring diagnosis, assessment, and reporting

Condition	Manifestations	Required Equipment	Management*
Coma†	Unable to respond to stimuli	Blantyre coma scale score	Parenteral therapy
Convulsions	Convulsions (grand and petit mal)—can be subtle signs	Observation	Anticonvulsants, protection from injury
Renal failure	Urine output in 24 hours < 400 mL (adults); or < 12 mL/kg (children)	Biochemical analysis	Rehydration (no overhydration)
	Serum creatinine > 265 μmol/L (> 3.0 mg/dL)	Urine collections	Hemofiltration if needed
Other: sepsis†	Febrile, hypotensive, shocked (after malaria treatment)	Blood culture, complete blood count	Antibiotics, supportive care, rehydration
Low birth weight†	< 2,500 < 1,500 g (severe)	Scale (calibrated)	Resuscitation, breast feeding, food supplements, warmth (incubator)
Hematologic: anemia†	Hematocrit < 15% Hemoglobin < 5 g/dL	Hematocrit equipment Hemoglobinometer	Blood transfusion with whole blood or packed cells
Biochemical: hypoglycemia†	Plasma glucose < 2.2 mmol/L (< 40 mg/dL)	Analytic equipment Glucosometer	Glucose infusion
Acidosis	Arterial pH < 7.25 or plasma bicarbonate < 15 mmol/L	Blood gas analysis	Correct hypovolemia Hemofiltration
Parasitologic: Hyperparasitemia†	> 100,000 parasites/mL	Microscopy (or Rapid Diagnostic Test) Microscope, slides, reagents	Consider parenteral treatment with artemisinins, quinine or quinidine

* In addition to antimalarial drugs; referral to a secondary or temporary care facility for patients requiring parenteral therapy and intensive supportive care.
† Essential measurement.
‡ Consider exchange transfusion for parasitemia > 10

along the timelines needed for managing national and international malaria control initiatives[45] (Table 10). Burden of disease is reflected in human morbidity and mortality, and measurements of the manifestations of malaria in the clinical setting should be the place to start. The advantages of improving diagnosis and clinical management of patients are evident. Given the amount of "malaria" coming to clinics and hospitals, especially in Africa, and the costs of newer treatments (ACTs), greater emphasis on improving the quality of medical care is required. Emphasis must be on provision of up-to-date diagnostic equipment and reagents, recommended medicines, and supportive care. Most importantly, establishing the highest standards of care for patients with malaria will involve greater pre-service, in-service, and post-service training of laboratory and clinical officers. Granted, most malaria occurs outside of the hospital.[4] As the quality of care improves at hospitals, it will be the responsibility of those running the hospitals to assess the needs of populations near peripheral dispensaries and in villages to improve their care, emphasizing quality, training, and supervision, and efficient utilization of resources. Involvement of communities in decision-making and investments of the public and private sectors in rural and urban health will be necessary. Similarly, major investments in epidemiologic surveillance, particularly for proper record keeping, reporting, and analysis at all hospitals and selected dispensaries, will be needed: this too requires training, provision of diagnostic definitions, computer software, and support. Most importantly, supervision, feedback, and backup from central epidemiologic services will be required.

FIGURE 4. Conjunctival pallor in patient with severe anemia.

Accurate and complete demographic surveys will give denominators for calculating rates of malaria and other diseases using outpatient visits and inpatient events occurring at hospitals as numerators. Using agreed on definitions of disease and accurate clinical diagnoses, public health officials will be able to follow disease trends monthly or quarterly and make corrections in patient management and prevention programs without delay. Precise assessments of overall mortality and morbidity requires statistically valid surveys that are rarely performed more often than once every several years—usually by outside consultants, researchers, or academics. Funding organizations often request these surveys to see if the stated goals have been achieved. These specialized surveys have a role, but should also include national staff in design, leadership, and managerial roles, so that nationals can do such surveys on their own.

Measurements of the impact of prevention measures aimed toward decreasing transmission and eliminating disease must focus on entomologic and parasitologic indices. This will require large-scale recruitment and training of entomologists, microscopists, and persons skilled in the newer rapid diagnostic tests. Parasite rates (PRs) are one of the best measures of endemicity, but only when the goal of control is to decrease or eliminate transmission. PRs are dependent on immune status

TABLE 10
Indicators of the impact of malaria control programs

Morbidity
Patients diagnosed with malaria in public-sector facilities over 1 year.*
Proportion of children diagnosed with malaria among patients seen at public-sector clinics†‡
Proportion of population reporting a febrile episode in the previous 2 weeks
Patients with microscopically confirmed severe malaria seen in referral facilities over 1 year§
Proportion of children with severe anemia among pediatric admissions in health facilities†
Proportion of babies delivered in health facilities who have low birth weight (< 2500 g)
Mortality
Deaths after a malaria-like illness¶ occurring in facilities over 1 year
Deaths after a malaria-like illness, confirmed microscopically, occurring in referral facilities over 1 year
Proportion of all deaths in health facilities that follow a malaria-like illness
Proportion of patients hospitalized with a malaria-like illness who die in the hospital**
Number of children dying with severe anemia in health facilities over 1 year

* This and several other morbidity indicators are not expressed as proportions, as is desirable. The most useful denominator would be "the population served by the health facilities"; however, in most malaria-endemic countries, population estimates are unavailable or outdated, utilization rates for health facilities may vary over times, and the resulting proportion would be imprecise.
† This indicator can be difficult to interpret because changes may be caused mainly by a change in the denominator, which may be unrelated to malaria.
‡ More complete reporting is often available from public sector than private sector facilities. This may vary by country, and program managers using this indicator will need to define the types of facilities to sample for indicator measurement.
§ In this example, measurement of the indicator is limited to referral health facilities because they are most likely to have microscopes available and receive a major share of severe malaria cases.
¶ "Malaria-like" can be defined regionally or at country level, but might include fever alone, seizure, coma, or anemia without other apparent cause.
** This indicator may reflect community beliefs and attitudes related to health system utilization, health worker performance, or quality.

and age and human–vector contact. In areas with intense, stable transmission (hyper- or holoendemic malaria), it has been shown that PRs can be reduced greatly—to ~1% as in Garki, Nigeria—but no further, even after chemoprophylaxis, mass drug administration, and periodic household applications of IRS.[46] Great reduction in sporozoite-carrying female anopheles can occur with IRS and insecticide-treated nets (ITNs). Although recent control programs in southern Africa and Zanzibar relying on IRS, ACTs and ITNs have been extremely successful, no areas or country in Africa or Asia has shown that malaria-carrying mosquitoes can be eliminated.[47,48] A recently published study from Vanuatu indicated that IRS and ITNs were needed to get the best effect in reducing transmission and malarial illness, but ITNs alone were not as effective as both.[49]

Models for malaria dynamics and the effects of different interventions continue to be valuable in understanding and preventing malaria.[46,50] Much recent attention by mathematical modelers has been in defining the impact of malaria vaccines.[51] The main purpose of these exercises should be to understand, control, and prevent disease transmission and facilitate logistics; to date, the results have been mainly of academic use. Rainfall, temperature and humidity are excellent predictors of anopheles' breeding. Parasite prevalence and incidences will help to track the impact of control measures on transmission.[52] It is important that reliable morbidity and mortality information be registered at the same time in the same areas where drug sensitivity studies are done, and where vectors, EIRs, and parasite prevalence data are collected.

To perform the disease and transmission measurements properly requires a commitment to training and research in surveillance and malariology. Surveillance staff (including modelers) should go to the field to observe how data are collected and train field workers in diagnostics, demography, malariology, and the relationship of the data collected to program planning. All surveillance activities require a long-term commitment. Although the current interventions can have a substantial impact on malaria incidence within a few years, large-scale decreases in mortality may take much longer. Sustainability of programs will be the key to controlling and eliminating malaria. Measuring accurately how well patients are being managed in health units, changes in mortality rates using updated censuses, and hospital and community-based survey data will be the key to understanding the effectiveness of such programs and making changes to improve them.

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Authors' address: Joel G. Breman and Cherice N. Holloway, Building 16, Room 214, 16 Center Drive, MSC 6705, Bethesda, MD 20892. Tel: 301-496-0815, Fax: 301-496-8496, E-mail: jbreman@nih.gov.

REFERENCES

1. Rowe AK, Rowe SY, Snow RW, Korenromp EL, Schellenberg JR, Stein C, Nahlen BL, Bryce J, Black RE, Steketee RW, 2006. The burden of malaria mortality among African children in the year 2000. *Int J Epidemiol 14:* 691–704.
2. Breman JG, Mills AM, Snow RW, Mulligan J, Lengeler C, Mendis K, Sharp B, Morel C, Marchesini P, White N, Steketee RW, Doumbo O, 2006. Conquering malaria. Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans D, Jha P, Mills A, Musgrove P, eds. *Disease Control Priorities in Developing Countries.* Second edition. Washington, DC: Oxford University Press/World Bank, 413–432.
3. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI, 2005. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature 434:* 214–217.
4. Breman JG, 2001. The ears of the hippopotamus: manifestations, determinants and estimates of the malaria burden. *Am J Trop Med Hyg 64 (Suppl 1-2):* 1–11.
5. Breman JG, Alilio MS, Mills A, 2004. Conquering the intolerable burden of malaria: II. What's new, what's needed: a summary. *Am J Trop Med Hyg 71 (2 Suppl):* 1–15.
6. Kiszewski A, Johns B, Schapira A, Delacollette C, Crowell V, Tan-Torres T, Ameneshewa B, Teklehaimanot A, Nafo-Traoré F, 2007. Estimated global resources needed to attain international malaria control goals. *Bull World Hlth Organ 85:* 623–630.
7. United Nations, 2000. *Millennium Declaration*. New York: The United Nations Millennium Summit.
8. World Health Organization, 2003. *The Africa Malaria Report, 2003,* Geneva: World Health Organization.
9. World Health Organization, 2005. *The World Malaria Report 2005. Roll Back Malaria*. Geneva: World Health Organization.
10. Bryce J, Rongou JB, Nguyen-Dinh P, Naimoli JF, Breman JG,

1994. Evaluation of national malaria control programmes in Africa. *Bull World Hlth Org 72:* 371–381.
11. Teklehaimanot A, Singer B, Spielman A, Tozan Y, Schapira A, 2005. *UN Millennium Project. Coming to Grips With Malaria in the New Millennium. Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines.* Working Group on Malaria, p. 10.
12. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM, 2007. Vivax malaria: neglected and not benign. *Am J Trop Med Hyg 77 (Suppl 6):* 79–87.
13. Koram KA, Molyneux ME, 2007. When is malaria malaria: the different burdens of malaria infection, malaria disease, and malaria-like illness. *Am J Trop Med Hyg 77 (Suppl 6):* 1–5.
14. Coleman RE, Manceechai N, Rachaphaew N, Kumpitak C, Miller RS, Soyseng V, Thimasarn K, Sattabongkot J, 2002. Comparison of field and expert laboratory microscopy for active surveillance for asymptomatic *Plasmodium falciparum* and *Plasmodium vivax* in western Thailand. *Am J Trop Med Hyg 67:* 141–144.
15. Prudhomme O'Meara W, Remich S, Ogutu B, Lucas M, Mtalib R, Obare P, Oloo F, Onoka C, Osoga J, Ohrt C, McKenzie FE, 2006. Systematic comparison of two methods to measure parasite density from malaria blood smears. *Parasitol Res 99:* 500–504.
16. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, Savioli L, 2007. Current concepts: control of neglected tropical diseases. *N Engl J Med 357:* 1018–1027.
17. Steketee RW, Nahlen BL, Parise ME, Menendez C, 2001. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg 64 (Suppl 2):* 28–35.
18. Murphy SC, Breman JG, 2001. Gaps in the childhood malaria burden in Africa: cerebral malaria, neurologic sequelae, anemia, respiratory distress, hypoglycemia and complications of pregnancy. *Am J Trop Med Hyg 64 (Suppl 1-2):* 57–67.
19. Marsh K, Foster P, Wariuru C, Mwangi I, Winstanley M, Marsh V, Newton C, Pasvol G, Snow R, 1995. Indicators of life-threatening malaria in African children. *N Engl J Med 332:* 1399–1404.
20. Gwer S, Newton CRJC, Berkley J, 2007. Over-diagnosis and co-morbidity of severe malaria in African children: a guide for clinicians. *Am J Trop Med Hyg 77 (Suppl 6):* 6–13.
21. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J, Davachi F, 1989. Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. *Bull World Hlth Org 67:* 189–196.
22. World Health Organization, 2005. *Guidelines for the Treatment of Malaria.* Geneva: World Health Organization.
23. World Health Organization, 2000. Severe falciparum malaria. *Trans R Soc Trop Med Hyg 94 (Suppl 1):* 1–51.
24. White NJ, Breman JG, 2007. Malaria. Kasper D, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds. *Harrisons Principles of Internal Medicine.* Seventeenth edition. New York: McGraw Hill, in press.
25. Bryce J, Black RE, Walker N, Bhutta ZA, Lawn JE, Steketee RW, 2005. Can the world afford to save 6 million children from dying each year? *Lancet 365:* 2193–2200.
26. Gove S, Tamburlini G, Molyneux E, Whitesell P, Campbell H, 1999. Development and technical basis of simplified guidelines for emergency triage assessment and treatment in developing countries. WHO Integrated Management of Childhood Illness (IMCI) Referral Care Project. *Arch Dis Child 81:* 473–477.
27. Victora CG, Adam T, Bryce J, Evans DB, 2006. Integrated management of the sick child. Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans D, Jha P, Mills A, Musgrove P, eds. *Disease Control Priorities in Developing Countries*. Second edition. Washington, DC: Oxford University Press/World Bank, 1177–1192.
28. Muhe L, Oljira B, Degefu H, Jaffar S, Weber MW, 2000. Evaluation of clinical pallor in the identification and treatment of children with moderate and severe anaemia. *Trop Med Int Health 5:* 805–810.
29. Zucker JR, Perkins BA, Jafari H, Otieno J, Obonyo C, Campbell CC, 1997. Clinical signs for the recognition of children with moderate or severe anaemia in western Kenya. *Bull World Hlth Org 78 (Supp 1):* 97–102.
30. de Savigny D, Binka F, 2004. Monitoring future impact on malaria burden in sub-Saharan Africa. *Am J Trop Med Hyg 71 (Suppl 2):* 224–231.
31. Lackritz EM, Campbell CC, Ruebush TK 2nd, Hightower AW, Wakube W, Steketee RW, Were JB, 1992. Effect of blood transfusion on survival among children in a Kenyan hospital. *Lancet 340:* 524–528.
32. Kampikaho A, Irwiq LM, 1991. Incidence and causes of maternal mortality in five Kampala hospitals. *East Afr Med J 68:* 624–631.
33. Idro R, Ndirito M, Ogutu B, Mithwani S, Maitland K, Berkley J, Crawley J, Fegan G, Bauni E, Peshu N, Marsh K, Neville B, Newton C, 2007. Burden, features, and outcome of neurological involvement in acute falciparum malaria in Kenyan children. *JAMA 297:* 2232–2240.
34. Mung'ala-Odera V, Snow RW, Newton C, 2004. The burden of the neurocognitive impairment associated with *Plasmodium falciparum* malaria in sub-Saharan Africa. *Am J Trop Med Hyg 71 (Suppl 2):* 64–70.
35. INDEPTH, 2001. *INDEPTH Monograph Series: Demographic Surveillance Systems for Assessing Populations and their Health in Developing Countries. Volume 1: Population, Health and Survival in INDEPTH Sites.* Ottawa: International Development Research Centre.
36. Sankoh OA, Ngom P, Clarks J, de Savigny D, Binka F, 2006. Levels and patterns of mortality at INDEPTH demographic surveillance systems. Jamison DT, Feachem RG, Makgoba MW, Bos ER, Baingana FK, Hofman KJ, Rogo KO, eds. *Disease and Mortality in Sub-Saharan, Africa*. Second edition. Washington, DC: World Bank Press.
37. Nsubuga P, White ME, Thacker SB, Anderson MA, Blount SB, Broome CV, Chiller TM, Espitia V, Imtiaz R, Sosin D, Stroup DF, Tauxe RV, Vijayaraghavan M, Trostle M, 2006. Public health surveillance: a tool for targeting and monitoring intervention. Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans D, Jha P, Mills A, Musgrove P, eds. *Disease Control Priorities in Developing Countries*. Second edition. Washington, DC: Oxford University Press/World Bank, 997–1018.
38. Royall J, Bennet M, Van Schyak I, Alilio M, 2004. Tying up lions: multilateral initiative on malaria communications: the first chapter of a malaria research network in Africa. *Am J Trop Med Hyg 71 (Suppl 2):* 259–267.
39. UNAIDS, 2007. *Joint United Programme on HIV/AIDS.* Available at http://www.unaids.org/en/HIV_data/default.asp
40 World Health Organization, 2003. *Malaria Entomology and Vector Control.* Geneva: World Health Organization.
41. Mboera LE, 2005. Sampling techniques for adult Afrotropical malarial vectors and their reliability in the estimation of entomological inoculation rate. *Tanzan Health Res Bull 7:* 117–124.
42. White NJ, 1998. Preventing antimalaria resistance through combinations. *Drug Resist Update. 1:* 3–9.
43. Vestergaard L, Ringwald P, 2007. Responding to the challenge of antimalarial drug resistance by routine monitoring to update national malaria treatment policies. *Am J Trop Med Hyg 77 (Suppl 6):* 153–159.
44. Smith S, Joshi UB, Grabowsky M, Selenikio J, Nobia T, and Aapore T, 2007. Evaluation of bednets after 38 months of household use in northwest Ghana. *Am J Trop Med Hyg 77(Suppl 6):* 243–248.
45. Roll Back Malaria, MEASURE Evaluation, World Health Organization, UNICEF, 2006. *Guidelines for Core Population Coverage Indicatiors for Roll Back Malaria.* To be obtained from Household Surveys, MEASURE Evaluation: Calverton, MD 1–31.
46. Molyneux L, Gramiccia G, 1980. *The Garki Project: Research on the Epidemiology and Control of Malaria in the Sudan Savannah of West Africa.* Geneva: World Health Organization, 172.
47. Sharp BL, Kleinschmidt I, Streat E, Maharaj R, Barnes KI, Durrheim DN, Ridl FC, Morris N, Seocharan I, Kunene S, La Grange JJ, Mthembu JD, Maartens F, Martin DL, Barreto A, 2007. Seven years of regional malaria control collaboration—Mozambique, South Africa, and Swaziland. *Am J Trop Med Hyg 76:* 42–47.

48. Battarai A, Ali AS, Kachur SP, Mårtensson A, Abbas AK, Khatib R, Al-mafazy A-w, Ramsan M, Rotllant G, Geistenmaier JF, Molteni F, Abdulla S, Montgomery SM, Koneko A, Björkman A, 2007. Impact of art artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. *PLoS Medicine 4:* e309.
49. Over M, Bakotee B, Vélayudhan R, Wilikai P, Graves P, 2004. Impregnated nets cannot fully substitute for DDT: field effectiveness of malaria prevention in Solomon Islands. *Am J Trop Med Hyg 71 (Suppl 2):* 214–223.
50. McKenzie FM, Samba EM, 2004. The role of mathematical modeling in evidence-based malaria control. *Am J Trop Med Hyg 71 (Suppl 2):* 94–96.
51. Smith T, Killeen GF, Maire N, Ross A, Molineaux L, Tediosi F, Hutton G, Utzinger J, Dietz K, Tanner M, 2006. Mathematical modeling of the impact of malaria vaccines on the clinical epidemiology and natural history of Plasmodium falciparum malaria: overview. *Am J Trop Med Hyg 75 (2 Suppl):* 1–10.
52. Guerra CA, Hay SI, Lucioparedes LS, Gikandi PW, Tatem AJ, Noor AM, Snow RW, 2007. Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project. Review. *Malaria J 6:* e27.