Malaria and the Millennium Development Goals

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ABSTRACT

Malaria, as a key disease of poverty, was singled out for special attention in the Millennium Project of 2000. Recent data suggest that malaria incidence and mortality are now declining all over the world. While these figures are cause for celebration, they must be interpreted carefully and with caution, particularly in relation to Africa. There are daunting challenges ahead for those working to achieve malaria eradication, not least of which is the poor quality of the data on which the work is based. In the absence of an affordable and fully effective vaccine, international funding for malaria control needs to be escalated still further. The money is essential to pay for universal access to a set of simple and proven interventions which would save the lives of millions of children over the next 15 years.

INTRODUCTION

In 2015, the United Nations (UN) will ask which of the eight Millennium Development Goals (MDGs), agreed by all 189 member states in September 2000, have been achieved. In terms of combating malaria (MDG 6C) (table 1), the primary question will be prosaic: is the incidence of malaria lower in 2015 than it was in 2000? Despite the optimism of the latest WHO World Malaria Report,[1] from which all of the unreferenced data in this article are taken, the answer will likely be somewhat nuanced: probably yes, though not everywhere, and we don't really know by how much. As the world moves toward the Sustainable Development Goals of 'the post-2015 agenda',[2] the Roll Back Malaria (RBM) Partnership is formulating a series of more incisive questions to be asked of the international malaria community between now and 2025. Its second Global Malaria Action Plan (GMAP) will provide the framework against which these questions must be answered, for the sake of the 3 billion people who still live under the shadow of this ancient human pathogen.[3]

MALARIA AND POVERTY

At the end of the 20th century, up to 3 million people died every year from malaria.[4] Almost all were young African children killed by *Plasmodium falciparum*, the deadliest of five species of human malaria parasite transmitted by female anopheline mosquitoes. Endemic malaria is a disease of the tropics and sub-tropics, the same geographical boundaries that enclose the sizeable fraction of the world's population still living in extreme poverty. That poverty complicates malaria control needs little explanation. However, the arguments that malaria actually causes poverty are also persuasive.[5] At the microeconomic level, a bout of malaria for an Asian subsistence farmer during harvest time can have catastrophic consequences for the family, while, at the macroeconomic level, the World Bank estimates that malaria costs Africa US$12 billion a year, accounting for a reduction of almost half the annual per capita gross domestic product of some countries.[6] Conversely, almost all countries that have eradicated malaria since 1965 experienced substantially accelerated economic growth in the immediate aftermath.[7] For the rest, malaria, as a leading cause of childhood mortality, contributes to the maintenance of high-fertility rates and impedes a demographic transition to smaller, healthier and better-educated families.

MALARIA CONTROL IN THE 20TH CENTURY

These vast human and economic costs explain why malaria was highlighted for special attention in the Millennium Declaration's chapter on Development and Poverty Eradication.[8] The international community had been beaten by the disease decades before, when the Global Malaria Eradication Programme (1955–1969) had ultimately failed despite some notable successes in temperate regions, where the transmission season was short and the main mosquito vectors preferred biting cattle to humans.[9] Elsewhere, rapidly escalating chloroquine and dichlorodiphenyltrichloroethane (DDT) resistance led to pandemic resurgences where malaria interventions had been discontinued short of full elimination. Control programmes were so poorly integrated with existing healthcare infrastructures that, at worst, they served only to undermine them. With weakening political support and diminished funding for malaria control in the 1970s and 1980s, mortality rates rose, even where the disease had been almost eliminated 20 years before. In the face of this looming catastrophe, health leaders, malariologists and development workers began a coordinated campaign throughout the 1990s to refocus attention on the global malaria problem, with particular emphasis on Africa.

In 1998 the WHO–RBM Partnership announced the first GMAP based around universal global coverage with a small set of proven interventions (table 2). Through international advocacy, multi-agency collaboration and vigorous implementation, RBM aimed for a 75% reduction in global malaria incidence by 2015. In 2000, African heads of state signed the Abuja Declaration, resolving to 'halve the malaria mortality for Africa's people by 2010',[10] and, later the same year, the MDGs were approved. For the first time, all the key stakeholders were aligned toward an ambitious and shared goal for universal malaria control, with the focus on Africa.

INDICATORS OF PROGRESS

Despite dissent and criticism in some quarters,[11] RBM and the Millennium Project successfully

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Table 1 List of indicators for Millennium Development Goal 6C[14]

Goal 6: Combat HIV/AIDS, malaria and other diseases	Indicators
Target 6C: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases	6.6 Incidence and death rates associated with malaria 6.7 Proportion of children under 5 sleeping under insecticide-treated bed nets 6.8 Proportion of children under 5 with fever who are treated with appropriate antimalarial drugs

attracted substantial funding to finance the realisation of MDG 6. Since 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria[12] has driven the increase in worldwide spending on malaria from US$100 million in 2000 to almost US$2 billion in 2013. This money has helped to scale-up global vector control programmes, such as the distribution of the long-lasting insecticide-treated nets (LLINs), the most efficient way to prevent malaria in endemic areas.[13] By 2011, over a third of children exposed to malaria slept under LLINs, up from 5% in 2000,[14] and treated nets are now distributed free of charge through antenatal and immunisation clinics in 39 countries across Africa. By 2012, WHO policies on parasitological confirmation of suspected cases and use of artemisinin-based combination therapy (ACT) for confirmed cases were being adopted all over the world. Manufacturers supplied 205 million rapid diagnostic tests to national control programmes, and 61% of suspected malaria cases in the African public sector were tested. Between 2005 and 2012, the number of ACT treatment courses delivered to malaria-endemic countries rose from 11 million to 331 million.

The headline statistics of the latest WHO Malaria Report[1] suggest these and other measures are having a huge impact on the scale of the global malaria problem. Of 103 countries with ongoing malaria transmission in 2000, 59 have since reported declining malaria incidence, fewer hospital admissions for malaria or lower malaria-specific mortality rates. A further 26 endemic countries have recently been reclassified as having already eliminated, or being close to eliminating, malaria altogether. By 2012, the estimated global incidence had fallen by 29%, and estimated global malaria mortality rates (which take account of population growth) had fallen by 42%, equating to 3.3 million lives saved since 2000. Estimated malaria mortality rates are projected to fall by 52% in all ages and by 60% in children under 5 years old by 2015. Although the effect sizes vary considerably, these estimates broadly concur with those derived from earlier models proposed by the UN[14] and others,[15] suggesting that final victory could be in sight.

Yet the protozoan devil is, as ever, in the detail. The indicator data on which WHO and partner organisations evaluate progress are often flawed, partly because malaria is easily conflated with other causes of febrile illness and death in children, but also because their collection has been inadequate or inconsistent. By 2012, just 62 of the 103 countries that were endemic for malaria in 2000 had generated data of sufficient quality to assess trends in incidence and mortality. Of these, the 52 that reported the greatest progress accounted for only 4% of the 226 million malaria cases estimated to have occurred in 2000. These were generally countries with lower transmission intensities but stronger health information systems. By contrast, the remaining 41 countries generated 80% of the estimated case load, but had inadequate surveillance data on confirmed cases. The absence of hard data necessitates the use of statistical modelling to estimate regional and global trends in incidence and mortality. These models, derived from extrapolated surveillance data, measures of parasite transmission intensity and coverage by national vector control programmes, tend to produce imprecise estimates with wide uncertainty intervals. Information is weakest where need is greatest.

MALARIA IN AFRICA

The WHO Africa Region, home to most of the 41 countries described above, dominates the global malaria statistics. The entomological inoculation rate, a measure of the frequency with which an individual is bitten by an infectious mosquito, is several hundred times higher across much of sub-Saharan Africa than in the endemic countries of Asia or South America.[16] Of the many contributory factors to this contrast, the ubiquitous presence of *Anopheles gambiae* as the primary malaria vector in sub-Saharan Africa is most important. This species complex is highly efficient as a malaria progenitor—long-lived with a particular voracity for biting humans. In a continent ravaged by conflict with chronic underinvestment in healthcare and exploding population growth, an insect lies at the heart of a uniquely ferocious disease ecology.

In 2012, Africa accounted for 165 million of the estimated 207 million cases of malaria (95% uncertainty interval, 135–287 million) and 562 000 of the estimated 627 000 malaria deaths (95% uncertainty interval, 473 000–789 000) (table 3). Just two countries, Nigeria and the Democratic Republic of Congo, generated 40% of total estimated cases globally. Yet there are grounds for cautious optimism. In 2012, 11 African countries reported declining malaria incidences or malaria hospital admissions. Cabo Verde and Algeria each edged closer to 'Malaria Free' certification. Meta-analysis of infection

Table 2 Key interventions for malaria prevention and treatment[3]

Intervention	Notes
Long-lasting insecticidal nets	Sleeping under nets prevents mosquito bites, and insecticide reduces mosquito burden locally
Indoor residual spraying	Application of long-lasting chemical insecticides to inside walls to kill mosquitoes
Other vector control measures	Include application of chemicals to water sources to kill mosquito larvae, under certain conditions
Intermittent preventative treatment during pregnancy	Pregnant women, who are at increased risk from malaria, are given regular preventative treatment to reduce parasitaemia and improve pregnancy outcomes in endemic areas
Diagnosis	Prompt parasitological diagnosis in those with fever using microscopy or rapid diagnostic tests informs malaria treatment
Treatment	Prompt prescription of artemisinin combination therapy for those with *Plasmodium falciparum* or chloroquine and primaquine for those with *Plasmodium vivax* infections

Table 3 Estimated total number of indigenous malaria cases and deaths by WHO region from 2000 to 2012[1]

Cases/deaths per year (thousands)	2000		2004		2008		2012	
WHO region	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Africa	174 000	802	190 000	791	181 000	677	165 000	562
Americas	2000	2.1	2000	1.6	1000	1	1000	0.8
Eastern Mediterranean	16 000	22	15 000	20	13 000	18	13 000	18
European		0.003		0.001			0.002	0
South-east Asia	31 000	49	31 000	45	29 000	46	27 000	42
Western Pacific	3000	6.9	3000	6.1	2000	3.9	1000	3.5
Global total	226 000	881	240 000	864	225 000	747	207 000	627
Lower limit	151 000	670	158 000	656	146 000	569	135 000	473
Upper limit	304 000	1113	325 000	1094	307 000	937	287 000	789

prevalence data from thousands of local surveys conducted across 49 endemic African territories showed modest reductions in malaria transmission rates between 2000 and 2010.[17] These results and those from smaller clinical studies across the continent[18 19] support the conclusion that Africa too is experiencing some reduction in malaria disease burden, although it is difficult to quantify and is patchy. The estimated malaria mortality rate in African children under 5 years old fell by 54% between 2000 and 2012—20% of the overall reduction in child mortality over the same period. If accurate (except for the caveats above), these estimates suggest that improved malaria control plays a major role in efforts to achieve MDG 4: reduce by two-thirds, between 1990 and 2015, the under-five mortality rate.

NEW CHALLENGES

It seems clear that unprecedented international efforts, especially over the last decade, have yielded improvements in the coverage of malaria control interventions and have had a positive impact on disease outcomes too. However, it is also clear that the benefits have been shared inequitably, even within individual countries, and in some places progress has fallen well short of planned targets. In a tight financial and governance climate, it is essential that the effects of interventions are better measured, particularly as countries move closer to elimination status and seek to stratify their approach to local conditions. Health information systems are in dire need of upgrading across most of malaria-endemic Africa in order that the global data are fully representative of the range of transmission settings. Impact models based on national coverage with proven interventions need to account for the fact that their efficacy may vary according to local disease ecology and the strength of healthcare-delivery systems. Models should be validated where possible against solid empirical data from large-scale household surveys or high-quality studies, and incorporate likely interactions between the many dependent variables.

As global malaria incidence falls, *Plasmodium vivax* is responding more slowly to control measures than *P. falciparum*, especially in territories with low seasonal transmission.[1] This is probably a reflection of the different biological characteristics of the two parasite species. About 9% of worldwide malaria cases are estimated to be caused by *P. vivax*, with 80% of infections arising in four countries (Ethiopia, India, Indonesia and Pakistan). Although conventionally considered a relatively benign infection, the actual morbidity risks and case fatality rate of *P. vivax* malaria are poorly quantified. Recent studies suggest that severe disease might be more common than was previously thought.[20] As countries progress toward malaria elimination, strategies to target vivax specifically (such as universal administration of primaquine to effect radical cure of the dormant liver stage of the infection) will become increasingly more important.

Resistance to one or more of the four existing classes of insecticide used for mosquito control has been documented in at least 64 countries to date and is a major threat to malaria control in Africa. Rotational use of insecticides guided by resistance monitoring, as recommended by WHO, may help to prolong the utility of pyrethroids, the only insecticide class used in LLINs, but the development of new classes of insecticide should be a public health priority. Similarly parasite resistance to artemisinins has been recently detected in the Greater Mekong sub-region of South East Asia[21] and there are reports of ACT treatment failures in Pailin Province, Cambodia.[22] This is the area where earlier resistance to chloroquine and sulfadoxine-pyrimethamine first emerged before spreading to Africa and costing millions of lives. The spread of multidrug resistance could rapidly undo much of the progress made in global malaria control over the last decade. In order to contain artemisinin resistance, WHO recommends routine monitoring of therapeutic drug efficacy and the market withdrawal of artemisinin monotherapy in favour of ACT.

In the face of rising mosquito and parasite resistance to chemical interventions, the holy grail of malaria control is an effective vaccine. Despite decades of research, none are commercially available as yet. Of several candidates in development, RTS, S/AS01 (GlaxoSmithKline) is by far the most advanced, with the publication of the final phase III trial data expected later this year. The efficacy results published so far suggest that, when given to 6–12-week-old infants as part of the primary immunisation schedule, the vaccine gives 30% protection against clinical malaria and 26% protection against severe disease in the first year.[23] The results for children 5–17 months old were slightly better.[24] A WHO policy decision on the introduction of the vaccine is likely to be made soon, but, based on the existing data, it will be evaluated as an adjunct to existing control strategies rather than a replacement.

But the single biggest threat to global malaria control in the next 15 years remains financial. Although funding is projected to increase to US$2.85 billion by 2016, it will still fall some way short of the US$5.1 billion WHO calculate is required every year until 2020 to fund universal access to proven interventions. Further sums will be needed for research and development of new drugs, insecticides and vaccines, and most of this money will need to come from outside donors. Interruptions in cash flow can have catastrophic consequences, as demonstrated by

the recent sharp decline in LLIN distribution, which coincided with a period between 2009 and 2012, when rate of increase in financial disbursements by donors fell between 2009 and 2012. National malaria control programmes need assurance that steady funding streams will be in place to support their efforts. As in the last century, malaria resurgence is a real threat unless such commitments are honoured.

As the UN calls time on arguably the greatest act of global political solidarity since its inception, substantial progress has been made toward the elimination of extreme poverty and its effects on public health. However, it has not been enough, and, in terms of malaria control, there is a long way to go to achieve total eradication.[25] Last year, over half a million children died from a disease that is largely preventable and entirely treatable. The fact that the universal implementation of proven and cost-effective interventions to combat malaria fails for want of money is as wrong today as it was in 2000.

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