Malaria: retreat of a centuries-old scourge
Energized in 2007 by a call for malaria eradication, the world united around a new agenda to control and eliminate this ancient scourge. WHO-driven policies led to massive coverage with free or subsidized insecticide-treated nets. As malaria ceased to be the main cause of fever in African children, WHO recommended treatment only after diagnostic confirmation. Malaria deaths dropped 62% from 2000 to 2015, and WHO set an ambitious global technical strategy for malaria through 2030, drawing on the advice of more than 400 experts from 70 countries.

In 1969, the World Health Assembly adopted a carefully worded resolution that effectively ended the Global Malaria Eradication Programme launched in 1955. While long-term plans for malaria eradication were kept on the table, the resolution frankly admitted the failures and setbacks encountered during implementation of the global eradication strategy and shifted the responsibility for moving forward to national public health organizations. The campaign succeeded in eliminating malaria from many parts of the world, but no major gains were made in sub-Saharan Africa, the historical heartland of this disease. The goal of defeating malaria was replaced by the more realistic ambition of holding the disease at bay. In Africa, the malaria situation deteriorated to the point that its only positive feature was stability: things could hardly get any worse.

Interest in malaria control revived in 1992, when the government of the Netherlands hosted a ministerial conference on malaria, co-sponsored by WHO. The conference, attended by senior health leaders from 65 countries, aimed to map out plans for a renewed assault on malaria that acted on lessons from the past. Participants at the conference regarded the fight against malaria as a fight against poverty that demanded better coverage with essential health services. In Africa, WHO estimated that malaria killed one out of every 20 children in rural areas before their fifth birthday and was the most prevalent illness in young adults, sapping productivity and eroding prospects for development. The conference adopted a World Declaration on the Control of Malaria, which was endorsed by the World Health Assembly the following year.

The window of political will and financial resources began to open when WHO established the Roll Back Malaria partnership in 1998, with the goal of cutting malaria deaths in half by 2010.

By 2004, the malaria burden was still expanding as the biggest obstacle to development in a large number of countries, especially in sub-Saharan Africa.
The window opened even wider in 2000, when targets for turning the malaria epidemic around were included in the Millennium Development Goals. However, midway into Roll Back Malaria’s drive, signs were clear that its targets would be missed by a longshot.

By 2004, the malaria burden was still expanding as the biggest obstacle to development in a large number of countries, especially in sub-Saharan Africa. In that part of the world, only 2% of children were sleeping under an insecticide treated net. Though childhood deaths from other causes were declining, deaths from malaria were rising.

Malaria parasites had again exercised their uncanny ability to develop resistance to virtually any single chemotherapeutic agent administered on a large scale. Drug-resistant strains of *Plasmodium falciparum*, which causes the most lethal form of the disease, had swept through the African continent, rendering the first-line treatment, chloroquine, nearly useless. The newer artemisinin-combination therapies were highly effective but, at twenty times the price of older drugs, were beyond the reach of most national control programmes. Despite the renewal of ambitious targets, the overall situation looked bleak.

By 2006, the numbers were large, round, and deeply familiar: 3 billion people at risk in 109 malarious countries and territories and around 266 million cases annually, leading to nearly 750 000 deaths.

**Unrealistic goals?**

In October 2007, malaria experts were stunned when, at a malaria forum in Seattle, Washington, Bill and Melinda Gates uttered a forbidden word in back-to-back speeches calling for the eradication of malaria. The WHO Director-General stepped up to support that goal, further fanning the shockwaves. Reactions were sharply divided. Some cautioned against setting unrealistic goals that were doomed to crash and burn in the absence of new breakthrough tools, most notably a vaccine.

Others pointed to recent reductions in malaria cases and deaths of 50% and even higher in a handful of African countries with small populations and excellent coverage with available interventions. That, they said, was evidence of what could be achieved with existing tools. They argued for elimination goals in groups of neighbouring countries that could gradually shrink the malaria map. As they further argued, more ambitious coverage targets could bring a more ambitious R&D agenda in their wake, especially if supported by the deep pockets of the Bill and Melinda Gates Foundation. Contrary to the expectations of many, that was precisely what began to happen.

A move towards more ambitious coverage turned out to be the preferred way forward for governments in endemic countries, WHO, and the many international partners joining the malaria assault. The will to tackle malaria now had a focused goal: a massive scale up of existing interventions, and most especially, of coverage with insecticide treated nets. In 2008, the UN Secretary-General called for universal access to malaria interventions.
As malaria in Africa affects the poorest of the poor, often living beyond the reach of formal health services, efforts to scale up coverage began with a paucity of reliable data to pinpoint hotspots, assess the effectiveness of different interventions, and establish benchmarks for measuring progress. Nonetheless, some tantalizing evidence was beginning to emerge.

In 2008, WHO recommended that insecticide treated nets be distributed at heavily subsidized prices or no cost to users and on a massive scale. That recommendation ended a long debate. One side argued that the best route to sustainable supplies was through local manufacturing, with nets sold at a subsidized price. Besides, as the argument went, people tended to value and use correctly items for which they had to pay. The other side argued that, for people mired in poverty, no price—however low—was affordable. Nets must be distributed at no cost.

WHO’s recommendation for massive free distribution of nets coincided with two welcome trends. First, more and more African heads of state were taking charge of the malaria response, sometimes leading to an elimination effort in groups of neighbouring countries. Second, the money was rolling in. International funding commitments for malaria control increased from around $300 million in 2004 to $1.7 billion in 2009, largely from such sources as the Global Fund, the World Bank Booster Programme, the US President’s Malaria Initiative, and other agencies.

But national and international efforts still had a very long way to go. As set out in the 2008 World Malaria Report, surveys showed that supplies of insecticidal nets were sufficient to protect only around 26% of people in 37 African countries. Even worse, only 3% of children with fever were being treated with artemisinin-combination therapy.

The impact of policy coherence

With massive scale up of coverage with free insecticidal nets now an agreed programmatic goal, the dam broke. Within a year, sufficient insecticidal nets had been delivered to protect nearly 580 million Africans. An estimated 75 million Africans living in high transmission zones were further protected by indoor residual spraying. The trend continued. WHO estimated that the number of nets procured in just the two years between 2008 and 2010 was sufficient to protect 73% of the 800 million people considered at risk.

Access to diagnostic tests was also rapidly growing, especially following the advent of rapid tests that could quickly detect malaria right down to the community level. To direct this rapid growth towards the selection of quality-assured products, WHO established a testing programme in 2008 to determine the comparative reliability of new tests coming on the market. A detailed checklist to aid procurement was also introduced to add another layer of quality control. Again, the results were impressive. At the turn of the century, fewer than 5% of suspected malaria cases reported in Africa were confirmed by a diagnostic test. By 2010, the worldwide figure had grown to 76%, with the largest increase in sub-Saharan Africa.

By 2010, the situation had improved so much that WHO could issue a new policy recommendation: treatment should be given to suspected malaria cases only after a diagnostic test had confirmed infection. That policy change had three dimensions. First, by ending the blanket administration
of artemisinin-combination therapy to every child with a fever. WHO hoped to reduce selective pressure on the parasite and thus delay the development of resistance. Second, excluding malaria in children with fever would increase the prospect of prompt and effective treatment for the many other common diseases that killed young children in Africa. Finally, the recommendation was made feasible by some very good news: most cases of childhood fever, even in Africa, were no longer caused by malaria.

The impact of all these improvements was dramatic. By 2010, reductions in malaria cases of more than 50% were being reported in 43 of the 99 countries with ongoing transmission, with downward trends recorded in an additional 8 countries. The epidemic’s iron brake on African development that had stubbornly persisted for centuries was losing its grip.

WHO strengthened its policy-making architecture even further. In 2010, WHO initiated an extensive review of its policy-making process for malaria control and elimination. The aim was to establish a more rigorous, efficient, and transparent process that would allow for timely responses to the ongoing challenges faced by national malaria programmes.

Following the recommendations of an external advisory group, a Malaria Policy Advisory Committee was established in 2011 to provide independent advice to WHO on all policy areas related to malaria control and elimination. This strengthened policy-setting architecture repositioned WHO as the credible international public health authority on malaria policy, guidance, and technical support in malaria-endemic countries.

Since establishment of the new architecture, WHO has issued more than 15 policy recommendations on issues ranging from the use of seasonal malaria chemoprevention in the Sahel sub-region in Africa, to advice on how to estimate the longevity of insecticidal nets, to a warning about the risks of scaling back vector control in areas where transmission has been reduced.

### The Malaria Eradication Research Agenda: malERA

By 2010, the world had embraced an ambitious plan for scaling up malaria control that progressed towards country-by-country and regional elimination, with the ultimate goal of global eradication. A meeting was held in Washington, DC to refine a research agenda to underpin the eradication goal. Participants agreed on a multi-pronged approach that included health systems, operational research, and monitoring and evaluation in addition to the basic and applied sciences. A false assumption that the epidemiology and pathophysiology of malaria were fully understood contributed to the failure of the first eradication effort. Scientists were determined to get things right this second time around.

The meeting was attended by the WHO Director-General who had argued for more aggressive malaria control since the start of her administration. In her remarks at the close of the week-long event, Dr Chan thanked participants for putting so much smart science in the service of a disease that affects the very poor, but reminded them that no single technical breakthrough in any single area would be sufficient to eradicate a disease as complex and tenacious as malaria. Even a highly effective vaccine, she said, would need to be supported by the
simultaneous use of drugs, vector control, and good monitoring and evaluation delivered by well-performing health systems.

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**Good will – and innovation – kick in**

Public health is replete with good will and a creative desire to innovate, especially when doing so might change a situation where a child was dying from malaria every second of every day.

In 2008, the UN Secretary-General appointed Ray Chambers, an American business entrepreneur, philanthropist, and humanitarian, as his first Special Envoy for Malaria. Articulate and compelling, Mr Chambers undertook his role with passion, contributing to the visibility of malaria, understanding of its impact, and above all the need for funding. Also in 2008, at the request of its Member States, WHO launched the first of what would become annual World Malaria Days as awareness-building events.

Part of that awareness was a keen appreciation of the need for new tools. Several public-private partnerships were established to develop new products for malaria control, including the Medicines for Malaria Venture, the Malaria Vaccine Initiative, the Innovative Vector Control Consortium, and a malaria project supported by the Foundation for Innovative New Diagnostics, which aims to develop high-quality affordable diagnostic tests for diseases of the poor.

But one existing tool also needed innovation to maximize its impact. Though increases in coverage with insecticidal nets were nothing less than spectacular, access to artemisinin-combination therapies remained disappointingly low in most African countries. In 11 of 13 countries surveyed in 2009, fewer than 15% of children with fever were treated with these superior life-saving medicines. Data from that same year further showed that countries were receiving less than half of needed treatments. Annual joint tenders issued by WHO and UNICEF for multi-source generic treatments meeting international quality standards led to more quality products on the market, but supplies were still inadequate and prices were still too high for most national control programmes.

Apart from high prices, the barriers to better access were numerous and difficult to break down. Procurement required exceptionally long lead times. Artemisinin and its derivatives are manufactured from the leaves of the sweet wormwood, or *Artemisia annua*, plant. Cultivation, extraction, processing, and manufacturing of the final product require at least 18 months. Manufacturing and quality control are especially complex operations. The raw plant materials vary greatly in quality; impurities must also be removed. Artemisinin and its derivatives are chemically unstable, a characteristic that accounts for their superior antimalarial activity but adds to the challenge of manufacturing a consistently high-quality product. Finished products can deteriorate easily, creating special demands for packaging and storage.

Additional problems were market-related. The supply of treatments was highly fragmented, with a huge and lucrative market in the private sector, typically beyond the control of national regulatory authorities. The high price of medicines lured the producers of counterfeit products and cheaper monotherapies to flood the market, raising deep concern that these products...
would hasten the development of drug resistance. The long lead time from cultivation to finished products contributed to a notoriously unstable supply chain, with supplies and their prices fluctuating wildly in what has been called a “bullwhip effect”. A year of oversupply was typically followed by a year of dire shortages with a high risk of stock outs. The uncertainty of future demand gave pharmaceutical companies little incentive to expand production.

One solution came in 2010 with publication of the *WHO guide to good procurement practices for artemisinin-based antimalarial medicines*. Through its concise 16-step checklist, the manual covered all aspects of the procurement cycle, from selecting the best products, through defining product specifications and inviting tenders, to post-shipment quality control and the detection of variations.

In improving access to both diagnostic tests and medicines, the WHO prequalification programme played a decisive role, especially given the very low demand for antimalarial medicines and diagnostic tests in countries with stringent regulatory authorities. The situation improved significantly. The number of manufacturers of quality-assured artemisinin-combination therapies grew from a single company in 2006 to nine prequalified generic manufacturers in 2013. Together, they produced 22 prequalified patient-friendly fixed-dose combinations and two prequalified paediatric formulations.

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**Percentage decrease in malaria death rate since 2000 by WHO region**

<table>
<thead>
<tr>
<th>Year</th>
<th>Africa</th>
<th>South-East Asia</th>
<th>Eastern Mediterranean</th>
<th>Americas</th>
<th>Europe</th>
<th>Western Pacific</th>
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<td>2000</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>2005</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
<td>80%</td>
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<tr>
<td>2010</td>
<td>60%</td>
<td>60%</td>
<td>60%</td>
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<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>2015</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
</tr>
</tbody>
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* There were no recorded deaths among indigenous cases in the WHO European Region for the years shown.

Source: WHO
Community-directed delivery of interventions

In addition to insecticidal nets, WHO recommended three preventive interventions for use in parts of Africa with high transmission of *Plasmodium falciparum* malaria. One policy recommendation covered the use of sulfadoxine-pyrimethamine for the intermittent preventive treatment of pregnant women. A second covered the preventive treatment of infants. In 2012, WHO recommended the seasonal chemoprevention of malaria in areas with highly seasonal malaria transmission as an additional approach to control. Implementation of the recommendations required more frequent contact with health services, which is always a problem for diseases that predominantly affect the rural poor. For example, the recommendation for the preventive treatment of pregnant women required that drugs be administered at each of four antenatal care visits.

To improve access to treatment, the Special Programme for Research and Training in Tropical Diseases, or TDR, had a tailor-made solution based on scientific understanding of why good drugs, good diagnostics, and good preventive strategies fail to have a proportionate impact on tropical diseases in poor countries. In 2009, TDR published the results of a three-year multicentre experimental study designed to test whether community-directed distribution, which had successfully delivered ivermectin to 75 million rural Africans at risk of onchocerciasis, could also distribute other priority interventions, including insecticidal nets and medicines for the home-based management of malaria. *When malaria interventions were delivered using the community-directed strategy, coverage with both nets and treatments more than doubled,* at lower costs than with conventional delivery systems. The results further showed that 77% of children in the seven study sites received artemisinin-combination therapy within 24 hours following the onset of fever.

Moving forward, the approach holds great promise as a platform for the integrated delivery of services, aligned with the core principles of primary health care and the ambition of reaching universal coverage.

The best news yet: 6.8 million lives saved

The way so many partners and innovative approaches kicked in to break down the barriers to ever-higher coverage was emblematic of an initiative that looked destined for unprecedented success.

By 2013, 79 of the 88 endemic countries had adopted artemisinin-combination therapies as the first-line treatment for *Plasmodium falciparum*. The purchasing of treatments increased dramatically, from 11 million treatment courses in 2005 to nearly 400 million in 2013. At that time, generic treatments accounted for 73% of purchases by UNITAID, a drug-purchasing facility that draws substantial and sustainable resources from a levy on airline tickets.

Another milestone was reached in 2013. For the first time, the number of diagnostic tests supplied to Africa for use in the public sector exceeded the number of treatments administered. The test-
before-treat strategy was clearly working to conserve treatments and hopefully prolong their effective market life.

In terms of net distribution, 2014 was the strongest year ever, with more than 189 million nets delivered to countries in sub-Saharan Africa, bringing the total number of nets delivered to that region since 2012 to 402 million. Not surprisingly, deaths from malaria in sub-Saharan Africa dropped by 54% compared with the situation in 2000.

In 2014, WHO estimated that 670 million fewer cases and 4.3 million fewer deaths occurred between 2001 and 2013 globally than would have occurred had the incidence and mortality rates seen in 2000 remained unchanged. Another new estimate was equally compelling: from 2000 to 2014, reductions in malaria cases in sub-Saharan Africa saved countries an estimated $900 million – money that would otherwise have gone to malaria case management. Mosquito nets contributed to the largest savings, followed by artemisinin-based combination therapies and indoor residual spraying.

But the 2016 World Malaria Report brought the best news yet. Data in the report showed – beyond any shadow of a doubt – that the MDG target for halting and beginning to reverse the incidence of malaria had been met. Between 2000 and 2015, the rate of new malaria cases declined globally by an estimated 41%. Over the same period, the global malaria death rate fell by 62%. Equally important, an increasing number of countries had moved towards malaria elimination. Between 2000 and 2015, six countries were certified by WHO as malaria free. An additional 11 countries met the criteria of zero indigenous cases for three years or more and were awaiting official certification of malaria-free status by WHO. All previously endemic countries that eliminated malaria prevented reestablishment of the disease. Elimination is considered especially important in areas of South-East Asia with low malaria incidence but high rates of drug resistance.

By 2016, WHO could revise its estimates upward: between 2001 and 2015, a cumulative total of 6.8 million lives were saved due to reductions in malaria mortality, which is testimony to the commitment of governments supported by the efforts of multiple partners on multiple fronts – an enormous victory for families, communities and countries.

In May 2015, the World Health Assembly approved WHO’s Global technical strategy for malaria 2016–2030, a 15-year blueprint for all countries working to control and eliminate malaria. The strategy set ambitious but attainable targets for 2030, including reducing malaria case incidence and death rates by at least 90%, eliminating malaria in at least 35 countries, and preventing the reintroduction of malaria in all countries that are malaria free.

The global technical strategy marked the first malaria strategy endorsed by the World Health Assembly since 1993. It resulted from the collective effort of more than 400 malaria experts from 70 countries and consultations in seven regions. In June 2015, the Global Malaria Programme was restructured to better respond to the challenges outlined in the global technical strategy.

With the target of reducing malaria cases and deaths by at least 90%, the world is clearly moving into an era that wants to see no child die from a mosquito bite anymore. The malaria experience supports one further conclusion: investment in health development works.
In 2016, WHO announced a significant breakthrough. The world’s first malaria vaccine, approved by the European Medicines Agency the previous year, is set to be piloted in three countries in sub-Saharan Africa beginning in 2018. The vaccine, known as RTS,S, has been shown to provide partial protection against malaria in young children. It will be evaluated as a potential complement to the existing package of WHO-recommended malaria preventive, diagnostic, and treatment measures. The benefits of the vaccine are expected to be greatest in areas with high transmission of Plasmodium falciparum malaria and associated high child mortality.

Though the eradication of malaria remains the ultimate goal for WHO, endemic countries, and their multiple partners, the way ahead is not an easy one for a disease as complex and tenacious as malaria. The burden, though diminished, remains huge. Worldwide, malaria caused 212 million new cases and 429,000 deaths in 2015. In Africa, an estimated 43% of people at risk of malaria do not have access to the core WHO-recommended vector control tools, namely insecticide treated nets and indoor residual spraying. Significant coverage gaps undermine the effectiveness of WHO recommendations for the protection of the two most vulnerable groups: pregnant women and infants.

The fear of further spread of resistance to artemisinin continues to haunt control programmes. The resistance of mosquitoes to insecticides is another significant worry. Since 2010, 60 countries have reported mosquito resistance to at least one class of insecticides used in nets and indoor spraying. Of these, 50 reported resistance to two or more classes of insecticides.

These and other challenges will need to be addressed in the same spirit of determination, ingenuity, and global solidarity that has brought so much progress – and saved so many millions of lives – in the recent past.