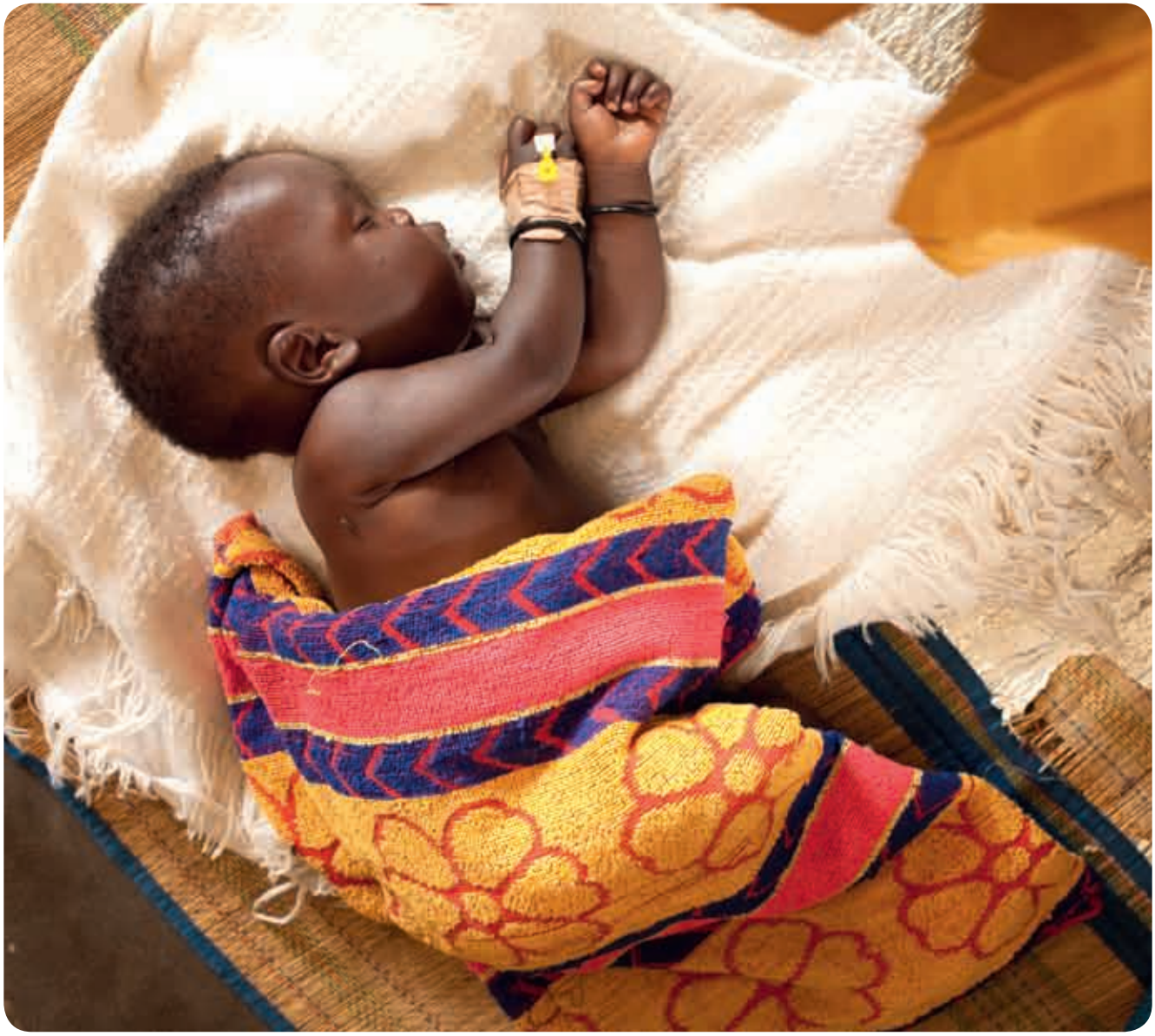

# MAKING THE SWITCH

## Ensuring access to improved treatment for severe malaria in Africa

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

Cover design and layout: Daniel Jaquet
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# MAKING THE SWITCH

Malaria continues to be the leading cause of death in African children. Of an estimated 781,000 malaria-related deaths reported in 2009, 91% occurred on the African continent, and 85% were among children under the age of five[1].

The majority of the 225 million cases of malaria reported worldwide in 2009 were uncomplicated (or simple) malaria, and while this represents a significant burden of illness, these cases are, for the most part, non-fatal. However, around eight million simple malaria cases will progress to severe malaria annually[2].

Patients who have severe malaria show clinical signs of organ damage, which may involve the brain, lungs, kidneys or blood vessels. By definition, all malaria deaths are the result of severe malaria. Uncomplicated malaria is most likely to progress to severe malaria in patients who have not repeatedly been exposed to malaria in the past, and so have not had a chance to develop an immune response against the parasite. For this reason, children are the most vulnerable[3]. Severe malaria has been described as a life-threatening medical emergency and a neglected disease that poses a significant economic burden on most African countries[4].

Severe malaria has traditionally been treated with quinine. Today, the latest scientific evidence clearly shows that many more children's lives can be saved by switching treatment from quinine to a more effective drug, artesunate. However, making this switch will require a concerted effort and dedicated support from the international community.

Médecins Sans Frontières (MSF) has long been an important provider for malaria diagnosis and treatment and treated over one million cases of malaria in Africa in 2009. In response to the latest evidence, MSF has revised its treatment guidelines for all projects to replace quinine with artesunate, and is working with national ministries of health to be able to introduce artesunate in all countries where MSF works.

**This report, based on a review of the latest scientific evidence, coupled with information from MSF's malaria programmes across Africa, highlights some of the important challenges in making this life-saving switch to artesunate for the treatment of severe malaria especially in children, and provides some recommendations for the way forward.**

## Niger: "The real difficulty is that treating children with severe malaria with quinine is too complex"

*During the rainy season in Niger when the risk of getting malaria is highest, over 75% of the children admitted in MSF projects test positive for malaria. Last year, over 200,000 children under five were treated for the disease by MSF in the country. Young children are particularly susceptible to progressing to severe malaria which is often fatal as their immune systems are less developed. This vulnerability is particularly heightened in Niger, where children are already in a weakened state due to malnutrition. Dr. Yvonne Nzomukunda, MSF's deputy medical coordinator in Niger, explains the difficulties in dealing with the seasonal peak of malaria cases, and why a change in protocol to treating the disease with artesunate would make a real difference to the quality of care children receive.*

"The real difficulty is that treating children with severe malaria with quinine is too complex. With quinine, we rely on infusions of the drug delivered in a glucose solution through a vein. Each child needs a succession of separate infusions, each lasting four hours and each time checks have to be carried out – is the drip placed correctly? Is it flowing at the right speed? Has the child moved and does the infusion need to be reset? When there's a spike in admissions during the peak malarial seasons, this places a lot of pressure on the staff and makes it extremely difficult to ensure each child is getting the right treatment at the right time in the right doses."

Quinine is the first choice in the country's protocols for the treatment of severe malaria in children, although intramuscular injections of artemether, another antimalarial drug derived from the Chinese plant, artemisin, are allowed in the case of quinine stock outs, or if a child shows an intolerance to quinine. Dr. Nzomukunda explains that in a context like Niger where many of the children are malnourished, this can happen all too often:

"Large volume infusions are risky for malnourished children, who are often in a fragile metabolic state and therefore must be carefully monitored when given fluids. Plus quinine carries the risk of severe side effects, such as hypoglycaemia and irregular heart beat that can be fatal. If we could use artesunate to treat children, we would have the ability to deliver a dose of the drug through injection in just over four minutes, rather than the four hour period taken currently to deliver quinine, so this would obviously be an advantage and that's why we are really hoping that we will be able to switch away from quinine and use injectable artesunate instead."

Moves are now underway to work with the health authorities so that artesunate can be used in the treatment of severe malaria in children.

However, any moves in Niger or elsewhere on the continent are likely to be aided by enhanced guidance from the World Health Organization; with both the revision of its own guidelines setting out artesunate as the preferred treatment for severe malaria in children and also providing countries with the necessary medical guidance and training to implement.

# THE SCIENCE

Quinine has been the mainstay of malaria treatment for hundreds of years and currently almost all African countries rely on quinine for the treatment of severe malaria[1]. However, several large clinical trials conducted over the past decade in Asia and Africa show that artesunate saves more lives, is safer, and is easier to use compared to quinine. Taken together, an overwhelming body of evidence supports the superiority of artesunate over quinine for the treatment of severe malaria in both adults and children across the world.

**Artesunate saves more lives than quinine**

According to a nine-country trial done in Africa in 2010, for every 41 children treated for severe malaria with artesunate instead of quinine, one life would be saved. This study found that treatment with artesunate reduces the risk of death by 39% in adults and 24% in children; this translates into many thousands of children's lives saved by making the switch[12]. The benefits are likely to be even greater in programme settings, where the difficulties of using quinine are more burdensome than in trial conditions (see below). Overall, it has been estimated that if all cases of severe malaria were treated with artesunate instead of quinine, around 195,000 additional lives would be saved[2].

**Artesunate is safer than quinine**

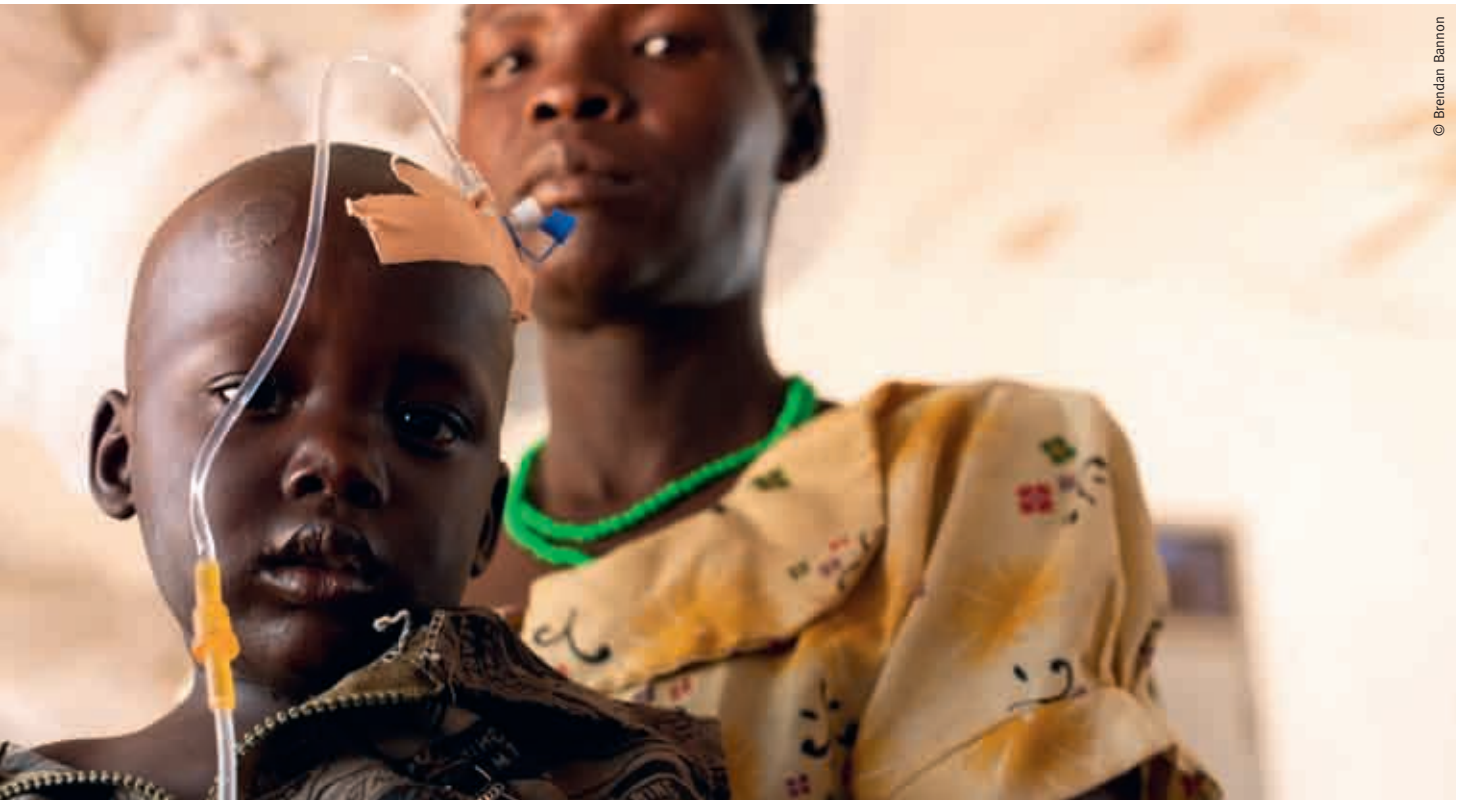
In addition to reducing mortality, artesunate is safer to use than quinine. The most common side effect experienced by patients with severe malaria is low blood sugar (hypoglycemia), which is particulary dangerous for pregnant women. Quinine can worsen low blood sugar in severe malaria patients; this risk is reduced by more than half if artesunate is used instead[13]. Other significant side effects of quinine include dizziness, anaemia and, in some cases, cardiotoxicity and death[15].

**Artesunate is easier to use than quinine**

Quinine is a difficult drug to administer for many reasons. Doses must be calculated precisely according to the patient's body weight and administered as slow infusions over four hours that must be repeated every eight hours until the patient can tolerate oral therapy. In addition, the first dose needs to be adjusted in cases where the patient has taken quinine treatment prior to admission to avoid toxicity. However, it is not always possible to establish a clear history, so some patients will risk being overdosed.

These difficulties in administering quinine, particularly in rural areas of Africa where health workers may lack the necessary training or equipment, can lead to overdosing of quinine, which has resulted in instances of permanent blindness, convulsions, cardiotoxicity and coma[16]. A recent study examining malaria deaths in healthcare facilities in three provinces of South Africa found that almost one in four patients were not given quinine doses as prescribed; four patients received excessive amounts and at least one patient was thought to have died as a result of rapid quinine infusion[17]. A study from Uganda reported similar findings, with 12.7% of patients being underdosed and 12.3% being overdosed with quinine[4].

For these reasons, intravenous quinine treatment requires trained professionals for accurate dosing, slow infusion, and continuous monitoring for side effects. The lack of available skilled professionals may contribute to a delay in starting quinine infusions, and this can lead to avoidable suffering and death. In the African trial comparing quinine and artesunate, children assigned to receive quinine were almost four times more likely to die before ever receiving treatment compared to children assigned to receive artesunate[12].



**Evidence supporting the switch from quinine to artesunate**

**1980s** Following the rediscovery of qinghaosu (artemisinin) in China and subsequent synthesis of artemether and artesunate, both are found to be highly effective alternatives to quinine[5].

**1992-2003** Evidence from small trials done in Myanmar, Thailand, and Vietnam suggest a benefit of artesunate over quinine, but studies are too small to be definitive[6,7].

**2005** A large clinical trial involving nearly 1,400 patients (mostly adults) with severe malaria in Asia shows that artesunate (administered intravenously) reduces deaths by a third compared to quinine[8]. The study is stopped early because of the very large mortality difference between patients receiving artesunate and quinine.

**2006** The WHO recommends artesunate (delivered intravenously) as the treatment of choice for adults with severe malaria, although the guidelines state that quinine would be an acceptable alternative in situations where artesunate is unavailable[9].

**2007** A systematic review of existing trials comparing artesunate and quinine lends further support to the benefit of artesunate in terms of reduced side effects and mortality[10].

**March 2010** The WHO issues stronger guidelines in favour of artesunate treatment for adults with severe malaria. However, these guidelines state that there is insufficient evidence to recommend artemisinin derivatives over quinine for treating children, especially in endemic areas in Africa[11].

**November 2010** A trial involving more than 5,000 children from 11 centres in nine African countries reports that artesunate is more effective at reducing mortality compared to quinine. The study concludes that for every 41 children given artesunate instead of quinine, one life is saved[12].

**March 2011** Updated review of available data concludes that treating severe malaria with artesunate instead of quinine reduces the risk of death by 39% in adults and 24% in children[13].

**April 2011** WHO guidelines are revised to recommend artesunate (to be delivered intravenously) as the first-line treatment for severe malaria in both adults and children[14]. Several African countries, including Guinea, Niger and Uganda, indicate that they are preparing to revise their malaria treatment guidelines to reflect the latest recommendations.

## Guinea: "The challenge that will need to be met is ensuring that these new medicines are made available"

*In December 2010, MSF with the active support of the Ministry of Health, began using a new protocol to treat children for severe malaria in rural health centres in the Guéckédou area in Guinea's eastern, forested uplands. Instead of quinine infusions, children now receive artemether injections, and in a few months' time artesunate will be introduced as the treatment of choice. MSF Field Coordinator Divin Barutwanayo explains what pushed MSF and the health authorities to make the switch as he looks back on the first months of implementation.*

"With the eventual introduction of artesunate injections and the phasing out of quinine, we're really hoping to ease the burden of severe malaria on the population here. Until now all the complicated cases of severe malaria had to be referred to hospitals and this creates real difficulties for people from the villages. There are no ambulances, very few vehicles around and the roads are bad so if you're sent to hospital it's very hard to get food or for family members to come for support. But the problem has been that local health clinics don't have the capacity to treat the illness using quinine which is tricky to administer.

We first started using artemether to treat severe malaria in the local health clinics around here in December last year. To start with, the health workers, some of the nurses and the doctors, were a little reticent about using the new treatment, because quinine has been used for years, so it's not so easy to change overnight. And the patients too – everyone is familiar with infusions when a child has severe malaria, so when they received an injection instead, many at first thought they hadn't received proper treatment, and they wanted the infusions.

So we're working to familiarise health workers with the new medication and reaching out to the local population with radio spots, through posters in waiting rooms and through a network of local organisations and community officers who go out and spread the information in the villages.

And attitudes are changing: in January we treated only six cases of severe malaria with the new treatment, in February we had 27 and in March 46. We're hopeful that we can replicate this success when we introduce artesunate, sometime during the course of the year, with the support of the Ministry of Health.

The challenge that will need to be met is ensuring that these new medicines are made available throughout the health structure of Guinea and not just MSF-supported clinics. Currently some health centres in Guinea sometimes lack even basic medicines and obviously, this presents a big hurdle that needs to be addressed by the government and the donors."

# CHALLENGES TO MAKING THE SWITCH

In response to the latest evidence, the WHO has published revised treatment guidelines to recommend artesunate as first-line treatment for children and adults with severe malaria everywhere[14]. However, there are a number of important barriers that can be anticipated in making this switch.

**Translating evidence into policy**

The latest WHO guidelines will need to be rapidly disseminated to all relevant malaria actors so that national protocols can be revised, and these new protocols must then be distributed to healthcare providers throughout the country. The reality today is that almost no African countries even recommend artesunate as treatment for severe malaria in adults, even though this has been the recommendation by WHO since 2006[9].

**Translating policy into practice**

Health providers and managers – both in the public and private sector – are generally not aware of the latest evidence. To date, there are no international plans in place to finance or provide technical support for such training at the scale required. Similarly, caregivers and patients have yet to be made aware that a new, more effective treatment exists. Healthcare workers may be reluctant to switch to a new and unfamiliar treatment, or may hold a personal conviction that, in spite of the evidence, quinine remains the best treatment available. MSF teams in Niger have reported that, despite a willingness to change practice at the national level, many local doctors remain convinced that quinine is the best treatment for severe malaria. However, while quinine has been used to treat severe malaria for hundreds of years, this does not mean it is easy to use. Even in well-resourced clinical trial conditions, quinine use has been shown to be difficult to administer and can have life-threatening side effects. In contrast, artesunate can be given intravenously over just a few minutes, and has far fewer side effects. (This is followed by a full course of oral treatment (ACTs) to achieve complete parasite clearance and minimise the risk of development of resistance.)

**Replacing quinine production**

Switching to artesunate may prove particularly difficult in areas where this is seen as a threat to local quinine production, which is an important economic activity in a number of malaria-endemic countries. In Burundi, for example, quinine is the most frequently available drug in both the public and private sector. It has been available in Burundi since the 1940s and is one of the few drugs manufactured in the country, making it more popular and more easily accessible than imported antimalarials[20]. However, countries may balance the interests of local quinine producers with the fact that producers of artemisinin, the raw material for artesunate, are today located in several African countries in addition to traditional production sites in Asia[21].

**Lessons to be learnt from slow malaria policy change in the past**

For most of the twentieth century, chloroquine was the standard malaria treatment throughout Asia and Africa. In the 1960s and 1970s, however, it became apparent that the use of a single drug (or monotherapy) leads to resistance and, as a result, chloroquine was becoming less and less effective throughout Africa. Another drug, sulphadoxine-pyrimethamine, was introduced in the 1970s, but this drug combination rapidly suffered a similar fate, becoming ineffective due to resistance. By the 1990s, widespread resistance to both chloroquine and sulphadoxine-pyrimethamine had been documented across the continent. Largely as a result of the reduced treatment effectiveness, malaria deaths began to soar, with deaths reported in the period 1982 - 97 four times higher than deaths in the preceeding two decades. In 2000, a ministerial meeting in Abuja issued a declaration that artemisinin-based treatments should become the first-line therapy for simple malaria. MSF and other providers began advocating for the switch to artemisinin-based combination therapy (ACT) for simple malaria in 2001, and WHO recommended switching to ACT for all cases of simple malaria the following year[18].

But the road from policy change to implementation is long, and it took several years and considerable efforts to translate the WHO recommendations into practice.

Between 1996 and 2004, MSF teams undertook 43 resistance studies in 18 countries to provide evidence that a move away from chloroquine to ACT was necessary[19]. By 2006, close to 40 countries in Africa had changed their national treatment protocols to recommend ACT for simple malaria treatment, but still chloroquine use persisted in health centres across Africa. Limited ACT supplies, the higher cost of ACT compared to chloroquine, and an enduring conviction among health providers that chloroquine was still the drug of choice, meant that ACTs were still not reaching the patients who needed them most.

Even today, ten years after international policy change, there are reports that health workers in high-burden countries continue to provide chloroquine because they believe it is the better drug.

The long shelf life of quinine (five years) means that large quinine stocks exist in many countries. Reports from malaria programmes in Guinea suggest that programme managers would be reluctant to purchase artesunate when they have already paid a lot of money for quinine. This may result in a lag-time during which quinine is phased out. This may make economic sense, but it means that children will continue to receive what is now known to be sub-optimal treatment.

**Improving quality supply**

A WHO prequalified source of artesunate is now available to support the switch[22]. As demand increases, additional manufacturers should be encouraged to enter this market, increase supply security and reduce the price for quality assured artesunate.

**Decreasing drug costs**

The higher cost per dose of artesunate compared to quinine is likely to be an important concern. Currently, the cost of drugs to treat a child with severe malaria are around $3.3 for artesunate compared to $1.3 for quinine[23]. It can be expected that some governments will be reluctant to switch to artesunate as long as it remains more expensive than quinine. While the unit price of artesunate is currently higher than that of quinine, overall costs are found to be equivalent. Cost analyses from the trials in Asia[24] and Africa[23] show that if total costs are considered (in particular the costs of administering the drugs and the management of side effects), artesunate is found to be cost-effective.

**Supporting acceptance of the evidence**

Finally, calls for local evidence are often made by national governments out of concern that studies done in other contexts may not apply to their setting. It should be noted that two large trials were done in more than nine African and four Asian countries, and their results are considered to be widely generaliseable. For this reason, the latest review of the evidence to date concluded that further research to examine the efficacy of artesunate versus quinine in children and adults is unnecessary[13]. International ethical standards clearly state that patients should only be subjected to experimental trials if there is real uncertainty about which drug is better[25]. Thus, while operational research may help provide practical lessons for the implementation of artesunate, it would clearly be unethical to delay implementation by insisting on further drug effectiveness studies and to subject patients to clinical research where there is already enough evidence.

**The difference between artemether and artesunate**

There are two commonly used artemisinin derivatives for the treatment of severe malaria: artesunate and artemether. Artesunate is a water-based preparation and can be administered via intravenous or intramuscular injection. Artemether, on the other hand, is an oil-based preparation and as such can only be used intramuscularly. Intravenous treatment is most effective in treating severe malaria.

During the 1980s, two parenteral formulations were produced (artesunate and artemether) in China and initially, the oil-based intramuscular formulation of artemether was preferred and pursued in studies that compared artemether against quinine[5]. Data from these trials found that there was an overall mortality benefit in favour of artemether, and the fact in programme settings artemether was more likely to be administered correctly than quinine meant that it was more effective.

We now know that artesunate is more effective than artemether; a recent randomised trial comparing both drugs delivered through intramuscular injection found a 47% mortality reduction among patients receiving artesunate (although the trial was not large enough to be statistically significant)[26].

A number of African countries have already included intramuscular artemether in their national guidelines, and this may act as an additional barrier to introducing artesunate[14]. Health staff may prefer artemether because it is provided ready for injection once drawn up in a syringe, whereas artesunate requires prior mixing with an injection solution. However, artemether cannot be seen as equivalent to artesunate. Artesunate is almost immediately absorbed and fully converted to the active form of the drug, whereas artemether is slowly, erratically absorbed and only partially converted to an active form[27]. There is plenty of evidence that delays in treatment kill. This is why the latest WHO guidelines recommend artesunate, and not artemether, for severe malaria. In resource-limited settings where intravenous administration is impractical, WHO recommends intramuscular or rectal artesunate.

## Democratic Republic of Congo: "Let's not forget, current treatment is hard on the patient"

*In addition to years of violence and conflict, the people of the North Kivu region of the Democratic Republic of Congo are burdened with high rates of malaria – one in every three consultations carried out in MSF clinics in January this year were due to the disease. MSF supports many health clinics throughout the area and, in 2010, treated tens of thousands of people for malaria. Around one-third of those are, like Colette, children under the age of five.*

When little Colette arrived at the Mpety health centre, her life hung in the balance. With a high fever, she was having difficulty breathing and was experiencing seizures, all symptoms that she was clearly suffering from severe malaria. Nurses battled to save the two year old's life by setting up the first of many drip infusions, where quinine is administered in a glucose solution through a vein over a number of hours. The drug has been the mainstay of malaria treatment in the DRC for many years as set out by government regulations, but it's not that easy a treatment to administer as MSF's medical coordinator, Dr. Martins Dada explains:

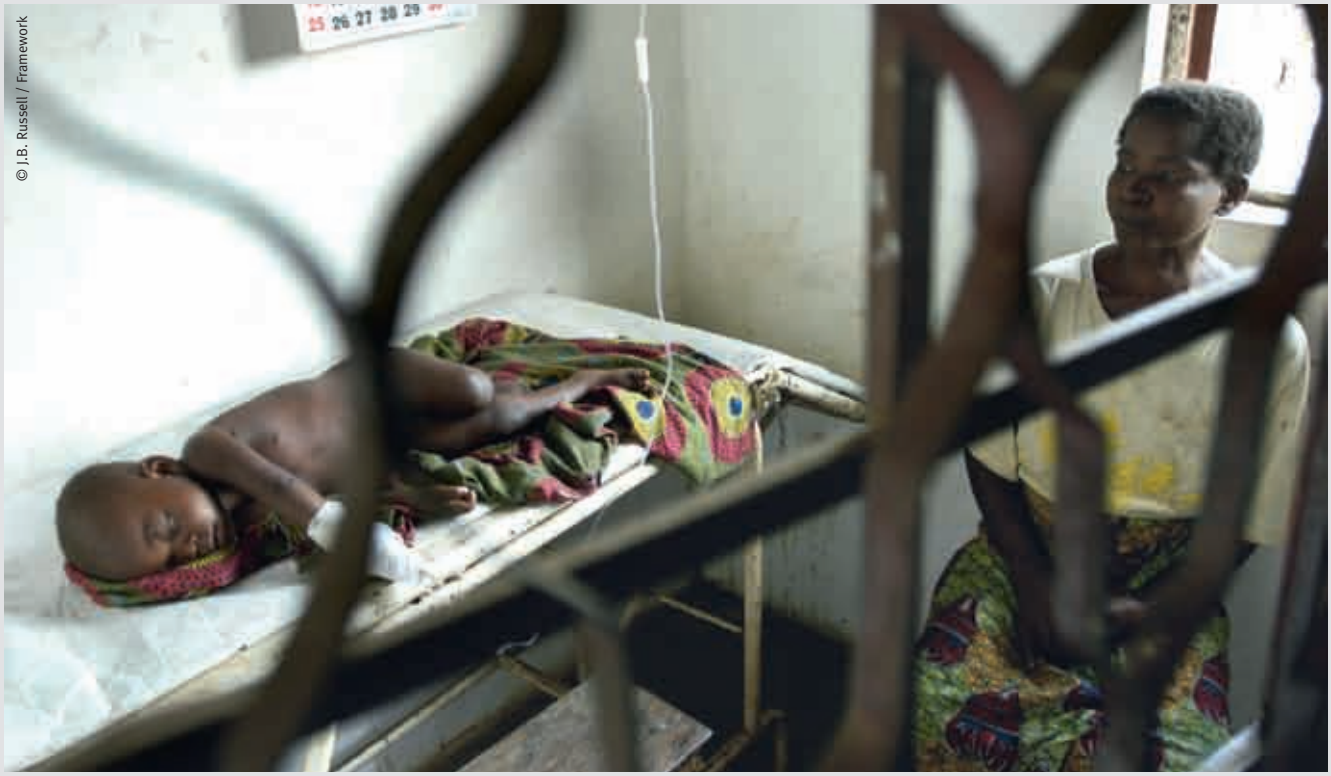
"Staff in clinics based in very remote areas run by the Ministry of Health often have great difficulties with setting up the thrice daily infusions with quinine. Sometimes this is because they lack basic medical supplies such as glucose solutions, infusion lines and intravenous catheters. Other times, placing the infusion in a child can be tricky because they cannot find a good enough vein or because the infusion needs to remain in place for four hours at a time, multiple times and movement can disturb this. Also, treatment isn't standardised and each treatment has to be adapted specifically to each child, and this makes things complex for medical staff too."

Quinine is also a difficult treatment for patients to tolerate: because of both the nature of quinine and the challenges in administering it in the correct dosage, patients can suffer a wide range of side effects - including short-term dizziness, hearing loss, or ringing in the ears - and progress into far more serious, life-threatening ones such as irregular heartbeat and even coma.

Despite recent studies that have shown that artesunate could save many more lives, quinine remains the main plank of treatment in DRC. Many at the health centre express hope for a switch to a medication like artesunate, which would not only be safer with fewer side-effects, but also more effective.

"Let's not forget, current treatment is hard on the patient. The real benefit [of switching to artesunate] to me as a doctor would be the knowledge that I can treat patients faster and with less side effects," Dr. Dada explains.

Colette pulled through after seven days of treatment and went on to make a full recovery at the nearby Pinga hospital. Her mother, aunt and baby brother who were by her side during her entire treatment were overjoyed with her recovery. Although Colette won her battle with severe malaria today, there are many who aren't so lucky.



# WHAT NEEDS TO HAPPEN

The evidence is clear: switching from quinine to artesunate will simplify the management of severe malaria and has the potential to save hundreds of thousands of children's lives each year. Policy change does not happen overnight, and making the switch will require a dedicated effort by the international community and governments of malaria-endemic countries.

**The World Health Organization's** updated guidelines should be rapidly disseminated to affected country governments, supported by programme guidance and appropriate training materials. WHO should also prioritise the prequalification of additional sources of injectable artesunate.

**National ministries of health** should begin the process of changing their guidelines based on the existing evidence. Specific activities to support implementation of the treatment switch are needed. This includes establishing procurement and supply chains, staff trainings, as well as community education to ensure that patients understand why their care is being changed from a drip infusion to an injection.

**Manufacturers** should prepare for increased demand of injectable artesunate. Additional manufacturers should be given a clear message that the market exists to encourage them to start production of injectable artesunate and obtain WHO prequalification. Market forecasting will be essential to convince manufacturers that artesunate production needs to increase and to support market diversification that will contribute to a more stable drug supply and subsequently, lower prices. Manufacturers should also work to improve the preparation and dosing presentation of artesunate.

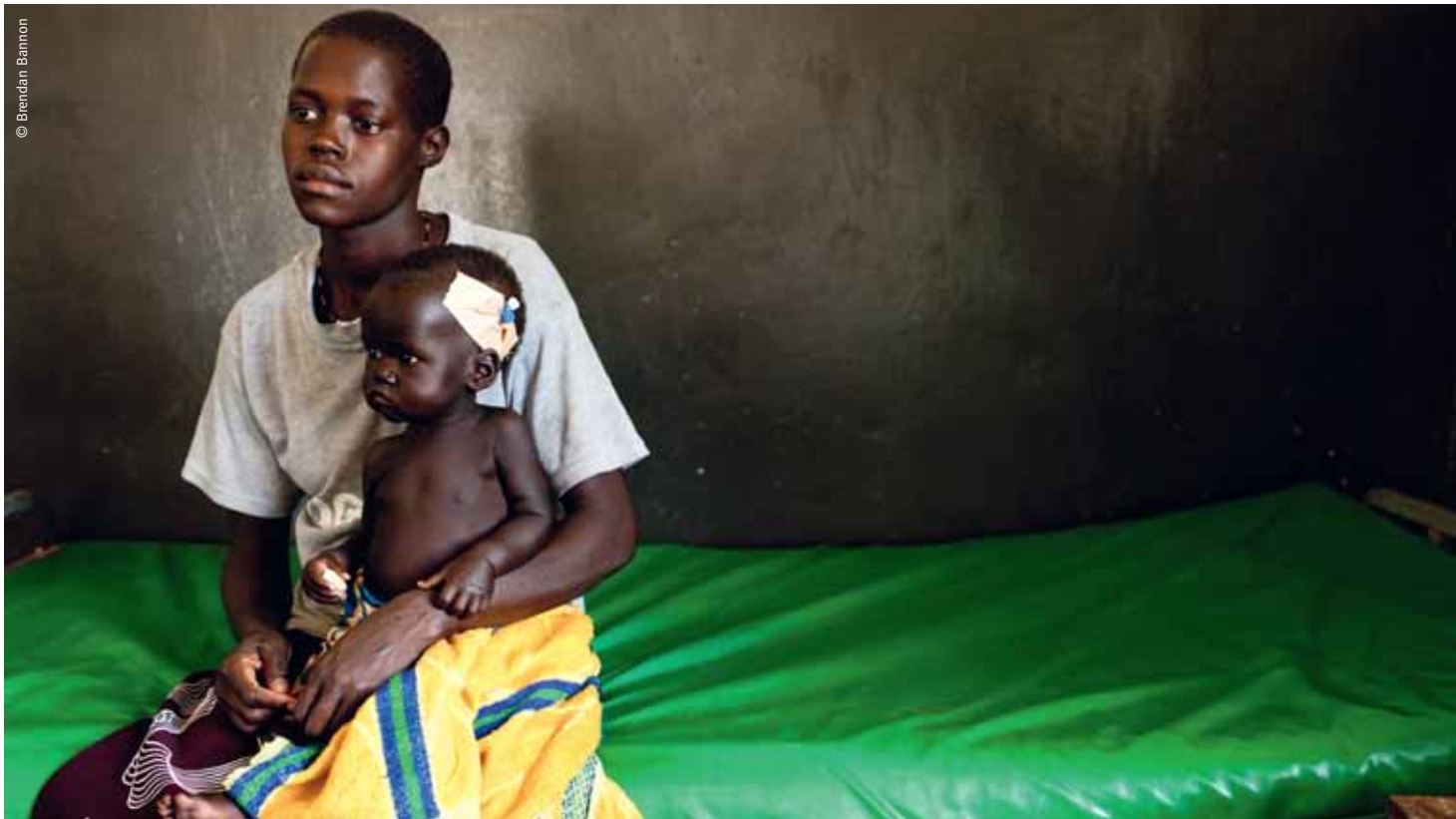
**Malaria partnerships and initiatives** should help with awareness raising of the benefits of changing treatment for severe malaria, as well as provide technical support to countries to change treatment protocols, to apply for funding where needed, and to implement the switch. Roll Back Malaria could be well placed to establish and champion a multi-stakeholder strategy to support the switch. Country co-ordinating mechanisms and their supporters in the Roll Back Malaria network should be encouraged to include specific requests for funding to support severe malaria treatment in their applications to the Global Fund.

**Donors** should act now to support efforts to revise national guidelines and replace drug supplies. Multilateral donors such as UNITAID, the Global Fund, and the World Bank, as well as bilateral donors with a major commitment to malaria control such as USAID and DFID all have an important role to play. International donors have not traditionally supported severe malaria treatment due to the low cost of quinine. The challenges ahead in the short term require specific donor support in order to switch to a drug that, in terms of unit costs, is more expensive.

The cost of making the switch is well within reach of the international community. To treat all cases of severe malaria world-wide with artesunate instead of quinine represents an additional annual drug cost of $31.8 million and a total drug cost of $49.2 million in order to save around 195,000 lives each year*.

An international plan is needed to support the switch without delay.

* Calculation based on reported number of cases of severe malaria[2], reported costs of drugs for adults[23] and children[24], and reported proportion of severe malaria cases in children[4].



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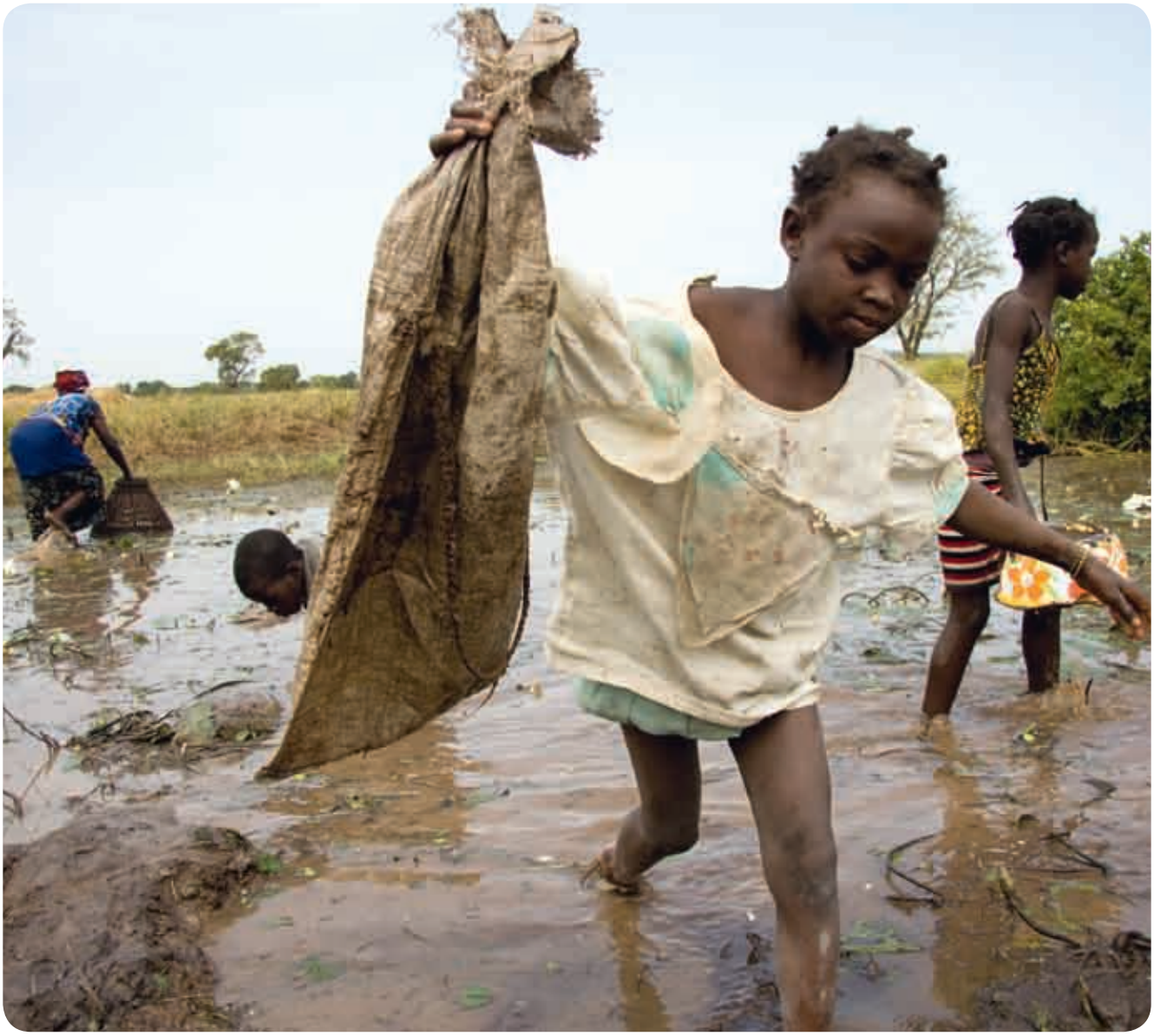

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