CHILDREN AND THE ‘BIG THREE’ EPIDEMICS

With signs of progress, challenges still remain for children with malaria

JUNE 2020

This article is one of a series of three. It dives into the current situation for malaria, highlighting the specific burden on children, setting out what needs to happen next in terms of product development and the remaining product gaps. It underscores the need for a diverse range of new treatments that are suitable for children, especially with the growing threat of drug resistance and the prevalence of sub-standard and falsified medicines on the market.
Malaria continues to infect millions of people every year. In 2018, approximately 228 million malaria cases were reported worldwide. Yet progress has been made over the last number of years. Between 2010 and 2018, malaria deaths dropped from 585,000 to approximately 405,000 deaths. But although this shows signs of improvement in mortality rates, there has been a steadily increase in the number of malaria infections since 2014, particularly among pregnant women and children.

A 2019 report found that pregnant women and young children are the most vulnerable to this disease. In 2018, children under the age of five accounted for 67% (272,000) of all malaria-related deaths, deaths which could have been prevented with access to appropriate treatments.

Approximately half of these deaths were caused by substandard and falsified antimalarial medicines, accounting for 122,000 deaths among children under the age of five in sub-Saharan Africa alone.

Pregnancy reduces a woman’s immunity to malaria, making her more susceptible to infection, while maternal malaria also interferes with the growth of the foetus, increasing the risk of premature delivery and low birth weight. In 2018, nearly 900,000 children were born with a low birth weight as an estimated 11 million pregnant women were infected with malaria, mostly in sub-Saharan Africa. Today, the disease remains one of the leading causes of high morbidity and mortality in children under the age of five.

The need for better access to treatments

While children are disproportionately affected by malaria, they often struggle to access appropriate treatments. A study conducted in sub-Saharan Africa found that the median percentage of children under the age of five with malaria and a history of fever who received any antimalarial treatment was less than 30%. This number was less for children under the age of five receiving artemisinin-based combination therapies (ACT), at around 14%. Combination therapies, as opposed to monotherapies, offer a higher success rate and a lower risk of developing resistance. With such access-related challenges and the prevalence of substandard and falsified medicine on the market, ensuring access to high-quality combination therapies is an unmet high-priority need.

Challenge fuelled by drug resistance

The pathogen most commonly responsible for causing malaria, \( P. falciparum \), has developed resistance to almost all classes of antimalarial medicine. Resistance to commonly used medicine such as chloroquine started emerging in the 1950s and 1960s. By 1990, chloroquine resistance reached fixation levels across malaria-endemic countries. It is estimated that the loss of chloroquine to resistance was responsible for more than doubling malaria-associated mortality.

Seasonal malaria chemoprevention

Seasonal malaria chemoprevention (SMC) is a highly effective intervention to prevent malaria in children living in areas of exclusive seasonal malaria transmission, mainly in the Sahel region. SMC requires a monthly dose of long-acting antimalarial treatments and has proven to be effective in reducing morbidity and mortality. As of 2012, WHO recommends that all children living in seasonal transmission areas receive SMC.

Global initiatives such as the President’s Malaria Initiative (PMI) and the Malaria Consortium have been actively supporting SMC activities across the Sahel region. Approximately 39 million children under the age of five live in areas where SMC is deemed appropriate. Yet, only one company, Guilin, is producing quality assured SMC treatment, sulfadoxine/pyrimethamine + amodiaquine (SPAQ™). Such reliance on a single manufacture may have an impact on ensuring a reliable continuous supply.
in sub-Saharan Africa, which bears over 90% of the global malaria burden. Since then, ACTs were introduced and have acted as the preferred malaria treatment.

ACTs are generally associated with a high rate of efficiency and higher barrier to resistance, contributing substantially to reductions in global morbidity and mortality from malaria. Further, as the fast-acting artemisinin derivative is combined with a second, longer-acting antimalarial partner medicine, the parasite is attacked by two different modes of action allowing for a greater success-rate and lower risk of resistance. Yet, recent studies have reported some ACT resistance in malaria endemic countries such as the Greater Mekong Subregion - at least in part due to the continued use of less effective monotherapies - which drives an urgent need for new and novel treatment options. WHO has urged all regulatory authorities to withdraw any oral artemisinin-based monotherapies in order to preserve the efficiency of ACTs.

At present, resistance to artemisinin or key partner drugs included in combination therapies does not appear to be a substantial problem in sub-Saharan Africa, where most malaria cases occur. However, the emergence of resistance to ACTs in sub-Saharan Africa would likely have devastating consequences, and continued surveillance of the emergence of resistance in this region is a high priority.

Poor-quality treatments drive resistance

The existence of substandard and falsified (S&F) medicines in regions where malaria is most prevalent (Southeast Asia and sub-Saharan Africa) are also a major factor in the high mortality rates and rising resistance.

Substandard medicine are authorised medical products that fail to meet either their quality standards or specifications, or both. Falsified medicines deliberately fraudulently misrepresent their identity, composition or source. Alarmingly, nearly one in five antimalarials circulating in low- and middle-income countries (LMICs) are substandard or falsified. High prevalence of S&F medicine is often caused by a combination of factors on the local level, including weak technical capacity, poor governance and issues with access.

What children need and the role for pharmaceutical companies

Malaria treatments have been generally developed for the use in adults first. However, as malaria predominantly affects children, efforts are being made to develop malaria treatments for both adults and children in parallel. Yet, suitable formulations are still needed for children, particular those under the age of five. In cases where children are affected by complications due to severe malaria, such as coma or kidney failure, alternative treatments must be available, such as intravenous artesunate. This is of particular importance as the majority of severe cases with rapid progression to death occur in young children without acquired immunity.

Pharmaceutical companies have an important role to play in enabling the availability and accessibility of child-friendly formulations of ACTs that include single-dose, easy to administer, palatable regimes. Such formulations can help ensure correct dosing and adherence which can ultimately help limit the emergence of resistance. Companies also have a critical role in the development of new and novel treatments that are needed to replace the ones that are no longer effective due to resistance.
According to WHO guidelines, children and adults with *P. falciparum* malaria should be treated with an ACT, as artemisinin derivatives are effective and generally well tolerated in children. The choice of ACT, however, is based on the safety and tolerability of the partner drug that is used in combination with the artemisinin-based drug, as combination therapies work best in combating resistance. Additional considerations include palatability, ease of preparation/administration, and tolerability.

Specifically, WHO recommends six ACT treatments for both children and adults, of which three come in the form of an optimal paediatric formulation and three are in the form of a low-dose tablet that is suitable for children, but not for those who cannot swallow tablets. Furthermore, two (pre-referral) treatments for severe malaria and one preventative treatment are also recommended for use in children.

**Most recommended treatments are available in fixed-dose combinations**

In total, six paediatric formulations for the treatment of malaria are already available by at least eight pharmaceutical companies. All eight companies have been granted WHO prequalification for the products, which ensures that these medicines meet unified standards of high-quality, safety and efficacy.

<table>
<thead>
<tr>
<th>Company with WHO Prequalification**</th>
<th>Treatment</th>
<th>Brand name</th>
<th>Pediatric formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended first-line ACTs</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Originator: Novartis <strong>Generic:</strong> Ajanta; Cipla; Ipca; Macleods; Strides</td>
<td>Artemether/lumefantrine</td>
<td>Coartem® Dispersible</td>
<td>FDC dispersible tablet 20/120mg †</td>
</tr>
<tr>
<td>Originator: Sanofi <strong>Generic:</strong> Ajanta; Cipla; Guilin; Ipca; Macleods; Micro Labs</td>
<td>Artesunate/amodiaquine</td>
<td>ASAQ® Winthrop</td>
<td>FDC tablet 25/67.5mg †</td>
</tr>
<tr>
<td>DNDI/Cipla</td>
<td>Artesunate/mefloquine</td>
<td>FDC tablet 25/50mg †</td>
<td></td>
</tr>
<tr>
<td>Alfa Sigma</td>
<td>Dihydroartemisinin/ piperaquine</td>
<td>Euratesim®</td>
<td>FDC tablet 20/160mg FDC tablet 40/320mg †</td>
</tr>
<tr>
<td>Guilin</td>
<td>Artesunate + sulfadoxine/ pyrimethamine</td>
<td>ARTECOSPE®</td>
<td>Tablet 50mg + FDC tablet 25/500mg †</td>
</tr>
<tr>
<td>Shin Poong</td>
<td>Pyronaridine/Artesunate</td>
<td>Pyramax®</td>
<td>Oral granules 60/20mg †</td>
</tr>
<tr>
<td><strong>Pre-referral treatment severe malaria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guilin/Ipca</td>
<td>Injectable Artesunate</td>
<td>Artesun® Larinate®</td>
<td>(Vial + Ampoule); 60mg/vial</td>
</tr>
<tr>
<td>Cipla/ Strides</td>
<td>Rectal Artesunate</td>
<td>Rectal capsule 100mg</td>
<td></td>
</tr>
<tr>
<td><strong>Seasonal malaria chemoprevention (SMC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guilin</td>
<td>Sulfadoxine/pyrimethamine + amodiaquine</td>
<td>SPAQ-CO™ Dispersible</td>
<td>FDC dispersible tablet 25/500mg + dispersible tablet 153mg FDC dispersible tablet 12.5/250mg + dispersible tablet 76.5mg †</td>
</tr>
</tbody>
</table>

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* This is not an exhaustive list. Data was collected and verified using data provided by companies and publicly available data.

**The focus on WHO Prequalified medicine means that local companies that are producing anti-malarial medicines and selling them in the local market are not included, as well as other manufacturers of these medicines.

***While not identified as a recommended treatment in the 2015 WHO Malaria Treatment Guideline, the WHO issued a statement in 2019 that “artesunate- pyronaridine can be considered a safe and efficacious artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas.”

† Also available in higher dose tablet form.
efficacy, and allows for international procurement and accelerates registration in countries. The majority of the ACTs listed in table 5 are available in a paediatric dose, either as a fixed-dose combination (FDC) low-dose tablet, a dispersible tablet or as oral granules. Additionally, there are child-friendly formulations available of pre-referral treatments for severe malaria and seasonal malaria chemoprevention. Importantly, there are no treatments currently available for infants that weigh below 5kg — meaning low-weight or malnourished babies are the most vulnerable without optimal treatments. It is important that companies fill this crucial gap in the market. Further, due to the high prevalence of S&F medicines, companies should work with procurers and international organisations to combat the issue, including the reporting of identified cases to national authorities and WHO Rapid Alert.

FIGURE 5  The majority of products are registered in less than 30 LMICs
This figure demonstrates how many recommended malaria products are registered in low- and middle-income countries (LMICs).

Novartis  artemether/lumefantrine (Coartem® Dispersible)
Sanofi  artesunate/amodiaquine (ASAQ® Winthrop)
Gulin  Injectable artesunate (Artesun®)
Alfa Sigma  dihydroartemisinin/pyrithione (Eurartesim®)
Gulin  dihydroartemisinin/piperazine (D-ARTEPP® Dispersible)
Gulin  artesunate/amodiaquine (ASUAQ®)
Shin Poong  pyronaridine/artesunate (Pyramax®)
Cipla and Strides  artesunate rectal capsules (ARC)
Gulin  sulfadoxine-pyrimethamine/amodiaquine (SPAQ-CD™ Dispersible)
Cipla  artesunate/mefloquine

FIGURE 6  Half of the recommended antimalarials are available in a child-friendly formulation
This figure shows which WHO recommended ACTs for the treatment of P. falciparum are available in a child-friendly formulation, taking into account the needs of children and infants who cannot swallow tablets or hold down bitter syrups. Three out of the six recommended ACTs are available in a dispersible or granular form.
MALARIA - R&D INSIGHT

What new antimalarials are in development for children?

There are approximately 52 projects in the global malaria pipeline, including 14 approved. Of the projects in the pipeline, 10 projects, including five approved, are specifically targeting the paediatric population through the development of a paediatric indication and/or formulation. The growing attention to malaria over the past decades, through funding and development partnerships, has resulted in the increased development of child-friendly formulations of antimalarials.

One novel treatment in the paediatric pipeline

While just a snapshot of the global malaria pipeline, table 6 reflects the projects that take the specific needs of children into consideration. Notably, there is one novel treatment in the paediatric pipeline, KAF156/lumefantrine, being developed by Novartis and MMV. In addition to treatments for *P. falciparum*, there are two paediatric projects to treat malaria caused by *P. vivax*, tafenoquine by GSK and MMV and primaquine by Sanofi. Given the fact that children are disproportionately affected by this disease, companies must ensure that their projects, especially those with novel mechanisms of action, take the specific needs of children into account and ensure rapid access to child-friendly formulations, once safety and efficiency are established.

**TABLE 6 What is in the paediatric malaria pipeline?**

This table* provides a snapshot of companies' R&D pipelines for specific malaria treatments tailored for infants, children and adolescents.**

<table>
<thead>
<tr>
<th>Company</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Approval</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>KAF156/lumefantrine</td>
<td>Tafenoquine - <em>P. vivax</em></td>
<td>Tafenoquine - <em>P. vivax</em> Age: 6 months - 15 years - Dispersible tablet - Partner: MMV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>Novel - <em>P. falciparum</em></td>
<td>Artmether/lumefantrine</td>
<td>Artmether/lumefantrine - <em>P. falciparum malaria</em> - Weight:&lt;5kg - FDC dispersible tablet - Partner: MMV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfasiaga</td>
<td>- <em>P. falciparum malaria</em> - Age: &gt;2 years - FDC dispersible tablet - Partner: MMV</td>
<td>Dihydroartemisin-piperaquine (DHA-PQP) - <em>P. falciparum malaria</em> - FDC dispersible tablet - Partner: MMV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanofi</td>
<td></td>
<td>Pimaquine - <em>P. vivax</em> malaria - Age: unknown - Dispersible tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This table excludes five paediatric projects that have been approved
** This is not an exhaustive list. Data was collected and verified using data provided by companies and publicly available data

WHAT VACCINES ARE IN THE PIPELINE?

There are several groups around the world who are developing targets and vaccines for preventing malaria. The Malaria Vaccine Initiative, for example, reports working on a total of six vaccines in clinical development, targeting different age groups. GSK is involved in all six vaccine projects. Five of the six projects involve the RTS,S/AS01 vaccine against *P. falciparum*. Of these, one project is for paediatric indication and was introduced in a pilot programme in selected areas of Ghana, Kenya and Malawi. The Malaria Vaccine Implementation Programme (MVIP) is funded by Gavi, the Vaccine Alliance, the Global Fund and Unitaid and is a country-led, WHO-coordinated initiative to assess the feasibility, impact and safety of RTS,S/AS01 in routine implementation. GSK has stated a commitment to donate up to 10 million doses and are undertaking additional post-approval pharmacovigilance, effectiveness and impact studies. GSK is also working with WHO and PATH, Gavi, the Vaccine Alliance, and other potential funders to address the supply of the vaccine for a potential broader implementation beyond the pilot.
Ensuring broad access to paediatric antimalarials

While developing child-friendly antimalarial treatments, companies can consider access early in the development process. Nearly all projects in the paediatric pipeline are co-developed with the Medicines for Malaria Venture (MMV). Such partnerships help bolster access and appropriate use, as they tend to set standards for product characteristics, including dosing, palatability and efficiency targets, as well as for access clauses. Furthermore, MMV promotes responsible use and engages in education and training activities for healthcare professionals and caregivers. In addition to partnerships, companies can take a number of steps to ensure wide availability and accessibility of their products such as equitable pricing, non-exclusivity, broad registration and sustainable supply. Table 7 demonstrates some examples of the access strategies companies have applied to their paediatric antimalarial products on the market and/or projects in the pipeline.

<table>
<thead>
<tr>
<th>Access strategies</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration</td>
<td>Novartis has registered artemether/lumefantrine (Coartem® Dispersible) in over 50 countries.</td>
</tr>
<tr>
<td>Equitable pricing strategy</td>
<td>Sanofi has an equitable pricing strategy in place for artemesate/amodiaquine (ASAQ Winthrop®) that takes into account a payer's ability to pay by considering socioeconomic factors. Further, Sanofi's artesunate/amodiaquine (ASAQ Winthrop®) for children is available at 50 cents, for partners such as the Global Fund, WHO and MSF. This is in general the lowest-priced fixed-dose ACT combination.</td>
</tr>
<tr>
<td>Ensuring adequate supply</td>
<td>Novartis engages with primary and local healthcare facilities to align supply and demand forecasting for artemether/lumefantrine (Coartem® Dispersible).</td>
</tr>
<tr>
<td>Non-exclusivity</td>
<td>A non-exclusivity agreement between DNDi and Sanofi for artesunate/amodiaquine (ASAQ Winthrop®) allowed for increased access and subsequent technology transfer to the pharmaceutical company Zenufa in Tanzania, which can lead to improved supply.</td>
</tr>
<tr>
<td>Access through partnerships</td>
<td>Generic medicine manufacturer Cipla partnered with product development organisation DNDi to develop artesunate/mefloquine fixed-dose combination tablets.</td>
</tr>
</tbody>
</table>
How companies and organisations are working to improve access to antimalarials for children

**Expanding the availability of a truly child-friendly antimalarial**  
**MMV, NOVARTIS**

Since 2009, steps have been made to improve access to dispersible artemether/lumefantrine (Coartem® Dispersible) - a palatable, single pill for the treatment of malaria in children.

**ACTs for Children**

In 2000, the first fixed-dose artemisinin-based combination therapy (ACT) for adults was brought to the market by Novartis — artemether/lumefantrine (Coartem®). Yet until 2009, no quality-approved child-friendly ACT existed, even though infants and children under the age of five are predominantly affected by malaria.

**Answering calls for ‘child-size’ medicines**

In 2007, seven years after the adult formulation was marketed, WHO and UNICEF announced the initiative ‘Make Medicines Child Size’ to improve access to better medicines for children. Responding to this call, Novartis and the Medicines for Malaria Venture (MMV) teamed up to develop a child-friendly version of artemether/lumefantrine, in the form of a dispersible and flavour-masked formulation.

Approved in 2009, Coartem® Dispersible was found to be highly effective for children, achieving a 98% clinical cure rate in a large study involving several African countries.17 It’s palatable taste and cost for public-sector buyers have helped facilitate the uptake of this ACT for the treatment of malaria in children.18 To date, 390 million treatments of Coartem® Dispersible have been distributed in more than 50 countries.18

**Making Coartem® Dispersible widely available**

In the 2018 Access to Medicine Index, Novartis reported to have an inter- and intra-country pricing strategy, making Coartem® available at USD 0.38 for its youngest patients.19 In addition to Novartis, five manufacturers have received a WHO prequalification and a further three are currently under review. In early 2020, the Global Fund pooled procurement price for the lowest dose artemether/lumefantrine dispersible for children was reported at USD 0.28. In part, Novartis’ challenge to compete with this low price due to generic competitors has led to the steady decline in Global Fund’s allocation of Novartis’ artemether/lumefantrine dispersible (Coartem® Dispersible).

Since the approval of Coartem® for both adults and children, Novartis is currently developing a version of artemether/lumefantrine for children under 5kg. If successful, this will be the first antimalarial product approved for neonates and children under 5kg.

**Securing the supply of ARC for severe malaria**  
**CIPLA, MMV AND STRIDE PHARMA**

A collaborative effort aims to improve the availability of high-quality artesunate rectal capsules, used for the treatment of severe malaria.

**What is ARC?**

Injectable artesunate (Inj AS) is administered intravenously for the treatment of severe malaria. Yet when patients do not have immediate access to injectable artesunate, WHO recommends the use of artesunate rectal capsules (ARC) for the pre-referral management of severe illness prior to patient transport to higher level care centers that can administer injectable artesunate. However, the lack of quality-assured ARC products on the market has hindered widespread availability, forcing malaria-endemic countries to allow poor-quality treatments that do not meet international standards onto the market.

**Making ARC available**

To ensure the continuous supply of ARC, MMV collaborated with Cipla and Strides to develop high-quality ARC and guarantee their access, by submitting products through WHO’s prequalification process. This process allows for UN procurement and accelerated registration in countries with weak national regulatory authorities. The collaboration was formed as part of the Unitaid-funded project ‘Improving Severe Malaria Outcomes’ aimed at increasing the availability of injectable artesunate.

With funding from MMV, Transaid, Health Partners Zambia (HPZ), Development Data and Disacare started an access to severe malaria care-and-intervention in Zambia using ARCs at the community level through the MaMaZ Against Malaria (MAM) project. The project aims to address the lack of access to quality severe malaria treatments and case management in the Serenje District, Zambia, which has high malaria prevalence rates.20

**The impact of WHO prequalification on ARC**

In 2018, ARC products developed by both Cipla and Strides secured WHO prequalification. It is estimated that over 80% of procured ARC are now WHO prequalified.21
REFERENCES