

# Sudan Malaria Resilience Initiative (SMRI): Integrated Pharmacovigilance and Therapeutic Stewardship in a Conflict-Affected Syndemic Landscape

## 1. Introduction: The Intersection of Conflict and Public Health Collapse

The ongoing armed conflict in Sudan, which escalated dramatically in April 2023, has precipitated a humanitarian catastrophe of historic proportions. As of March 2025, the country faces the world's largest displacement crisis, with 12.8 million people forcibly displaced from their homes, including 8.1 million internally displaced persons (IDPs) and nearly 4 million refugees who have crossed borders into neighboring nations.<sup>1</sup> This mass migration has occurred against the backdrop of a systematic dismantling of the national health infrastructure. Reports indicate that up to 80% of health facilities in conflict-affected regions are non-functional, having been either destroyed by direct kinetic action, looted of their assets, or abandoned due to the targeted violence against healthcare personnel.<sup>2</sup>

The resulting vacuum in healthcare provision has created a "perfect storm" for infectious disease outbreaks. The country is currently grappling with a complex syndemic involving *Plasmodium falciparum* malaria, cholera, and dengue fever, all exacerbated by severe malnutrition rates that are among the highest globally.<sup>3</sup> The collapse of the pharmaceutical supply chain has further compounded this crisis. Domestic manufacturing of essential medicines has effectively ceased, and import channels are strangled by bureaucratic impediments and insecurity.<sup>4</sup> Consequently, the market has been infiltrated by

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<sup>1</sup>Public Health Situation Analysis: Sudan conflict (10 March 2025)

<sup>2</sup>Sudan: Delivering Vital Health Services Despite Conflict and Displacement - Stories - The Global Fund to Fight AIDS, Tuberculosis and Malaria

<sup>3</sup>Sudan Humanitarian Update (1 October 2024) - ReliefWeb

<sup>4</sup>Health care without medicine: the impact of war on Sudan's pharmaceutical manufacturing and supply - PubMed Central

substandard and falsified medicines, posing a lethal threat to patients who are already vulnerable due to displacement and starvation.<sup>5</sup>

This report details a comprehensive project proposal - the **Sudan Malaria Resilience Initiative (SMRI)** - designed for implementation within this fragile ecosystem. The project aims to be a robust pharmaceutical stewardship framework. It integrates supply chain vigilance to detect counterfeit antimalarials, adaptive clinical protocols to manage chronic stockouts, and sentinel monitoring for the emergence of artemisinin partial resistance (ART-R), which has now been confirmed in East Africa.<sup>6</sup> By synthesizing epidemiological data, molecular mechanisms of drug resistance, and humanitarian logistics, this proposal aims to safeguard the efficacy of life-saving treatments for the 30.4 million Sudanese requiring assistance in 2025.

## 2. Epidemiological Profile: A Syndemic of Neglect

To understand the necessity of the SMRI, one must first analyse the epidemiological burden facing the Sudanese population. The crisis is defined by the interaction of multiple diseases within a malnourished host population.

### 2.1 The Burden of Malaria in a Displaced Population

Malaria remains the primary driver of morbidity and mortality in Sudan. The transmission dynamics have been fundamentally altered by the conflict. The destruction of vector control programs - such as the distribution of insecticide-treated nets (ITNs) and indoor residual spraying (IRS) - has led to a resurgence of the *Anopheles* vector.<sup>7</sup>

Recent epidemiological data highlights the severity of the outbreak. In the Amhara region, neighbouring Sudan, which serves as a proxy for the cross-border dynamics, 1,109 confirmed malaria cases were reported between March and April 2025.<sup>8</sup> More alarmingly, the Gambella region, in Ethiopia, reported 6,450 confirmed cases in refugee-settled districts during the same period.<sup>9</sup> Unfortunately, figures in Sudan are largely inaccurate to the ongoing crisis. These figures likely represent a significant underestimation of the true burden within Sudan itself, where surveillance systems have largely collapsed.

The situation is particularly dire for children. In South Sudan's Aweil State Hospital, pediatric admissions for severe malaria doubled in 2024 compared to the previous year, with the facility admitting an average of 43 children per day for severe malaria and

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<sup>5</sup>Fighting The Scourge Of Fake Medicines: Global Fund Replenishment Is Moment Of Truth

<sup>6</sup>Understanding the global rise of artemisinin resistance: Insights from over 100000 Plasmodium falciparum samples - PubMed Central

<sup>7</sup>Over Three Million Children at Heighted Risk of Cholera and other Deadly Diseases in Sudan - Unicef

<sup>8</sup>Sudan conflict and refugee crisis - World Health Organization (WHO)

<sup>9</sup>Sudan conflict and refugee crisis - World Health Organization (WHO)

requiring 14 blood transfusions daily to manage severe malarial anemia.<sup>10</sup> This surge is driven by the interruption of preventative measures and the lack of timely treatment for uncomplicated cases, allowing them to progress to severe, life-threatening forms of the disease.

## 2.2 The Cholera Co-Morbidity

The management of malaria is complicated by simultaneous cholera outbreaks. Cholera thrives in the unsanitary conditions of displacement camps where Water, Sanitation, and Hygiene (WASH) infrastructure is nonexistent. As of early 2025, Sudan reported 29,170 suspected cholera cases and 629 associated deaths across 15 states.<sup>11</sup> This follows a severe wave in late 2024 where 8,457 cases and 299 deaths were recorded in just two months.<sup>12</sup>

The clinical implication of this co-morbidity is profound. Cholera causes rapid dehydration and electrolyte imbalance, which can be fatal in a patient already weakened by malaria-induced fever and anemia. Furthermore, the "diagnostic dilemma" in resource-poor settings is acute. Both malaria and the early stages of cholera (as well as dengue) present with non-specific febrile illness. In the absence of Rapid Diagnostic Tests (RDTs), clinicians are often forced to treat just symptoms, leading to the overuse of antibiotics and antimalarials, which drives resistance and depleting stocks.<sup>13</sup>

## 2.3 Dengue Fever and the Vector Crisis

Adding to the complexity is the concurrent outbreak of dengue fever. An outbreak beginning in July 2024 resulted in over 10,464 cases by March 2025.<sup>14</sup> Dengue and malaria share the same vector control weaknesses but require different clinical management strategies (e.g., fluid management in dengue is critical, while antimalarials are useless). The overlap in symptoms creates a triage nightmare in overcrowded field clinics, where a misdiagnosis can be fatal. For instance, administering aspirin or NSAIDs for fever in a dengue patient can precipitate hemorrhagic complications, whereas failing to treat malaria rapidly leads to cerebral involvement.<sup>15</sup>

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<sup>10</sup>South Sudan: MSF calls for urgent delivery of life-saving malaria medicines as nationwide stockouts threaten thousands

<sup>11</sup>UNICEF Sudan Humanitarian Flash Update (Cholera Outbreak), 18 June 2025 - ReliefWeb

<sup>12</sup>Over Three Million Children at Heightened Risk of Cholera and other Deadly Diseases in Sudan - Unicef

<sup>13</sup>Sudan: Health Emergency - Situation Report - EMRO

<sup>14</sup>Public Health Situation Analysis (PHSA)

<sup>15</sup>Sudan Humanitarian Update (1 October 2024) - ReliefWeb

## 2.4 The Multiplier Effect of Malnutrition

Perhaps the most critical factor in Sudan's epidemiological profile is malnutrition. Sudan is now among the top four countries globally for the prevalence of Global Acute Malnutrition (GAM), estimated at 13.6%.<sup>16</sup> In North Darfur, GAM rates have breached the famine threshold of 30%.<sup>17</sup>

Malnutrition compromises the immune system, reducing the body's ability to control parasite density. Malnourished children are significantly more likely to develop severe malaria and have higher case fatality rates. Conversely, malaria and diarrhea (from cholera) exacerbate malnutrition by increasing metabolic demand and reducing nutrient absorption. This vicious cycle is the primary driver of pediatric mortality in the current crisis.<sup>18</sup>

## 3. The Pharmaceutical Supply Chain: Anatomy of a Collapse

The ability to treat these diseases relies entirely on the availability of quality-assured medicines. However, the conflict has decimated Sudan's pharmaceutical ecosystem.

### 3.1 Destruction of Domestic Manufacturing

Prior to the war, Sudan possessed a developing pharmaceutical manufacturing sector capable of producing essential medicines. The conflict has brought this to a standstill. Facilities have been destroyed, looted, or forced to close due to a lack of raw materials and fuel.<sup>19</sup> This has shifted the country's dependence almost entirely to imports and humanitarian aid, precisely at a time when borders are insecure.

### 3.2 Logistics and Looting

The distribution of medicines within Sudan is fraught with peril. Supply convoys are frequent targets. Reports confirm that over 100 ambulances and 400 medical vehicles have been looted since the conflict began.<sup>20</sup> Medical supply warehouses, including the central stores of the National Medical Supplies Fund (NMSF), have been looted or destroyed, wiping out strategic reserves of ACTs and intravenous fluids.<sup>21</sup>

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<sup>16</sup>Sudan Humanitarian Update (1 October 2024) - ReliefWeb

<sup>17</sup>Sudan Humanitarian Update (1 October 2024) - ReliefWeb

<sup>18</sup>Sudan Humanitarian Update (1 October 2024) - ReliefWeb

<sup>19</sup>Health care without medicine: the impact of war on Sudan's pharmaceutical manufacturing and supply - PubMed Central

<sup>20</sup>Public health in Sudan: priorities, challenges, and pathways to resilience in crisis - PMC

<sup>21</sup>Health care without medicine: the impact of war on Sudan's pharmaceutical manufacturing and supply - PubMed Central

Consequently, facilities experience chronic stockouts. In South Sudan, which relies on similar supply lines, clinics in Yei and Morobo reported being completely without anti-malarial medicines for months in 2025.<sup>22</sup> The average duration of stockouts in Khartoum has reached 59 days.<sup>23</sup>

### 3.3 The Private Sector and Economic Barriers

With the public sector collapsed, patients turn to the private market. However, the economic crisis and hyperinflation have rendered private medicines unaffordable for the majority of the population. The price of essential drugs has skyrocketed medicines for chronic conditions and acute infections have seen price increases of over 200%.<sup>24</sup> This economic barrier forces families to ration doses or purchase cheaper, unverified medicines from informal street vendors, significantly increasing their exposure to falsified products.

## 4. The Threat of Falsified and Substandard Medicines

The scarcity of legitimate medicines creates a lucrative vacuum for transnational criminal networks to introduce falsified medical products. This is a critical, often overlooked, dimension of the crisis.

### 4.1 Prevalence and Impact

Research indicates that up to 21% of medicines circulating in Africa may be substandard or falsified.<sup>25</sup> In conflict zones, this percentage is likely higher due to the suspension of regulatory oversight. The United Nations Office on Drugs and Crime (UNODC) estimates that falsified antimalarials contribute to nearly 500,000 deaths annually in sub-Saharan Africa.<sup>26</sup>

In Sudan, the risk is concentrated on high-demand items: **Artemether-Lumefantrine (Coartem)** and **Artesunate**. Falsified versions of these drugs typically contain no active ingredient (leading to treatment failure and death), sub-therapeutic doses (driving resistance), or toxic contaminants.<sup>27</sup>

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<sup>22</sup>South Sudan: MSF calls for urgent delivery of life-saving malaria medicines as nationwide stockouts threaten thousands

<sup>23</sup>The critical pharmaceutical situation in Sudan 2023: A humanitarian catastrophe of civil war

<sup>24</sup>Pharmacists warn of medicine scarcity in Sudan - ReliefWeb

<sup>25</sup>Counterfeit Medicines On The Rise In Africa

<sup>26</sup>Counterfeit Medicines On The Rise In Africa

<sup>27</sup>QSM/MC/IEA.127 3 May 2013 Information Exchange System Alert No. 127 Falsified batches of Coartem recently circulating in Wes

## 4.2 Specific Product Alerts

The SMRI project relies on intelligence regarding specific falsified batches currently circulating in the region.

**Falsified Coartem:** The World Health Organization (WHO) and Nigeria’s NAF-DAC have issued alerts for falsified Coartem batches, specifically batch numbers **F2261**, **F1901**, and **NOF 2153**.<sup>28</sup>

**Identifiers:** These fakes often display the ”Green Leaf” logo of the Affordable Medicines Facility-Malaria (AMFm) program on packaging dated after the program’s conclusion. They may lack the ”Novartis” embossing on the tablets or contain spelling errors in the patient leaflet.<sup>29</sup>

**Falsified Quinine:** Alerts have also been issued for falsified Quinine Sulphate, circulating in grey or white plastic containers with the outdated WHO Essential Drugs Programme logo. These tablets often contain zero active quinine.<sup>30</sup>

**Falsified Artesunate:** Fake artesunate tablets often mimic the Guilin Pharmaceutical brand. Genuine packs have sophisticated hologram stickers with optical security features; fakes often have static, non-reflective stickers or incorrect coding.<sup>31</sup>

## 4.3 Detection in Low-Resource Settings

In a war zone, sophisticated analytical chemistry (like HPLC or Mass Spectrometry) is impossible. The SMRI proposes a tiered detection strategy suitable for field pharmacists:

**Visual Inspection (Tier 1):** This is the first line of defense. Pharmacists are trained to inspect packaging for specific ”tells”: spelling errors (e.g., ”Tablests”), poor print quality, missing batch numbers, or inconsistencies between the primary (blister) and secondary (box) packaging dates.<sup>32</sup>

**Simple Physical Tests (Tier 2):**

- **Disintegration Test:** Genuine dispersible Coartem tablets should disintegrate rapidly in water. Fakes often remain hard or dissolve into a gritty paste due to incorrect excipients (e.g., chalk or starch).<sup>33</sup>
- **Color/Shape:** Comparisons with known genuine samples are vital.

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<sup>28</sup>Ref. RHT/SAV/MD/IEA.130 8th November 2013 Information Exchange System Drug Alert No. 130 Falsified batches of Coartem recently

<sup>29</sup>Ref. RHT/SAV/MD/IEA.130 8th November 2013 Information Exchange System Drug Alert No. 130 Falsified batches of Coartem recently

<sup>30</sup>Medical Product Alert N° 1/2020: Falsified antimalarials displaying an outdated WHO Essential Drugs Programme logo

<sup>31</sup>CHARACTERIZATION OF COUNTERFEIT ARTESUNATE ANTIMALARIAL TABLETS FROM SOUTHEAST ASIA - CORE

<sup>32</sup>Tool for visual inspection of medicines

<sup>33</sup>Detection Technology - Countering the Problem of Falsified and Substandard Drugs - NCBI

**Portable Technology (Tier 3):** If available, devices like the CD-3 (a handheld tool using UV/LED light to compare spectral signatures of packaging) or the GPHF-Minilab (Thin Layer Chromatography) can be deployed. The Minilab is particularly robust for field use, allowing for the semi-quantitative verification of active ingredients without electricity.<sup>34</sup>

## 5. Molecular Biology of Malaria and the Resistance Threat

While the immediate crisis is access, the long-term threat is the efficacy of the drugs themselves. The emergence of Artemisinin Partial Resistance (ART-R) in East Africa is a catastrophic development that necessitates urgent monitoring.

### 5.1 Mechanism of Action of Artemisinins

To understand resistance, one must appreciate the drug's unique mechanism. Artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin) are sesquiterpene lactones containing a pharmacophore endoperoxide bridge.

**Activation:** The drug is inactive until this endoperoxide bridge is cleaved. This cleavage is catalyzed by **heme (ferrous protoporphyrin IX)**, which is released as a byproduct when the malaria parasite digests host hemoglobin within its acidic food vacuole.<sup>35</sup>

**Cytotoxicity:** The cleavage generates highly reactive carbon-centered free radicals and Reactive Oxygen Species (ROS).<sup>36</sup> These radicals function like a "molecular bomb," indiscriminately alkylating parasitic proteins (such as the translationally controlled tumor protein - TCTP) and lipids, causing widespread cellular damage and rapid parasite death.<sup>37</sup>

**Heme Detoxification:** Normally, the parasite detoxifies free heme by polymerizing it into inert hemozoin crystals. Partner drugs like Lumefantrine and Piperaquine work by inhibiting this polymerization, causing toxic heme to accumulate, further stressing the parasite.<sup>38</sup>

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<sup>34</sup>Field detection devices for screening the quality of medicines: a systematic review

<sup>35</sup>Artemisinin: mechanisms of action, resistance and toxicity - PubMed

<sup>36</sup>The Molecular Mechanism of Action of Artemisinin-The Debate Continues - MDPI

<sup>37</sup>Artemisinin: mechanisms of action, resistance and toxicity - PubMed

<sup>38</sup>Artemisinin-Based Drugs Target the Plasmodium falciparum Heme Detoxification Pathway — Antimicrobial Agents and Chemotherapy - ASM Journals



## 5.2 The Biological Mechanism of Resistance (K13 Mutations)

Resistance to artemisinins is defined as "delayed parasite clearance" (clearance half-life  $\geq$  5 hours), rather than complete treatment failure. This phenotype is primarily driven by point mutations in the **Kelch13 (K13)** protein.

**The Endocytosis Model:** Current research posits that the K13 protein is a critical component of the cytosome, the specialized structure the parasite uses to ingest host red blood cell cytoplasm (hemoglobin).<sup>39</sup>

**Wild Type:** In sensitive parasites, K13 facilitates robust hemoglobin endocytosis. High levels of hemoglobin digestion release high levels of heme, which activates the artemisinin, resulting in effective killing.

**Mutant Type:** Mutations in the K13 propeller domain (e.g., C580Y, R561H) reduce the function or stability of the K13 protein. This leads to a *reduction* in hemoglobin endocytosis.<sup>40</sup> With less hemoglobin being digested, there is less heme available to activate the drug. Consequently, the artemisinin is not fully activated, allowing the ring-stage parasite to enter a state of dormancy (quiescence) and survive the drug exposure.<sup>41</sup>

**The Ubiquitin-Proteasome System (UPS):** K13 also functions as an adaptor for an E3 ubiquitin ligase. Mutations may alter the ubiquitination and degradation of specific substrates (potentially including Phosphatidylinositol-3-kinase, PI3K), creating an altered stress response that favors survival.

## 5.3 The East African Expansion

For over a decade, ART-R was confined to the Greater Mekong Subregion. However, it has now been confirmed in East Africa.

**Genotypic Evidence:** Validated K13 mutations such as **R561H** have been found in Rwanda and Tanzania. In South Sudan (Western Equatoria), studies have detected the **R561L** mutation and the widespread **A578S** mutation.<sup>42</sup> While A578S is often considered a polymorphism with less phenotypic impact, the presence of R561-lineage mutations is a red flag for emerging resistance.<sup>43</sup>

**Implications:** The movement of millions of people across borders due to the Sudan conflict facilitates the rapid spread of these resistant genotypes. Furthermore, the chaotic use of monotherapies (artesunate alone without a partner drug) or substandard medicines

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<sup>39</sup>K13, the Cytosome, and Artemisinin Resistance - PubMed

<sup>40</sup>The Plasmodium falciparum artemisinin resistance-associated protein Kelch 13 is required for formation of normal cytosomes - eLife

<sup>41</sup>K13, the Cytosome, and Artemisinin Resistance - PubMed

<sup>42</sup>Screening for K13-Propeller Mutations Associated with Artemisinin Resistance in Plasmodium falciparum in Yambio County (Western Equatoria State, South Sudan) in

<sup>43</sup>Screening for K13-Propeller Mutations Associated with Artemisinin Resistance in Plasmodium falciparum in Yambio County (Western Equatoria State, South Sudan) in



creates extreme selection pressure, accelerating the evolution of resistance.<sup>44</sup>

## 6. Clinical Pharmacology and Treatment Protocols

In light of these challenges, clinical protocols in Sudan must be adaptive, evidence-based, and strictly managed.

### 6.1 First-Line Therapy: Artemether-Lumefantrine (AL) vs. Dihydroartemisinin-Piperaquine (DP)

Sudan's national protocol generally recommends AL (Coartem) as the first-line treatment for uncomplicated malaria.<sup>45</sup> However, therapeutic efficacy studies (TES) in the region suggest a need for nuance.

**Efficacy & Reinfection:** Both AL and DP show high cure rates (ACPR  $\geq$  90%). However, DP contains piperaquine, which has a very long half-life (approx. 23-28 days) compared to lumefantrine (3-4 days).<sup>46</sup> In high-transmission settings like refugee camps, patients treated with AL are reinfected much faster. Studies in Uganda and Kenya showed that AL-treated patients had 3 to 9.6 times more reinfections within 28-42 days compared to those treated with DP.<sup>47</sup>

**Dosing Compliance:** AL requires a twice-daily regimen for 3 days and must be taken with fatty food for absorption. In a famine setting where fat intake is minimal, AL absorption is compromised, potentially leading to sub-therapeutic levels and treatment failure. DP is typically dosed once daily and is less dependent on fat co-administration.<sup>48</sup>

**Recommendation:** While AL remains the standard, the SMRI proposes prioritizing DP for vulnerable populations in high-transmission camps to utilize its post-treatment prophylactic effect, reducing the overall caseload.

### 6.2 Severe Malaria: Artesunate vs. Quinine

The gold standard for severe malaria is **Intravenous (IV) Artesunate**, which reduces mortality in children by 24% compared to Quinine.<sup>49</sup>

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<sup>44</sup>Five challenges in the fight against malaria — by MSF Access Campaign - Medicines Are Not a Luxury

<sup>45</sup>Adapted Guidelines for Malaria Case Management in Sudan - KnE Open

<sup>46</sup>Efficacy of Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated Plasmodium falciparum Malaria among Children in Western Kenya, 2016 to 2017 - PMC - NIH

<sup>47</sup>Efficacy of Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated Plasmodium falciparum Malaria among Children in Western Kenya, 2016 to 2017 - PMC - NIH

<sup>48</sup>Artemether-Lumefantrine versus Dihydroartemisinin-Piperaquine for Treating Uncomplicated Malaria: A Randomized Trial to Guide Policy in Uganda — PLOS One

<sup>49</sup>Adapted Guidelines for Malaria Case Management in Sudan - KnE Open

**Protocol:** IV Artesunate (2.4 mg/kg) should be given at 0, 12, and 24 hours, followed by a full 3-day course of an oral ACT once the patient can tolerate oral intake.<sup>50</sup>

**The Quinine Alternative:** Due to stockouts and cold-chain requirements for Artesunate, Quinine remains the essential backup. However, Quinine has a narrow therapeutic index and significant toxicity (cinchonism). Critically, Quinine stimulates insulin secretion, causing severe hypoglycemia, which is particularly dangerous in malnourished children and pregnant women.<sup>51</sup>

**Management:** Quinine infusions must always be administered in 5% or 10% dextrose solution to prevent hypoglycemia. Nurses must be trained in drop-counting to control infusion rates and prevent cardiotoxicity (hypotension/arrhythmias).<sup>52</sup>

## 6.3 Management in Pregnancy

Treatment guidelines for pregnancy have been updated in 2024/2025.

**First Trimester:** Historically, Quinine + Clindamycin was recommended due to safety concerns with artemisinins. However, recent evidence and WHO guidelines now recommend **Artemether-Lumefantrine (AL)** as the preferred treatment for uncomplicated malaria in the first trimester.<sup>53</sup>

**Significance:** This shift is operationally vital. It simplifies the supply chain by removing the need to stock Clindamycin (which is rarely available) and allows pharmacists to use the standard AL stock for all pregnant women, ensuring they receive effective care without delay.<sup>54</sup>

## 6.4 Pediatric Compounding in Emergencies

A major challenge in displacement camps is the shortage of pediatric formulations (dispersible tablets or suspensions). Pharmacists must be skilled in compounding pediatric doses from adult tablets.

**Dosing Protocol:** Using the standard adult AL tablet (20mg Artemether / 120mg Lumefantrine), dosing is weight-based<sup>55</sup>:

- 5 - 14 kg:  $\frac{1}{4}$  Tablet
- 15 - 24 kg:  $\frac{1}{2}$  Tablet
- 25 - 34 kg:  $\frac{3}{4}$  Tablet

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<sup>50</sup>4.3 Parasitic infections - MSF Medical Guidelines

<sup>51</sup>4.3 Parasitic infections - MSF Medical Guidelines

<sup>52</sup>4.3 Parasitic infections - MSF Medical Guidelines

<sup>53</sup>Safety of artemisinin and non-artemisinin antimalarials in the first trimester of pregnancy - World Health Organization (WHO)

<sup>54</sup>Adapted Guidelines for Malaria Case Management in Sudan

<sup>55</sup>Malaria tablets: dose for children - Wanda

- $\geq$  35 kg: 1 Full Tablet

**Administration:** Tablets must be crushed and mixed with a small amount of water or breast milk. To improve adherence given the bitter taste, caregivers are advised to mix the medication with any available sweet substance (sugar, date paste) immediately before administration.

## 7. Project Proposal: Sudan Malaria Resilience Initiative (SMRI)

**Project Title:** Sudan Malaria Resilience Initiative (SMRI): A Field-Based Stewardship Model.

**Objective:** To reduce malaria morbidity and mortality in Sudan's conflict zones by securing the integrity of antimalarial therapies and optimizing their clinical use through pharmacist-led stewardship.

### Pillar 1: Supply Chain Security and Vigilance

**Action:** Establish "Sentinel Pharmacy Points" in key IDP camps (e.g., White Nile, Gedaref, Kassala).

**Protocol:** Every batch of antimalarials entering the camp-whether from donors, private traders, or cross-border sources-must undergo a Three-Point Check before distribution:

1. **Database Cross-Reference:** Check batch numbers against the offline-cached WHO/NAFDAC Medical Product Alert database (specifically looking for batches F2261, NOF 2153, F1901).<sup>56</sup>
2. **Visual Inspection:** Utilize the USP/ICN Visual Inspection Checklist. Staff will inspect for poor print quality, peeling holograms, spelling errors, and "Green Leaf" logos on recent stock.<sup>57</sup>
3. **Disintegration Test:** Perform a simple field test by placing a tablet in water. Genuine dispersible tablets disintegrate rapidly ( $\leq$  3 minutes); fakes often remain hard or form a non-uniform paste.<sup>58</sup>

**Outcome:** Immediate quarantine of suspicious stock to prevent administration to patients and reporting to the Health Cluster.

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<sup>56</sup>Ref. RHT/SAV/MD/IEA.130 8th November 2013 Information Exchange System Drug Alert No. 130 Falsified batches of Coartem recently

<sup>57</sup>Tool for visual inspection of medicines

<sup>58</sup>Detection Technology - Countering the Problem of Falsified and Substandard Drugs - NCBI

## Pillar 2: Clinical Stewardship and Therapeutic Adaptation

**Action:** Implementation of a dynamic "Red/Yellow/Green" treatment protocol based on real-time stock levels.

- **Green (Normal Stock):** Treat all uncomplicated cases with AL; severe cases with IV Artesunate.
- **Yellow (Shortage):** Ration AL for priority groups (children <5, pregnant women). Shift adult males to oral Quinine (7 days) + Doxycycline (if available).<sup>59</sup>
- **Red (Critical Shortage):** Implement strict "Test and Treat" policy (no clinical diagnosis without RDT). Initiate pediatric compounding from adult tablets. Reserve IV Artesunate strictly for cerebral malaria cases in children/pregnancy.<sup>60</sup>

**Pregnancy Protocol:** Enforce the use of AL for first-trimester uncomplicated malaria to conserve Quinine stocks for severe cases.<sup>61</sup>

## Pillar 3: Resistance Monitoring (The "Canary in the Coal Mine")

**Action:** Given the lack of genomic sequencing capabilities in the field, the project will use clinical proxies to monitor for resistance.

**Protocol:** Day 3 Positive Loop.

- Any patient treated with an ACT who remains febrile or parasitemic (RDT positive) on Day 3 of treatment is flagged.
- These cases are treated as potential Delayed Clearance cases (indicative of K13 mutations like R561H).<sup>62</sup>
- **Action:** Immediate switch to Second-Line therapy (Quinine + Clindamycin or Dihydroartemisinin-Piperaquine if available). The case is recorded in a specific "Resistance Register."
- **Surveillance:** If clusters of Day 3 failures occur, the Health Cluster/WHO is notified to investigate a potential resistance outbreak and prioritize the area for TES or genomic sampling.<sup>63</sup>

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<sup>59</sup>Appendix A: Malaria in the United States: Treatment Tables - CDC

<sup>60</sup>4.3 Parasitic infections - MSF Medical Guidelines

<sup>61</sup>Safety of artemisinin and non-artemisinin antimalarials in the first trimester of pregnancy - World Health Organization (WHO)

<sup>62</sup>Plasmodium berghei K13 Mutations Mediate In Vivo Artemisinin Resistance That Is Reversed by Proteasome Inhibition - Stanford Medicine

<sup>63</sup>Emerging Plasmodium falciparum K13 gene mutation to artemisinin-based combination therapies and partner drugs among malaria-infected population in sub-Saharan Africa - PMC - NIH

## 8. Implementation Strategy and the Pharmacist’s Role

### 8.1 The Pharmacist as Humanitarian Steward

In this context, the pharmacist’s role evolves from dispenser to strategic asset.

**Gatekeeper:** The pharmacist is the primary barrier between falsified medicines and the patient. Their ability to visually identify fake Coartem batches protects the community from toxic or ineffective treatments.

**Clinical Consultant:** They advise clinicians on substitution protocols during shortages (e.g., calculating Quinine drip rates to avoid hypoglycemia).

**Educator:** They train community health workers on how to properly crush and mix adult tablets for children, ensuring accurate dosing and adherence.<sup>64</sup>

### 8.2 Data Collection in a Digital Vacuum

Recognizing the lack of electricity and internet, data collection will rely on robust paper-based systems (tally sheets) that can be digitized later when connectivity permits.

**Key Performance Indicators (KPIs):**

- % of batches screened for falsification.
- Number of suspected fake packs quarantined.
- Number of Day-3 treatment failures identified.
- Stock-out duration (days) for key antimalarials.

## 9. Conclusion

The conflict in Sudan has dismantled the biological and logistical shields that protect the population from infectious disease, leaving millions vulnerable to a syndemic of malaria, cholera, and malnutrition. The convergence of infrastructure collapse, the proliferation of fake medicines, and the emerging threat of molecular drug resistance represents an existential threat to the region’s health security.

The **Sudan Malaria Resilience Initiative (SMRI)** proposes a pragmatic, field-based response to this crisis. By operationalizing visual inspection for fake drugs, standardizing adaptive clinical protocols for shortages, and establishing clinical surveillance for resistance, this project offers a viable pathway to sustain life-saving malaria treatment in the most challenging conditions. It represents a shift from passive aid distribution to active **pharmaceutical stewardship**, ensuring that even in the “fog of war,”

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<sup>64</sup>The pharmacist’s crucial role in humanitarian crises

the medicines reaching the patient are safe, effective, and administered with scientific precision. This initiative underscores the vital role of the pharmacist in humanitarian response-not just as a provider of goods, but as a guardian of patient safety and public health resilience.

## Appendix: Clinical Reference Tables

Table 1: Visual Inspection Checklist for Antimalarials (Field Guide)

Feature	Genuine Coartem (Novartis)	Suspect / Falsified
Hologram	Dynamic, changes color/image with angle	Static, dull, or sticker peeling off
Spelling	Correct English/French	Errors (e.g., "Tablests", "Noartis", "Malarie")
Batch No.	Matches printed date	Known bad batches (e.g., <b>F2261</b> , <b>NOF 2153</b> , <b>F1901</b> ) <sup>65</sup>
Tablet Appearance	Yellow, round, "N/C" or "CG" debossed	Discolored, chipping, no debossing, powdery texture
Logo	Standard Novartis packaging	Outdated "Green Leaf" AMFm logo on recent dates
Disintegration	Rapid ( $\leq 3$ mins) in water	Slow, hard, or gritty residue

Table 2: Pediatric Dosing Adaptation for Adult AL Tablets (Coartem 20/120mg)

*Note: Crush and mix with clean water or breast milk immediately before use.*

Child Weight (kg)	Portion of Adult Tablet per Dose	Dosing Frequency	Duration
5 - 14 kg	$\frac{1}{4}$ Tablet	Twice Daily (every 12h)	3 Days
15 - 24 kg	$\frac{1}{2}$ Tablet	Twice Daily (every 12h)	3 Days
25 - 34 kg	$\frac{3}{4}$ Tablet	Twice Daily (every 12h)	3 Days
$\geq 35$ kg	1 Full Tablet	Twice Daily (every 12h)	3 Days

Table 3: Therapeutic Substitution Protocol (Shortage Management)

Clinical Scenario	First Line (Green)	Shortage Alternative (Yellow)	Critical Failure (Red)
Uncomplicated Malaria (Adult)	AL (3 days)	DP (3 days)	Quinine PO (7 days) + Doxycycline/Clindamycin
Uncomplicated Malaria (Pregnancy 1st Tri)	AL (3 days) <sup>66</sup>	Quinine PO (7 days) + Clindamycin	Quinine Monotherapy (7 days)
Severe Malaria	IV Artesunate (min 24h)	IM Artemether	IV/IM Quinine (Loading dose required + Dextrose)



*Note on Quinine Safety: When using IV Quinine, monitor for hypoglycemia. If glucose monitoring is impossible, empirically administer maintenance fluids with 5-10% Dextrose.*<sup>67</sup>

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<sup>67</sup>4.3 Parasitic infections - MSF Medical Guidelines

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