Injectable Artesunate Assessment Report

June 2019

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Acknowledgements

We would like to express our immense gratitude to the officials of the ministries of health, including the national and state malaria control programs in DRC, Nigeria, and Uganda, who took the time to share information about the health system and the introduction, availability, and use of injectable artesunate in their countries. We would also like to thank in-country partners, including Alisons SPRL, the Alliance for International Medical Action, Chemonics, Catholic Relief Services, the Integrated Health Project/Abt Associates, Malaria Consortium, Management Sciences for Health, the Malaria Action Program for Districts/Malaria Consortium, Médecins Sans Frontières, the President's Malaria Initiative/Centers for Disease Control, the Regional Health Integration to Enhance Services/University Research Co., Sanru, Swiss Tropical and Public Health, and the World Health Organization for their collaboration and insights into severe malaria and injectable artesunate. Special thanks to the Bill and Melinda Gates Foundation, the Global Fund for Aids, Tuberculosis, and Malaria, Malaria Consortium, Medicines for Malaria Venture, Médecins Sans Frontières, the President's Malaria Initiative, Swiss Tropical and Public Health, UNICEF and the World Health Organization for sharing their perspectives and relevant information. This assessment was funded through a grant from Unitaid.

Acronyms

3PL – Third Party Logistics Provider
ACT – Artemisinin Combination Therapy
ALIMA – The Alliance for International Medical Action
AQUAMAT - Artesunate versus quinine in the treatment of severe falciparum malaria in African children
BCZ – Bureau Central de Zone de Santé/Health Zone Office
BMGF – Bill and Melinda Gates Foundation
CARAMAL – Community Access to Rectal Artesunate for Malaria
CDR – Centre de Distribution Régionale/Regional Distribution Center
CFR – Case Fatality Rate
CHAI – Clinton Health Access Initiative
CHW – Community Health Worker
CRS – Catholic Relief Services
CSR – Centre de Santé de Reference/Reference Health Facility
DALYs – Disability Adjusted Life Years
DFID – Department for International Development
DHIS2 – District Health Information System 2
DHS – Demographic Health Survey
DMCSA – Drug Medical Consumables Supply Agency
DPM – Direction de la Pharmacie et du Médicament/Department of Pharmacy and Medicine
DPS – Département Provinciale de la Santé/Provincial Health Department
DRC – Democratic Republic of Congo
DRF – Drug Revolving Fund
EUV – End User Verification
FC – Franc Congolais/Congolese Franc
FCT – Federal Capital Territory
Global Fund/GF – The Global Fund for AIDS, Tuberculosis, and Malaria
GMP – Good Manufacturing Practices
GPRM – Global Price Reporting Mechanism
HC – Health Center
HMIS _ Health Management Information System
IM – Intramuscular
iCCM – Integrated Community Case Management
ISMO – Improving Severe Malaria Outcomes
IV – Intravenous
JMS – Joint Medical Stores
LMIS – Logistics Management Information System
NDA - National Drug Authority
NMCP – National Malaria Control Program
NMEP – National Malaria Elimination Program
NMS – National Medical Store
M&E – Monitoring and Evaluating
MC- Malaria Consortium
MMV – Medicines for Malaria Venture
MoH – Ministry of Public Health
MOP – Malaria Operational Plan
MSF – Médecines Sans Frontières

MSH – Management Sciences for Health
NGO – Non-governmental organization
NSP - National Strategic Plan
PFP – Private-for-profit
PNAM – Programme National d'Approvisionnement en Médicaments Essentiels/National Supply Chain Program
PNFP – Private-Not-For-Profit
PNLP – Programme National de la Lutte Contre le Paludisme/National Malaria Control Program
PMI – The President's Malaria Initiative
PPM – Pooled Procurement Mechanism
PPP – Public Private Partnership
PQ – Prequalified
PQR – Global Fund Price and Quality Reporting
PR – Primary Recipient
QPPU – Quantification Procurement Planning Unit
Sanru – Santé Rurale/Rural Health
SEAQUAMAT - South East Asian Quinine Artesunate Malaria Trial
SMEP – State Malaria Elimination Program
SNAME – Système National d'Approvisionnement en Médicaments Essentiels/National Supply Chain System
SR – Secondary Recipient
Swiss TPH – Swiss Tropical and Public Health Institute
UN – United Nations
USAID – United States Agency for International Development
WHO – World Health Organization

Executive summary

Malaria is one of the leading causes of morbidity and mortality in children under five in Africa. With timely and effective treatment, the risk of death can be significantly reduced. Following the results of clinical trials showing the high efficacy of injectable artesunate over quinine, the World Health Organization (WHO) recommended injectable artesunate as the preferred first line treatment for severe malaria in adults and children in 2011. However, uptake of the product remained slow. To help catalyze injectable artesunate procurement and uptake, Unitaid funded the "Improving Severe Malaria Outcomes" (ISMO) project from 2013-2016. Implemented in Cameroon, Ethiopia (two regions)[1], Kenya, Malawi, Nigeria (13 states),[2] and Uganda, the project supported each of these countries with the quantification, procurement, distribution, case management trainings, supervision, and M&E systems to introduce and drive the uptake of injectable artesunate.

Since the ISMO project, few efforts have been undertaken to understand to what extent injectable artesunate has become (or remained) the preferred drug to treat severe malaria in the ISMO countries or in other malaria-endemic countries globally and, particularly, in sub-Saharan Africa, where most deaths from malaria occur. This report describes the findings of an assessment intended to answer this question. The assessment consisted of the following key activities: 1) a global desktop review of published and grey literature on injectable artesunate introduction, availability, use, and prescription; 2) interviews with relevant stakeholders at the global level (i.e., donors, NGOs); 3) an analysis of available procurement data and 4) an in country 'deep dive' in three high endemic countries (DRC, Nigeria, Uganda) that included interviews with stakeholders at the central and subnational level, a supply chain analysis, and the extraction and analysis of health management information system (HMIS) and logistics management information system (LMIS) data where available.

Key findings from the assessment presented in this report are:

Guidelines and policy: The majority of malaria high-endemic countries (80%) have adapted their malaria policies and guidelines to reflect the WHO recommendation for injectable artesunate as the preferred severe malaria treatment. However, 74% of countries do not make an explicit recommendation to use artemether over quinine when injectable artesunate is not available, and only 25% specify the dosing recommendations for children under 20kg, as per the latest WHO recommendations.[3]

Procurement: Injectable artesunate procurement has steadily increased since its adoption in the WHO guidelines in 2011 with an year-over-year growth rate of 73% over period 2011-2018.[4] There are currently two WHO pre-qualified (PQ) suppliers of injectable artesunate: Guilin and IPCA. Guilin received WHO pre-qualification in 2011 and produces injectable artesunate in 30mg, 60mg, and 120mg formulations under the brand name Artesun. IPCA received WHO pre-qualification in December 2018 and only produces a 60mg vial product, under the brand name Larinate. Key findings from the procurement analysis include:

[1] Oromia and Southern Nations, Nationalities, and Peoples Regional State

[2] Akwa Ibon, Cross Rivers, Enugo, FCT Abuja, Imo, Jigawa, Kaduna, Kano, Lagos, Nasarawa, Ogum, Oyo, River

[3] WHO 2015 malaria treatment guidelines: injectable artesunate as preferred first-line treatment, 2) children under 20kg should receive 3mg/kg BW per dose and 3) IM artemether over IV quinine as an alternate treatment

[4] Procurement data included data from PMI, Global Fund and Unicef

- Almost all (98%) injectable artesunate procurement is the 60mg vial; small quantities of 30mg and 120mg vials were procured in 2017-2018 through the Global Fund.
- Majority of procurement went to just five countries- DRC, Uganda, Kenya, Tanzania, and Nigeria have received almost 55% of the 123 million 60mg Artesun vials procured in the 2011-2018 period.
- 87% of countries have received multiple donor shipments of injectable artesunate.
- Actual injectable artesunate procurement has been lower than the forecasted procurement - Forecasted procurement[5] has been relatively consistent in the 2017-2020 Unitaid global quantification report but actual procurement has been under 85% of the forecasted need for 2017-2018.[6]
- Prices have remained relatively stable (average of $1.53 per 60 mg vial) throughout the 2011-2018 period even though there was only one prequalified supplier for the drug.

Early adoption challenges: We found four key challenges among countries introducing injectable artesunate. First, the required volumes of injectable artesunate were **poorly quantified**. In Nigeria, for example, the first Global Fund procurement in 2014/2015 was based on a quantification that used a flat 5% severe malaria rate (i.e., 5% of uncomplicated cases) that proved to be too high, causing overstock in the Global Fund supported states, which had to be redistributed to non-Global Fund supported states. Secondly, **procurement delays** during the ISMO project plagued the initial injectable artesunate orders due to extended price negotiations with Guilin and either delayed introduction in project countries or had them rely on other donors for procurements. Third, there was (and in some countries still is) a **preference for quinine** over injectable artesunate due to the relatively inexpensive cost of quinine compared to injectable artesunate, ample supply, and the preference of some health providers to continue to use quinine. Fourth, there was, and in some countries continues to be, **competition from non-WHO prequalified injectable artesunate** products and **alternative treatments** that discouraged local procurement and uptake of PQ injectable artesunate. In countries such as DRC and Nigeria there are strong local markets for quinine or other artemisinin derived products that were established prior to injectable artesunate introduction.

Poor adherence to treatment guidelines: Following its introduction, misuse of injectable artesunate has been common and pervasive. In some countries, such as Uganda and DRC, injectable artesunate is used to treat cases of uncomplicated malaria, contrary to national guidelines. This **excessive use of injectable artesunate for non-severe cases** drives up consumption leading to stock outs, complicates patient treatment, and increases the cost of treatment for simple cases.[7] We found five drivers of this misuse. First and foremost, health workers receive insufficient **training and a lack of regular supervision**. A 2017 survey in DRC found only 42% of providers had been trained on PNLP guidelines.[8] Similar challenges have been found in Uganda: a 2018 survey reported only 45% of health providers trained in severe malaria case management.[9] Second, **insufficient health system financing** encourages providers to prioritize services and treatments for which they can charge:[10] In some countries, consultations and hospitalization for severe malaria provide opportunities for providers to charge for services which results in patients opting for alternative and/or less expensive treatments (i.e., quinine). Third,

[5] Forecasted projections based on current Global Fund procurement plans from high burden countries and data from PMI and Unitaid.

[6] Forecast Report: Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast 2017-2020. May 25 2017.

[7] Zurovac, Dejan et al. Monitoring health systems readiness and inpatient malaria case-management at Kenyan county hospitals. Malaria Journal (201) 17:213.

[8] DRC PMI End Use Verification Survey, October 2017.

[9] Uganda PMI End Use Verification Survey, November 2018.

[10] DRC MOP 2019

injectable artesunate is used at lower levels of the health system, where its use is unauthorized, and where lower level providers and facilities often do not have the skill level, training, or resources to properly care for severe malaria and related complications. Fourth, the relatively **high cost** to patients of injectable artesunate and severe malaria treatment, in certain countries, can be a barrier to accessing treatment and forces patients to rely on less effective treatments or on drugs of unknown quality. Fifth, **use of quinine** is encouraged by its persistent availability and accessibility, its lack of donor funding which enables it to be charged back to patients, and its perception as efficacious.

Finally, **ACTs may not be provided after the patients has received injectable artesunate**, contrary to national guidelines. Reasons for this are not certain but likely due to a lack of knowledge and negligence on the part of the provider or stock outs of ACTs.

Based on the findings in the assessment and identified best practices, six **key recommendations** are suggested to improve injectable artesunate availability and use:

1) Country malaria programs should **improve quantification and forecasting** of injectable artesunate by strengthening severe malaria data availability and quality through interventions such as regular HMIS data quality audits and support to facilities on reporting and data use. Improving facility reporting and data use can help improve the quality of consumption data used in quantification, supply and distribution planning, and stock monitoring.
2) Country malaria programs should **strengthen the capacity of supply chain** staff to minimize stock outs and improve quantification and forecasting capacity through facility and warehouse logistics training, mentoring, and supervision. More accurate quantification, reporting, and ordering can reduce product rationing[11].
3) Country malaria programs, in collaboration with partners, should work to **encourage injectable artesunate rational use**. Examples could include:
    a. Revise training curricula and supervision through approaches such as on-the-job training, mentoring, and clinical audits to ensure proper use of the drug and patient care. Targeted clinical audits, for example, may improve reporting, severe malaria case management, and overuse of injectable artesunate. Training and supervision particularly need to highlight the prescription of ACTs following injectable artesunate treatment as well as the superiority and higher efficacy of injectable artesunate compared to quinine.
    b. Work with WHO to ensure alignment between severe disease classifications and management practices at different levels of the health system such that severe malaria patients receive injectable artesunate while those with uncomplicated malaria or other illnesses do not. Countries that have not yet made a clear recommendation of injectable artesunate as a first-line treatment, do not having dosing specifications for children under 20kg, or do not recommend artemether as the preferred alternate treatment, should also work with WHO to align its guidance to global WHO recommendations. Donors could play an advocacy role or provide technical support to make any revisions.
    c. Develop and implement patient registration/tracking systems for those patients with severe malaria who were prescribed injectable artesunate. For example, in Uganda, a hospital rolled out an injectable artesunate-patient registration/tracking system (for every person who receives the product, the pharmacist records the name and the number of vials received), which significantly reduced overconsumption.

[11] Practice that caps the quantity of a commodity a facility can receive

Improved rational product use could lead to lower and more targeted injectable artesunate use and reduce stock outs, rationing, and reliance on the open market.

4) Donors should work closely together with country programs and other in-country stakeholders to **ensure free severe malaria treatment** by leveraging comprehensive primary health care and maternal and child health projects and initiatives (e.g., free treatment schemes for children under five, flat service fees, insurance schemes). Country malaria programs should ensure that malaria drugs and treatment are included in these non-malaria-specific interventions.
5) National regulatory authorities such as the MoH Department of Pharmacy and Medicine and National Drug Authorities should work to **strengthen their pharmacoviligence systems** in countries to reduce the availability of sub-standard or fake artemisinin derived injectable drugs, particularly those not registered for use with the national drug authorities.
6) Donors and implementing partners should **support severe malaria case management initiatives that provide comprehensive care** (rather than funding procurement of injectable artesunate alone) to ensure that the necessary drugs and services to treat severe malaria complications, such as blood transfusions are consistently available and provided to patients.

Overall, it seems that the ISMO project has had a lasting effect on procurement and use of injectable artesunate for the treatment of severe malaria in the two ISMO project countries examined here, particularly in Uganda. The procurement analysis found that procurement has steadily increased over the years since 2012, through and then following the ISMO project. The ISMO project found that training and supervision can reduce misuse, particularly for uncomplicated malaria cases, although findings suggest that discontinuation of such activities may result in these effects waning. Since the ISMO project, use of injectable artesunate use has increased, albeit with challenges around misuse. Finally, analysis of the (very limited) data available (from DRC and Uganda) was unable to identify a discernable difference in the case fatality rate among facilities with and without injectable artesunate. However, poor data quality and confounding factors, such as the possibility that facilities with injectable artesunate might have started off with higher case fatality rates than those without, limit the conclusions that should be drawn from this analysis.

Introduction

From 2013 to 2016, Unitaid invested in a consortium led by Medicine for Malaria Venture (MMV), with the Clinton Health Access Initiative (CHAI) and Malaria Consortium (MC) responsible for in-country activities, to introduce and catalyze the procurement of injectable artesunate, the recommended first-line treatment for severe malaria. This project, called "Improving Severe Malaria Outcomes" (ISMO), was implemented in Cameroon, Ethiopia (two regions),[12] Kenya, Malawi, Nigeria (13 states),[13] and Uganda.

The ISMO project aimed to create a stable market to catalyze the use of quality-assured injectable artesunate. During the project, the consortium supported each of the project countries with the quantification, procurement, distribution, case management training, supervision, and M&E systems to introduce and drive uptake of injectable artesunate. The End of Project Evaluation showed a significant increase in the use of injectable artesunate across the implementation regions in its final year, with up to 86% of severe malaria cases receiving injectable artesunate by December 2015, according to data collected from project countries.[14]

Since the end of the ISMO project, few efforts[15] have been undertaken to understand to what extent injectable artesunate has become (or remained) the preferred drug to treat severe malaria in the ISMO countries or in other malaria-endemic countries globally and, particularly, in Africa where most deaths from malaria occur.

This report describes the findings of an assessment that 1) reviewed data on the introduction, availability, and use of injectable artesunate; 2) quantified the impact injectable artesunate has had on malaria deaths; and 3) analyzed available data on historical and future injectable artesunate procurement.

The remainder of this report includes the following sections: an overview of relevant WHO guidance (section I); a description of the assessment methodology (section II); findings from a global desk review and a deep dive in three high endemic countries (Democratic Republic of Congo (DRC), Nigeria, and Uganda) including surveillance data and supply chain analyses (section III); and a summary of the main challenges and key recommendations (section IV).

I. WHO Policy review

Malaria remains one of the leading causes of morbidity and mortality in children under five in Africa. In 2017, an estimated 2 to 6 million of the 219 million uncomplicated malaria cases were assumed to have advanced to severe disease, resulting in approximately 435,000 malaria-attributable deaths.[16] The majority of these malaria cases and deaths were in sub-Saharan Africa, where 91% of cases and 93% of

[12] Oromia and Southern Nations, Nationalities, and Peoples Regional State

[13] Akwa Ibon, Cross Rivers, Enugo, FCT Abuja, Imo, Jigawa, Kaduna, Kano, Lagos, Nasarawa, Ogum, Oyo, River

[14] Cambridge Economic Policy Associates Ltd. End of Project Evaluation appointed by Unitaid of the "Improving Severe Malaria Outcomes" (ISMO) Project, 1 March 2017.

[15] In 2018 and 2019, MMV has worked with the National Malaria Control Programs (NMCPs) in Uganda, the Democratic Republic of the Congo (DRC), and Liberia to conduct severe malaria case management rapid assessments in key vulnerable groups (particularly pregnant women and children under five years); with an intention to guide policy direction and improve service delivery.

[16] World Malaria Report 2018

deaths occurred.[17] One-third of all malaria deaths were recorded in just three countries: Nigeria, DRC, and Uganda, the countries selected for this assessment's 'deep dive.'[18]

Once malaria advances to a severe state, it often leads to death, if not timely and effectively treated. In 2006, the WHO revised its guidance on severe malaria to recommend intravenous artesunate as the preferred first-line treatment for adults with severe malaria. The WHO recommendation stated that intravenous or intramuscular artesunate should be given until the patient can tolerate oral therapy, followed by a full course of combination therapy, artemisinin combination therapies (ACTs).[19] These recommendations were mainly based on one major study (SEAQUAMAT)[20] and five smaller trials. The SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial) study, performed in 2005, showed injectable artesunate reduced the risk of death from severe malaria in adults by 34.7% compared to quinine, the WHO recommended treatment for severe malaria until 2006.[21]

In its 2006 guidance, WHO stated that in children insufficient evidence was available to recommend artemisinin derivatives over quinine in high transmission settings, as only 14% of the participants in SEAQUAMAT were under 15, and individual patient data meta-analysis of trials comparing artemether and quinine did not show a difference in mortality in African children.[22] A subsequent trial with more than 5000 children in 11 centers in nine African countries concluded that treating severe malaria with injectable artesunate over quinine reduces risk of death in children by 24%.[23] Following the results of this study, in April 2011, the WHO guidelines were revised to recommend intravenous artesunate as first-line treatment for severe malaria in both adults and children.[24] In 2015 the third edition of the WHO's Guidelines for the treatment of malaria was released. This version included a specification for injectable artesunate dosing for children under 20kg, a preference for IM artemether over quinine as an alternative treatment to injectable artesunate, and a recommendation for injectable artesunate use during all trimesters of pregnancy. The most recent WHO malaria guidelines from 2015 state the recommended treatment for severe malaria as:

- "*Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24h and until they can tolerate oral medication. Once a patient has received at least 24h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of an ACT (add single dose primaquine in areas of low transmission)*"
- "*Children weighing <20kg should receive a high dose of artesunate (3mg/kg BW per dose) than larger children and adults (2.4 mg/kg BW per dose) to ensure equivalent exposure to the drug).*
- *"If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria."*[25]

[17] World Malaria Report 2018
[18] World Malaria Report 2018
[19] WHO Guidelines for the Treatment of Malaria, 2006.
[20] WHO Guidelines for the Treatment of Malaria, 2006.
[21] Dondorp A, Nosten F, Stepniewska K, Day N, White N; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* 2005; 366: 717-25.
[22] WHO Guidelines for the Treatment of Malaria, 2006.
[23] Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010; 376: 1647-57.
[24] WHO Guidelines for the Treatment of Malaria, Second Edition, 2010.
[25] WHO Guidelines for the Treatment of Malaria, Third Edition, 2015.

II. Methodology

This injectable artesunate assessment was conducted between February 18th and June 14th, 2019 and consisted of two phases: 1) a desktop review of current global information on injectable artesunate procurement and implementation and 2) an in-depth assessment of injectable artesunate availability and use in three high endemic countries DRC, Nigeria, and Uganda. The assessment included seven major activities:

1) A global desk review of published and grey literature on injectable artesunate introduction, availability, use, and prescription
2) Interviews with global level stakeholders
3) Collection and analysis of donor procurement data
4) Collection and review of national severe malaria treatment guidelines
5) Interviews with stakeholders in DRC, Nigeria, and Uganda
6) Supply chain analysis in DRC, Nigeria, and Uganda
7) Extraction and analysis of the health management information system (HMIS) and logistics management information system (LMIS) data in DRC, Nigeria, and Uganda

The remainder of this section provides details on how each of the activities were conducted.

1. Desk Review

The objective of the desk review was to identify challenges, successes, and lessons learned in the introduction of injectable artesunate, as well as its current availability and use. The desk review consisted of the collection and review of published articles and grey literature, particularly from DRC, Nigeria, and Uganda, as well as country national malaria guidelines.

Published literature was searched in the Pubmed database, on April 9th, 2019 using different combinations of severe malaria terms.[26] Articles were retained with titles related to the introduction, use, availability, treatment, or prescription of injectable artesunate or severe malaria treatment. The search identified a total of 198 articles, of which nine were retained. Additionally, a snowball approach was used to obtain published articles not found in the PubMed database, resulting in three additional articles, making a total of 12 published studies that were reviewed for the assessment. Annex A contains the published literature decision tree and Annex B an overview of included literature.

Grey literature included national malaria policies, relevant projects reports (i.e., ISMO semi-annual and annual reports), assessment reports (i.e., the MMV supported severe malaria case management assessments), and relevant Ministry of Health (MoH) reports, such as annual malaria reports and mid-term national strategy review reports. Many of the documents included were found on the Severe Malaria Observatory[27] website, MoH, donor, and NGO websites, such as the President's Malaria Initiative's (PMI) Malaria Operational Plans (MOPs).

For the in-depth analysis of the three focal countries, national documents were identified and collected during in-country visits. These country-specific documents included national quantification reports, annual malaria program reports, scientific abstracts from national malaria scientific days, and national

[26] Different combinations of terms related to severe malaria and injectable artesunate were searched in the database: Injectable Artesunate, "Severe Malaria Treatment", and Severe Malaria Injectable Artesunate.

[27] Severe Malaria Observatory is website, initiative and hosted by MMV, populated with information made available by the global malaria community.

strategic malaria plans (NSPs). ISMO and CARAMAL[28] project documents, plans, and reports (i.e., supply chain assessments) were also reviewed. A total of 70 documents were reviewed. Annex B contains an overview of all documents gathered and reviewed.

2. Global Level Stakeholder Interviews

A list of key global level malaria stakeholders was identified in close collaboration with the global CHAI malaria team and Unitaid. This list included representatives of donor agencies, UN agencies, and NGOs. A standard questionnaire was developed to guide the interviews. The questionnaire can be found in Annex H. A complete list of organizations and interviewed stakeholders can be found in Annex I.

3. Injectable Artesunate Procurement Data Analysis

Injectable artesunate procurement data was obtained from PMI, the Global Fund to Fight AIDS, Tuberculosis, and Malaria's (Global Fund) Price and Quality Reporting (PQR) database, and the WHO's Global Price Reporting Mechanism (GPRM) database; data from PMI covered the period 2012-2019, Global Fund from 2010-2019 for both quinine and injectable artesunate, and UNICEF injectable artesunate and quinine procurement from 2004-2016. The data were cleaned and analyzed in Excel; the analysis included volumes by country and year, average weighted[29] annual price, and forecasted[30] vs. actual procurement. For the pricing analysis, data were excluded if the freight costs were imbedded or unknown if they were imbedded in the unit costs. UNICEF data were excluded from the price analysis due to uncertainty around accuracy of certain unit costs.

4. Collection and review of national severe malaria treatment guidelines

Malaria country guidelines were obtained for 51 countries in Africa (41) and Asia (10). Country guidelines were collected from CHAI country teams and through online searches. All countries in Africa, malaria endemic countries in Asia, and countries that received injectable artesunate from Global Fund and PMI were targeted for guideline collection. The country guidelines were reviewed and compared to WHO's 2015 malaria treatment guidelines to determine alignment on three key elements: 1) administering injectable artesunate as first-line treatment for severe malaria in adults, infants, and children; 2) providing children weighing under 20kg a higher dose of 3.0mg/kg of body weight to ensure equivalent exposure to the drug; and 3) using artemether if artesunate is not available in both adults and children with severe malaria (as opposed to quinine). In countries where the latest guidelines were not available, we used the 2018 World Malaria Report for information on severe malaria treatment. However, the World Malaria Report did not include information on the dosing specification for children under 20kg and the preferred alternate treatment could not be ascertained when multiple treatments were listed.

5. Country Visits and Interviews in DRC, Uganda, and Nigeria

[28] The Community Access to Rectal Artesunate for Malaria project is an operational research study to examine how reductions in severe malaria case fatality can be achieved under real-world conditions by introducing RAS through established ICCM platforms within targeted communities along with a minimal package of supporting interventions.

[29] Weighted price was calculated by multiplying the volume by price for each order, totaling the amount for the year, and then dividing by the total volume for the year.

[30] Forecast from the Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast, 2017-2020

During each country visit, key informants from the national malaria control programs, national and sub-national medical stores, NGOs, donors, facilities, and the private sector (i.e., wholesalers) were interviewed. A full list of organizations and interviewees can be found in Annex I. Key informants were identified in close collaboration with CHAI country teams. Interviews were conducted using a standard questionnaire. The questionnaire can be found in Annex H. In Nigeria, in addition to interviews focused at the national level, interviews were held with state level (Kano) stakeholders due to Nigeria's decentralized government. Subnational visits also enabled visits to four health facilities supported by the ISMO project; two in Kano and two in the Federal Capital Territory (FCT).

6. Supply Chain Analysis

A supply chain management analysis was completed for each of three focus countries. Supply chains were evaluated along the following 12 supply chain areas: 1) coordination, 2) registration, 3) quantification and forecasting, 4) procurement, 5) customs clearance/taxes, 6) warehousing, 7) distribution and resupply, 8) transport, 9) data management/information systems, 10) quality control and quality assurance, 11) financing, and 12) human resource capacity. Challenges were drawn from the three countries and summarized throughout the report; the full supply chain analysis can be found in Annex G.

7. Country Quantitative Data Assessment

In addition to qualitative data sources, a secondary analysis of available quantitative surveillance data was conducted on the availability, use, and impact of injectable artesunate in each of the three focus countries. Data were extracted from the country HMIS and LMIS systems for 2012 to 2018 (if available). All HMIS data was reported on periodic (weekly or monthly) summary forms by each facility. Only aggregate data were reported, such as the number of severe cases seen in the month, the number of severe malaria deaths, and the number of injectable artesunate units consumed. The estimates of injectable artesunate use and case fatality rate are therefore indirect estimates, best interpreted as ratios rather than true proportions or rates.

In **DRC**, individual facility monthly summary reports of service delivery (number of severe malaria cases and number of deaths) and logistics data (injectable artesunate and quinine stock balances and consumption) were extracted from the national DHIS2 for 2015-2018.

In **Uganda**, individual facility monthly and weekly summary reports of injectable artesunate weekly stock balance for 2015-2018 and the monthly number of inpatient malaria cases and number deaths from 2012-2018, were extracted from the national HMIS. Injectable artesunate consumption data was not available in Uganda.

In **Nigeria**, data was extracted from two systems: the HMIS for service delivery data (monthly facility reported the number of severe malaria cases and deaths) with data available for 2012-2018 and the LMIS for logistics data (stock on hand, number of days stocked out, and consumption), with only 2018 data available; however, we were not able to match the facilities between the two systems and therefore could not use the LMIS data in the analysis.

Data were cleaned and aggregated for each of the countries, as described in more detail in Annex C. In DRC and Uganda, availability was defined as the percent of higher-level facilities at a given month (Uganda – HC III, HC IV, hospitals; DRC – CSR, hospitals) where injectable artesunate was reported as in stock or used in the weekly or monthly HMIS report. The availability of injectable artesunate (and

quinine in DRC) was stratified by facility type and years. In DRC (the only country with consumption data available), we looked at the ratio of the number of units of injectable artesunate administered to the number of severe cases.

The impact of injectable artesunate was assessed by examining the ratio of reported severe malaria deaths to reported severe malaria cases – a proxy for the case fatality rate over time – and evaluating differences in this ratio between facilities with and without injectable artesunate available. Regression models were used to assess whether the availability of injectable artesunate or quinine was statistically associated with the case fatality rate observed at the facility level. Additional details of this analysis are described in Annex C.

Table 1 lays out the facility-level data elements extracted for the analysis from each country:

Indicator	DRC	Nigeria	Uganda
Availability	Inj. Art. stock on hand Quinine stock on hand (DRC HMIS, monthly, 2015-2018)	n/a	Inj. Art. stock balance (Uganda HMIS, weekly, 2015-2018)
Use	Inj. Art. consumption Quinine consumption (DRC HMIS, monthly, 2015-2018)	n/a	n/a
Impact	# of cases (>/< 5 yrs.) # treated (>/< 5 yrs.) # deaths (>/< 5 yrs.) (DRC HMIS, monthly, 2015-2018)	# of cases (< 5 yrs.) # deaths (< 5 yrs.) (Nigeria HMIS, monthly, 2012-2018)	# of cases (>/< 5 yrs.) # deaths (>/< 5 yrs.) (Uganda HMIS, monthly, 2012-2018)

III. Assessment findings

The following section describes the findings from the review of the national severe malaria guidelines in Africa and Asia (3.1); the injectable artesunate procurement analysis (3.2); and countries' experiences with injectable artesunate, according to its introduction, availability, and use (3.3).

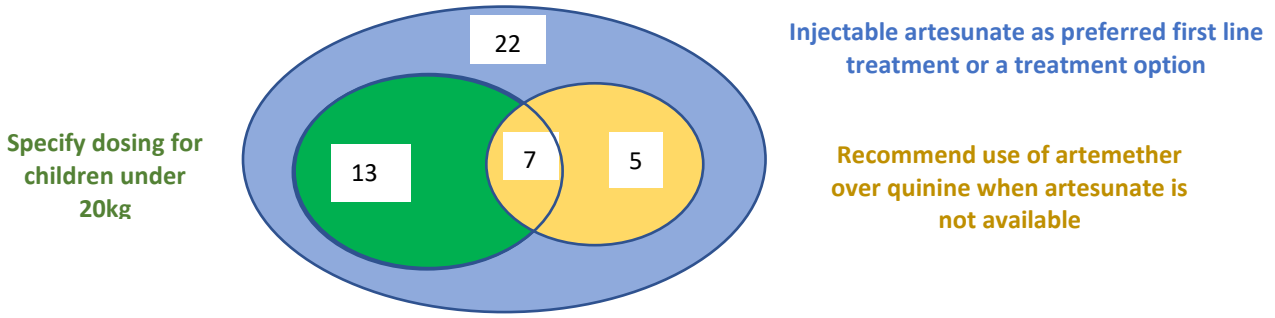
1. Injectable Artesunate in National Malaria Guidelines

Of 51 countries in Africa and Asia with available guidelines,[31] 80% or 41 countries list injectable artesunate as the preferred first-line treatment for severe malaria. Of the 10 countries that do not list injectable artesunate as the preferred first-line treatment for severe malaria, six include it as a treatment option. In these six countries, quinine, injectable artesunate, and artemether are all listed as treatment options without a clear preference for injectable artesunate as the preferred first line treatment. In the 47 countries where injectable artesunate is the preferred first-line treatment or listed as a treatment option, only 20 specify dosing for children under 20kg, as recommended by WHO.

[31] Donors procured injectable artesunate for an additional 13 countries, for which guidelines were not available but injectable artesunate is very likely the preferred treatment in these countries: Afghanistan, Burundi, Djibouti, Guinea-Bissau, Eretria, Haiti, Iran, Kyrgyzstan, Niger, Philippians, Solomon Islands, Suriname, and Yemen.

Furthermore, only 12 countries specify a preference for artemether over quinine as a second line treatment for severe malaria.

Thirty-three countries prefer quinine or do not clarify between artemether or quinine as the preferred alternative to injectable artesunate. Hence, of the 51 countries, only 14% or seven countries have adopted the WHO's 2015 guidelines for artesunate on all three key points: 1) listing injectable artesunate as a preferred treatment, 2) including specifications for dosing for children under 20kg, and 3) recommending use of artemether over quinine when artesunate is not available. A review of the 2018 World Malaria Report identified nine additional countries with injectable artesunate as a preferred first-line treatment, however, the report did not provide details on alternative treatments or dosing for children under 20kg and so these countries could not be included in the guideline analysis. See the diagram below for a summary.[32]



The three focus countries DRC, Uganda, and Nigeria comply with WHO guidelines to various degrees:

Uganda revised its national malaria policy and its Integrated Malaria Manual to recommend injectable artesunate as a first line treatment for severe malaria in 2013. The guidelines specify dosing specifications for children under 20kg but recommend both artemether and quinine as alternative treatments to injectable artesunate, without a clear preference for artemether.

DRC updated its malaria treatment guidelines to include injectable artesunate as the preferred treatment in 2012. In 2016, DRC revised its guidance to include dosing specifications for children under 20kg and other artemisinin derivates as alternatives to artesunate, aligning its guidance with WHO on all three key elements. However, the 2016 guidelines were never fully disseminated due to lack of resources and most providers continue to use the 2012 version.[33] The National Malaria Control Program (PNLP) plans to revise and disseminate the guidelines in 2019.

Nigeria updated its national malaria guidelines in 2012. The Nigeria guidelines align with the WHO guidelines recommending artesunate as a preferred treatment as well as the dosing specifications for children under 20kg. However, the guidance mentions both artemether and quinine as treatment alternatives without a clear preference for artemether.

Furthermore, despite alignment with WHO, adherence to treatment guidelines remain a challenge. While many patients receive injectable artesunate (although misuse is common) there is a low level of compliance to WHO guidelines on ACT use post injectable artesunate treatment, which may generate resistance and allow for continued parasite survival within the patient. A study in **Uganda** found that while the majority of patients received three doses of artesunate, only 4.8% of patients received co-

[32] Among the 47 countries that recommend injectable artesunate as a preferred first line treatment, one country does not specify the dosing recommendations for children under 20kg nor recommend artemether as an alternative treatment.
[33] Interview with PNLP Prise en charge department.

prescription of an oral ACT.[34] In **DRC**, a 2017 survey found that of patients who received injectable artesunate only 11.8% were subsequently treated with an ACT.[35]

Preliminary results from the CARAMAL baseline assessment found similar results. Patients still had high rates of slide positivity at the 28-day survey: 50% in DRC, 38% in Nigeria, and 65% in Uganda. Reason for this are not certain but likely due to a lack of knowledge and negligence on the part of the provider and stock outs of ACTs. Regular training and supervision would likely improve the situation.[36]

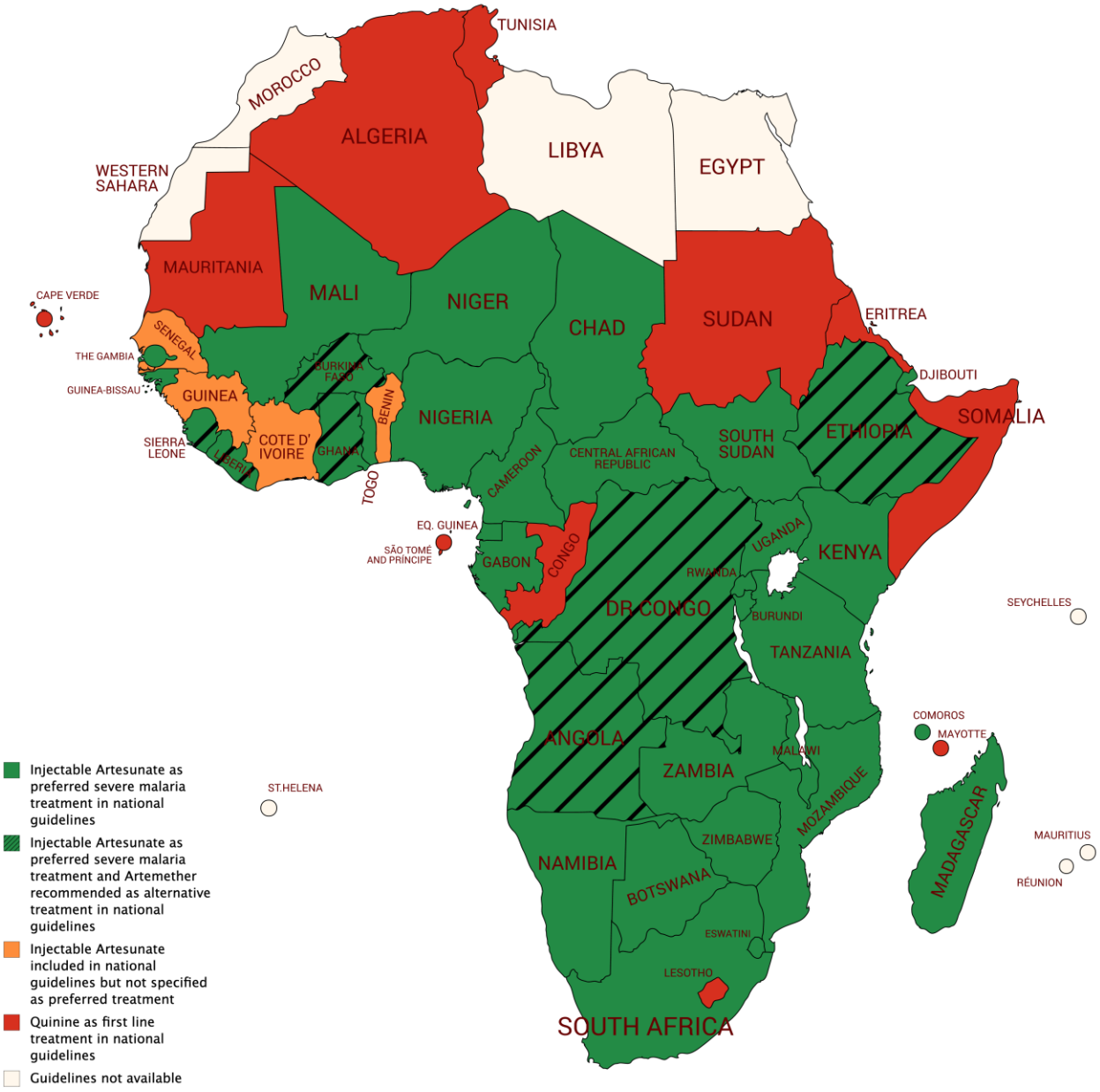
Annex D provides a summary of the guidelines by country. Maps 1 and 2 show the countries in Africa and Asia which include injectable artesunate in their national malaria guidelines.

[34] Ampadu, Hilda H. et al. Prescribing patterns and compliance with World Health Organization recommendations for the management of severe malaria: a modified cohort event monitoring study in public health facilities in Ghana and Uganda. Malaria Journal (2019) 18:36.

[35] USAID, The Global Fund, Sanru, PNLP, PMI. Democratic Republic of the Congo EUV Report October 2017.

[36] Interview with Swiss TPH Basel

Map 1: Injectable artesunate guideline adoption in Africa



Map 2: Injectable artesunate guideline adoption in Asia

2. Supply and Procurement

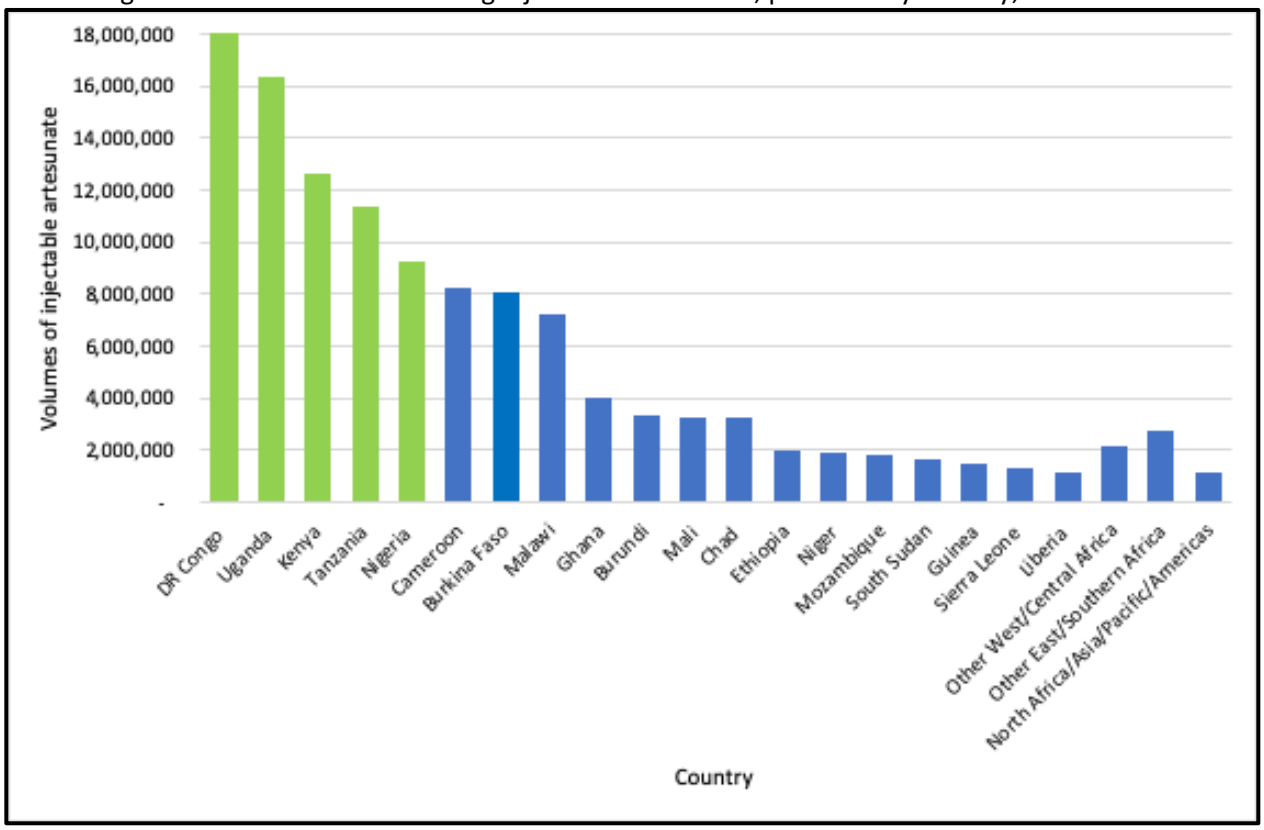
There are currently two WHO pre-qualified suppliers of injectable artesunate: Guilin and IPCA. Guilin received WHO pre-qualification in 2011 and produces injectable artesunate in 30mg, 60mg, and 120mg formulations under the brand name Artesun. The 60mg formulation is the most commonly procured strength by donors and governments, with only the Global Fund procuring 30mg or 120mg vials. IPCA received WHO pre-qualification in December 2018 and only produces a 60mg vial product, under the brand name Larinate.

Up until 2018, Guilin had a monopoly as the sole WHO pre-qualified injectable artesunate supplier in the market. The Global Fund, PMI, and UNICEF have been the largest purchasers of injectable artesunate to date. The Global Fund started to procure Guilin manufactured injectable artesunate in 2010 and has supplied 45 countries since then. PMI has procured Guilin manufactured injectable artesunate since 2012 and has provided the product to 26 countries. UNICEF began to procure Guilin injectable artesunate in 2006 and has supplied 54 countries.

Volume

In total, almost 124 million vials of injectable artesunate were procured between 2006 and 2019 by the Global Fund, PMI, and UNICEF. Most of these, 98% or close to 123 million of these vials were the 60mg-artesunate variety. Five countries received 55% of these injectable artesunate vials: DRC, Uganda, Kenya, Tanzania, and Nigeria (represented in green in Figure 1, below). Figure 1, below, shows total volumes by country.

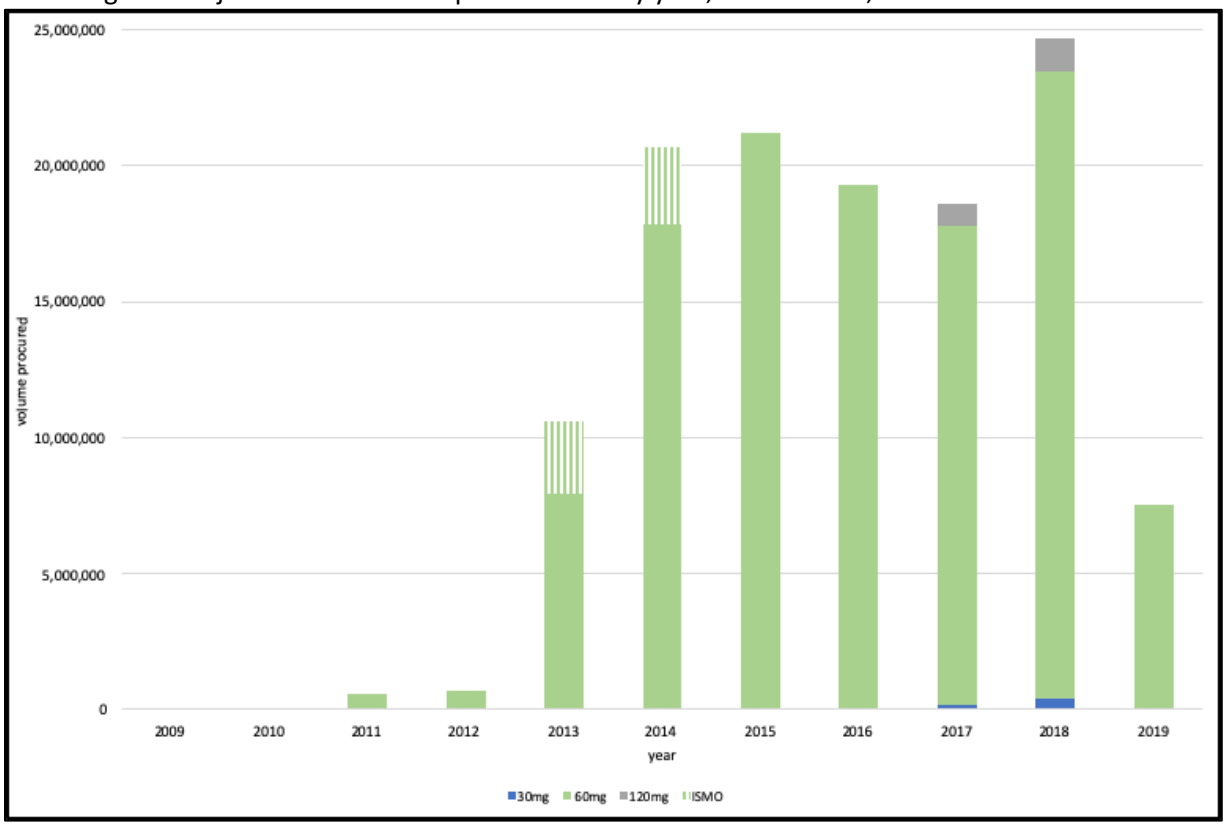
Figure 1: Volumes of Guilin 60mg injectable artesunate, procured by country, 2006-2019



Procurement volumes of injectable artesunate have generally increased from 2009-2018, with the exception of a slight decrease in 2016-2017, and an average year over year growth rate of 73% over 2011-2018 period. Procurement funded through the ISMO project totaled 2.7M in 2014 (15% of all procurement) and 2.8M in 2015 (13% of all procurement).[37] Figure 2 shows total volume by year. Please note that 2019 volumes include Global Fund orders delivered only until February 2019 and PMI orders planned to be delivered until November 2019. UNICEF data was not available for 2017-2019.

[37] ISMO 2016 Semi-Annual M&E Report

Figure 2: Injectable artesunate procurement by year, 2009-2019[38], all Guilin formulations



Price

The weighted average price for injectable artesunate 60mg procured by Global Fund and PMI between 2011-2018 was $1.53[39]. Injectable artesunate was at its highest weighted average price between Global Fund and PMI just prior to the ISMO project in 2013 at $1.76/vial. The ISMO project negotiated a price of $1.42 for volumes procured under the project.

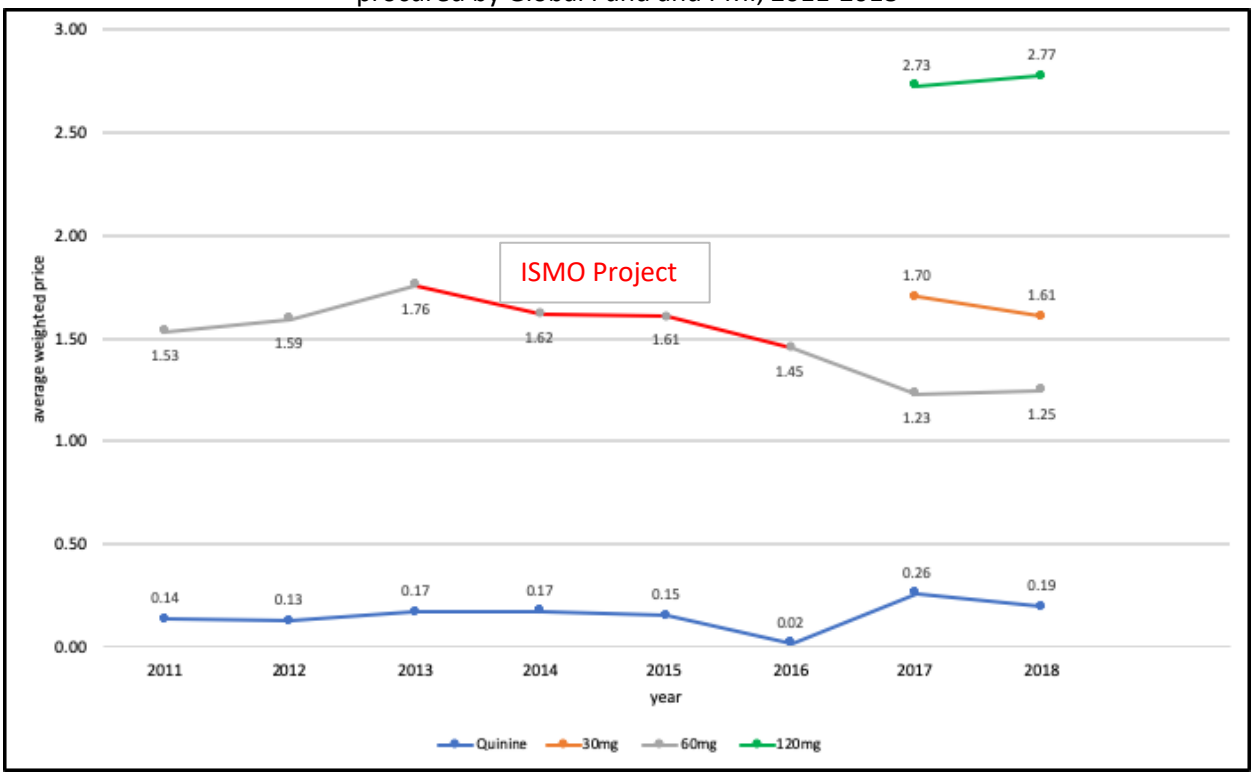
Pricing of the 30mg (average price of $1.63 per vial) is similar to price 60 mg procured by the Global Fund and PMI, likely due to the small order quantities for this particular strength. As expected, the 120mg is more expensive (average price of $2.76 per vial). Quinine remains far less expensive than injectable artesunate at an average of $0.15/vial.

Figure 3 shows the average weighted price of Guilin injectable artesunate 30mg, 60g, 120mg vials and quinine procured by the Global Fund and PMI between 2011-2018. While, quinine is significantly less expensive compared to injectable artesunate, more units are required to treat severe malaria with quinine, so the total treatment cost difference is smaller than the per vial cost difference. No procurement of IPCA's product was included in the procurement data recorded by PMI, Global Fund's PQR, or WHO's GPRM.

[38] 2019 volumes include Global Fund orders delivered only until February 2019 and PMI orders planned to be delivered until November 2019. Unicef data was not available for 2017-2019

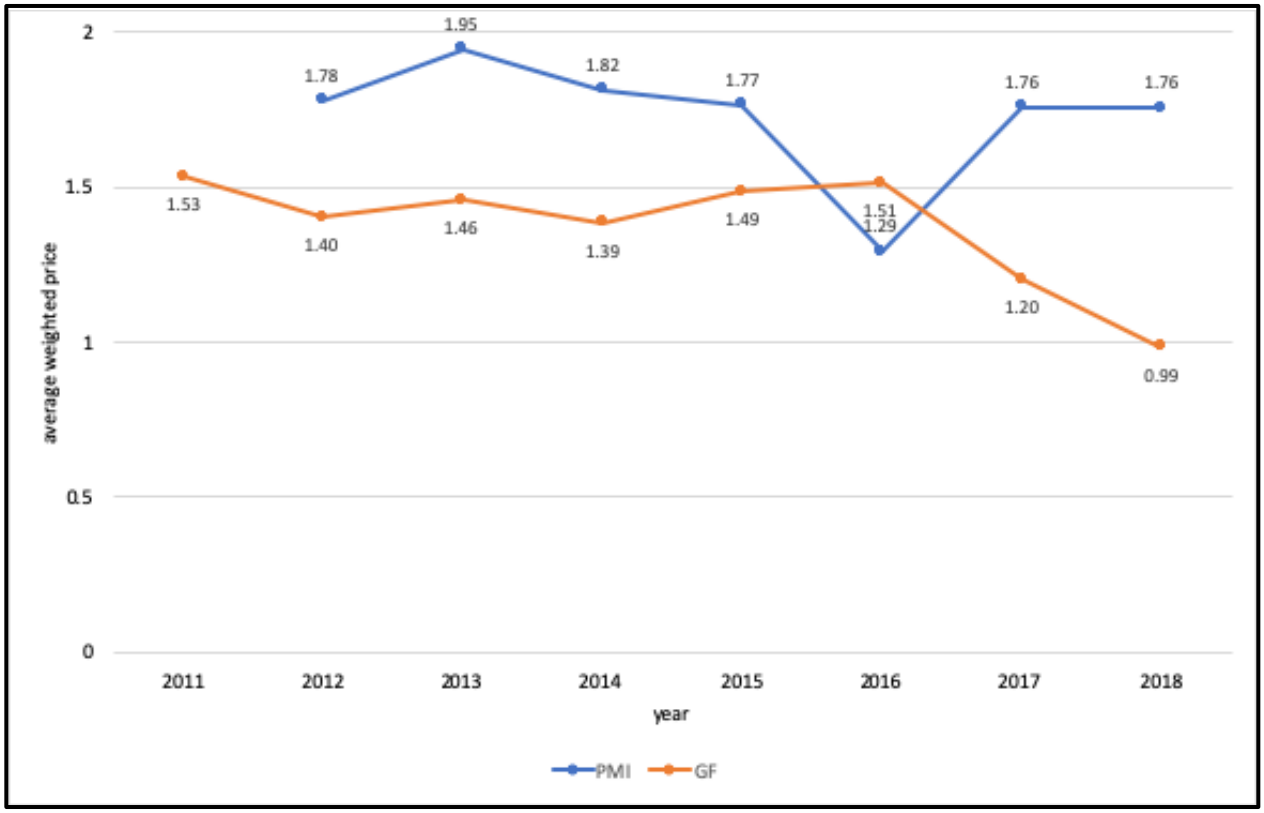
[39] UNICEF pricing data was excluded due to data quality issues. The GPRM data suggests that UNICEF pays a lower price for injectable artesunate (average at $0.69 per vial) but this is driven by many very low price points (i.e., $0.1) that may not reflect the actual price paid, but rather data entry erors

Figure 3: Weighed average price of Guilin injectable artesunate 30mg, 60g, 120mg vials and quinine vials procured by Global Fund and PMI, 2011-2018



In comparing pricing from the Global Fund and PMI, Global Fund has on average paid less for injectable artesunate than PMI (an average of 36% per year less over the 2012-2018 period), except in 2016. Some of this difference may be explained by order sizes. Between 2014-2018, Global Fund had an average order size of 53% more than PMI per year. Figure 4 shows the average price of injectable artesunate 60mg vial procured by PMI and Global Fund, between 2011-2018.

Figure 4: The weighted average price of Guilin injectable artesunate 60mg procured by PMI and Global Fund, 2011-2018



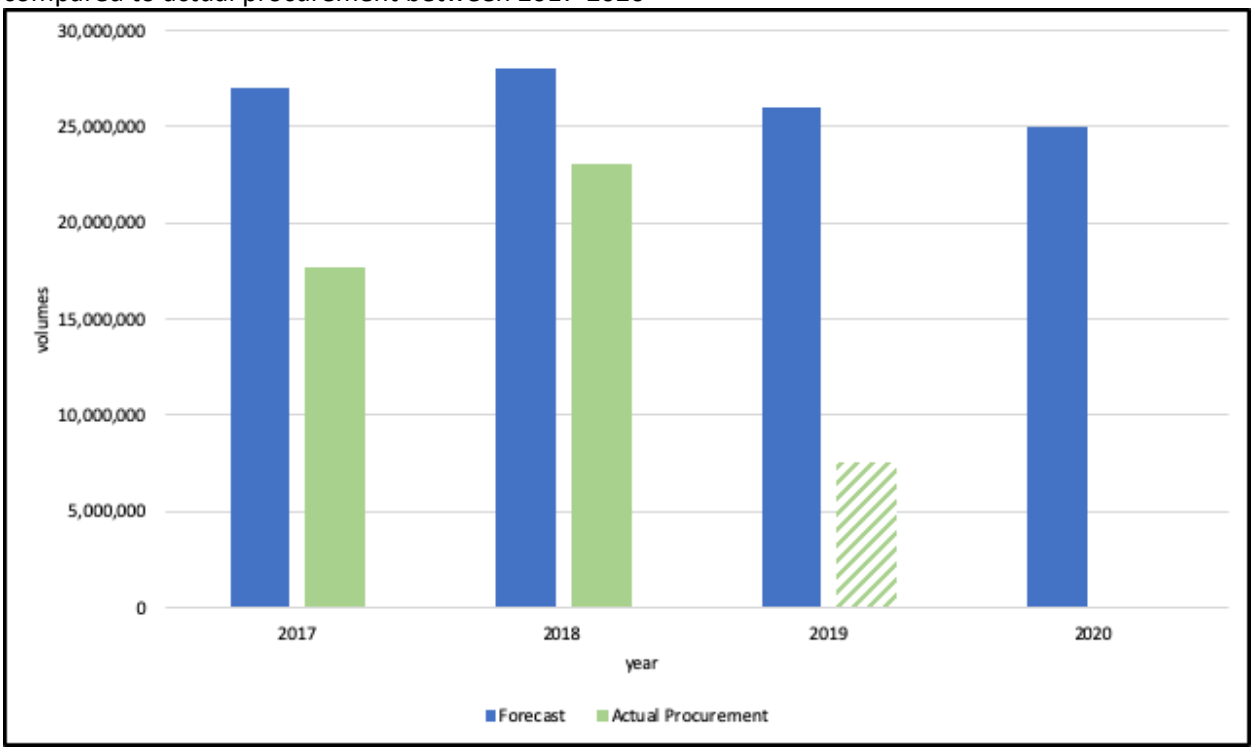
Forecast

Over the last 2 years, injectable artesunate actual procurement has been lower than the forecasted procurement in the 2017-2020 Unitaid global quantification report.[40] The forecasted procurement[41] has been relatively consistent between 2017-2019, but actual procurement has been under 85% of the forecasted needs. Figure 5 shows the global forecast compared to actual procurement 2017-2020.

[40] Forecast Report: Global Malaria Diagnostic and Artemisinin Treatment Commodities Demand Forecast 2017-2020. May 25 2017.

[41] Forecasted projections based on current Global Fund procurement plans from high burden countries and data from PMI and Unitaid.

Figure 5: Global procurement forecast (from the Unitaid global quantification report 2017-2020) compared to actual procurement between 2017-2020



Annex F contains the procurement volumes by country, by year, by donor.

3. Country Experiences with Injectable Artesunate

The following section summarizes our findings from the literature review and the deep dives in the three focus countries structured in the following subsections 1) introduction, 2) availability, 3) use, and 4) impact of injectable artesunate.

a) Injectable Artesunate Introduction

Following the update of the WHO Malaria Guidelines to recommend injectable artesunate for adults and children in 2011, many countries in high endemic areas, including the ISMO project countries, began to update their national guidelines, as explained in section I. However, the update in guidelines or the subsequent availability of donor funding did not necessarily translate into the rapid adoption of the drug. We found four key challenges across countries that hampered or delayed the scale-up of injectable artesunate in country:

1. Poor quantification of injectable artesunate. Due to poor quality data on the number of severe malaria cases in the public sector, early quantification remained very poor. Donors provided technical assistance and quantification tools to support the process but it continued to remain a major challenge. In Nigeria for example, the first Global Fund procurement in 2014/2015 was based on a quantification that used a flat 5% severe malaria rate (i.e. assuming 5% of all malaria cases would progress to severe malaria). Due to the high number of malaria cases, this led to a large procurement and an overstock in the Global Fund-supported states that would have expired if not for the redistribution to other non-Global Fund supported states. In DRC, Sanru's first procurement for the Global Fund provinces was

supposed to last 9 months; it was used within 2 months; however, this may also have been caused by the prescription of injectable artesunate for uncomplicated malaria.[42] Stockouts of injectable artesunate led to continued use of alternative treatments, particularly quinine.

2. Injectable artesunate procurement delays. The initial large injectable artesunate procurement orders funded through the ISMO project were delayed across all six ISMO countries. MMV, commenced price negotiations with Guilin, drawing on their long-term relationship, to obtain a price of $1.45, which according to Unitaid set the bar high for further reductions.[43] Therefore, in an attempt to secure price reductions by leveraging larger volumes, Unitaid, and MMV adopted a pooled procurement approach with the Global Fund.[44] This delayed the introduction in project countries or had them rely on other donors for procurements. The first shipments that were supposed to arrive in Kenya and Nigeria in early 2014 only arrived 7 months later in September and October 2014, respectively. In Uganda, for example, following the initial delay, procurement was pushed back until July 2015 as other donors were able to fill the needs in the interim.[45] Multiple key informants suggested that this initial delay led to some belief among in-country stakeholders that there would be continued supply issues for injectable artesunate. This perceived lack of supply of injectable artesunate in the introduction phase may have meant that providers preferred sticking to quinine or expected to revert to quinine, resulting in continued stocking and use of that drug.[46]

3. Preference of quinine over injectable artesunate. Despite guidelines changes, many countries continued to stock and use quinine. The main reasons found in the literature and in interviews for continued quinine use point to the relatively inexpensive cost of quinine compared to injectable artesunate, consistent supply, and the preference of some providers to continue to use quinine (which may be attributed to a lack of training of these providers, as described in section 3.3). In Kenya for example, even though the national guidelines were updated to include injectable artesunate in 2012, almost half of severe malaria cases were still prescribed quinine in 2014.[47] Médecines Sans Frontières (MSF), an early adopter of injectable artesunate in its projects, experienced similar challenges. By 2012, of the 18 countries in which it had planned to support the introduction of injectable artesunate, it had only been introduced in 11.[48] Some reasons identified for the reluctance for switching from quinine were country-specific. In DRC for example, which updated its guidelines in 2012, injectable artesunate was only introduced in 1/3 of the health zones, after which it was halted due to what was described as a strong quinine lobby by local manufacturers and a reduction of PNLP support for further scale up.

4. Competition from non-WHO PQ injectable artesunate products and alternative treatments that discouraged local procurement and uptake of the Guilin product. Countries such as DRC and Nigeria had strong local markets for quinine or other artemisinin-derived products prior to injectable artesunate introduction. For example, in Nigeria, the injectable artesunate brand Rekmal, manufactured in India, had a significant market share. Artemether and alpha, beta-arteether were also widely used, the latter enabled by aggressive market techniques of its manufacturer, despite the fact that it is not

[42] Interview with Sanru

[43] Cambridge Economic Policy Associates Ltd. Mid-term Project Evaluation of the "Improving Severe Malaria Outcomes" (ISMO) Project, 13 November 2015.

[44] Idem

[45] Idem

[46] Cambridge Economic Policy Associates Ltd. End of Project Evaluation of the "Improving Severe Malaria Outcomes" (ISMO) Project, 1 March 2017.

[47] Amboko et al. Malaria investigation and treatment of children admitted to country hospitals in western Kenya. *Malaria Journal* 2016; 15: 506.

[48] De Smet, Martin. The Implementation of injectable artesunate: the experience of MSF. RBM Case Management Working Group, Geneva 2012, presentation.

recommended in Nigeria's national malaria guidelines.[49] In DRC, there was strong resistance to injectable artesunate introduction from local quinine manufacturers, who were concerned that injectable artesunate would reduce their market share; one interviewee said it was "a fight to the death with them."[50] This may be partially because IV quinine is also used to treat uncomplicated malaria.

The ISMO project attempted to address these challenges and was notably successful in the following ways:

- **Accelerated revision of severe malaria policy guidelines; design and roll out of high-quality training tools.** By December 2013, all ISMO project countries (Cameroon, Ethiopia, Kenya, Malawi, Nigeria, and Uganda) had revised severe malaria treatment policy and guidelines together with revised training programs that were ready to be rolled out.[51] The subsequent healthcare provider trainings surpassed the planned number of providers to be trained under the project: a total of 2,082 health centers were trained across the counties, or 67% above target. The cascade training approach was deemed cost-efficient, reaching a large number of providers with the available budget as well as reaching providers beyond those directly trained through skill transmission within facilities.

- **Regular supply of injectable artesunate.** After the initial procurement delays, stockouts were minimal over the course of the ISMO project. Technical assistance to the NMCPs and the establishment of quantification committees improved national quantification processes. It was found that out of the six ISMO countries, four achieved zero-stockouts at central warehouses over the course of the project: Cameroon, Ethiopia, Malawi, and Uganda.[52] Although stockouts did occur at the facility level (in Nigeria for example), stock generally was available contributing to higher usage rates of injectable artesunate.

b) Injectable Artesunate Availability

Following its introduction, availability of injectable artesunate generally increased but has remained low in some key countries, such as DRC.

A 2018 survey in **Uganda** found the availability of injectable artesunate in facilities to be relatively high at 86% on the day of the visit and 94% in the last 3 months.[53] The CARAMAL Rapid Assessment in 2017 found similar stock availability with 88% of facilities with unexpired artesunate in stock on the day of the visit.[54] These results were similar to the Severe Malaria Case Management Rapid Assessment conducted by MMV which showed 67% and 83% availability in HC III and HC IV facilities.[55] These assessments shows that continued support (during and post ISMO) has led to a significant increase and sustained availability compared to 2013, prior to injectable artesunate introduction, when only 3.8% of public facilities and 7.7% of PNFP facilities stocked injectable artesunate.[56] HMIS (DHIS2) data analysis generally supports

[49] Interview with CHAI Nigeria

[50] Interview with Prise en charge department, DRC

[51] Unitaid Improving Severe Malaria Outcomes Project: Annual Programmatic Report 2013, 19 March 2014.

[52] Cambridge Economic Policy Associates Ltd. End of Project Evaluation of the "Improving Severe Malaria Outcomes" Project, Draft report, 1 March 2017.

[53] PMI End Use Verification Survey, Uganda 2018.

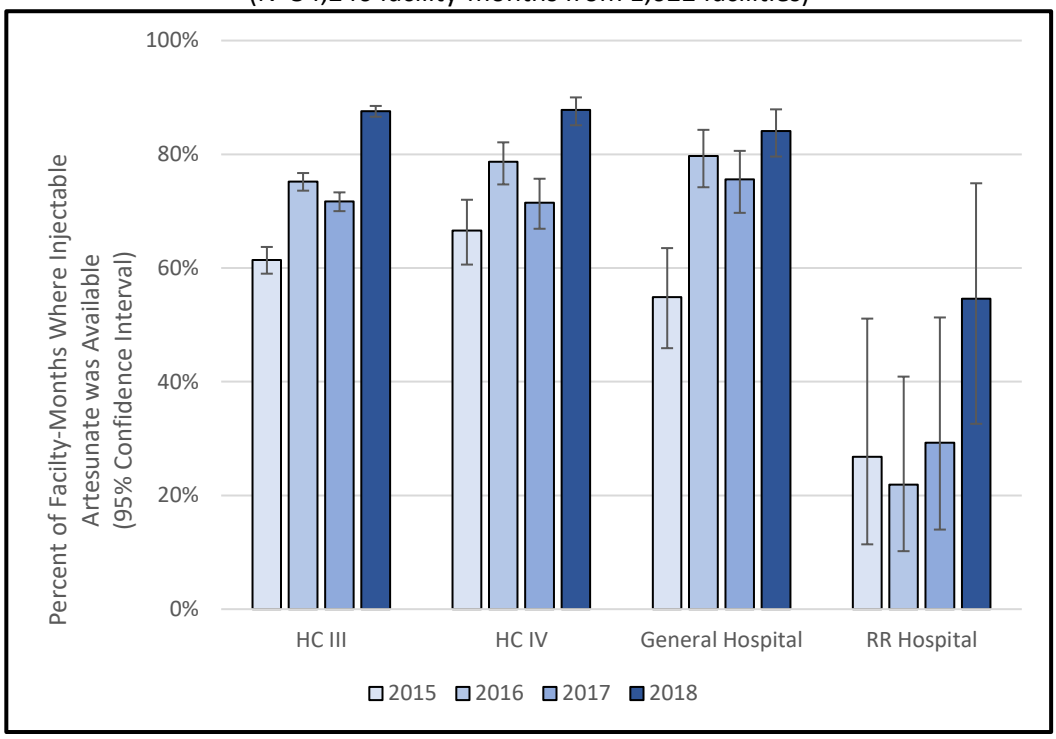
[54] CARAMAL Rapid Assessment, 2017

[55] Republic of Uganda, Makerere University, Development Data, Medicines for Malaria Venture. Severe Malaria Case Management in Uganda: A rapid assessment of management of severe malaria at health centres in Jinja District, Uganda.

[56] ACT Watch 2013, Uganda

these survey findings: injectable artesunate availability improved between 2015 and 2018 across HC IIIs, HC IVs, and General Hospitals (Figure 7).

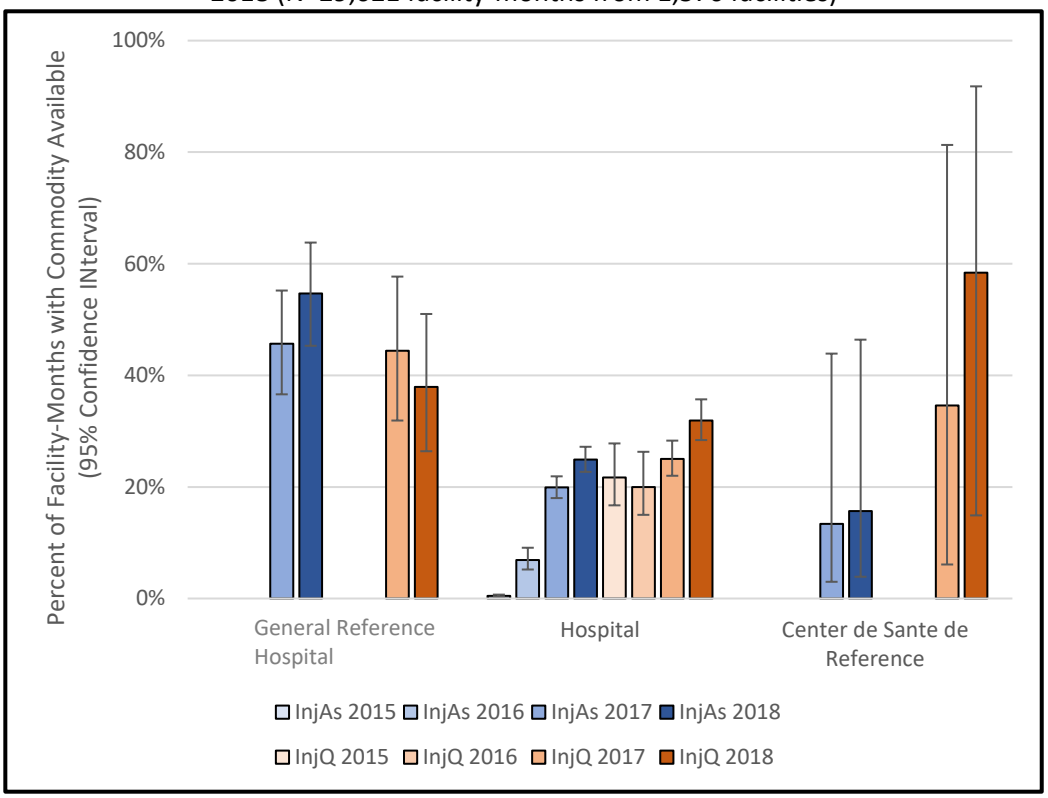
Figure 7: Injectable Artesunate Availability by Facility Type and Year, Uganda HMIS, 2015-2018, (N=54,246 facility-months from 1,622 facilities)



In **DRC**, where injectable artesunate procurement started in 2013, a 2017 survey found that 35.3% of health facilities and 26.3% of warehouses were stocked out of injectable artesunate on the day of the visit while 66.3% of facilities and 64.3% of warehouses were stocked out for more than three days within the last three months.[57] Based on a more recent HMIS (DHIS2) assessment, about 27% of facilities had injectable artesunate available in any given month in 2019, compared to about 33% of facilities that had injectable quinine available (Figure 8).

[57] PMI End Use Verification Survey, November 2017

Figure 8: Injectable Artesunate and Injectable Quinine Availability by Facility Type, DRC HMIS, 2015 – 2018 (N=29,621 facility-months from 1,576 facilities)



The desktop review and interviews found the following key drivers of injectable artesunate availability (or lack thereof):

1. Availability of donor funding. Our findings suggest that in the geographies and periods of support, injectable artesunate availability was generally high, but outside of donor-funded geographies or periods, availability dropped. In Uganda, for example, donors cover the majority of public and private-not-for-profit (PNFP) facilities; PMI provides stock for 650 PNFP and Global Fund covers 3200-4000 public facilities, effectively covering most of the country. Due to this support, stock levels of products stored at the National Medical Store (NMS) and Joint Medical Stores (JMS) are closely monitored. If stock issues arise, Global Fund and PMI coordinate to resolve the situation[58] and this has led to high availability in health facilities across Uganda.

To address any remaining stockouts in **Uganda,** PMI's implementing partners have supported reallocation of stock between facilities within districts that are over/understocked[59] as well as put into place an injectable artesunate patient tracking system to curb irrational use. At one referral hospital, for example, consistently high use rates of injectable artesunate were found, despite the fact that it was not a high malaria endemic area. The hospital, with support from PMI's implementing partners, rolled out an injectable artesunate patient registration/tracking system (for every person who receives the product, the pharmacist records the name and the number of vials received). This accountability and oversight led to a 90% reduction in total consumption from 2000 vials of artesunate to 200 per month.[60]

[58] Interview with PMI Uganda
[59] Interviews with MAPD
[60] Interview with RHITES

A similar situation was found in donor supported states in **Nigeria**. In states supported by Global Fund (13 states) and PMI (11 states) there is a relatively reliable stock of injectable artesunate. However, in states not supported by a partner, such as the Federal Capital Territory, facilities have to purchase artesunate through their Drug Revolving Funds (DRF) or directly from private suppliers that facilities then sell to patients. As a result, facilities keep limited amounts of injectable artesunate in stock due to the limited purchasing power of the population that is often not able to pay for the injectable artesunate.

In **DRC**, donor support has achieved mixed results. PMI and Global Fund pay for the procurement of injectable artesunate but base their order size on the PNLP's quantification for children under five,[61] due to the limited donor resources available to cover needs for all ages. While injectable artesunate is only procured based on the estimated needs of the targeted group, use at facilities is not restricted and so facilities frequently stockout. For example, PMI's procurement should cover the needs of their supported provinces for an entire year but the stock is typically exhausted within six months.[62] Hence, availability data in DRC shows a mixed picture.

2. Poor quantification and forecasting of injectable artesunate: Across Uganda, DRC, and Nigeria, methods to accurately quantify and forecast the need for injectable artesunate have remained weak, leading to massive over or under procurement. Poor data quality and a lack of understanding of the extent of severe malaria has led countries to over and under procure. Quantification processes also do not consider all facilities that may ultimately receive the product, leading to inaccurate quantification.

For example, in **Uganda**, injectable artesunate is only quantified for health center (HC) IVs and hospitals but injectable artesunate also goes to HC IIIs, though it is not systematically available at all HC IIIs and is distributed through the HC IV for the sub-district area. Furthermore, no consumption or treatment data specific to injectable artesunate is collected from facilities and included in DHIS2.

In **DRC** there is a disconnect between actual needs, what is forecasted, and what is procured. Quantification is done through a top-down approach due to a lack of capacity at the health zones and Provincial Departments of Health (DPS). Poor forecast accuracy stems from the diverging opinions on the epidemiological profile of the country and the actual percentage of severe malaria cases. This is in part due to a lack of quality demographic and morbidity data because there has not been a census in over 30 years. While HMIS (DHIS2) has been fully functional since 2017, it is still plagued with poor quality and incomplete data, leading to a lack of confidence on the part of donors, partners, and the government in the data available.

In **Nigeria,** the quantification has a low level of accuracy, leading to over/under procurement; this is because the data that should drive the quantification are not very robust. There are two data systems in Nigeria (DHIS2 and LMIS), which are not yet linked; meaning it is not possible to compare the number of cases or deaths (in DHIS2) with the availability and use of injectable artesunate (in the LMIS). It is difficult to obtain accurate consumption data due to periodic stock outs, poor recording and tracking systems, and insufficient reporting by higher-level facilities, where the bulk of the severe malaria cases are treated.[63] Furthermore, there is a negative incentive for facilities to have robust consumption data. Once a facility has used its donor supplied stock, facilities can procure through the DRF, which provides them with funds for facility running costs from the mark-up, however, this may actually be a negative

[61] PMI will also target ages 6-13 in their supported provinces.

[62] Interview with Chemonics

[63] Interview with CSR Nigeria

incentive for facilities to report lower number consumption figures so they receive less donor stock and are able to procure more stock through the DRF, therefore increasing their revenue.[64]

3. Poor warehousing and storage conditions: Our findings suggest that poor but also limited storage space impacts the availability of injectable artesunate. Insufficient and poor storage conditions at different levels of the supply chain have jeopardized the quality of injectable artesunate and in turn affected availability. Donors limit the volume of stock stored at central or sub-national level warehouses due to limited space or to keep warehousing costs low, which can lead to stock-outs at facility level. In addition, poor storage conditions at facilities may render products unusable, negatively affecting the availability of effective injectable artesunate.

At the NMS in **Uganda** for example, limited storage space restricts stocks stored at the national level to a volume of only 4-8 months of stock. In turn, lower level facilities have poorer quality storage conditions. A 2018 survey found that only 53% of HC IIs had acceptable storage conditions, while 65% of HC IIIs, 82% of HC IVs, and 100% of hospitals, had sufficient storage conditions.[65] At the facility level, sufficient storage is available but stocks are not always well kept. Of 75 facilities surveyed in 2018, 92% had a stock card for injectable artesunate, but only 51% had it up to date.[66]

Similar issues were found in **DRC**. Reports and interviews found that the quality of storage at regional distribution centers (CDRs), health zones, and facilities varies widely. A 2016 survey found that only 2/3 of depots and hospitals and 35% of health centers had acceptable storage conditions.[67] At the same time, as in Uganda, partners often try to limit the amount of stock they store at central/provincial level storage facilities (i.e., CDRs) to avoid storage costs.

In **Nigeria**, at the national warehouses in Abuja and Lagos, Chemonics (who manages stock for PMI and Global Fund) pays for pallet space for periods, so they try to stagger shipment to use limited pallet space. Although there should be 6-10 months of supply at central level, stock levels are normally kept at no more than six months, with more frequent shipments occurring in an effort to keep warehousing costs down. The six zonal warehouses across the country have been established as a public-private partnership (PPP) and therefore it is often difficult for the government to use these facilities, as they have limited ability to pay for storage. This means that commodities procured with state funds or through the DRF are often kept in poor conditions at state warehouses, risking their quality and possibly rendering them unusable.

4. Product rationing: In the three focus countries inefficient distribution processes, such as delayed resupply, incorrectly filled orders, or improper stock holdings (i.e., under or over stocked), also contribute to stock availability issues.

In **Uganda**, a 2018 survey found that while about half of facilities (53%) received the quantities of commodities as ordered, 34% received less, and 13% received more than ordered. Across these commodities, the most undersupplied commodity was injectable artesunate: almost half (49%) of facilities received less than ordered.[68] This is likely due to injectable artesunate being a rationed product in Uganda. NMCP and the NMS cap the amount of injectable artesunate a facility receives based on the

[64] Interview with Unicef

[65] PMI End Use Verification Survey, Uganda, November 2018.

[66] PMI End Use Verification Survey, Uganda, November 2018.

[67] Rapport de l'enquête pour la vérification de l'utilisation final des médicaments et commodités de lutte contre le paludisme dans la République Démocratique du Congo réalisée en mars 2016.

[68] PMI End Use Verification Survey Uganda, November 2018.

facility's reported case data. This practice supposedly helps facilities order the correct amounts and to curb misuse of injectable artesunate. However, since consumption data is not collected from facilities, capping the distribution can also lead to stockouts and patients purchasing stock from the private sector and pharmacies.

In **DRC**, stock issues are more related to delays in ordering processes, with facilities not always receiving the amount requested. This, in turn, is caused by varying stock levels at the CDRs; much like in Uganda, injectable artesunate is often rationed to health zones and facilities. The lack of sound methods to predict accurate demand of the drug and its misuse in uncomplicated cases also contributes to the lack of availability.

In **Nigeria**, injectable artesunate distribution in Global Fund-supported provinces is rationed by Management Sciences for Health (MSH), the Global Fund Secondary Recipient (SR). For large facilities, the allocation is not always sufficient, while other facilities may receive too much stock. In an effort to make data available from secondary facilities (where severe malaria can be treated) to better inform distribution, the LGA M&E Officer physically goes to the facility to collect the information so it can be entered into DHIS2.

5. Continued widespread availability of quinine: Even though injectable artesunate was introduced several years ago, quinine is still widely available in some countries. This is because quinine is manufactured locally, is purchased by facilities, and is a revenue-generating product for facilities. In Nigeria and DRC, public facilities will charge for severe malaria care (excluding donor-funded drugs) so there is an incentive for providers to buy, stock, and administer quinine instead of injectable artesunate.

A survey in 2015 in **DRC** found that in the ex-Katanga province injectable artesunate was available in 14.3% of public facilities stocking antimalarials while IV quinine was available in 56.5% of facilities; similar percentages were seen in Kinshasa with artesunate available in 18.2% while IV quinine was available in 46.1%.[69] Three years later, DRC continued to have a higher availability of quinine: a 2018 study on severe malaria case management, commissioned by MMV in collaboration with the PNLP and the Ecole de Santé Publique de Kinshasa, found that quinine was twice as available at reference facilities (80%) compared to injectable artesunate and artemether (both 40%).[70] Injectable artesunate also had higher rates of stockouts at 40% of reference facilities while quinine was only stocked out at 20%.[71] In Nigeria, the ACTWatch survey in 2015 also showed a higher availability of quinine over artesunate, (quinine at 5.1% of public health facilities and 25.8% of Private for Profit (PFP); artesunate at 1.1% of public health facilities, 1.9% of PFP).[72]

6. High out of pocket costs for patients purchasing injectable artesunate when facilities are stocked out or non-donor supported: Across all three focus countries, the cost of injectable artesunate is pushed to the patient when a facility is stocked out or does not receive donor commodities. In **Uganda**, if a facility is stocked out, the patient will have to buy injectable artesunate from private pharmacies, which are not sold at set regulated prices (one interviewee estimated about 30,000 Uganda Shillings (~$7.94) per dose).[73] For facilities in non-donor supported states in **Nigeria**, making injectable artesunate available for patients is a major problem. Facilities can procure injectable artesunate through the DRF or wholesalers but the population cannot always afford the cost, so facilities are reluctant to

[69] ACT Watch 2015, DRC

[70] Évaluation de la prise en charge des cas de paludisme grave en RDC: rapport préliminaire de l'étude

[71] Évaluation de la prise en charge des cas de paludisme grave en RDC: rapport préliminaire de l'étude

[72] ACT Watch 2015, Nigeria

[73] Interview with MAPD

procure too much. A hospital visited in Kano, for example, will buy a 60mg vial of injectable artesunate for 600 Naira ($1.67) and then sell to patients at 775 Naira ($2.15) (@359.5 Naira/dollar). Patients may buy from pharmacies and drug shops to find a less expensive product and bring it to the facility for administration, but the cheaper products are of unknown quality and efficacy. In **DRC**, when facilities are stocked out of donor commodities, they will procure injectable artesunate from wholesale suppliers and distributors, who offer a variety of brands, including Guilin and manufacturers with Indian government Good Manufacturing Practices (GMP) certification. These wholesalers sell to all types of structures, depots, clinics, pharmacies, and NGOs. From these suppliers a 30mg vial of Artesun costs around $1.10, 60mg $1.60, and 120mg $2.50.[74]

c) Injectable Artesunate Use

Following its introduction, use of injectable artesunate to treat severe malaria has generally increased, yet significant issues still plague the use of the product. The following drivers of misuse were found during the desktop review and interviews:

1. Use of injectable artesunate in cases of uncomplicated malaria. A widespread and consistent occurrence of injectable artesunate misuse is reported across countries, though its extent varies. Both across ISMO and non-ISMO countries, reports of misuse of injectable artesunate for uncomplicated malaria have continued to surface since its introduction. This excessive use of injectable artesunate for non-severe cases drives up consumption leading to stockouts, complicates patient treatment, and increases the cost of treatment for simple cases.[75]

While there were some reports of misuse during the ISMO project in Kenya and Uganda,[76] it seemed to be more of an issue in non-project countries. Studies in Kenya and Ghana found that injectable artesunate and other injectable antimalarials were used for 16% and 35% uncomplicated malaria cases, respectively.[77,78] Another study estimating severe malaria admissions rates, cases, and deaths across 41 countries found that in African countries, most patients admitted for in-patient treatment would not be classified as having severe disease.[79] The literature review and interviews found different reasons for the preferred use of injectable artesunate over ACTs for uncomplicated malaria:

Often, providers and patients perceive that injectables are superior and more effective drugs.[80] For example, a study in Kenya found that providers and patients believe injectables are more effective than oral drugs. This was also mentioned in interviews during the in-country visits in Uganda and DRC. Providers, especially those on the private sector, may also prefer injections because of higher prices (and mark ups) of injections over oral medication.[81] Interviewees also suggested that patients will exaggerate malaria symptoms to have injectable artesunate prescribed instead of oral treatment

[74] Interview with Alisons SARL

[75] Zurovac, Dejan et al. Monitoring health systems readiness and inpatient malaria case-management at Kenyan county hospitals. Malaria Journal (201) 17:213.

[76] Cambridge Economic Policy Associates Ltd. Mid-term Evaluation of the "Improving Severe Malaria Outcomes" (ISMO) Project, 13 November 2015.

[77] Zurovac, Dejan et al. Monitoring health systems readiness and inpatient malaria case-management at Kenyan county hospitals. Malaria Journal (201) 17:213.

[78] Afriyie, Daniel Kwame et al. Prescribing trend of antimalaria drugs at the Ghana Police Hospital. The Journal of Infection in Developing Countries, 2015 9(4):409-415.

[79] Noubiap, Jean Jacque N. Shifting from quinine to artesunate as first-line treatment of severe malaria in children and adults: saving more lives. Journal of Infection and Public Health. (2014) 7, 407-412.

[80] Interviews with Prise en charge department and Sanru

[81] Interview with Prise en charge department, DRC

because they see it as a "good" drug; some even mentioned that when healthcare workers fall sick with uncomplicated malaria, they will prescribe themselves injectable artesunate. Finally, what seems common is that patients are also provided injections if oral medications cannot be taken (i.e, because of vomiting), which does not necessarily mean these patients had severe malaria.

In **DRC**, it is perceived that **the system will absorb as much injectable artesunate as the donors put in and so there is a focus to rationalize the use of injectable artesunate.**[82] Donors do not want to encourage further overuse of the product by procuring large quantities, which could lead to a reliance on monotherapies, generating resistance.[83] If the product was rationally used, the overall needs would likely be closer to the amounts currently procured (amount for only children under five) and donors would be more able to cover all needs.[84] In the Global Fund provinces, Sanru, the Primary Recipient (PR), has tried to limit distribution to three reference facilities within each health zone who are authorized to treat severe malaria and closely follow-up on use by linking the number of cases and use of the drug; however, irrational use continues.[85]

In Nigeria, artemether is often used to treat severe malaria. While Nigeria has less irrational use of injectable artesunate than the other focus countries, there is widespread availability and use of artemether for malaria treatment. IM artemether is used more often for uncomplicated malaria than injectable artesunate due to the cost and injectable artesunate's perception as a gold standard treatment. Artemether is often used to treat less severe cases that can be treated as outpatient or when a hospital's inpatient ward is at maximum capacity.

2. Continued preference for quinine: Despite the improved availability of injectable artesunate, quinine is still widely used in some countries and in some cases, there is a preference for quinine, even when injectable artesunate and artemether are available,[86] despite ample evidence that injectable artesunate is more effective and easier to administer. Furthermore, because the WHO guidelines recommend quinine for the treatment of uncomplicated malaria in pregnant women during the first trimester, facilities still have a reason to keep the product in stock. Several studies in DRC exhibit the continued high use of quinine to treat severe malaria, which is mainly due to political and financial motivations. An October 2017 survey in DRC found that while 13.4% of severe malaria cases received injectable artesunate, 19.3% were treated with quinine.[87] Studies in a set of hospitals in Kinshasa found between 89.7% and 99.2% of severe malaria cases were treated with quinine.[88,89] A recent case management study in DRC found that 68.9% of severe malaria cases were treated with quinine perfusion and 11.8% with injectable artesunate and that some providers at the primary healthcare level were treating severe malaria with a quinine perfusion, not referring patients.[90] HMIS data analyzed from DRC, Figure 9, shows that injectable quinine continues to be used – even when injectable artesunate is available and specifically among facilities where both are available.

[82] Interview with DRC GF malaria team

[83] Interview with Global Fund DRC malaria team

[84] Interview with DRC GF malaria team

[85] Interview with Sanru

[86] Feedback à la synthèse missions 2017.

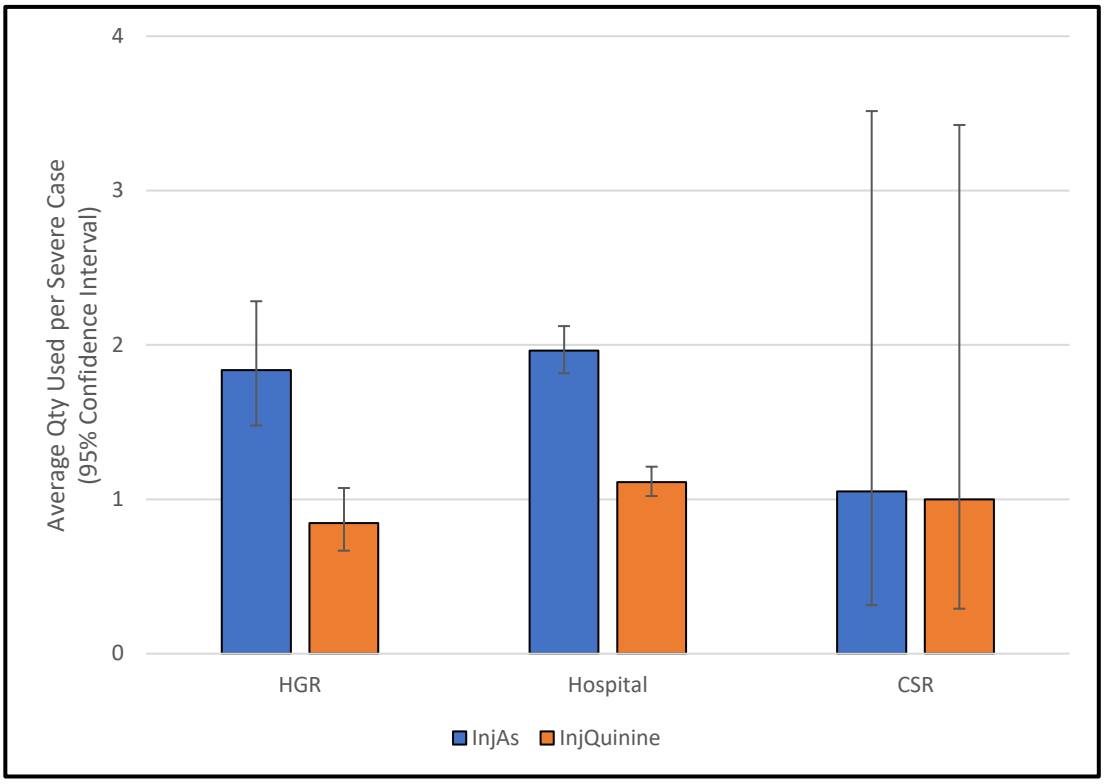
[87] PMI DRC End Use Verification Report, October 2017.

[88] Mandoko. Connaissances, Attitudes et Pratiques des prestataires de soins sur la lutte antipaludique dans la ville-province de Kinshasa/République Démocratique du Congo. Abstract, Journée Scientifique du Paludisme, 2016.

[89] Umesumbu, Solange. Severe malaria mortality and case management in 3 general reference hospitals in Kinshasa. Abstract, Journée Scientifique du Paludisme, 2016.

[90] Ecole de Santé Publique de Kinshasa. Évaluation de la prise en charge des cas de paludisme grave en RDC: rapport préliminaire de l'étude.

Figure 9: Average ratio of units used per severe case, by facility type, among facilities with both injectable artesunate and injectable quinine available, DRC, 2017-2018, (N=7,317 facility-months from 979 facilities)



3. Insufficient training and lack of regular supervision. Insufficient training and poor-quality supervision are persistent in the focus countries and have led to continued misuse of injectable artesunate.[91] Across Uganda, DRC, and Nigeria, training and supervision are fully dependent on Global Fund and PMI funded implementing partner support. Reports show several challenges in administering injectable artesunate. For example, providers have had challenges with the reconstitution of injectable artesunate and were not always at ease with the process. Practical sessions built into the training during the ISMO project, which successfully ensured that providers could gain competency in the preparation of the drug, generated confidence using the product. In general, injectable artesunate is much easier to use than quinine, but this may have resulted in a perverse effect on its perceived efficacy – that providers and patients believe that the longer perfusion is more effective.

A 2016 survey in **DRC** found that only 37% of providers were trained on the recent national malaria guidelines and 69% had received one supervision on malaria prevention and case management in the last 6 months;[92] while the 2017 survey found only a slight increase to 42% trained on PNLP guidelines and 79.5% supervised.[93] Similar challenges have been found in **Uganda** with 45% of providers trained in malaria case management by 2018 and 67% of facilities receiving supervision for malaria case management in the last 6 months; this is an increase however from 36% of providers trained in 2010.[94]

[91] DRC MOP 2019
[92] Rapport de l'enquête pour la vérification de l'utilisation final des médicaments et commodités de lutte contre le paludisme dans la république démocratique du Congo réalisée en mars 2016.
[93] DRC PMI End Use Verification Survey, October 2017.
[94] Uganda PMI End Use Verification Survey, November 2018.

4. A lack of financing for the health system. Insufficient health system financing encourages providers to prioritize services and treatments for which they can charge.[95] In some countries, consultations and hospitalization for severe malaria and treatment with quinine provide opportunities for providers to charge for services. In **DRC**, providers are not always paid by the government, and with limited resources available at facilities, hospitals charge for services, which encourages them to prioritize treatments that need hospitalization or non-donor supported drugs. While injectable artesunate provided by donors should be available for free, facilities will charge for consultations, hospitalization, and treatment for complications. This also encourages providers to use quinine instead of injectable artesunate as they can charge patients for the product.

Insufficient health system financing also leads to a high cost of severe malaria treatment, which can be a barrier to accessing treatment. While the cost of severe malaria treatment varies widely and depends on several factors, including the availability of donor supplied drugs and insurance schemes, it can often be prohibitive to patients. In **DRC** for example, where 70% of health system operating costs are charged to users via fees,[96] treatment of severe malaria has an average cost of $51.94,[97] while in **Uganda**, where services are provided mostly free of charge, a caregiver still has to pay out of pocket between $1.71 - $3.12 and loses between $2.73 - $3.81 in terms of opportunity costs.[98] In DRC, there have been attempts to alleviate the financial burden of malaria treatment, as well as other diseases and services, via a system of "*tarification forfaitaire*" that has been rolled out in several provinces, providing comprehensive services for a set fee. This system works well when donor commodities are available, but it has been complicated to implement when facilities are stocked out and patients have to purchase drugs.

In **Nigeria**, if a facility does not receive free injectable artesunate from a donor or the state government, the cost to purchase the drug from a pharmacy or facility and the treatment costs can be prohibitively expensive for the patient. Facility visits in Kano and Abuja found that even when they have donor support, patients may have to pay for some aspects of their treatment.

4. Unauthorized use of injectable artesunate at lower levels of the health system. In some countries, notably DRC and Uganda, facilities that are not authorized to provide severe malaria treatment in fact do. When treatment is provided at lower level facilities with providers who might not be adequately trained or have sufficient resources, there is a larger chance for injectable artesunate misuse. In **DRC,** a 2016 study found that 31% of health centers surveyed provide severe malaria treatment services even though they are not authorized by the PNLP.[99] Furthermore, one interviewee estimated that 50% - 80% of primary health facilities treat severe malaria.[100] Reasons for this include long distances, often over 100 km, between a primary care facility and reference facilities and a lack of or access to referral transport.[101]

[95] DRC MOP 2019

[96] DRC ACT Watch 2015

[97] Ferrari, Giovanfrancesco et al. An operational comparative study of quinine and artesunate for the treatment of severe malaria in hospitals and health centers in the Democratic Republic of Congo: the MATIAS study. Malaria Journal. (2015) 14:226.

[98] Nanyonjo, Anges. Estimating the cost of referral and willingness to pay for referral to higher-level health facilities: a case series study from an integrated community case management progamme in Uganda. BMC Health Services Research (2015) 15:347.

[99] Rapport de l'enquête pour la vérification de l'utilisation final des médicaments et commodités de lutte contre le paludisme dans la république démocratique du Congo réalisée en mars 2016.

[100] Interview with PMI DRC.

[101] Rapport de l'enquête pour la vérification de l'utilisation final des médicaments et commodités de lutte contre le paludisme dans la république démocratique du Congo réalisée en mars 2016.

In **Uganda**, while injectable artesunate can be administered at HC IVs and above, it is often found at HC IIIs. A recent severe malaria case management report, supported by MMV, recommended that the national policy should be updated to officially allow HC IIIs to offer injectable artesunate.[102] While HC IIIs may not be able to diagnose or manage all severe malaria-related complications, less severe cases could be managed, and are already being treated, at HC IIIs.[103]

d) Injectable Artesunate Impact

Both DRC and Uganda have seen significant reductions in their malaria burden in recent years. In **DRC**, a mid-term review report of the National Strategic Plan reported a 35% reduction in malaria deaths between 2015 and 2018, from 43 deaths/100,000 inhabitants to 28 deaths per 100,000 inhabitants.[104] **Uganda**'s 2017-2018 annual malaria report noted a 40% reduction in the number of inpatient malaria cases from the previous year and a decrease in the number of deaths by 52% (7260 to 3503).[105]

The availability and use of injectable artesunate likely has contributed to the reduction in mortality due to severe malaria. The ISMO project calculated averted deaths and disability-adjusted life years (DALYs) and reported that due to the 5.6 million vials of injectable artesunate procured instead of quinine, an additional 41,500 deaths and 660,300 DALYs were averted across all of its 6 implementation countries.[106] Furthermore, the procurement of 12.6 million vials by Global Fund, PMI, and governments during this period (2013-2016) could have averted an additional 92,300 deaths and 1,468,200 DALYs in the 6 project countries. Following a similar method at the global level, total volumes procured during 2013-2016 may have averted an estimated 369,900 deaths and 5,883,900 DALYs throughout Africa.[107] For the period following the ISMO project, 2017-2018, an estimated 3.1 million treatments of injectable artesunate were needed, and if filled, would have contributed to an additional 138,500 deaths and 2,200,400 DALYs adverted.[108]

For this report, to assess impact, we examined the ratio of reported severe malaria deaths to reported severe malaria cases – a proxy for the average case fatality rate – over time and assessed differences between facilities with and without injectable artesunate available.

Our findings in **DRC** and **Uganda** did not show a difference in the case fatality rates at the facility level between facilities with available injectable artesunate and those without. This may be due to poor quality data and confounding factors, such as the possibility that facilities with higher baseline case fatality rates may have been targeted to receive injectable artesunate. In Uganda, inpatient case fatality rates were largely similar between facilities that had injectable artesunate available and those that did not; there were 2.85 deaths per 1000 cases in facilities stocking injectable artesunate while there were 2.76 deaths per 1000 cases at facilities that did not stock injectable artesunate (Figure 10). In DRC, the severe malaria case fatality rate point estimates were extremely low, suggesting underreporting of

[102] Uganda National Malaria Control Program. Severe Malaria in Case Management in Uganda: A rapid assessment of management of severe malaria at health centers in Jinji District, Uganda.

[103] Uganda National Malaria Control Program. Severe Malaria in Case Management in Uganda: A rapid assessment of management of severe malaria at health centers in Jinji District, Uganda.

[104] PNLP, Revue à mi-parcours du plan stratégique national 2016-2020.

[105] Uganda Malaria Annual Report, July 2017-June 2018.

[106] Cambridge Economic Policy Associates Ltd. End of Project Evaluation of the "Improving Severe Malaria Outcomes" (ISMO) Project, 13 November 2015.

[107] Cambridge Economic Policy Associates Ltd. End of Project Evaluation of the "Improving Severe Malaria Outcomes" (ISMO) Project, 13 November 2015.

[108] Cambridge Economic Policy Associates Ltd. End of Project Evaluation of the "Improving Severe Malaria Outcomes" (ISMO) Project, 13 November 2015.

severe malaria deaths or low specificity of severe malaria case definition. However, there was no statistically significant difference in CFR between facilities with injectable artesunate (0.24), injectable quinine (0.27), both (0.25) or neither (0.28) (Figure 11). Due to data limitations in Nigeria, we were not able to calculate impact as with Uganda and DRC, but Figure 12 shows the observed severe malaria case fatality rate from 2014-2018. No significant difference in predicted CFR was evident over time.

Significant challenges with the quality of HMIS data create several limitations in this analysis of impact:

- Surveillance data are limited by the reporting quality, and systematic underreporting or overreporting could lead to biases in the estimates; careful assessment of the quality of HMIS data used here was beyond the scope of this analysis.
- **Uganda:** Since only the quantity of injectable artesunate available is reported in HMIS, rather than the quantity used or the quantity of other severe malaria treatments available, we are unable to describe the extent of injectable artesunate use. While its availability has increased, it is not known whether this has coincided with a decrease in the availability of other severe malaria drugs such as injectable quinine. The frequency of use of injectable artesunate compared to other drugs is also not known.
- **DRC**: The revisions to the HMIS and DHIS2 platform in 2017, including the adoption of the commodity reporting form, revision of the case and death forms, and expansion of facility coverage, may make pre- and post-2017 data non-comparable without more extensive data cleaning and manipulation. While the death reporting form was submitted with similar frequency to the other forms, it was left blank more often – when these blanks were interpreted as zeroes; it may have led to underestimates of the case fatality rate. Without further insight into the data collection and reporting procedures, it is difficult to know how to correctly interpret these blank values.

Figure 10: Inpatient malaria case fatality rate by injectable artesunate availability, facility type, and year in Uganda, HMIS Surveillance Data (N=39,220 facility-months from 1,288 facilities)

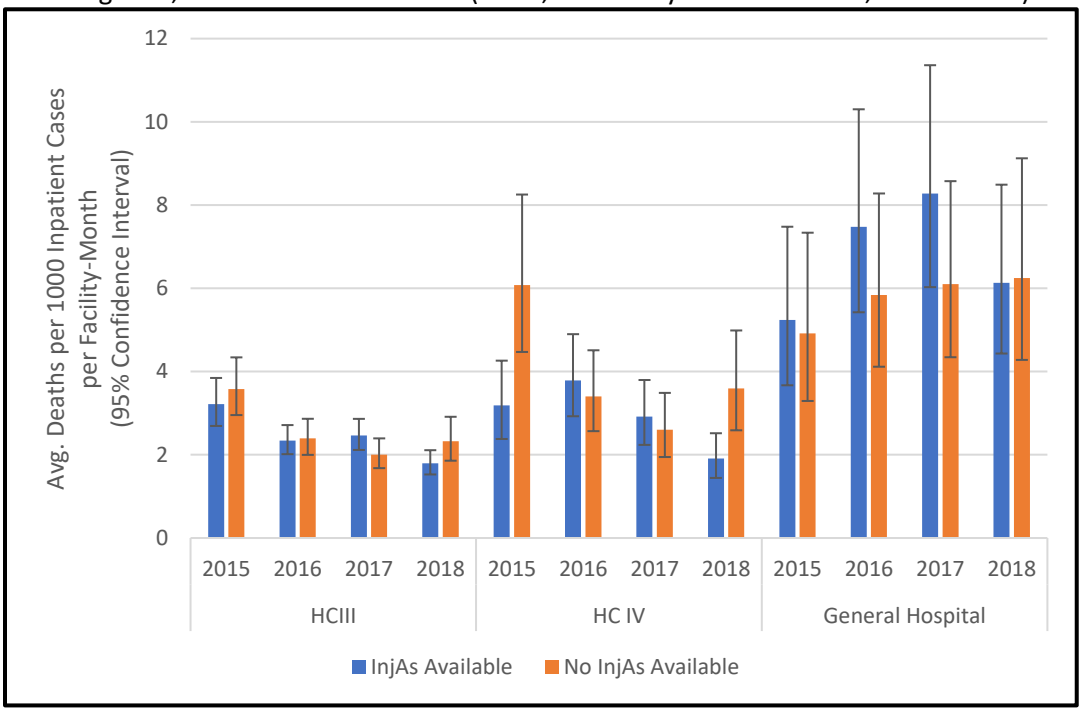


Figure 11: Case fatality rate (deaths per 1000 severe cases) by injectable artesunate and injectable quinine availability, hospitals, DRC 2017-2018, HMIS surveillance data (N=7,863 facility-months from 590 facilities)

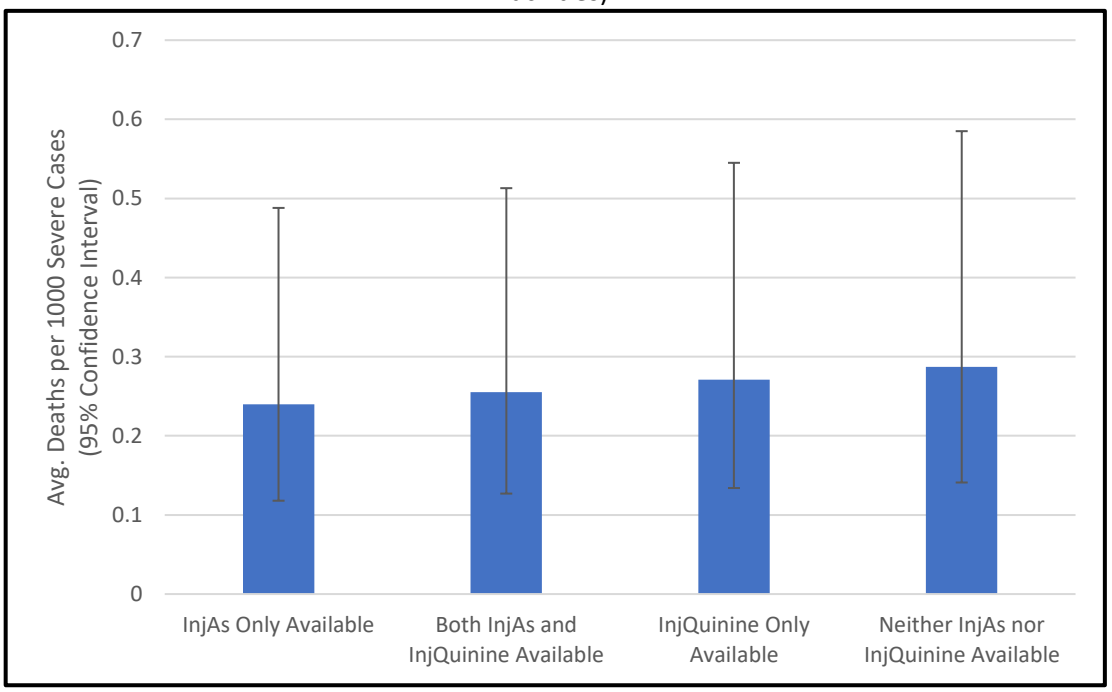
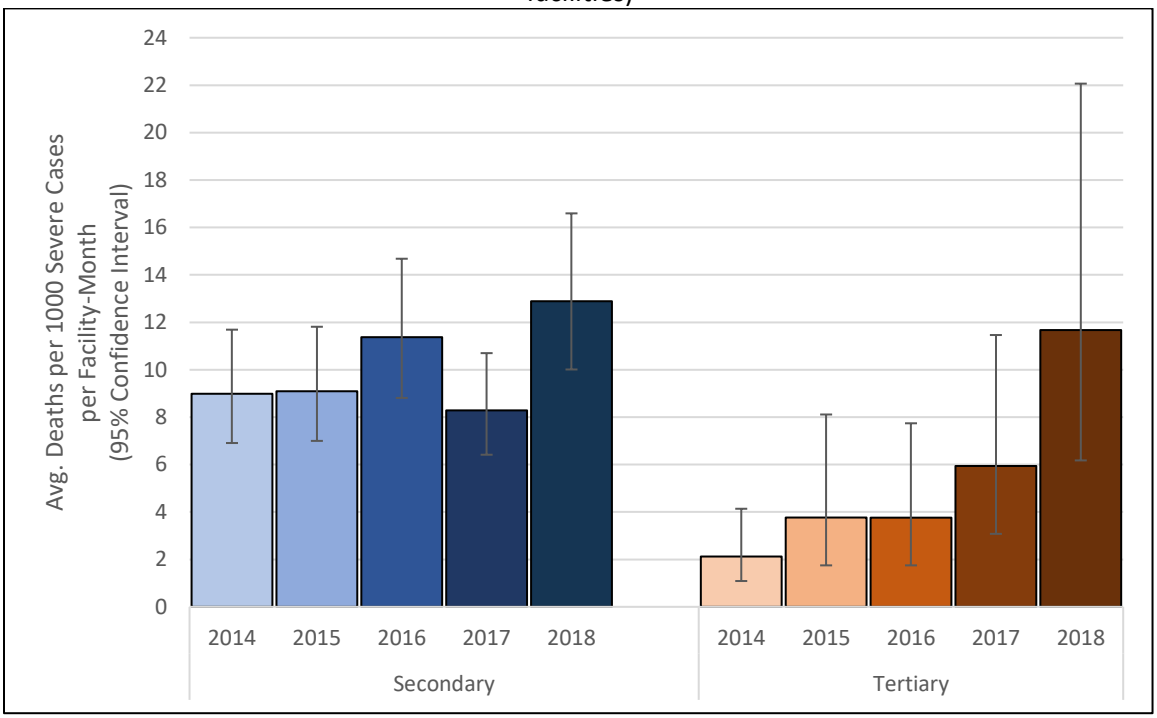


Figure 12: Nigeria, modeled case fatality rate for children under 5 years from 2014-2018 at secondary facilities that reported both case and death data into the HMIS (N=8,165 facility-months from 715 facilities)



IV. Summary and recommendations

Policy challenges

The vast majority of countries (80%) have adapted their national guidelines to reflect WHO guidelines to recommend injectable artesunate as the preferred treatment. As we have seen reflected in the data, in the absence of the injectable artesunate, many countries do not make an explicit recommendation to recommend artemether over quinine and many countries do not clearly state the dosing specifications for children under 20kg in their guidelines. WHO and donors, such as PMI and Global Fund, could play an advocacy and technical support role.

Market challenges

The procurement analysis found that procurement has overall steadily increased over the years since 2011 (especially through and then following the ISMO project), but actual procurement volumes still do not meet the forecasted procurement. Prices have remained fairly stable even though volumes have increased, which may be caused by the presence of just one WHO pre-qualified manufacturer of injectable artesunate (although prices did not increase either). With the recent addition of a second WHO pre-qualified supplier and potentially a third in the future[109], there may be opportunities for price reductions because of competition, possibly permitting countries and donors to procure larger volumes. Poor quantification however will likely continue to hamper uptake of injectable artesunate. The lack of data and the uncertainty in demand creates difficulties in appropriately distributing the product through the supply system. As a result, stock may ration stock levels to minimize costs causing further stock

[109] MMV, CHAI discussions with a manufacturer

shortages. More accurate data on severe malaria and improved rational use may result in better quantification and fewer stock outs, yet may also lead to lower consumption rates.

Health system challenges

The availability of injectable artesunate is relatively high in former ISMO countries included the assessment which seems to be driven by continued donor funding. Even when injectable artesunate is available, additional barriers exist to patients being able to access it, particularly in DRC and Nigeria. The high cost of injectable artesunate and severe malaria treatment can be a barrier to accessing treatment and forces patients to rely on less effective treatments or drugs of unknown quality.

Findings also suggest that quantification and availability issues are exacerbated by misuse of injectable artesunate, particularly if procured by donor funds. This misuse includes treatment of uncomplicated malaria with injectable artesunate and unauthorized use of injectable artesunate at lower levels of the health system. There is also often incomplete treatment with limited ACT use following injectable artesunate administration.

The ISMO project found that training and supervision may reduce misuse, particularly for uncomplicated malaria cases, but the data also shows that in the absence of continued activities (i.e., refresher trainings, supportive supervision) these effects may wane. While training and supervision are part of the standard package of activities supported by partners, new approaches such as on-the-job training and mentoring may further encourage appropriate use. For example, regular clinical audits conducted by PMI's implementing partners have helped facilities to become more aware of and make improvements to treatment issues. Another potential solution is improving the accountability for appropriate injectable artesunate use. In Uganda, a hospital with support from PMI's implementing partners rolled out an injectable artesunate patient registration/tracking system, which significantly reduced over-consumption. An important challenge remains, however, related to clarity and comparability in how a health worker is to diagnose severe malaria. Community health workers in iCCM learn to diagnose and refer a fever plus a danger sign (i.e., vomiting) which may differ from the WHO or national guidelines. It is very likely that misalignment between different classifications and guidelines also contributes to over or under-use of injectable artesunate.

Finally, the persistent availability and use of quinine is worrisome. Quinine's demand is driven in part by local manufacturers who have a vested interest in ensuring a market for injectable quinine exists. Quinine is substantially cheaper than injectable artesunate which may make it attractive for facilities and patients that are often required to procure treatment in the open market. It is not funded by donors and thus can be charged back to patients to generate funds for the facility. Additionally, it is perceived as efficacious (with some reports suggesting more than injectable artesunate because it takes longer to administer).

Recommendations

Based on the findings in the assessment, the implementation of the following recommendations could improve the availability and appropriate use of injectable artesunate and contribute to better case management of severe malaria:

1) Country malaria programs should **improve quantification and forecasting** of injectable artesunate by strengthening severe malaria data availability and quality through interventions such as regular HMIS data quality audits and support to facilities on reporting and data use.

Improving facility reporting and data use can help improve the quality of consumption data used in quantification, supply and distribution planning, and stock monitoring.

2) Country malaria programs should **strengthen the capacity of supply chain** staff to minimize stock outs and improve quantification and forecasting capacity through facility and warehouse logistics training, mentoring, and supervision. More accurate quantification, reporting, and ordering can reduce product rationing[110].
3) Country malaria programs, in collaboration with partners, should work to **encourage injectable artesunate rational use**. Examples could include:
    a. Revise training curricula and supervision through approaches such as on-the-job training, mentoring, and clinical audits to ensure proper use of the drug and patient care. Targeted clinical audits, for example, may improve reporting, severe malaria case management, and overuse of injectable artesunate. Training and supervision particularly need to highlight the prescription of ACTs following injectable artesunate treatment as well as the superiority and higher efficacy of injectable artesunate compared to quinine.
    b. Work with WHO to ensure alignment between severe disease classifications and management practices at different levels of the health system such that severe malaria patients receive injectable artesunate while those with uncomplicated malaria or other illnesses do not. Countries that have not yet made a clear recommendation of injectable artesunate as a first-line treatment, do not having dosing specifications for children under 20kg, or do not recommend artemether as the preferred alternate treatment, should also work with WHO to align its guidance to global WHO recommendations. Donors could play an advocacy role or provide technical support to make any revisions.
    c. Develop and implement patient registration/tracking systems for those patients with severe malaria who were prescribed injectable artesunate. For example, in Uganda, a hospital rolled out an injectable artesunate-patient registration/tracking system (for every person who receives the product, the pharmacist records the name and the number of vials received), which significantly reduced overconsumption.

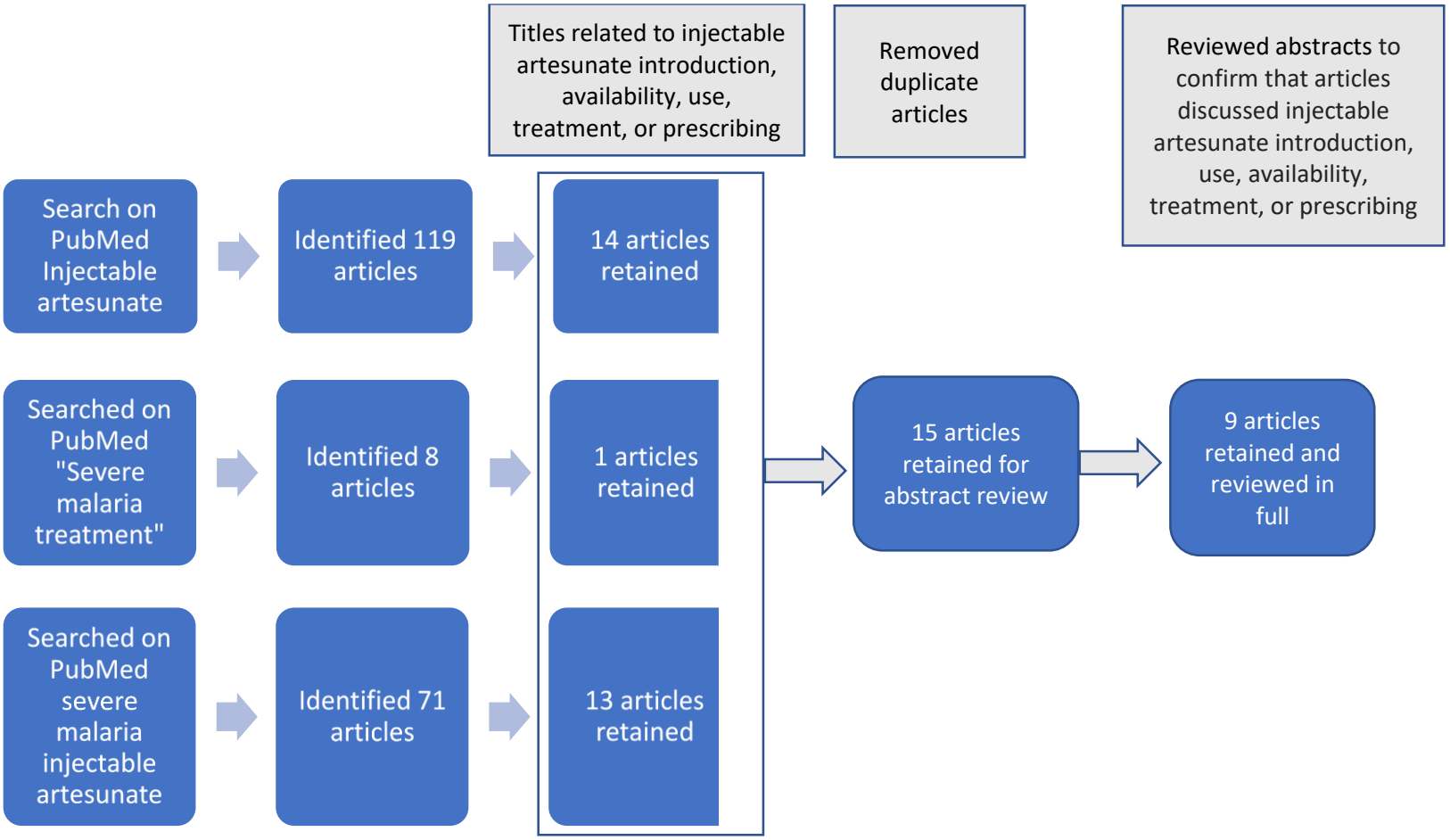
    Improved rational product use could lead to lower and more targeted injectable artesunate use and reduce stock outs, rationing, and reliance on the open market.
4) Donors should work closely together with country programs and other in-country stakeholders to **ensure free severe malaria treatment** by leveraging comprehensive primary health care and maternal and child health projects and initiatives (e.g., free treatment schemes for children under five, flat service fees, insurance schemes). Country malaria programs should ensure that malaria drugs and treatment are included in these non-malaria-specific interventions.
5) National regulatory authorities such as the MoH Department of Pharmacy and Medicine and National Drug Authorities should work to **strengthen their pharmacoviligence systems** in countries to reduce the availability of sub-standard or fake artemisinin derived injectable drugs, particularly those not registered for use with the national drug authorities.
6) Donors and implementing partners should **support severe malaria case management initiatives that provide comprehensive care** (rather than funding procurement of injectable artesunate alone) to ensure that the necessary drugs and services to treat severe malaria complications, such as blood transfusions are consistently available and provided to patients.

Overall, the ISMO project has had a lasting effect on procurement and use of injectable artesunate for the treatment of severe malaria in the two ISMO project countries examined here, particularly in Uganda. Renewed commitments to ensure health workers receive the training and supervision they

[110] Practice that caps the quantity of a commodity a facility can receive

need may help reduce injectable artesunate misuse which in turn can help better quantify its actual need, inform improved distribution and result in fewer stockouts of this life-saving drug. Finally, while this assessment has focused specifically on the availability and use of injectable artesunate, a holistic approach to severe malaria case management, including the treatment of related complications, will be needed to fully leverage the effectiveness of this drug and allow for even more lives to be saved.

Annex A: Published literature review decision tree



Annex B: Overview of published and grey literature

Published Literature

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Annex C: Quantitative data analysis in focus countries

For the analysis of routine surveillance data, facility-month level data was extracted from the national HMIS and LMIS of DRC, Nigeria, and Uganda. Health (case and death counts) and commodity (injectable artesunate availability and use) form reporting rates were used to limit each countries dataset to years where reporting rates were adequate.

A dataset was created for each country with one row per reporting facility per month, with indicators that included the number of severe or inpatient malaria cases, severe or inpatient malaria deaths, injectable artesunate availability, injectable quinine availability, quantity of injectable artesunate used, and quantity of injectable quinine used, where available. Facilities were classified according to the structure of secondary and tertiary facilities in the country and datasets were restricted to secondary and tertiary facilities.

Light data cleaning was conducted as follows:

- Outliers were removed for case, death, and commodity use variables.
- Where a form was submitted by a facility in a given month but a variable was left blank, the blank was assumed to indicate zero. For example, if a form was submitted with 10 cases and the death field left blank, it was assumed that the facility had 0 deaths. If the form was not submitted, all variables were set to missing.
- In Uganda, injectable artesunate availability was reported on a weekly form, rather than on a monthly form. If injectable artesunate was reported as available in any week in a month, the facility was counted as having it available for that month.

Estimates of injectable artesunate availability, use and impact were then made. For each indicator, the unit of analysis was the facility-month. All estimates accounted for within-facility clustering of data, or the non-independence of facility-month estimates within the same facility, using a model with random facility intercepts. Generalized linear mixed-effect model with binomial (for availability estimates) or poisson (for use and case fatality rate estimates) distribution were fit using the ‘glmer’ function in the ‘lmer’ package in R to get facility-cluster controlled estimates.

Annex D: List of country guidelines reviewed

	in alignment with WHO			
	discrepancies with WHO guidelines			
	not mentioned			
	information not available			
Country	**Date of available guidelines**			
WHO Guidelines	**2015**	**Treat adults and children with severe malaria with IV/IM for at least 24h and until they can tolerate oral medication**	**Child <20 kg (3mg /kg bw per dose)**	**If parenteral artesunate is not available, use artemether in preference to quinine**
Afghanistan	WMR 2018	yes		Artemether or quinine
Algeria	2014	IV quinine	n/a	Artesunate IV/IM, Mefloquine, or AL
Angola	2014	yes	no	Artemether
Bangladesh	2016	yes	yes	Artemether
Benin	2015	Quinine or derivatives of artemisinin are indicated (quinine is listed first in the guidelines)	no	Artemether (listed third in guidelines)
Botswana	2015	yes	yes	Quinine
Burkina Faso	2014	yes	no	Artemether
Burundi	WMR 2018	yes		Quinine
Bhutan	WMR 2018	Artemether	n/a	Quinine
Cabo Verde	WMR 2018	Quinine	n/a	
Cambodia	2014	yes		Quinine
Cameroon	2014	yes	no	Quinine is recommended before artemether
CAR	2013	yes	no	Artemether or quinine
Chad	2014?	yes	no	Quinine
China	WMR 2018	Artemether	n/a	Artesunate, Pyronaridine
Comoros	2016	yes	no	Quinine
Congo	WMR 2018	Quinine	n/a	
Cote d'Ivoire	2013	Injectable artesunate or artemether injection or quinine; preferred treatment not clearly stated	no	Artemether or quinine - preference not stated
Country	**Date of available**	**Treat adults and children with severe malaria with**	**Child <20**	**If parenteral artesunate is not available, use artemether in**

	guidelines	IV/IM for at least 24h and until they can tolerate oral medication	kg (3mg /kg bw per dose)	preference to quinine
DR Congo	2016 unpublished	yes	yes	Artemether
Djibouti	WMR 2018	yes		
Equatorial Guinea	2004	yes	no	not mentioned
Eritrea	WMR 2018	Quinine	n/a	
Ethiopia	2012/2014	yes	no	Artemether
Gabon	WMR 2018	yes		Artemether or quinine
Gambia	2016	yes	yes	Quinine
Ghana	2014	yes	no	Artemether
Guinea-Bissau	WMR 2018	yes		Quinine
Guinea	2014	Derivatives of artemisinin or quinine, preference not stated	no	Quinine
India	2014	Parenteral artemisinin derivatives or quinine, preference not stated	no	Artesunate, quinine, artemether, alphabetaartether are all listed as options
Indonesia		yes	no	not mentioned
Iran	WMR 2018	yes		Quinine
Kenya	2016	yes	yes	Quinine or Artemether
Korea (Republic of)	WMR 2018	Quinine	n/a	
Laos	2018	yes	no	Quinine
Lesotho	2005	Quinine	n/a	not mentioned
Liberia	2016	yes	yes	Artemether
Madagascar	2015	yes	yes	Quinine
Malawi	2013	yes	no	Quinine
Mali	2016	yes	yes	Artemether or quinine, no preference specified
Mauritania	WMR 2018	Quinine	n/a	
Mayotte	WMR 2018	Quinine, Artesunate, Artesunate+Doxycycline, Quinine +Doxycycline	n/a	
Mozambique	2011	yes	no	Quinine
Country	**Date of available guidelines**	**Treat adults and children with severe malaria with IV/IM for at least 24h and until they can tolerate oral**	**Child <20 kg (3mg**	**If parenteral artesunate is not available, use artemether in preference to quinine**

		medication	/kg bw per dose)	
Myanmar	2015	yes	yes	Artemether
Namibia	2015	yes	yes	Quinine
Nepal	2015	yes	yes	Artemether
Niger	WMR 2018	yes		Quinine
Nigeria	2015	yes	yes	Artemether or quinine, no preference specified
Pakistan	2007	yes	no	Quinine
Papa New Guinea	2012	yes	no	Quinine
Philippines	WMR 2018	Quinine+ Tetracycline		Quinine + doxycycline, quinine + chloroquine
Rwanda	2013	yes	no	Quinine
San Tome and Principe	WMR 2018	Quinine		
Saudi Arabia	2018	yes	yes	Artemether
Senegal	2013	Quinine, artesunate, and artemether all mentioned but with no preference, quinine listed first in guidelines	no	Artesunate, artemether, and quinine no preference specified
Sierra Leone	2015	yes	yes	Artemether
Solomon Islands	WMR 2018	Artesunate + Artemether-Lumefantrine or Quinine	n/a	
Somalia	2015/2016	Quinine, Artemether available but not used	n/a	not mentioned
South Africa	2016	yes	yes	Quinine
South Sudan	2015	yes	yes	Artemether or quinine, no preference specified
Sri Lanka	2014	yes	no	Quinine
Sudan	after 2013	Quinine	n/a	Artemether
Swaziland	2014	yes	no	Quinine
Tanzania	2014	yes	yes	Quinine, artemether also included
Country	**Date of available guidelines**	**Treat adults and children with severe malaria with IV/IM for at least 24h and until they can tolerate oral medication**	**Child <20 kg (3mg /kg bw per dose)**	**If parenteral artesunate is not available, use artemether in preference to quinine**

Thailand	2009	yes	yes	Artemether listed before quinine but no clear preference
Timor-Leste	WMR 2018	Artemether	n/a	Artesunate, quinine
Togo	2012	yes	no	Artemether or quinine, no preference specified
Tunisia	2012	Quinine + Doxycycline	n/a	Chloroquine, if not in resistant areas
Uganda	2016	yes	yes	Artemether or quinine, no preference specified
Vanuatu	WMR 2018	yes		
Viet Nam	WMR 2018	yes		Quinine
Yemen	WMR 2018	yes		Quinine
Zambia	2014	yes	no	Artemether or quinine, no preference specified
Zimbabwe	2015	yes	yes	Quinine

Annex E: Injectable artesunate procurement + guidelines by country

Country	Injectable Artesunate first-line treatment in national guidelines	At least one procurement from donor
Afghanistan	yes	yes
Algeria	Quinine	no
Angola	yes	yes
Bangladesh	yes	yes
Benin	Quinine or derivatives of artemisinin	yes
Botswana	yes	no
Burkina Faso	yes	yes
Burundi	yes	yes
Bhutan	Artemether	no
Cabo Verde	Quinine	no
Cambodia	yes	yes
Cameroon	yes	yes
CAR	yes	yes
Chad	yes	yes
China	Artemether	no
Comoros	yes	yes
Congo	Quinine	no
Cote d'Ivoire	Injectable artesunate or artemether injection or quinine	yes
DR Congo	yes	yes
Djibouti	yes	yes
Equatorial Guinea	yes	yes
Eritrea	Quinine	yes
Ethiopia	yes	yes
Gabon	yes	yes
Gambia	yes	yes
Ghana	yes	yes
Guinea-Bissau	yes	yes
Guinea	Derivatives of artemisinin or quinine	yes

India	Parenteral artemisinin derivatives or quinine	yes
Country	**Injectable Artesunate first-line treatment in national guidelines**	**At least one procurement from donor**
Indonesia	yes	yes
Iran	yes	yes
Kenya	yes	yes
Korea (Republic of)	Quinine	no
Laos	yes	yes
Lesotho	Quinine	no
Liberia	yes	yes
Madagascar	yes	yes
Malawi	yes	yes
Mali	yes	yes
Mauritania	Quinine	no
Mayotte	Quinine, Artesunate, Artesunate+ Doxycycline, Quinine +Doxycycline	no
Mozambique	yes	yes
Myanmar	yes	yes
Namibia	yes	no
Nepal	yes	yes
Niger	yes	yes
Nigeria	yes	yes
Pakistan	yes	yes
Papa New Guinea	yes	no
Philippines	Quinine+Tetracycline	yes
Rwanda	yes	yes
San Tome and Principe	Quinine	no
Saudi Arabia	yes	no
Senegal	Quinine, artesunate, and artemether	yes
Sierra Leone	yes	yes
Solomon Islands	Artesunate + Artemether-Lumefantrine or Quinine	yes
Somalia	Quinine, Artemether available but not used	yes
South Africa	yes	yes
South Sudan	yes	yes
Country	**Injectable Artesunate first-line treatment in national**	**At least one procurement from**

	guidelines	donor
Sri Lanka	yes	yes
Sudan	Quinine	yes
Swaziland	yes	no
Tanzania	yes	yes
Thailand	yes	yes
Timor-Leste	Artemether	no
Togo	yes	yes
Tunisia	Quinine + Doxycycline	yes
Uganda	yes	yes
Vanuatu	yes	yes
Viet Nam	yes	no
Yemen	yes	yes
Zambia	yes	yes
Zimbabwe	yes	yes

Annex F: Procurement totals by country, year, and donor

Procurement totals by year 30mg, 60mg, and 120mg, Global Fund, PMI, and UNICEF

	30mg	60mg	120mg
2006		72,000	
2009	-	25,275	-
2010	-	4,430	-
2011	-	552,280	-
2012	-	651,520	-
2013	-	7,903,719	-
2014	-	20,551,618	-
2015	-	24,042,318	-
2016	-	19,274,041	-
2017	137,875	17,652,826	800,800
2018	410,117	23,072,002	1,178,239
2019	-	7,550,137	-
unknown		1,425,808	
Total	**547,992**	**122,777,974**	**1,979,039**

Procurement totals by country 30mg, 60mg, and 120mg, Global Fund, PMI, and UNICEF, 2006-2019

Country	30mg	60mg	120mg
Afghan		20,400	
Angola		360,000	
Bangladesh		63,376	
Benin		50,000	
Brazil		53,200	
Burkina Faso		8,121,426	
Burundi		3,378,456	
Cambodia		50,000	
Cameroon		8,252,681	
CAR		504,627	
Chad		3,232,403	
Colombia		3,800	
Comoros		31,137	
Cote d'Ivoire		440,805	

Djibouti		26,387	
DR Congo		18,239,823	800,800
Egypt		4,550	
Equatorial Guinea		15,070	
Eritrea		162,757	
Ethiopia		2,022,608	
Gabon		200	
Gambia		98,656	
Ghana	150,000	3,996,844	400,000
Guinea		1,486,959	
Guinea-Bissau		213,012	
Haiti		14,505	
India		16,080	
Indonesia		450	
Iran		14,020	
Iraq		100	
Kenya		12,642,955	
Kyrgyzstan		1,080	
Laos		93,442	
Lebanon		3,335	
Liberia		1,165,670	
Madagascar		366,182	
Malawi		7,215,674	
Maldives		25	
Mali	137,875	3,234,961	
Morocco		18,000	
Mozambique		1,788,757	
Myanmar		361,917	
Nepal		6,071	
Niger		1,939,905	
Nigeria		9,247,222	
Pakistan		32,920	
Philippians		15,482	
Rwanda		824,951	
Senegal		590,050	
Sierra Leone		1,295,996	
Solomon Islands		83,000	
Somalia		38,140	
South Africa		275	

South Sudan	108,956	1,676,247	490,087
Sri Lanka		508	
Sudan	151,161	188,545	288,152
Suriname		700	
Syria		100	
Tanzania		11,413,310	
Thailand		6,658	
Togo		262,173	
Tunisia		10	
Uganda		16,402,769	
Vanuatu		28,250	
Venezuela		320	
Yemen		35,956	
Zambia		440,000	
Zimbabwe		482,036	
Total	**547,992**	**122,777,924**	**1,979,039**

Total procurement by donor by strength

Donor	30mg	60mg	120mg
Global Fund	547,992	57,989,708	1,979,039
PMI		28,533,199	
UNICEF		34,829,259	

Annex G: Detailed supply chain review

a) Quantification processes for injectable artesunate

In **Uganda**, an all malaria commodity quantification is done every three years to correspond with the development of the Global Fund concept note; the last quantification was developed for 2017-2020. The MoH, Global Fund, warehouses (NMS/JMS), donors, and partners evaluate the needs for 3 years and donors (Global Fund and PMI) make procurement commitments and commodities gaps are identified. A 3-year supply plan is developed and reviewed annually. The quantification is based on morbidity methodology using HMIS data with an estimated 4% of malaria cases progressing to severe illness, 60% of severe cases in children under 5, and 70% of cases treated in the public sector. The quantification covers the public sector plus the PNFP, which accounts for 25% of the needs. There is no private sector quantification but volumes could be estimated through imports registered with the National Drug Authority (NDA).

In **DRC**, the quantification is developed to align with the PNLP's national strategic plan; the last was developed for 2016-2020. The quantification is reviewed annually, product needs analyzed and divided between partners, and procurement gaps determined. The process is led by PNLP with support from partners (Chemonics and Sanru). The latest quantification is based on morbidity data with a population progression 3%, 5% of malaria cases progressing to severe illness, and 51% accessing public sector services. Sanru revised the quantification for 2018-2020 procurement for the Global Fund concept note and increased the severe malaria rate to 7% of cases. Data for the quantification comes from the PNDS (population) and the national strategic plan (service delivery estimates).

In **Nigeria,** under the guidance of the National Malaria Elimination Program (NMEP) partners come together to develop a 5-year malaria commodity forecast; the latest was completed for 2018-2022. The quantification is developed at the state level under the leadership of the State Malaria Elimination Programs (SMEP) and compiled at the national level by the government and partners. A supply plan is developed and updated every 6 months. The quantification is developed based on morbidity data with an estimation of 1% of all malaria cases progressing to severe disease. In Adamawa, the CARAMAL study state, the supply chain assessment cited that no clearly defined or reliable quantification method had been adopted by the state and the quantification was based on partner tools. Data for the quantification comes from the 2006 census (demographic data) and morbidity reports. Some states procure injectable artesunate through their DRF based on consumption from the Drug Medical Consumable Supply Agency (DMCSA) as well as with state budget lines; however, if the estimated need is over the available budget line then the procurement plans will be adjusted to fit within the budget.

b) Procurement processes for injectable artesunate

In **Uganda** the procurement of injectable artesunate is based on the national quantification. For public sector facilities, supported by Global Fund, the Global Fund/MoH accounting officers communicate orders to the Global Fund procurement and supply chain manager (PSM), who prepares the paper work for the order, once the order has been approved by the NMCP program manager. Global Fund procures through the Pool Procurement Mechanism (PPM) twice a year and delivers injectable artesunate directly to the NMS for distribution. For PNFP facilities supported by PMI, procurement is done through Chemonics, delivered to the JMS for distribution. JMS also procures small quantities of injectable artesunate from Guilin.

In **DRC**, injectable artesunate is procured through Chemonics for the PMI supported provinces, Sanru for the Global Fund supported provinces, and DFID for the Kasai province through IMA. Chemonics manages their procurement through Chemonics project in D.C. and Sanru through Global Fund's procurement system Wambo.

In **Nigeria**, PMI procures every 6 months through Chemonics in D.C. and procurement is based off national forecasts and supply plans. For the Global Fund procurement, Catholic Relief Services (CRS), the PR procures through Wambo/PPM. Some states do their own injectable artesunate procurement with funds from state budgets or other financing mechanisms, for example, Kano, Kaduna, and Rivers state have all procured injectable artesunate. Facilities who do not receive donor commodities or become stocked out of injectable artesunate, procure injectable artesunate through DMCSA via yearly framework contract tenders. If states are procuring a large volume, the tendering process will involve national and international competitive bidders, while if the volume is small, the procurement can be sourced locally and managed through a request for quotation process known as national shopping.

c) Distribution processes for injectable artesunate

Injectable artesunate in **Uganda** arrives directly to the NMS and JMS from the supplier. Both warehouses distribute directly to facilities on a bi-monthly basis (6 cycles per year) via a predetermined schedule. JMS, which distributes PMI funded stock to PNPF, organizes the country in 4 zones; at the beginning of the year a schedule with order dates and expected delivery dates is established. The facilities need to order within the set time frame and will receive stock within the set distribution time frame. While this system is just for donor commodities, which are distributed for free, other essential medicines will be bundled with these deliveries to reduce overall distribution costs. Donors pay for distribution and warehousing and mandate the JMS to do last mile delivery.

The NMS, which warehouses and distributes Global Fund malaria commodities, splits the 140 districts of Uganda into 5 zones; at the beginning of each fiscal year the NMS sets a schedule with an order deadline and delivery deadline for each zone. The NMS delivers directly to districts and hospitals; for last mile distribution to health facilities, the NMS prepares packages of commodities by facility with accompanied documentation on the contents that needs to be approved by the facility to document proof of delivery, as well as discrepancies between what was ordered vs. delivered. In each district there is a cross dock container, literally a 40ft. container, where the NMS distributed commodities are stored while in transit to HCs IV and below. A Third-Party Logistics Provider (3PL) is prepositioned and must deliver the packages within 4-7 days. A distribution plan is developed by the Quantification and Procurement Planning Unit (QPPU), which manages the national malaria stock status, and the NMS works with the Global Fund to establish consumption per facility, adjusted according to client flow and facility catchment area.

In **DRC** for PMI supported health zones, stock is delivered directly to the CDRs from the supplier. Chemonics manages the delivery from the CDR to the health zone offices on a quarterly basis. The USAID funded Integrate Health Project (IHP) consortium partner, i+Solutions, manages the distribution from health zones to facilities. Stock is collected by the infirmières titulaires (ITs), head nurses, during the monthly "réunion de monitorage" at the health zone office.

For Global Fund supported health zones, stock arrives at one of three points of entry, Kinshasa, Bunia, and Goma, where stock is stored in a transit warehouse to manage customs formalities. Sanru then manages the distribution to the CDRs in their supported provinces via a 3PL. Stock is then distributed to the health zones by a 3PL under SR management (there is one SR per province, expect for 4 in Kinshasa),

where it is collected by ITs during the monthly "réunion de monitorage". The IT receives a reimbursement for transport according to the distance traveled, for example, $50 for 50km traveled. Distribution plans are made based on the grouped orders from the health zone and validated by the "Groupe Technique de Medicament" at the DPS.

In **Nigeria**, stock arrives to national warehouses in either Abuja or Lagos and from there it is distributed via a 3PL to six regional distribution centers, each catering to a number of states. Stock is then distributed directly to facilities. For both PMI and Global Fund malaria commodities, Chemonics manages the warehousing and distribution. In PMI states, Chemonics has staff in each supported state, who help the state to develop distribution plans, which are then sent to central office. Bids for 3PLs are based on these distribution plans. In Global Fund supported states, MSH, the Global Fund SR, works with state LMCUs to develop distribution plans. For commodities, including injectable artesunate, that are purchased through the DRF, facilities collect purchased stock directly from the DMCSA. While for commodities purchased from states budget lines, the DMCSA develops a distribution plan based on facility consumption from the bi-monthly stock forms.

d) Analysis on the focus country supply chains

i. Governance/coordination

Across the three countries, coordination mechanisms exist between partners, government, and supply chain agencies at all levels of the supply chain with varying levels of functionality and merit to be improved. In **Uganda,** the NMS is a government corporate body, mandated to procure, store, distribute drugs and medical supplies to public health facilities. The JMS, supplying PNPF facilities, was initially established by the Catholic and Protestant Medical bureaus to supply quality medical supplies to the mission established health facilities. There are five technical working groups within the NMCP: case management, monitoring and evaluation, behavior change communication, malaria and pregnancy, and vector control. The case management technical working group reviews and approves the use of technologies and products for malaria diagnosis and treatment. The QPPU works closely with the donors, partners, and medical stores on quantification and supply planning.

In **DRC**, partners oversee and ensure the distribution of commodities through the National Supply Chain (SNAME), though the National Supply Chain Program (PNAM) has the mandate to ensure coordination of the SNAME. While there are several working groups to collaborate and troubleshoot supply chain issues, such as the "Groupe Technique Médicament" and the "Sous-Groupe Approvisionnement et Distribution," major bottlenecks in governance and coordination remain. There is a lack of coordination and alignment between donors and the government and slow implementation of supply chain improvement activities. At the provincial level, one of the major challenges is a weak capacity of the "Groupe Technique Médicament." These bottlenecks are due to the limited capacity and leadership of the PNAM and other SNAME actors, a lack of government resources, and an almost complete reliance on donors and partners to support procurement and supply chain improvement activities.

In **Nigeria**, there is a National Supply Chain Program with an accompanying strategic plan. A severe malaria advisory group was set up during the ISMO project, however it does not meet regularly and needs to play a larger role in coordinating severe malaria interventions, including stock needs. This is due to lack of engagement from donors, partners, and the MoH because of competing priorities.

ii. Registration/regulatory landscape

Overall, across the three countries, while there can be some delays with registration, it seems to be a limited bottleneck for injectable artesunate availability. Injectable artesunate is widely available in public, PNFP, and private sector facilities and pharmacies, however the MoHs have limited oversight into the quality of products being supplied.

In **Uganda** products are registered with the National Drug Authority (NDA). Injectable artesunate, 30mg 3 vial packs, 60mg 3 vial packs, and 120mg 3 vial packs were registered prior to the ISMO project and will not need to be reregistered. In **DRC**, injectable artesunate was registered with the Department of Pharmacy and Medicine (DPM) and needs to be renewed every 5 years. Drug commodity registration in DRC needs to be done by a manufacturer pharmaceutical representative or by a local pharmaceutical consultant. There can be delays with holding DPM homologation session for product approval and renewal, as the DPM is reliant on donors for financing meetings due to insufficient government resources. There is also a lack of leadership on the part of the DPM. In **Nigeria**, NAFDAC, is the pharmaceutical regulatory authority and a product must be registered to be imported; its registration needs to be renewed every 5 years. While a product does not necessarily need to have WHO PQ for importation, some states such as, Kano, will only procure WHO PQ drugs.

iii. Quantification/forecasting

Across the three countries, quantification and forecasting are areas with significant challenges, leading to over and under procurement. Poor data quality and a lack of understanding of the extent of severe malaria has led countries to over and under procure. Quantification processes do not consider all facilities that may ultimately receive the product, leading to inaccurate quantification.

In **Uganda**, one of the main challenges in quantification and forecasting is that injectable artesunate is only quantified for HC IVs and hospitals but is also distributed to HC III, though it is not systematically available at all HC IIIs and is distributed through the HC IV for the sub-district area. Furthermore, in the HMIS, DHIS2, there is no consumption or treatment data collected from facilities and included in the database. These two challenges impact the quality and accuracy of the Uganda injectable artesunate forecast.

In **DRC** quantification there is a disconnect between actual needs, what is forecasted, and what is procured. Quantification is done as a top down approach due to a lack of capacity at the health zones and DPS in quantification. Poor forecast accuracy stems from the diverging opinions on the epidemiological profile of the country and the actual percentage of severe malaria cases. This is due to a lack of quality demographic and morbidity data, for example, there has been no census in over 30 years. While DHIS2 has been fully functional since 2017, it is still plagued with poor quality and incomplete data, there is also a lack of confidence in this data.

In **Nigeria**, the quantification has a low level of accuracy, leading to over/under procurement; this is because the data that should drive the quantification is not very solid. During the in-country interviews, one interviewee stated that they want to be able to quantify with consumption data but are in a catch22 as the quantification will be limited by what has been received in the past and not what is actually needed. It is also difficult to obtain accurate consumption data due to periodic stock outs, poor recording and tracking system, and insufficient reporting by higher level facilities, where the bulk of the severe malaria cases are seen.

iv. Procurement

Despite increased procurement from donors, stock outs continue to occur across the three countries. In DRC stock outs are rampant across all levels of the supply chain, while in Uganda stock outs are less frequent and only occur at the facility level. Nigeria faces stock outs of donor commodities and free drugs procured by the states but facilities continue to make the product available through the drug revolving fund and local procurement. Quinine is the most prevalent alternative to injectable artesunate in DRC and Uganda while in Nigeria it is artemether. Donors are limited in the size of their procurements by the price of the drug and the estimated needs of the country (in Nigeria only 24/37 states are covered). Facilities, particularly in DRC and Nigeria procure from the private sector, which leads to uncertainty around the product quality.

In **Uganda**, the donors are able to procure sufficient stock of injectable artesunate. During the in-country interviews two procurement bottlenecks were cited: unpredictable lead times and bureaucracy around importation; for example, according to government policy, if an entity has registered a product, another agent cannot import it and it must go through the registering entity.

In **DRC**, the main procurement challenge is the insufficient quantities procured based on the estimated need and use. This is due to insufficient donor funds to fill the country's needs and a procurement based on an estimate of malaria attributed mortality in children under 5 as well as irrational use of the product and leakages to private sector.

In **Nigeria**, the major procurement challenge is that injectable artesunate is only provided by donors to 24 of 37 states and the remaining states do not necessarily have the ability to procure themselves. Therefore, the only source of artesunate in the 13 unsupported states is what facilities can buy through the DRF or from local procurement. States and facilities that procure on the open market may be procuring non-quality drugs as well as procuring injectable artesunate when the facility does not have the authorization to administer. If the facility is stocked out, patients will often buy directly from pharmacies and will buy the cheapest brand of injectable artesunate, which is often the poorest quality drug.

v. Customs clearance/import taxes

In general, across the three countries, the assessment found no major bottlenecks around customs clearance and importation taxes for injectable artesunate, as either medical supplies are exempt from taxes or donors have tax exemption waivers to import drugs. Some administrative customs fees may still need to be paid at importation.

In **Uganda**, medicines and medical supplies are tax exempt, including commodities imported by private importers. During the ISMO project there were some delays because the importer (MissionPharma) and clearing agent (Spedag) needed to be registered with the NDA, as well as the latter with the Ugandan Revenue Authorities Customs System, which caused about a 4-week delay in delivery. For donor commodities delivered to the NMS a local clearing agent manages the customs clearance prior to delivery at the NMS, while for drugs that are procured by the NMS with government funds, the NMS manages customs clearance and reclaims the clearance fees from the government. In **DRC**, Sanru, the Global Fund PR, has tax exemption for the importation of injectable artesunate and other commodities but has to pay administrative fees at port of entry, which is managed by a local consultant. Chemonics also has tax exemption status for product importation. To receive tax exemption status in DRC, an organization must submit, every 2-years, a list of weights of goods to import to the Ministries of Planning and Finance who authorize tax free importation. In **Nigeria**, donors submit waivers to the

NMEP on an annual basis for tax exemption; drugs are exempt from VAT, however there are some taxes at the port level.

vi. Warehousing/storage

In all three focus countries, poor storage conditions at different levels of the supply chain plague the quality of the injectable artesunate. Donors limit stock amounts kept at central and provincial level warehouses due to space constraints or to keep warehousing costs low. At the NMS in **Uganda**, limited storage space constrains stocked stored at the national level to only 4-8 months. Lower level facilities have lower quality storage conditions, a 2018 survey found that only 53% of HC IIs had acceptable storage conditions, while 65% of HC IIIs, 82% of HC IVs, and 100% of hospitals, had sufficient storage conditions.[111] Of the facilities surveyed, 92% had a stock card for injectable artesunate, but only 51% had it up to date.[112] Poor storage conditions are mainly due to a lack of government investment in health system infrastructure.

In **DRC**, the quality of storage conditions at CDRs, health zones, and facilities varies widely. A 2016 survey found that 35% of health centers had acceptable storage conditions, while 68% of depots and 61% of hospitals did.[113] Both Sanru and Chemonics have storage contracts with CDRs; warehouse costs vary but they are often around 8% CIF. Global Fund pays health zones $42/quarter for storage. The supply chain norms set stock maximums for CDRs at 9 months, health zones at 5 months, and facilities at 2 months, however, partners often try to limit the amount of stock stored at CDRs to reduce warehousing costs. Poor storage conditions, especially at health zones and facilities affects product quality. Malaria program commodities are more vulnerable to low shelf life at CDRs and in the past there have been low levels of stock turns.[114] Overall, poor storage conditions are due to a lack of government resources dedicated to health system infrastructure and a reliance on donors and partners to rehabilitate health system structures.

In **Nigeria**, commodities are initially stored at national warehouses in Abuja and Lagos before being sent to one of six zonal warehouses. Each state has a pharmaceutical warehouse but they are no longer used by PMI or Global Fund as they are of poor non-pharmaceutical grade quality. Donors now keep stock at six zonal warehouses. At the national warehouses there should be 6-10 months of stock; Chemonics pays for pallet space for a period of time, so in an effort to keep warehousing costs down, they try to stagger shipments and send more frequent smaller shipments to limit use of pallet space. Zonal warehouses should stock 4-6 months and are established as a PPP, so it is often difficult for the government to use these facilities as they have to pay for storage. Poor storage conditions are due to a lack of federal and state resources to invest in the health system infrastructure, however they are also blocked from using the zonal warehouses due to an inability to pay, so commodities procured with state funds or through the DRF are often kept in poor conditions at state warehouses.

vii. Distribution and resupply and order process for injectable artesunate

Across all three focus countries, the distribution and resupply processes have inefficiencies that contribute to frequent stock outs. Challenges with distribution planning and understanding the real needs of facilities lead to facilities receiving incorrect quantities resulting in either stock outs or

[111] PMI End Use Verification Survey, Uganda, November 2018.

[112] PMI End Use Verification Survey, Uganda, November 2018.

[113] Rapport de l'enquête pour la vérification de l'utilisation final des médicaments et commodités de lutte contre le paludisme dans la République Démocratique du Congo réalisée en mars 2016.

[114] DRC Supply Chain Assessment, February 2018.

overstock. Injectable artesunate is often rationed and therefore facilities do not receive the amount they order and in theory need.

While **Uganda** has an overall consistent supply situation, there continue to be distribution related challenges that lead to stock availability issues. In the public sector, despite the fact that the NMS has put systems in place to ensure that facilities receive the right stock it remains difficult to ensure that: 1) stock does not go to facilities unable to manage severe malaria, 2) there are no leak to the private sector, 3) there are no discrepancies between what was ordered, on the distribution list, and actually distributed, and 4) an irregular supply of stock is pushed out to HC IIIs, which is predetermined and not based on need.[115] Furthermore, one of the main challenges of injectable artesunate distribution has been ensuring that facilities order the correct quantities of stock. For example, one hospital had 4 years of stock while others in the same district were stocked out. In response to this and to curb injectable artesunate misuse, the NMCP and the NMS, based on facility data, caps the amount of injectable artesunate a facility receives. However, since consumption data is not collected from facilities, capping the distribution can also lead to stock outs, driving patients to purchase stock from the private sector and pharmacies. Leakages to the private sector are due to insufficient regulation and oversight.[116]

Orders are generated at the facility, verified by the district, and then reviewed by the NMS. The NMS also can consult with the NMCP to validate orders if erroneous orders are sent to NMS. Orders sent to the NMS are received by email or paper through regional NMS offices who scan and send for processing. There is a push system for HC II/HC IIIs with the NMS deciding what facilities get. During supportive supervision to these lower level facilities, redistribution of commodities occurs, if needed. For HC IVs and hospitals, the resupply system is a pull system. These facilities have staff that can quantify and are trained on stock management. HC IVs place orders for the facilities in its sub-district; HC IIIs can draft their needs and submit to HC IVs for them to incorporates into their orders. However, in many cases what was requested, what is on the distribution list, and what was delivered do not correspond and HC IIs and HC IIIs may receive items they cannot consume. A November 2018 survey found that more than half of facilities (53%) received the quantities of commodities as ordered, 34% received less, and 13% received more than ordered; the most undersupplied commodity was injectable artesunate, as 49% of facilities received less than ordered, 45% received the ordered amount, and 6% received more.[117]

The JMS has a specific order-reporting form for donor commodities, developed by JMS in conjunction with partners, which is sent from facilities by email. Stock to distributed through a pull system and facilities must report on bi-monthly basis to the JMS, whether or not they need to order additional stock.

In **DRC** at the facility level, there is a reliance on the ITs to collect stock from the health zones and ensure their own last mile distribution. However, if stock is not available when they come for the monthly health zone meeting, they may need to return to health zone again during the month. There are frequent stock outs at health zones and facilities; this is partially due to a quarterly resupply from CDRs to health zones, limiting the flow of products to facilities, as well as targeted procurement for the needs of children under 5, and injectable artesunate misuse. A lack of transport infrastructure and materials further contributes to difficult last mile distribution.

[115] Uganda National Malaria Control Program and MMV. Severe Malaria Case Management in Uganda: A rapid assessment of management of severe malaria at health centres in Jinja District, Uganda. 2018.

[116] Uganda National Malaria Control Program and MMV. Severe Malaria Case Management in Uganda: A rapid assessment of management of severe malaria at health centres in Jinja District, Uganda. 2018.

[117] PMI End Use Verification Survey Uganda, November 2018.

In Global Fund supported health zones, facilities send orders to the health zone office, where the orders are centralized, and sent to the "Groupe Technique de Médicament" at the DPS for validation. The SR then takes the order to the CDR to manage packing. If there is a problem and the health zone does not order then there will be a push delivery according to the number of expected malaria cases. The capacity of the Groupe Technique de Médicament is a challenge in this process and functions better in some provinces compared to others.

For the PMI supported health zones, the health zones send orders to DPS which validates the order and then sends to the CDR. There is a Chemonics local representative who works with the DPS to review and validate orders for the distribution plan. If a health zone does not send orders on time to the DPS, then stock is pushed to the health zone. There are often delays in ordering process and facilities do not always receive the amount requested, as depending on the stock level at the CDRs, injectable artesunate can often be rationed to health zones and facilities. This is because there is not a clear understanding of the actual need of the drug due to the misuse for simple cases as well as proportion of patients that go to the private sector or never make it to a facility for treatment.

In **Nigeria**, consumption data is not accurate, so service data is used by the SR to develop distribution plans for the Global Fund supported states. Injectable artesunate distribution is rationed by the SR and for large facilities the allocation is not sufficient, while small facilities may be getting too much stock. Secondary and tertiary facilities do not report into DHIS2 because the reports are input by the Local Government Authority (LGA), and secondary facilities report to the state government, while tertiary facilitates report to the federal level. In an effort to make data available from secondary facilities, the LGA physically goes to the facility to collect the information so it can be entered into DHIS2. Therefore, the SR does not know the real needs of the facility and the distribution plan is based on what was used in the past and what facilities have requested from state warehouses when stocked out of donor commodities.

Facilities report and order via a bi-monthly facility stock report; each facility sends this report to the LGA, who then sends it to the state, and replenishments quantities are determined based on past consumption. Facilities are topped up back to 4 months of stock. For orders that are placed through the DRF, when a facility is at their minimum order level they will send a requisition to the DMSCA. There is normally a lead time of 2 weeks, and the minimum order level is consumed during this time. Facilities do not always receive what is requested when ordering from state free drug programs or Global Fund; facilities feel that they never receive enough injectable artesunate from donors or the state.

viii. Transport

Across the three focus countries, there is a heavy reliance on 3PLs by donors for distribution. In **Uganda** both the NMS and JMS have a fleet of vehicles or contract to 3PLs for distribution directly to facilities. The NMS has a fleet of 21 distribution trucks but would ideally have used 30 distribution trucks for deliveries in 2017-2018. In **DRC**, 3PLs or the CDRs transport between the port of entry, CDRs, and health zones, however, there is a heavy reliance on 3PLs for transport as the CDRs have limited material and resources for transport. At the facility level, products are collected by the IT at the health zone during monthly "réunion de monitorage" (both GF and PMI) and transported back to the facility on motorcycle, bicycle, pirogue, bus, truck, or carried. Therefore, products often arrive in poor condition due to transport. There is a lack of transport infrastructure in the country, poor or non-existent roads, and very limited options for inexpensive air transport. In **Nigeria**, PMI prequalifies 3PLs for transport across the country. State governments have limited transport material and facilities collect commodities procured through the DRF at the DMSCA.

ix. Data management

Overall, data quality and the availability of certain data points are major challenges, hindering a clear picture of injectable artesunate use and therefore an accurate quantification. A significant proportion of the population seek care in the private sector in the three focus countries, however, there is an absence of data and reporting from these facilities.

In **Uganda**, from the facility level, the number of malaria and severe malaria cases and deaths is reported on a monthly basis into DHIS2 and injectable artesunate stock on hand is reported into the system on a weekly basis. One of the major gaps with data at the facility level is that consumption of injectable artesunate is not collected and reported into DHIS2. Therefore, it is difficult to link injectable artesunate use with the number of reported severe cases; it is also a helpful data point for quantification and supply and distribution planning. At the sub-national level, malaria prevalence, diagnosis, treatment of children with fever by region, and malaria prevalence in children by region is collect in the Demographic Health Survey (DHS). However, the latest DHS form 2016 does not give a clear picture of injectable artesunate use, as data collection occurred not long after the introduction of injectable artesunate and so lower use is seen compared to quinine. At the national level, on the supply chain side, the NMS uses Macs for warehouse management and Sage for financial management, however, the two softwares do not interface with each other and data sets need to be exported into Excel for analysis. For each donor that stores commodities at the NMS, the NMS reports to them, as well as to the MoH, on a quarterly basis; reporting information on the quantities received, distributed, and currently in stock. JMS uses Industrial Financial Solution as inventory and financial management tool. NMS and JMS report stock status and AMC to the MoH for the bi-monthly stock status report.

In **DRC**, while there has been an improvement in the availability of health systems data with the national rollout of DHIS2, at all levels of the health system and supply chain, there is a lack of confidence in the data available. There is also limited data exploitation at all levels of the health system, limiting feedback into performance on stock and financial management to the lower levels. At the facility level, one of the major challenges is the lack of understanding on the part of provides on the use and importance of data. Those who complete the reports many not understand the importance of what they are doing due to a lack of data use by the facility, problems understanding the reports, and limited availability of data collection tools. While reporting rates, timeliness, and data quality have improved since the initial rollout of DHIS2, they are still quite variable, particularly on data quality. An October 2017 survey found that only 63.9% of health facilities submit their stock status report on time to their respective health zones and DPS.[118] There are discrepancies between data recorded in the registers vs. the SNIS form vs. the data entered into DHIS2. This is due to the fact that those who complete the reports as well as encode the data into DHIS2 at the health zone many not understand the importance of what they are doing, due to a lack of data use by facilities and health zones. Furthermore, reported data is often incorrect, for example, there are facilities that should not manage severe malaria cases but they do and then report on the SNIS forms as cases of simple malaria. A mission to the Global Fund provinces in 2017 cites that there was: 1) an incoherence in data between the registers and the report in all health centers and reference hospitals visited, 2) it was difficult to link the data in the registers and the monthly reports, 3) data quality was weak, due to improper use of registers, 4) poor data collection, and 5) the stock report did not show the reality of stock received by the health zone.[119] In terms of sub-national data, the last DHS was in 2013-2014 and collected data on the prevalence, diagnostics, treatment, and type of antimalaria received, however, the data collection was based on the 11 old provinces, prior to

[118] PMI End Use Verification Survey, DRC October 2017.

[119] Feedback à la synthese missions 2017.

the decoupagé in 2015, which makes it difficult to obtain estimates for some provinces. CDRs use ApiSoft as their financial and inventory management tool, however, the systems are not linked nor accessible online, making it difficult to have a national level stock picture.

In **Nigeria**, facilities report service delivery data on a monthly basis via the HMIS form and logistics data on a bi-monthly stock report form. The service delivery form is entered into DHIS2 by the LGA and the logistics data form is entered into Navision at the state level. There have been challenges with reporting for secondary and tertiary level facilities into DHIS2, as secondary level facilities report to the state government and tertiary facilities to the federal government, while it is the LGA that collects the HMIS forms and inputs the data into DHIS2. Data availability is improving from the secondary facilities as LGAs have started to collect the HMIS form from the secondary level facilities. Furthermore, Navision is not easily accessible and only has limited programmatic data, currently limiting its usefulness and leaving important data gaps as DHIS2 does not capture any stock or consumption data. The data quality is also uncertain and does not give an accurate picture as data collection and use are not well understood or seen as priorities by facilities. Additionally, the majority of patients go to the private sector which does not report into national systems, therefore, there are significant data gaps on malaria cases, deaths, and product use. At the sub-national level, the last DHS was in 2013, prevalence and treatment of children with fever by state are include in the report, however, because data collection was done prior to the full-scale introduction of injectable artesunate, data was not collected on its use.

x. Quality control + quality assurance

Across the three countries, quality control and assurance practices could be improved in the public sector. In the private sector product quality and processes are unknown and not sufficiently regulated. The Government of **Uganda** has put in place strict minimum standards and all medicines and diagnostics must be labeled with "Government of Uganda not for sale." Products must arrive in-country with at least 24 months of shelf-life. In **DRC**, the quality of injectable artesunate products available through the private sector is uncertain and there are uncertain quality control testing standards. Public facilities procure injectable artesunate from private sector distributors and there is no systematic quality control testing of imported products facilities procure from the private sector. In **Nigeria**, the NMEP has focused mostly on the quality of ACTs but they are working with NAFDAC to try to include injectable artesunate in the list of commodities for quality control.

xi. Financing

Financing of the supply chains in the focus countries mainly comes from donors, charged fees for warehousing and distribution, and costs that are passed down to the patient. In DRC and Nigeria, in particular, the out of pocket costs for patients can be a significant barrier to treatment, while in Uganda malaria treatment and services are free in the public sector, though price can be an issue in the private sector.

In the **Uganda** public sector treatment and services are free; program commodities are provided by donors and essential medicines are funded by the Ministry of Finance, which provides funds to facility specific accounts at the NMS. A mark-up of 8% from the NMS is applied to essential medicines and directly debited from the health facility account at the NMS. NMS fees, about 8.5% Exworks on average, related to the receiving, distribution, and storage of donor procured commodities are regulated by MoUs with donors. If a public health facility is stocked out of injectable artesunate the patient will have to pay in the private sector or at a pharmacy; the costs are variable but could be as high as 30,000 Ugandan Shillings ($7.95). While, the JMS serves charged based hospitals, PNFP facilities served by the

JMS do not charge for donor commodities, such as injectable artesunate, but do charge for the service (consultation, hospitalization), trying to keep prices low and accessible for the population. JMS has a grant from Ugandan government to procure essential medicines for PNFP facilities, which are distributed for free on a quarterly basis.

In **DRC**, while injectable artesunate should be free in the public sector, patients still have to pay for consumables, consultation, and hospitalization. Prices for services and commodities are unregulated in the public sector. Public sector facilities are underfunded and staff are often not paid by the government and therefore need to charge patients to generate revenue. Prices are not regulated in the private sector but are generally more expensive than the public sector.

In **Nigeria**, out of pocket patient expenditure for drugs and services is a major burden to effective medical treatment. If donors do not support the state or the facility is stocked out, patients have to pay out of pocket for drug and services. This drives patients to seek care in the private sector and from private sector pharmacies and drug shops where they might find lower priced but for inferior quality products. Prices for injectable artesunate vary depending on the state. In Kano, 1 vial of 60mg injectable artesunate purchased through the DRF at about 600 Naira ($1.67) and sold for 775 Naira ($2.15), while in Abuja it is sold for 1000 Naira ($2.78) -2700 Naira ($7.52). Facilities pay a 7.5% mark-up from the DMSCA and a total 18% mark-up is passed down to the patient. In Adamadwa, the CARAMAL injectable artesunate assessment found that injectable artesunate was priced between 350 – 600 Naira/vial with an average mark-up of 100 -350 Naira per vial; while arteether costed between 900 – 1500 Naira/vial, and quinine, the least expensive at 80-100 Naira/ampoule.[120] The cost of injectable artesunate can be out of reach for much of the population that needs it.

xii. Human resources + training

Across the three focus countries, human resource capacity in the supply chain varies, due to a lack of or insufficient training on stock management and quantification at facilities. In **Uganda**, only 59% of facilities had staff trained in logistics in 2018,[121] which was a decrease from previous years (2010: 63%, 2011: 37%, 2014: 59%, 2015: 98%, 2016: 78%, 2016: 90%, 2017: 87%, 2018: 68%).[122] While in **DRC** in 2016, the percent of facilities with staff trained in logistics was less with only 43% of facilities having at least 1 staff formally trained in drug management.[123] Of those staff trained, 32% were trained in a formal course, 30% were trained on the job, and 19% were self-trained. However, a subsequent survey showed that in 2018, there was an increase in drug and stock management training with 81% of facilities surveyed having at least 1 person trained in drug management and 73% of providers surveyed trained. In **Nigeria**, some higher-level facilities received training on stock management and forecasting but there is an overall insufficient training of facilities in these areas. Furthermore, due to the often-mobile health workforce population a facility may lose this skill set once their provider moves.

[120] CHAI. Injectable Artesunate supply chain assessment report. 31st July 2018.

[121] PMI End Use Verification Survey Uganda, November 2018.

[122] PMI End Use Verification Survey Uganda, November 2018.

[123] Rapport de l'enquête pour la vérification de l'utilisation final des médicaments et commodités de lutte contre le paludisme dans la République Démocratique du Congo réalisée en mars 2016.

Annex H: In-country and global stakeholder questionnaires

Global Level stakeholder questions

Variations of these questions were asked to different global level stakeholders

- Perspective on injectable artesunate availability and use across countries donor/partner works in
    - Current challenges around injectable artesunate use and availability?
    - Any notable challenges, successes, or trends from DRC, Nigeria, or Uganda?
    - Overall successes/challenges from the introduction period?
    - Major challenges in severe malaria case management?
- Are severe malaria and the availability of injectable artesunate priorities? Why/Why not? How will this change/continue?
- Has the donor/partner funded or is currently funding any specific projects related to severe malaria (outside of commodities)? If so, where, with what partners, and what is the scope of the project?
- For procurement donors/partners, over the next 3-5 years do you anticipate the funding level of injectable artesunate to remain near the same levels? Why/Why not? Is the cost of the drug limit funding for injectable artesunate in countries?
- Quinine, artemether, and non-WHO PQ artesunate brands are widely available and used in some countries, what do you think needs to be done to improve the availability and use of WHO PQ injectable artesunate over these other drugs? What do you think donor/partner could do?
- In some countries, particularly the three focus countries for this assessment, significant proportions of the population seek care for fever in the private sector, is the private sector a priority intervention? How do you see further engaging in the private sector going forward?

Injectable Artesunate Master In-Country Questionnaire

n.b. these questions are for focal country MoHs, in-country implementing partners, donors met in-country; some questions may only be relevant to certain stakeholders

I. Policy and Regulatory

1. When was injectable artesunate included in the country's treatment guidelines?
2. Has the policy been modified in any way since then?
3. What was the recommended treatment prior to injectable artesunate?
4. Are the guidelines in-line with the latest WHOs recommendations in 2011 for use? What happens if injectable artesunate in not available? What is recommended?
    a. *all patients with severe malaria with intravenous or intramuscular artesunate for at least 24h until can tolerate oral meds, complete treatment with 3 days of ACTs*
    b. *if cannot provide full treatment course but can provide injection - single dose of intramuscular artesunate and refer for further care*
5. Is injectable artesunate on the essential medicines list?
6. Where can InjAs be used? At what facility level/ who can administer it?

7. Does injectable artesunate have market registration?
    a. What products are registered? Guilin Pharmaceutical Co. Ltd? Ipca Laboratories Ltd?
    b. If so since when?
    c. With what entity regulates this drug/provides market authorization?
    d. When/if will the registration expire?
    e. What Acts apply to regulation of injectable artesunate?
    f. Who is licensed to import InjAs?
    g. Are there taxes or VAT applied on importation?
    a. What regulations apply when it is sold in the private sector?
8. Is injectable artesunate available in the private sector?
    a. Since when?
    b. If so, do you know how the stock is procured?
    c. Costs to patients?
    d. Is it's use regulated (i.e. supervision from MoH or regulatory authorities)?
9. Is injectable artesunate included in all MoH reporting systems? HMIS, LMIS, etc.?

II. Introduction and Scale-up

1. When was InjAs first procured? By whom, with what funding?
2. When and where was it distributed- geographically and to what type of facilities?
3. Did you receive partner and/or donor support for injectable artesunate introduction and scale-up?
4. Which partners and what kind of support did they offer? For how long?
5. How did the introduction go/walk us through the introduction, were there specific plans? Technical working group managing the introduction? Etc.
6. What kind of trainings took place? Who were trained? What kind of training (i.e., on sever malaria?), how long?
7. What about scale-up? How did that happen? Were there specific plans? Has national scale-up occurred? Or just in certain geographies?
    a. If it is only being used in select areas, what are these areas and how were they chosen?
    b. Is there a plan for further scale-up and if so what is it?
8. Who were the key players (NGOs, MoH, mulit-bi laterals) involved in the introduction?
9. What was successful in the introduction?
10. What were the challenges or bottlenecks?
11. What was successful in the scale-up?
    a. Did trainings/supervisions continue following the initial introduction support (through ISMO)?
        i. With partner/donor support?
    b. Has procurement and distribution continued?
        i. With partner/donor support?
12. What were the challenges or bottlenecks in the scale-up? Around trainings? Supervision?

III. Procurement and supply chain

1. What is the quantification process for injectable artesunate?
    a. Who is involved?
    b. Frequency of quantification?
    c. Methodology? Morbidity? Logistics?
    d. Could you share the latest quantification? As well as any past quantifications?
2. What is the procurement process for injectable artesunate?

a. Who currently procures and who has procured in the past (will also get info from procurement data)? Who will procure in the future?
b. Does the government procure? With what funds?
c. What frequency?
d. On what basis?
e. With what funding?
f. Has your organization procured injectable artesunate in the past? Do you have any procurement plans for the next year?

3. Walk us through the injectable artesunate supply chain? What happens from when the stock arrives in country to arrival at facilities? *(draw out)*
    a. How many months of stock are stored at each level of the supply chain?
    b. Is there a distribution plan? If so, who develops it? For what period?
        i. Could you share it? Do you have past years to share?
    c. What is the resupply process for each level of the supply chain? How long does it take?
    d. Who manages/pays for the transport of stock?
    e. Who pays for storage at the different supply chain levels?
4. Can we validate our procurement volume numbers? *(if have procurement data)*
5. What are the bottlenecks in the supply chain for injectable artesunate?
    a. Has there been stock out of injectable artesunate in the last year? At what level? What caused it? What about previous years? Any quantitative data assessments?
    b. Has any stock of injectable artesunate expired in the last year? If so, at what level of the supply chain? Any quantitative data assessments?
    c. Supply chain costs? Who funds the supply chain? MoH? Donors? Out-of- pocket costs? Any quantitative data assessments?
    d. Are there any parallel supply chains through which injectable artesunate flows? *(draw out)*

III. Availability, Access, and Case management

1. What challenges were encountered with quinine?
2. Is injectable artesunate used for simple malaria outside the country's guidelines of specified use?
    a. In practice how is injectable artesunate used?
3. At what level of the health system is severe malaria treated with injectable artesunate?
    a. What types of facilities?
    b. What level providers do they have?
    c. What type of training and when have these providers received on malaria case management?
    d. Have providers received training or refresher training in the last 12 months?
    e. How often do they receive refresher trainings in severe malaria case management? What about malaria case management trainings, is injectable artesunate included?
    f. Do partners/donors support trainings or refresher trainings?
        a. Who?
        b. Certain geographies?
        c. Government support?

g. How often do providers receive supervision or mentoring?
    a. Monthly? Quarterly?
    b. What happens in practice?
    c. Who supervises the providers?
    d. Do partners support supervision or mentoring?
        i. Who?
        ii. Certain geographies?
        iii. Government support?
h. What is the reporting process for indicators on severe malaria and injectable artesunate use?
    a. DHIS2? LMIS?
    b. Directly to national malaria program?
    c. What indicators are reported?
    d. Any information on reporting rates?

4. What is the process when someone presents at a PHC with symptoms of severe malaria?
    a. What actually happens? Do they receive injectable artesunate? Are they referred to a higher-level facility?
    b. What are the breakdowns and why? Is this a systematic issue or just in certain geographies?
5. Have you observed any improvements in severe malaria case management since the introduction of injectable artesunate?
    a. Do you have any data to support this?
6. Have you observed any challenges with availability of injectable artesunate at facilities?
7. Have you observed any challenges with access to injectable artesunate by patients?
    a. Financial? (even if should be free, does the patient need to pay for consultation, consumables, fiches, etc.?)
    b. Provider bias? (reserved for certain patients or preference for administer quinine as have to pay?)
8. In your opinion, what has been successful in the use of injectable artesunate based on existing policy?
    a. If yes, why was it successful? What strategies were key?
    b. If not, why was it unsuccessful? What barriers/challenges did you face? (use in uncomplicated malaria?)
9. What would you recommend other countries consider or do to achieve success and/or avoid the challenges your country had?

Questions for facility visits for injectable artesunate assessment

Facility identifying information

Facility Name	
Health system level	
Number of providers	
Providers level of qualification	

Case management

What is the process when someone presents at the facility with symptoms of severe malaria?	
What actually happens? Do they receive injectable artesunate?	

Reasons for discrepancies between process and practice?	
Number of cases of severe malaria in the last 12 months by month	
Number of cases of severe malaria in the last 12 months treated with injectable artesunate	
Number of severe malaria deaths in the last 12 months	
Number of providers trained in general malaria case management	
Number of providers trained in severe malaria case management	
Last training or refresher training date	
Frequency of supervision	
Challenges with treating patients with injectable artesunate?	
Do patients have to pay for any part of the treatment? Hospitalization? Consultation? Consumables?	
How much do patients pay for severe malaria treatment?	
What are the general challenges that you see with severe malaria treatment?	
Are there challenges for the patient to access injectable artesunate? Why?	
Have you seen an improvement in severe malaria treatment since the introduction of injectable artesunate?	
If you're not using injectable artesunate to treat severe malaria, why not? What are you using?	
If possible try to cross-check patient files and prescription	

Supply chain

How do you procure injectable artesunate?/What is the process?	
From where do you procure injectable artesunate?	
How frequently?	
When did you last receive stock?	
Do you have quinine in stock? Do you normally stock/use quinine?	
Do you have stock other drugs to treat injectable artesunate?	
Current stock status of injectable artesunate?	
Stock status of quinine?	
Stock status of other severe malaria drugs?	
AMC of injectable artesunate? (or total consumed in last 12 months)	

Number of stock outs in the last 12 months of injectable artesunate?	
Number of days stocked out in the last 12 months of injectable artesunate?	
Reasons for stock outs of injectable artesunate?	
AMC/consumption of quinine or other severe malaria drugs?	
Challenges with availability of injectable artesunate stock?	

Annex I: List of stakeholders contacted

Organization	Stakeholder	Country/Global
BMGF	Bruno Moonen Scott Miller	Global
Global Fund	Marcos Patino Mayer Laurie Barnier	DRC
Global Fund	Jo-Angenine Kalambo Rozina Merali James Ssekitooleko	Nigeria
Malaria Consortium	James Tibenderana	Global
MMV	Pierre Hugo Hans Rietveld	Global
MSF	Martin de Smet	Global
PMI	Larry Barat Meera Venkatesan	Global
Swiss TPH	Christian Burri Christian Lengeler	Global
WHO	Andrea Bosman	Global
UNICEF	Akthem Fourati Valentina Buj Joyce Bakka	Global
Alima	Dr Rodrigue Houmênou Yélian Alitanou	DRC
Alisons	Kamal Gupta	DRC
Chemonics/GHSC-TA	Jules Mwenze	DRC
IHP/Abt. Associates	Jean-Caurent Mantshumba	DRC
MSF	Barbara Graf Perez	DRC
PMI/CDC	Aboubacar Sadou Godefroid Tshiswaka Yung-Ting Bonnenfant	DRC
PNLP	Dr. Eric Mukomena (Director) Dr. Achille Mudiandambu	DRC
Sanru	Dr. Fernandine Phanzu Dr. Pomie Mungala	DRC
Swiss TPH	Dr. Didier Kalemwa	DRC
WHO	Dr. Bacary Sambou	DRC
CRS	Chukwudi Uche	Nigeria
CHAI	Remilekun Peregrino Chizoba Fashanu	Nigeria
Chemonics	Chukwuyem Okoh	Nigeria
Gwarinpa Hospital		Nigeria
Hasiya Bayero Paediatric Hospital	Dr. Binta	Nigeria
Kano Drug Medical Consumables Supplies Agency	Ph. Kamilu	Nigeria
Kano State Malaria Elimination Program	Dr. Basheer	Nigeria

Malaria Consortium	Olatunde Adesoro	Nigeria
Maitama District Hospital		Nigeria
MSH	Dr. Victoria Erinle	Nigeria
Murtala Muhammad Specialist Hospital	Dr. Safiya	Nigeria
National Malaria Elimination Program	Dr. Emmanual Shekarau Ph. Mohammad Mr. Sam Abutu	Nigeria
PMI	Dr. Uwem Inyang	Nigeria
Global Fund/MoH	Dr. Henry Katamba	Uganda
Joint Medical Stores	Paul Senyonga	Uganda
MAPD/Malaria Consortium	Dr. Persis Nabyonga	Uganda
National Malaria Control Program	Dr. Jimmy Opigo	Uganda
National Medical Store	Sunday Izidoro	Uganda
PMI	Dr. Kassahun Belay Dr. Mame Niang	Uganda
RHITES/URC	Dr. Rogers Twesigye	Uganda
WHO	Dr. Charles Katureebe	Uganda