FORECASTING METHODOLOGY

GLOBAL MALARIA DIAGNOSTIC AND ARTEMISININ TREATMENT COMMODITIES DEMAND FORECAST

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LIST OF ABBREVIATIONS

ACT(s)	Artemisinin Combination Therapy/Therapies
ACTwatch	Artemisinin Combination Therapy watch
AMFm	Affordable Medicines Facility for malaria
AL	Artemether Lumefantrine
ASAQ	Artesunate Amodiaquine
BCG	Boston Consulting Group
CHAI	Clinton Health Access Initiative
DHA-PQP	Dihydroartemisinin piperaquine phosphate
DHS	Domestic Household Survey
The Global Fund	Global Fund to fight AIDS, Tuberculosis, and Malaria
IRS	Indoor Residual Spraying
ITN(s)	Insecticide Treated Net(s)
MICS	Multiple Indicator Cluster Survey
MIS	Malaria Indicator Survey
MIT	Massachusetts Institute of Technology
MOPs	Malaria Operational Plans
mRDT(s)	malaria Rapid Diagnostic Test(s)
NMCP (s)	National Malaria Control Program(s)
PMI	The President's Malaria Initiative
QAACT(s)	Quality Assured Artemisinin Combination Therapy/Therapies
QARDT(s)	Quality Assured malaria Rapid Diagnostic Test(s) [defined by the WHO procurement criteria for RDTs]
RBM	Roll Back Malaria Partnership
RDT(s)	(malaria) Rapid Diagnostic Test/Tests
UCSF	University of California, San Francisco
WHO/WHO-GMP	World Health Organization/World Health Organization – Global Malaria Program

INTRODUCTION

Since their launch and adoption as the WHO-recommended treatment for uncomplicated malaria over a decade ago, the global market for quality-assured artemisinin combination therapies (QAACTs) has expanded dramatically. Artemisinin, the key component of artemisinin combination therapies (ACTs), can be readily extracted from the leaves of the sweet wormwood plant (*Artemisia Annua*), and cultivated *A. annua* remains the major source of artemisinin for these life-saving anti-malarial medicines. The market's reliance on a vegetal artemisinin source, with all that that confers (e.g., long production cycles dictated by growing seasons, varying crop yields, competition for cultivation acreage from other in-demand cash crops, small volume growers, an inflexible supply chain that cannot easily adjust to changes in market demand), has at times resulted in supply constraints, and in other times, an abundance of supply. These supply swings, resulting from uncertain or unforeseen demand, have led to dramatic oscillations in artemisinin prices. In 2010, the Affordable Medicines Facility for malaria (AMFm), a private-sector treatment subsidy mechanism whose goal was to increase access to appropriate, low priced anti-malarial medicines in the retail/private sector, was launched, increasing the uncertainty about QAACT demand and whether artemisinin supply would be sufficient to meet it. Facing uncertain demand for QAACTs and artemisinin in the newly-launched AMFm, UNITAID contracted The Boston Consulting Group (BCG) and its partners – the Clinton Health Access Initiative (CHAI) and Fundacion Zaragoza Logistics Center (MIT-Zaragoza) – to produce annual global forecasts for QAACTs and artemisinin and to publish these forecasts on a quarterly basis. This project concluded with the publication of the final report in 2014.

Given past and future uncertainties in the artemisinin market, demand forecasting for QAACTs continues to be important for many stakeholders invested in malaria treatment access. After a sustained period of growth, QAACT demand has reached a plateau that has stabilized artemisinin prices. However, the relatively-low current prices for artemisinin may drive farmers toward planting alternative cash crops, leading to a potential decline in the planted *A. annua* acreage, and another cycle of artemisinin price fluctuations. Meanwhile, several large-volume countries plan to continue subsidizing QAACTs through private sector co-payments; others that participated in AMFm may lack funding to continue such programs. At the same time, countries are scaling up confirmatory diagnostic testing, particularly with RDTs, meaning that many public sector entities are facing the challenge of funding large RDT procurement volumes while also continuing to pay for the high costs of treatment. Improved market intelligence can help

countries and donors improve or develop new strategies to prevent supply shortages and stabilize prices. Such market intelligence would have broad utility for stakeholders throughout the supply chain, including the *Artemisia annua* farmers, semi-synthetic artemisinin producers, the artemisinin extractors, the manufacturers of rapid diagnostic tests (RDTs), artemisinin based active pharmaceutical ingredients (APIs), and finished products containing these APIs, the National Malaria Control Programs (NMCPs) and donors.

The new UNITAID forecasting project, whose proposed methods are described herein, aims to forecast ACT and artemisinin monotherapy need, demand, and procurement, as well as RDT demand, and procurement, and artemisinin API demand. We have defined these outputs as follows:

- ACT Need – The number of treatments that are required to treat all febrile individuals who have a malaria infection at a parasite density that is detectable by diagnostic methods currently used in most settings (microscopy and RDTs), regardless of whether the febrile individual seeks treatment.

- ACT Demand – The number of treatments that are required to meet consumer demand for treatment of suspected malaria with an ACT.

- ACT Procurement – The number of quality-assured treatments that will be procured from manufacturers by public or private sector purchasers.

- Artemisinin Monotherapy Demand – The number of artemisinin monotherapy treatments (including Injectable and rectal artesunate)) that are required to meet consumer demand for treatment of suspected malaria, or severe malaria.

- Injectable Artesunate Procurement – The number of injectable artesunate treatments that will be procured from manufacturers by public sector purchasers.

- RDT Demand – The number of RDTs that are required to meet the consumer demand for rapid test diagnosis of suspected malaria (e.g., a proxy: the number of patients who

sought treatment and received an anti-malarial treatment could be equated to the catchment population for rapid diagnostic testing).

- RDT procurement – The number of RDTs that will be procured by public or private sector purchasers.

- Artemisinin API Demand – Metric tons of artemisinin API required to meet public sector procurement volumes and private sector demand for all artemisinin-based anti-malarial medicines.

The forecast will be published periodically.

METHODS

A. DATA SOURCES

A forecast is only as accurate as the data inputs and assumptions that go into it. Thus, we will compile the most comprehensive collection of data available; each source will lend greater insight into market dynamics for ACTs, artemisinin monotherapies, and RDTs.

Data Source	Data Description	Source Year(s)
Surveys: DHS, MIS and MICS	Febrile incidence in <5's, Treatment seeking behavior (if treatment is sought and in which sector), Diagnostic uptake, Treatment choices (whether treatment is received and what drug type). Channel for treatment seeking (Public/Private Formal/Private Informal care access settings) was categorized at the national level to the consortium partners' best current understanding of national public and private health systems.	Refer to Appendix 1
WorldClim Global Climate Data Project	Mean, minimum, and maximum elevation for administrative regions to estimate annual fever incidence rates from the survey data	Latest Available
WorldPop Project	Sub-national population estimates	2010
Malaria Atlas Project	Malaria Prevalence in 2-10 year olds	Latest available

World Malaria Report	Malaria diagnostic uptake	Latest available
World Bank	GDP per capita and Official development assistance per capita	Latest available
UN	National Population Estimates	2010 (covering 2010 through 2050)
ACTwatch Outlet Surveys	Price and sales volumes of ACT in retail sector	Latest Available
National Malaria Control Program Strategic and Operational Plans	National ACT and RDT procurement plans	Latest available
THE GLOBAL FUND, PMI	Grant applications, historical procurement volumes, and approved funding envelopes outlining ACT and RDT procurement plans for grants	Latest available
WHO GMP	Annual Procurement data, as reported by NMCPs, annual manufacturer sales volume data	Latest available
THE GLOBAL FUND PQR	Ex-manufacturer prices for ACTs and RDTs; Volume of QAACT procurement through THE GLOBAL FUND Pooled Procurement Mechanism (PPM)	Latest available
IMS	Usage of oral artemisinin monotherapy; Usage of QAACTs vs. non-QAACTs; Usage of parenteral and rectal artemisinin monotherapy, ACT product strength and shares	Latest available (currently available for 21 countries)
ALMA / RBM	ACT and RDT gap analysis	Latest available
Published Literature	Treatment seeking behavior in ≥5's and ACT, artemisinin monotherapies, and RDT use in the ≥5 febrile population	Latest available

B. ACT NEED

CHAI has developed a temporally-specific, dynamic forecasting model for ACT need at global, national, and sub-national levels. The model employs a decision-tree algorithm, based on febrile incidence extracted from national population-representative household surveys (i.e.,

Demographic and Health Surveys [DHS], Malaria Indicator Surveys [MIS], Multiple Indicator Cluster Surveys [MICS]), to calculate output estimates. The first step of the model is to build an estimate of annual fever incidence per sub-national region based on survey data collected over the course of a few months, and a survey question that asks about fever incidence during a two-week period. The second step is to translate this annual fever incidence to the number of fevers in children under 5. The third step is to extrapolate annual fevers in the ≥5 population based on the estimated <5 fever figures. For the purposes of ACT need, the model then applies malaria prevalence estimates (adjusted to account for the typically higher malaria prevalence among febrile patients than among the general populous) to the calculated number of fevers to arrive at an estimate of the number of febrile cases that, if all fevers were sampled and tested with RDT or microscopy, would be reported as positive for malaria infection. The final step is to iterate the model to project changes in ACT need as a result of steady or abrupt changes to the underlying dynamics between malaria incidence and strategic malaria control interventions (e.g., ITN use, IRS, ACT uptake).To produce iterative outputs projecting annual ACT need, the algorithm models of the impact of ACT use and other interventions (e.g., ITN coverage) on malaria prevalence, and uses this newly estimated prevalence to estimate fever prevalence for the following year. Thus, the compound effects that interventions may have on fever prevalence and malaria prevalence over time can be estimated by our model.

Estimating annual <5 fever incidence

Data on period prevalence of febrile illness were assembled for children younger than five years old from all population-representative household surveys conducted since 2000 in malaria endemic countries for which raw data were available (n=181). Older surveys were not included since the malaria landscape was substantially different in prior decades. Surveys included Demographic Health Surveys, Multiple Indicator Cluster Surveys, and Malaria Indicator Surveys (Appendix 1). The combined dataset included 1,474,157children from 69 countries for whom positive or negative reports of fever were recorded. With two exceptions (Liberia and Nigeria's most recent surveys), these surveys did not record fever or treatment-seeking behaviors for ages older than five. All surveys employed multistage sampling from first-level administrative levels (e.g., states or provinces), allowing fever prevalence to be recorded separately at this sub-national level (n=752 administrative units).

Survey questionnaires asked mothers to report whether their children <5 years old had experienced fever in the prior 14 days. By assuming that most fevers began and ended during the 14-day period, these period prevalences can be treated as incidence measures. Annualizing these fever rates is complicated by the fact that surveys are conducted over only a few months of the year, so significant over- or under-estimation of annual fevers may result depending on the survey timing with respect to seasonal patterns of fever prevalence. To more accurately annualize fever estimates, the fraction of children with reported fever in each administrative unit was stratified by month of interview, and this measure was modeled statistically with repeated measures logistic regression using the GENMOD procedure in SAS software, Version 9.3 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). Predictor variables included the month and year of the survey along with geographic and environmental variables calculated in ArcGIS Version 10 (ESRI, Redlands, CA, USA). The *x* and *y* coordinate of the administrative unit's centroid were calculated from a digital map of world administrative divisions. Mean, minimum, and maximum elevation was calculated for each unit using gridded data from the WorldClim global climate data project (www.worldclim.org). Monthly precipitation and monthly temperature were obtained from the same dataset and mean values for the month prior to each interview were calculated. The population of each region was calculated from gridded data created by The WorldPop Project (www.worldpop.org.uk) and log-transformed, and population-weighted mean *Plasmodium falciparum* prevalence in 2-10 year olds ($Pf\text{PR}_{2\text{-}10}$) was calculated using 2010 estimates from the Malaria Atlas Project (MAP)(1); future estimates will incorporate

the latest available prevalence data from MAP. Gridded data on <5 year old population were also obtained from WorldPop. Finally, gross domestic product per capita (GDP) and official development assistance per capita (ODA) for each country were obtained from the World Bank. Mean values for 2000-2010 and the trajectory of each over that period were used. An exchangeable structure was used to account for correlation between monthly fever rates within the same administrative unit. The mean of all selected 2-week fever rates was then calculated and multiplied by 26 to derive an annual estimate for each administrative unit for each survey.

Estimating current <5 annual fevers

Annualized <5 fever rate estimates are indicative of the year in which the survey was conducted. However, fever rates have declined in parts of sub-Saharan Africa over the past decade in concert with overall observations of improving health outcomes in children <5. Fever incidence in each administrative unit was extrapolated accordingly to the year 2014 using repeated measures logistic regression. The under-five population of each administrative unit was summed from WorldPop gridded population data corresponding to 2010 and proportionately adjusted so that the national population equaled UN <5 population estimates for the year in which each survey was conducted. The fraction of children from each administrative unit predicted to have fever in the year of each survey according to the annualized fever rate was then calculated and used as the outcome variable in the regression model. Predictive variables were the same as in the model predicting monthly fever rates with the exceptions that month was not included, and annual average precipitation and temperature from WorldClim were added in lieu of month-specific figures. An exchangeable structure was used to account for correlation between annualized fever rates within the same administrative unit. These models were also used to make predictions for what fever rates would be in 2014 for countries where no surveys were available.

Estimating current fevers for $\geq$5 year olds

Estimates of annual fever incidence in 2014 for those $\geq$5 years were extrapolated for all administrative units from the 2014 annualized <5 estimates according to a literature review-based relationship. Publications were identified in which the fraction of both <5 and $\geq$5 year olds reporting fever were provided from community-based surveys. Methods for this extrapolation are described elsewhere(2).

Population and malaria prevalence estimation

Three age groups were used in the model: 0 to 4, 5 to 7, and 8 and older. These groups correspond approximately to ACT dosage weight/age bands and are thus useful for forecasting specific ACT products. Gridded population data at 1 km resolution across Africa were obtained from the WorldPop project for the year 2010. Populations were summed across each administrative unit in ArcGIS, Version 10 (ESRI, Redlands, CA, USA). Annual national UN population projections from 2014 were obtained for each country and the population in each administrative region was proportionately recalculated to meet that total assuming the same distribution of population among regions as in 2010.

Gridded population prevalence estimates of *P. falciparum* malaria infection in 2-10 year olds (*Pf*PR_{2-10}) for the year 2010 (this will be updated with the latest figures, as available) were obtained from MAP(1). A population-weighted mean *Pf*PR_{2-10} was calculated for each administrative division by calculating the average of the Malaria Atlas Project gridded prevalence weighted by the WorldPop gridded population map in ArcGIS. The prevalence of malaria infection in 2-10 year olds was converted to equivalent prevalence in each age group through a published mathematical relationship(3). These prevalence measures describe the fraction of the population infected with *P. falciparum* malaria, but those who seek treatment for illness in endemic areas should have a higher prevalence. Malaria prevalence in febrile individuals was estimated from the population prevalence according to an empirical relationship described by Okiro and Snow in 2010(4). The authors reviewed population-representative household surveys and compared malaria prevalence as measured by rapid diagnostic test in febrile <5s to prevalence in all children regardless of febrile status; they found febrile children tended to have higher prevalence by a factor of 1.376 times the general population. This relationship was applied to all age groups to derive febrile prevalence among treatment-seekers for each. Malaria prevalence among febrile individuals who do not seek treatment is assumed to be equivalent to malaria prevalence among the general population.

Impact of ACT or ITN coverage on malaria prevalence

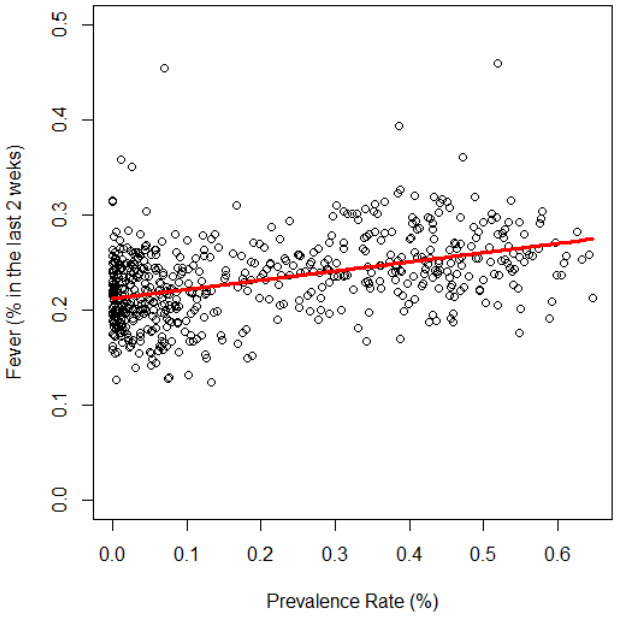
Mathematical transmission models are simplified representations of the world, but they provide a useful tool for understanding the impact of interventions on malaria and fever prevalence. This impact was evaluated using stochastic individual-based malaria transmission models developed by Imperial College(5) and Johns Hopkins School of Public Health (unpublished model), and will

be modified with current and future updates to these models. Currently, these models incorporate a number of complexities (in terms of interaction between hosts and vectors, vector behavior, treatment of infections, vector or parasite-focused interventions) that make them more realistic than classical mathematical models, which typically include overly simplistic assumptions(6) (e.g., mosquitoes bite all individuals with equal probability). The model parameters were estimated using generic estimates of malaria transmission assuming the malaria vector to be *Anopheles gambiae*, an African indoor-biting vector for which the Imperial College model was parameterized. The main output was malaria prevalence rate, and resulted in a compilation of reference tables that can be used to project the impact of a change in parasite-focused strategies (ACTs) or vector control (ITN usage) on malaria prevalence; The forecast model, using inputs on RDT, ACT and ITN coverage, ultimately outputs an estimate for ACT demand/use, and this new coverage level can be used to estimate the impact of the change in ITN coverage or ACT use on malaria prevalence, allowing the model to iterate as a change in malaria prevalence will likely produce a change in fever incidence.

Impact of a change in malaria prevalence on fever prevalence

The relationship between malaria prevalence and fever was estimated by comparing population-weighted prevalence at the first administrative division level from the Malaria Atlas Project to annualized febrile incidence as calculated from household surveys. A simple linear regression was fit to the data (Figure 1): fever = 0.2119 + 0.0966 * PR. Figure 1 shows that the fever rate gradually increases as malaria prevalence increases (maximum range for the modeled fever rate is between 21% in the absence of malaria and 27% for a prevalence of 65%).

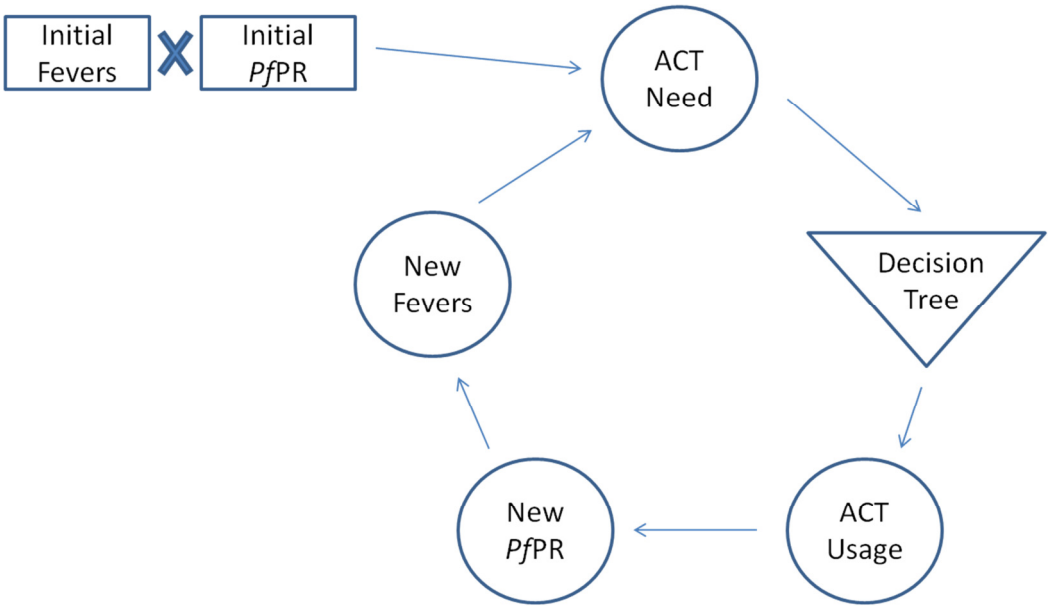
Figure 1 Fever rate in the last two weeks among children <5s as a function of malaria prevalence using the most recent malaria surveys.



Iteration of ACT need estimates

The CHAI decision tree model can be iterated over multiple years, given estimated changes in population growth and modeling around the impact of interventions on a change in ACT usage. With each cycle of the decision-tree model, a new fever rate is calculated based on the change in malaria prevalence resulting from the effect of treatment or diagnostics. ACT need can be iterated by applying the new fever incidence to the population estimate, expanding this figure to arrive at an annual fever estimate, and applying the new malaria prevalence estimate (Figure 2).

Figure 2 Iterating ACT need



C. ACT, ARTEMISININ MONOTHERAPY, AND RDT DEMAND

CHAI's decision-tree algorithm, described above to estimate ACT need, has been expanded to estimate total demand for anti-malarial medicines, diagnostic testing, and the ACT-specific portion of anti-malarial demand. The decision tree follows the cascade of symptomatic suspected malaria cases through the multi-channel health care system from point of entry (fever) to treatment options, using inputs projected based off trends in household survey data. The algorithm takes a step-wise approach, first tabulating treatment seeking rates by channel (sector), then calculating the portion of those tested among those who sought treatment. We then apply fever-adjusted malaria prevalence to the number of febrile cases that sought treatment and were tested, to estimate the fraction that were likely positive, and follow this up with an assumption (based on literature review and household survey responses) on treatment adherence to positive, negative, or non-tests to arrive at an estimate of ACT use. We

extrapolate all of these processes from <5 populations to the ≥5 population using relative treatment-seeking scalars (as described below). Through this process, we can output usage of diagnostic tests, anti-malarial medicines, and ACTs in particular.

Throughout the project, key outputs from this model (e.g., total fevers, estimated malaria incident cases), will be compared to similar outputs from other research groups (e.g., MAP, WHO GMP). Because we are attempting to build a model extrapolating the overall demand for anti-malarials resulting from individual febrile cases, we expect that the outputs will differ owing to the methods employed and the outputs targeted; we will endeavor to rationalize differences where they exist and are willing to adjust methods to increase accuracy and precision.

Estimating treatment seeking and treatment rates

Each population-representative survey asked about whether a drug was received for each <5 febrile episode, what kind of drug was received, and where treatment was sought (e.g., public health facility, private doctor, informal shop). The fraction of fevers treated with any drug, the fraction of those drugs reported to be anti-malarials, the fraction of reported anti-malarials that were ACTs, and the fraction of drugs reported to have been received in public health facilities, formal private sector facilities, or informal private facilities were calculated for each administrative district. Formal private sector facilities included private hospitals or doctors' offices, and private pharmacies, while informal facilities included shops or vendors. Religious or NGO facilities were included as public outlets since the availability of commodities and type of case management at those facilities are more likely to resemble other not-for-profit locations. Trends in survey-derived values were extrapolated to 2014 for each administrative unit using the same logistic regression analysis approach described above. For surveys that did not report location of treatment seeking for malaria, treatment seeking location for respiratory disease was substituted.

An additional literature review was conducted to identify publications presenting population survey-derived data on the relationship between the fraction of <5s and ≥5s seeking treatment in the private sector. Thirteen publications were identified detailing behaviors across a total of 63 sites. Simple linear regression was used to calculate the relationship between <5 and ≥5 treatment seeking in the private sector. Private sector treatment-seeking behavior in ≥5s was

found to be closely related to <5 treatment-seeking behavior but was on average 10.64% greater, relative to <5 treatment seeking. The linear relationship:

≥5 private sector fraction = 0.0918 + 0.9003 * <5 private sector fraction

was found to explain 83.25% of the variance in ≥5 private sector fractions. This relationship was then used to convert <5 private sector treatment-seeking rates for each administrative unit into estimated ≥5 private sector treatment-seeking rates.

Survey results and subsequent statistical adjustments provided empirical observations of the fraction of anti-malarials that were comprised of ACTs in each of the sectors categorized here. In the private formal and informal sectors, however, ACT share may be dynamically related to the price of drugs; some countries have attempted to increase ACT market share by manipulating pricing. To capture this dynamic, analysis was undertaken of the price and sales volume data from ACTwatch outlet surveys. A relationship was derived between the relative price of ACTs relative to other anti-malarials and the fraction of reported anti-malarial sales that were ACTs using linear regression model. This relationship was then used to modify ACT market share in the decision tree model as described below.

Estimating Testing rates

The fraction of febrile <5s whose caregiver reported they received a blood test was reported in DHS or MIS surveys for the following countries: Angola, Burkina Faso, Burundi, Gabon, Liberia, Madagascar, Malawi, Mozambique, Nigeria, Rwanda, Senegal, Tanzania, Uganda, and Zimbabwe (see the table, below). Testing rates were calculated separately from these surveys for the public, formal private, and informal private sectors. For the remaining countries in the model where testing rates were not known, the diagnostic test probability was assumed to equal the ratio of tests to anti-malarials dispensed as reported in the 2014 World Malaria Report. The ratio of testing to anti-malarials was of 0.72 in the public sector, 0.49 in the formal private sector and 0.15 in the informal private sector. The same testing rates were assumed for ≥5s. These figures will be updated as additional source data becomes available.

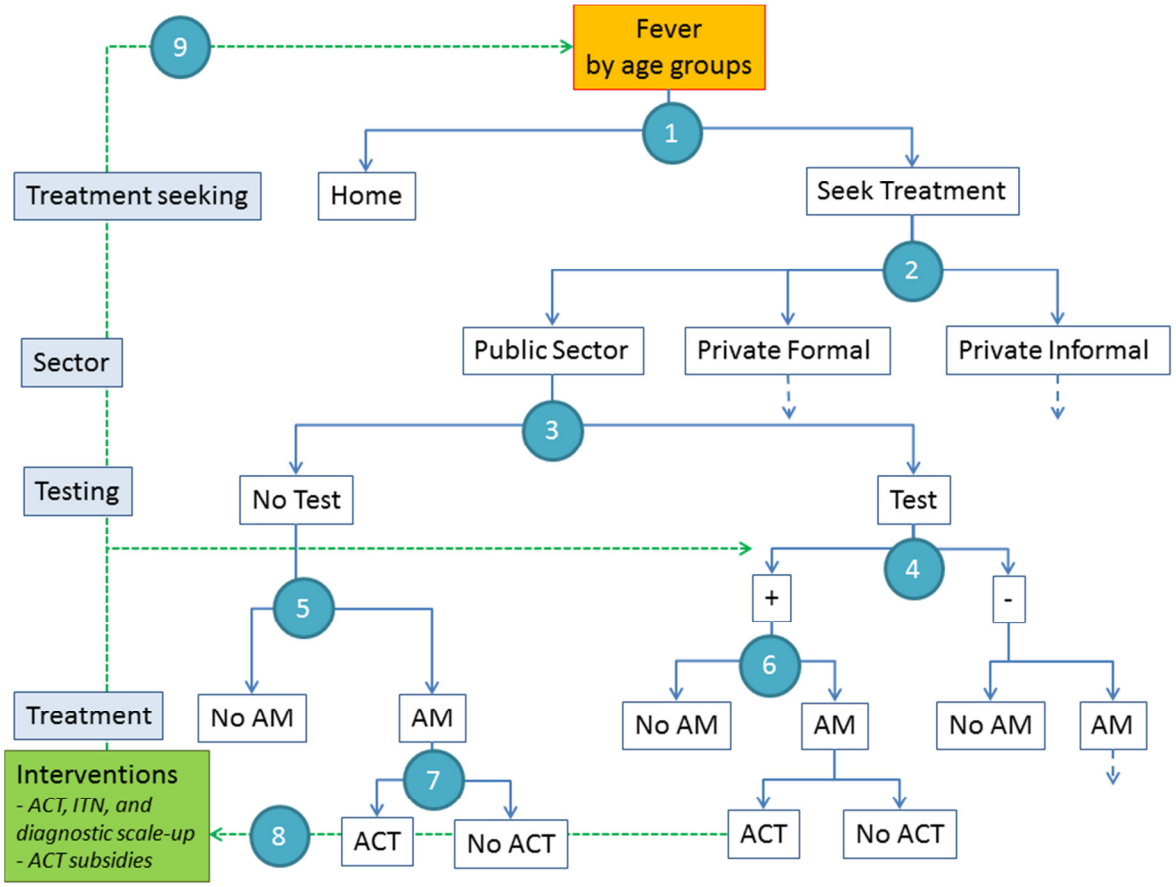
Sources for Data on Current Malaria Testing Rates

Country	Survey Source	Survey Year	Proportion of febrile treatment seekers who were tested	Overall proportion treated with an anti-malarial	Proportion of those who were tested who then received an anti-malarial treatment	Proportion of those who were NOT tested who then received an anti-malarial treatment
Angola	MIS	2011	41%	39%	67%	23%
Burkina	DHS	2010-	8%	62%	83%	60%
Burundi	MIS	2012-	48%	45%	59%	33%
Gabon	DHS	2012	17%	32%	54%	28%
Liberia	MIS	2011	41%	75%	84%	68%
Madagascar	MIS	2013	23%	27%	40%	26%
Malawi	MIS	2012	36%	54%	72%	43%
Mozambique	DHS	2011	43%	64%	75%	54%
Nigeria	MIS	2010	6%	62%	72%	62%
Rwanda	DHS	2010-	37%	19%	20%	18%
Senegal	DHS	2010-	15%	17%	26%	16%
Tanzania	MIS	2011-	30%	61%	76%	55%
Uganda	DHS	2011	29%	76%	81%	74%
Zimbabwe	DHS	2010-	13%	4%	20%	2%

The CHAI Decision Tree Algorithm

The entry point to the decision-tree model (Figure 3) was a febrile case (defined as a febrile episode in a single individual that may lead to that individual seeking treatment at home or from a public or private dispenser of health care or products; a given individual may have multiple febrile events in a given year), and each branch was stratified by age groups that roughly correspond with the treatment dose weight bands for ACTs: 0 to 4 year-old (lower pediatric ACT dose), 5-7 year-old (higher pediatric ACT dose), and 8 year-old or older (adolescent and adult ACT doses).

Figure 3 Decision tree for the need/demand model.



- **Step 1, Treatment seeking among the febrile population**: Due to differences in the way household surveys categorized data on treatment seeking, the most consistent framework for this assumption was to base the probability that a febrile case seeks treatment outside their home on the portion of the population who received a drug (any treatment) for febrile illness adjusted by the portion of febrile cases that were treated with a drug at home (20% of those that received a drug, based review of the published literature(7–37)).

- **Step 2, Of those seeking treatment outside the home, where do they go?**: The probability to go to either the public, formal private[1] or informal private sector was based on survey estimates which categorized the source of the treatment. *This step outputs the number of febrile treatment seekers per distribution channel/sector*.

[1] Formal private sector includes private not-for-profit and for-profit hospitals and clinics, and pharmacies. Informal private sector includes private drug shops, vendors and general retailers that sell medicines.

- **Step 3, Of those who sought treatment outside the home, the portion that are tested for malaria**: Each febrile treatment-seeking case has a probability of being diagnosed via a malaria diagnostic test; this probability was based on DHS/MIS-reported blood testing or data from the World Malaria Report. Where data on blood testing was not available, we used the population-weighted average ratio between testing and anti-malarial treatment in settings where both data points were known, and applied this average ratio to the known data on anti-malarial treatment to arrive at a proxy for test use in these settings. *This step outputs the number of febrile cases that likely receive a diagnostic test or malaria.* The portion of test demand that is attributable to RDTs is derived by applying the ratio between national RDT procurement estimates (see below) and national testing estimates to the derived test demand estimate, or by tabulating data on RDT usage from household surveys (where available). *This step outputs the demand for RDTs.*

- **Step 4, Of those who were tested for malaria, the probability that the test was positive**: Given evidence that malaria prevalence among treatment seekers is equivalent across healthcare outlets(38), the probability of positive test result was based on an extrapolation of prevalence in febrile cases from population-wide malaria prevalence based on analysis showing that malaria prevalence amongst febrile patients is somewhat higher than prevalence amongst the general population(1,4). Malaria prevalence used Malaria Atlas Project calculations as a baseline and adjusted them over time in response to scale up of either net or ACT coverage. *This step outputs the number of tested febrile cases that were likely positive for malaria infection.*

- **Step 5, Of those who were not tested for malaria, the probability of receiving an anti-malarial**: The probability of receiving an anti-malarial in the absence of a test was based on the adjusted proportion receiving an anti-malarial when seeking treatment for fever regardless of testing status (derived from survey estimates). *This step outputs the number of febrile cases that likely received an anti-malarial medicine without a preceding diagnostic test.*

- **Step 6, Of those who were tested for malaria, the probability of receiving an anti-malarial**: The probability of receiving an anti-malarial following a positive or negative test

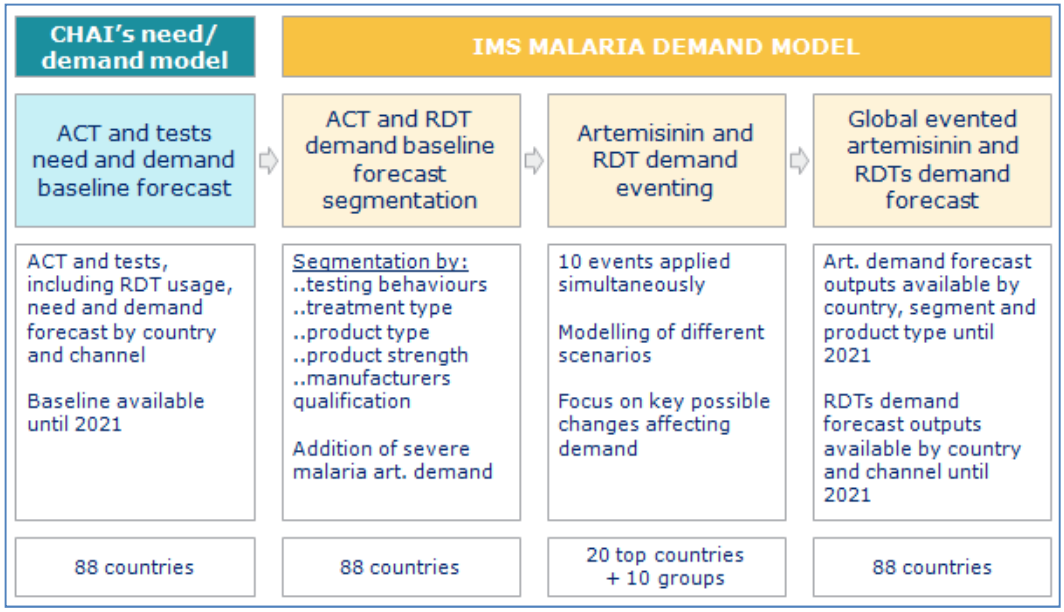
result was assumed to be 80% and 20%, respectively, based on analysis of the published literature(39–43). These estimates will be updated during the course of the project as new household survey data is collected on testing, test results, and treatment post-test. *This step outputs the number of febrile cases that likely received an anti-malarial medicine after the performance of a diagnostic test, and differentiates treatment rates by test result.*

- **Step 7, Of those who received an anti-malarial, the probability that it was an ACT**: The probability of receiving an ACT when receiving an anti-malarial for fever treatment was based on the estimated proportion of ACTs in public and private sector among all anti-malarials (derived from survey estimates). To reflect the impact of ACT price on demand for ACTs in the private sector, the ACT share of all anti-malarials sold in the private sector was adjusted using a linear regression model, based on price and sales volume data from ACTwatch outlet surveys, projecting ACT market share based on the ratio of the average price of the ACT to the average price of non-ACT anti-malarials. *This step outputs ACT demand given by the number of febrile cases that likely received an ACT. These figures are assembled at a sub-national (ADMIN1 unit) level, and can be aggregated nationally or globally.*

IMS Segmentation Overview

IMS will generate a yearly evented forecast of the global demand for artemisinin-containing anti-malarial drugs and rapid diagnostic tests (RDTs) by leveraging CHAI's baseline forecast and additional data sources and expertise. The overall IMS methodology to develop a global evented demand forecast revolves around three key steps, summarized in the figure below:

Figure 4 Global evented artemisinin and RDTs demand forecast methodology summary



As a first step, before the segmentation is applied, a comparison will be undertaken between ACT demand in CHAI's baseline outputs for the current calendar year and ACT demand recorded in the IMS Core data.

Where IMS Core data is available, the following comparisons will be made:

- The absolute number of ACT treatments in IMS Core data compared to CHAI's ACT demand
    - IMS will flag which countries have comprehensive data coverage and prioritize these countries for the comparison and validation exercise
    - Only similar channels will be compared, e.g. IMS private sector data will be compared to the sum of CHAIs baseline over private formal and private informal sector channels
- The relative proportion of ACT treatments out of all anti-malaria treatments in IMS data compared to the ratio in CHAI's need/demand model baseline

Any significant differences in ACT demand between IMS Core Data and CHAI's need/demand model baseline will be discussed and resolved between IMS and CHAI on an individual country basis.

IMS will then sub-segment the baseline forecast from CHAI's need / demand model to provide more granularity and insights on the dynamics of global artemisinin and RDTs

demand. The following segmentation of the anti-malarial and test demand outputs from CHAI's model will be added by IMS:

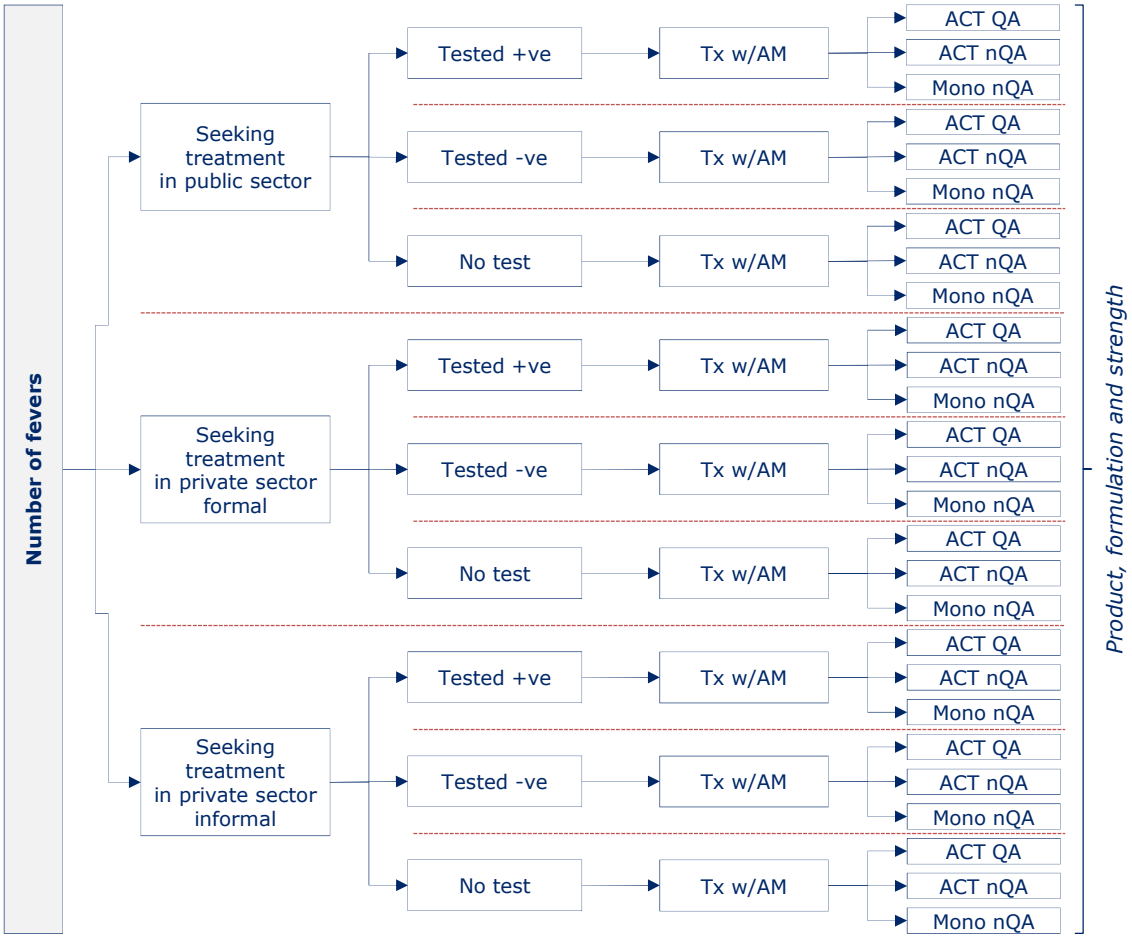
- Number of oral artemisinin monotherapy treatments
- Number of Quality-Assured (QA) and non-QA ACTs
- ACT and oral artemisinin monotherapy split across different products and their respective strengths

Applying the above segmentation across the three channels results in a total of 27 distinct segments, for which all forecast outputs will be made available.

Please note that the use of parenteral and rectal formulations of artemisinin cannot be added to the demand flow as they were not included in the design of the need forecast. Further details on how these formulations will be incorporated into the global demand forecast are detailed below under "Inclusion of parenteral and rectal monotherapy artemisinin".

The following flow illustrates the segmentation of artemisinin demand:

Figure 5 Full segmentation of the artemisinin demand flow



IMS will use a number of data sources, including the Core IMS data, to inform this segmentation. Please see below a summary of key data sources used to inform each step of the demand flows:

Layer	Key data source(s)
Number of fevers	• From CHAI's need/demand model
Fever treatment rate across channels	• From CHAI's need/demand model
Testing results (+) or (-), and non-tested	• From CHAI's need/demand model
Treatment rate with anti-malarial	• From CHAI's need/demand model
Usage of ACTs and oral artemisinin monotherapy	• ACT treatment rate is available in CHAI's need/demand model but is not currently linked to test outcome, this will be available in the upcoming revision of the algorithm • Core IMS Data to scale up demand for oral artemisinin monotherapy
Usage of Quality Assured (QA) vs. non-QA ACTs	• Core IMS Data
Product and strength split	• Core IMS Data, AMFm data and treatment guidelines

Please be aware that due to the way IMS data is collected and reported, the baseline segmentation will be provided at the private and public channel level. For modeling purposes the same inputs will be applied to both the informal and formal private sectors and these will both be considered as the private sector channel. Across a channel it will be assumed that the same product spilt applies across all testing outcomes i.e. the same QA to non-QA ACT split or ratio of mono artemisinin to ACT usage will be applied to test (+), test (-) and not tested cases within a channel. This assumption can be subsequently refined if new information becomes available

The sub-sections below will detail how this segmentation will be applied at the country level in the both private and public sectors, emphasizing methodological differences in countries where the Core IMS Data is not available.

Inclusion of oral artemisinin monotherapies

As previously explained, demand for oral artemisinin monotherapy products is not included in CHAI's baseline forecasts. To account for their usage, CHAI's baseline demand for ACTs will be scaled-up to a total oral artemisinin demand, including ACTs and oral monotherapy, by leveraging the Core IMS Data by distribution channel as follows:

Private sector channels

Countries with Core IMS Data available

The share that oral artemisinin monotherapies represent of total oral artemisinin treatments will be used to scale-up oral artemisinin demand. In the following example, analysis of the Core IMS Data produced the following split for a given country:

Artemisinin formulation	**Country average of total oral artemisinin, 2014**
Oral ACT	99.04%
Oral mono artemisinin	0.96%

If, for example, the CHAI baseline number for ACTs was 10,000 treatments, then the following would be calculated:

- Total oral artemisinin demand is 10,000 / 99.04% = 10,097 treatments
- Oral artemisinin monotherapy is 0.96% * 10,097 = 97 treatments

Any trends observed in the analysis of the last five years of demand will be projected forward in the baseline assumptions to account for instance for the decreasing usage of oral monotherapy as per WHO guidelines.

Countries without Core IMS Data available

A global average based on the countries with Core IMS data available will be applied as default value and can be subsequently refined on a country basis in light of new information.

Public sector channel

It will be assumed that there is no oral artemisinin monotherapy usage in the public sector.

Quality-Assured ACT usage

This segmentation will enable to discriminate demand for artemisinin drugs whose manufacturers are included in the WHO pre-qualification list.

Private sector channels

Countries with Core IMS Data available

The QAACT vs. non-QAACT % split for each country will be calculated by cross-checking the ACT producing manufacturers in the IMS Core Data against the WHO pre-qualification list. Please note that these numbers may be subsequently refined as some manufacturers importing products from pre-qualified manufacturers may be misinterpreted as non-pre-qualified supply. Any trends observed in the analysis of the last five years of demand will be projected forward in the baseline assumptions.

Countries without Core IMS Data available

A global average based on the countries with Core IMS data available will be applied as default value and can be subsequently refined on a country basis in light of new information.

Public sector channel

Although non-QAACTs may be available in the public sector, IMS is not aware of any data sources, Core IMS Data or otherwise, which can be used presently to quantify this demand. It will be assumed that the entirety of ACT demand in the public sector is for QAACT. This can be subsequently refined on a country basis in light of new information.

Inclusion of parenteral and rectal monotherapy artemisinin

As previously explained, demand for non-oral artemisinin products, namely parenteral and rectal formulations of artemisinin monotherapy products, and is not included in the baseline forecasts provided by CHAI. To account for these formulations in the global demand forecast, CHAI's baseline demand for oral ACTs, which has been previously scaled-up to a total oral artemisinin demand, will be scaled-up a second time to a total artemisinin demand, including parenteral and rectal, by leveraging the Core IMS Data.

Private sector channels

Countries with Core IMS Data available

The share that parenteral and rectal formulations of artemisinin represent of total artemisinin treatments will be used to scale-up oral artemisinin demand. The following example assumes the analysis of the Core IMS Data gave out the following split for a given country:

Artemisinin formulation	**Country average of total artemisinin, 2014**
Oral	98.00%
Parenteral	1.75%
Rectal	0.25%

Assuming the CHAI baseline for oral artemisinin from the scaling-up of ACTs is 10,000 treatments, the following will be calculated:

- Total artemisinin demand is 10,000 / 98% = 10,204 treatments
- Parenteral artemisinin is 1.75% * 10,204 = 179 treatments
- Rectal artemisinin is 0.25% * 10,204 = 26 treatments

Any trends observed in the analysis of the last five years of demand will be projected forward in the baseline assumptions to account for instance for the possible decrease in usage of rectal or parenteral formulations of artemisinin due to better case management and higher user of ACTs.

Countries without Core IMS Data available

A global average based on the countries with Core IMS data available will be applied as default value and can be subsequently refined on a country basis in light of new information.

Public sector channel

Countries with Core IMS Data available

The same scaling-up approach will be as employed as for countries with private sector Core IMS Data available (see above for details).

Countries without Core IMS Data available

Other data sources, including PQR data, will be used to calculate the split between parenteral, rectal and oral artemisinin products. If no other data sources are available, then the same global average figures as for the private channels will be applied and can be subsequently refined on a country basis in light of new information.

Artemisinin product split

This segmentation will enable to split demand for all artemisinin treatments into specific products. A product is here defined as a given combination of active ingredients, such as artemether + lumefantrine, as opposed to a specific brand name.

The IMS Core data has been used to identify all artemisinin products that are currently sold in the countries in scope. These have been grouped into 14 distinct product groups based on their active ingredients:

Composition	**Product group**		**Composition**	**Product group**
Artemether + lumefantrine	AL		Artesunate + pyrimethamine + sulfalene	Other AS ACTs
Artemisinin + lumefantrine	Other artemisinin ACTs		Artesunate + pyronaridine	AS + Pyronaridine
Artemisinin + naphthoquine	Other artemisinin ACTs		Dihydroartemisinin + amodiaquine	Other DHA ACTs
Artemisinin + piperaquine	Other artemisinin ACTs		Dihydroartemisinin + chloroquine	Other DHA ACTs
Artemotil + lumefantrine	Other artemotil ACTs		Dihydroartemisinin + piperaquine	DHA+PPQ
Artesunate + amodiaquine	AS+AQ		Artemether	Artemether
Artesunate + lumefantrine	Other AS ACTs		Artesunate	AS

Artesunate + mefloquine	AS+MQ		Artemotil	Artemotil
Artesunate + pyrimethamine + sulfadoxine	AS+SP		Dihydroartemisinin	DHA

The 14 product groups are available in a variety of formulation, leading to a final number of 19 product groups.

Product group	**Form**		**Product group**	**Form**
AL	Oral		AS+AQ	Oral
	Rectal		AS+MQ	Oral
Artemether	Oral		AS+SP	Oral
	Parenteral		AS + Pyronaridine	Oral
	Rectal		DHA	Oral
Artemotil	Parenteral		DHA+PPQ	Oral
AS	Oral		Other artemisinin ACTs	Oral
	Parenteral		Other artemotil ACTs	Oral
			Other AS ACTs	Oral
	Rectal			
			Other DHA ACTs	Oral

Note that any other product sold in countries for which IMS Core Data is not available would not have been identified in the above tables. Any new formulations of existing products that will launch in the forecast period will be modelled within their respective product group.

The product split will be managed manually by typing in values for each year and any major events will be managed manually.

<u>Private sector channels</u>

Countries with Core IMS Data available

IMS data will be used to allocate the total oral artemisinin demand for a country across the 19 different product groups. Any trends observed in the analysis of the last five years of demand will be projected forward in the baseline assumptions to account for changing product usage.

Countries without Core IMS Data available

Where available, AMFm data will be used to allocate the total oral artemisinin demand for a country across the 19 different product groups. In absence of other data sources, the same product split as for the public sector will be applied, based on a country's local treatment guidelines.

Public sector channel

Countries with Core IMS Data available

IMS data will be used to allocate the total oral artemisinin demand for a country across the 198 different product groups. Any trends observed in the analysis of the last five years of demand will be projected forward in the baseline assumptions to account for changing product usage.

Countries without Core IMS Data available

A blend of ACT donor procurement data and current treatment guidelines will be used to inform the product split. The split is likely to be static and based the latest available data.

Artemisinin product strength split

This segmentation will enable to split demand for all artemisinin products by strength, measured in milligrams of the artemisinin derivative included in the product.

The IMS Core data has been used to identify all strengths of artemisinin products that are currently sold in the countries in scope. There are 77 different product-formulation-strength combinations.

Product group	Form	Strengths included
AL	Oral	15MG, 20MG, 40MG, 60MG, 80MG, 90MG, 120MG, 180MG, 240MG, 360MG, 480MG
AL	Rectal	20MG
Artemether	Oral	40MG, 80MG, 120MG, 250MG, 300MG
Artemether	Parenteral	20MG, 40MG, 60MG, 75MG, 80MG, 100MG, 150MG, 600MG
Artemether	Rectal	40MG
Artemotil	Parenteral	75MG, 150MG, 300MG, 750MG
AS	Oral	50MG, 60MG, 80MG, 100MG, 200MG
AS	Parenteral	30MG, 60MG, 120MG
AS	Rectal	50MG, 200MG
AS+AQ	Oral	25MG, 50MG, 100MG, 150MG, 200MG
AS+MQ	Oral	50MG, 100MG, 200MG
AS+SP	Oral	25MG, 50MG, 100MG, 200MG
AS + Pyronaridine	Oral	60MG
DHA	Oral	60MG
DHA+PPQ	Oral	15MG, 20MG, 30MG, 40MG, 80MG, 90MG, 180MG
Other artemisinin ACTs	Oral	40MG, 80MG, 125MG, 250MG
Other artemotil ACTs	Oral	20MG
Other AS ACTs	Oral	20MG, 40MG, 80MG, 100MG, 180MG, 200MG, 360MG, 362MG, 725MG
Other DHA ACTs	Oral	80MG, 100MG

The product strength split will be managed manually by typing in values for each year, however no events is expected this split and it is expected to remain static.

Private sector channels

Countries with Core IMS Data available

Within a country, IMS data will be used to allocate the demand for each formulation of a product into its respective strengths. For QA ACTs, only pre-qualified strengths will be used, leveraging the respective proportion in the IMS data.

Countries without Core IMS Data available

A global average product split by strength will be calculated for each product type. These splits will then be applied to the product types available in the country.

Public sector channel

Countries with Core IMS Data available

Same as for private sector channels.

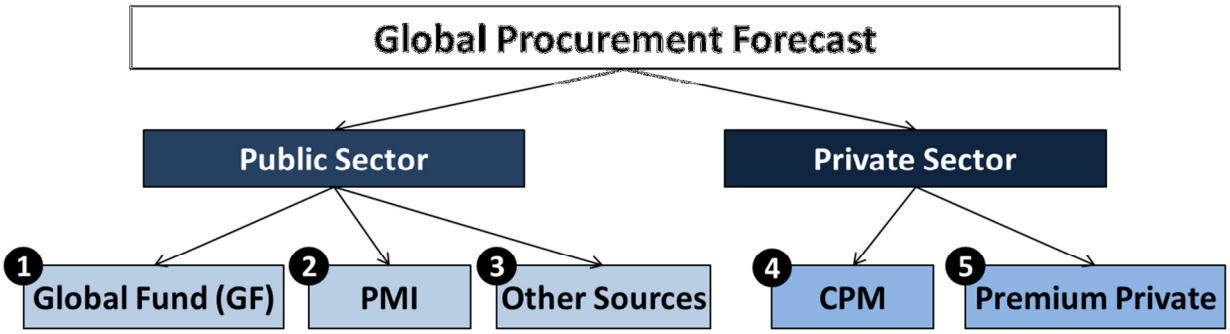
Countries without Core IMS Data available

A global average product split by strength will be calculated for each product type. These splits will then be applied to the product types available in the country.

D. QAACT, QA-INJECTABLE/RECTAL ARTESUNATE, AND RDT PROCUREMENT

QAACTs, QA-injectable/rectal artesunate, and RDTs are generally more expensive than less effective, sensitive/specific, or reliably reproducible alternatives (e.g., other anti-malarial medicines, quinine, and diagnosis via microscopy). Many (if not most) countries with endemic malaria transmission cannot afford the high treatment or diagnostic costs, and thus depend on funding from multi-lateral or bi-lateral donors that enables the procurement of these life-saving diagnostics and medicines. These funds are delivered into countries at predictable rates (e.g. annual disbursements from the GF), and comprise the majority of funds spent on procurement of these commodities. Thus, we can build baseline estimates by country for a procurement forecast by tabulating available financing for each country, estimating the percentage of funds spent on each commodity, and the weighted average price of each commodity. The weighted average prices for ACT and RDT procurement are determined based on the most recent annual pricing data from the Global Fund's PQR database, as well as PMI's historical pricing data. We would then compare these estimates to projections based on historical procurement. In addition, we will use data on actual sales volumes by all QAACT, QA-Injectable/rectal Artesunate, and RDT manufacturers (where available) to validate the procurement forecast outputs. Future reports will endeavor to incorporate a larger view of the malaria financing landscape to place commodity procurement in the context of other programmatic endeavors and project changes to funding allocations for commodities based on information gathered from NMCPs, grant recipients, malaria advisors, etc.

As mentioned above, since donor funding (particularly from the GF and PMI) represents the majority of funding towards procurement of these commodities, we outline the major sources / channels of funding, and the methodology used to project procurement from each funding source. We have identified five broad categories:



1. Global Fund public sector procurement

   To estimate the GF public sector procurement, we use the following steps:

   a. Projections of available funding by country by year – We analyze the publically available historical grants and disbursements data which lists all GF disbursements and grants by country and by date. Using historical disbursement rates, we project the funding available for each country for grants that are already in progress. We additionally use data from the funding envelopes and information from the concept note windows, to estimate funding start dates and amounts for grants that have not yet started but have an allocated amount (as per the funding envelope). For subsequent funding rounds (i.e. funding rounds that have not yet started, but will during the forecast period), we assume average disbursement rates to be similar to the previous round. This is validated by comparing the total funding envelope between funding rounds when that data becomes available. We proportionately adjust disbursement rates for subsequent rounds based on the percentage change in funding available for malaria between the new and previous round.

   b. Estimates on percentage spend on each commodity by country by year – We multiply the projections of total funding available by country by year with the percentage spend on each commodity to arrive at the funds available for each commodity. The percentage spend is calculated from dividing either the historical procurement (i.e. order data from GF's PQR database) or the country-level procurement plans by the total funding for the corresponding year. The country level procurement plans are based on either the country forecasts or on the GF's list of health products document. Since collating country level procurement plans is feasible for a limited set of countries, we prioritize them only for select countries which procure a large volume of commodities through donor funding.

We then analyze historical spending trends for each commodity at a country level to arrive at an estimated percentage spend by country, or directly use percentage spends where country procurement plans are available.

c. Price of each commodity (ACT, RDT, Inj. AS.) by country by year – We divide the funds available for each commodity (by country, by year) by the average price of that commodity to calculate the forecasted procurement volumes. The average price is based on the most recent year in the GF's PQR database, and hence takes into account the product and weight band splits at a country level.

2. PMI funded procurement (for the public sector)

   Historically, the US Government's President's Malaria Initiative (PMI) has helped coordinate country-level efforts in the provision and rapid scale-up of treatment and diagnostics, and has also been successful in filling developing gaps in coverage. We apply trends on the funding available for procurement of each commodity at a country level over the past few years, to project the future funding availability. We use the most recent PMI prices for each commodity at a country level available from PMI's historical procurement data. The PMI funded procurement volume is then calculated by dividing the funds available by the average price for each commodity at a country level.

3. Other funding for the public sector (from other donors, domestic funding)

   While Global Fund and PMI constitute for majority of public sector funding for most commodities, there are other domestic and donor funding sources. We will incorporate funding for commodities from country governments and other donors where data is available.

4. Co-payment mechanism (GF funded for the private sector for QAACTs only)

   For the private sector in countries taking part in the Global Fund's Private Sector Co-Payment Mechanism (CPM), which supports a subsidized, private sector market for QAACTs, we estimate CPM funding based on data from the Global Fund. We base our estimates on historical funding/procurement, planned funding/orders for the ongoing year under CPM, and the country's co-payment plans.

5. Premium i.e. non subsidized private sector

   The premium private sector (in countries not taking part in CPM for QAACTs and all countries for RDTs), volumes are calculated from private sector sales volumes tabulated

by IMS, and applied to outputs from the ACT and testing demand model (described above).

As mentioned above, for the public sector procurement across donors, we have used a mix of both historical procurement trends and country-level procurement plans. The use of either source (historical procurement trends or procurement plans) varies by the country, the forecast year, and the commodity. Hence, the proportion of the total public sector forecasted volumes attributed to a source varies by the forecast year and by the commodity. Countries are more likely to have reliable procurement plan data for the next 1 – 2 years rather than the next 3 – 5 years, since procurement plans are not drawn too far in advance, and if they are available for longer periods (3-5 years), the procurement estimates are less likely to be reliable as the likelihood of significant budget reprogramming increases with time. Hence, the proportion of the out years of the forecast that directly project procurement estimates based on procurement plan source data is marginal. The share of planned procurement data vs. historical procurement trends used for the forecast varies by the commodity due to a difference in the number of countries where planned procurement data is available for each commodity and the cumulative share of those countries in the public sector forecast for that commodity.

The choice of source for each country is primarily driven by two factors – availability of reliable data and the relative share of the country (i.e. country's share of total public sector commodity volume). We aim to gather procurement plans (particularly for the Global Fund funded commodities) for countries that contribute significantly to the total global public sector commodity procurement volume (e.g. Nigeria, Uganda, Tanzania) and have reliable data available through country forecasts, supply plans, or the Global Fund list of health products. However, these plans are not available for all high volumes countries. Additionally, there are few relatively low volume countries (i.e. countries which have a low share of total public sector commodity volume) for which procurement plans are easily available and used. Trends on historical procurement data are used for all other countries. As a general rule, most countries in the out years of the forecast used trends on historical procurement data due to limited availability of reliable procurement plans. We want to point out that the procurement plans are dynamic, and hence the planned procurement volumes are subject to change with each forecast. The definition of the historical procurement trend data source also varies by the forecast year. For example, in 2016, historical procurement data refers to the order data for all

artemisinin-derivative therapies and malaria rapid diagnostic tests between 2013 and 2015. In 2017, the historical procurement trends also incorporate planned procurement data for 2016 where available. Similarly, for 2018, historical procurement trends incorporate available planned procurement data for 2016 and 2017, and the 2019 historical procurement trends incorporate available planned procurement data for 2016 through 2018.

NOTE: Since the publication of the prior procurement forecast, the consortium has revised the procurement forecast methods and data sources to more accurately project annual procurement of ACTs, InjAS, and RDTs. Whereas previous methods relied primarily on country-level procurement plan data, with the grant-recipient's historical spending rate for diagnostic and treatment commodities ACTs as a secondary approach, the revised method estimates future procurement primarily based on historical procurement (i.e. order data) trends, with country-level procurement plan data used only for select high volume countries.

E. ARTEMISININ API DEMAND

Artemisinin API demand will be calculated based on the product mix (market share and strength distribution) for ACT and artemisinin monotherapy demand volumes, and the average yields for the various artemisinin derivatives. Product mix data will be estimated through the forecasting methods (described above), while data on derivative yields will periodically be collected from manufacturers to ensure the calculations are up to date with modernized methods. Currently, our understanding of the efficiencies of chemical derivation are that the process of converting artemisinin to artesunate has a 106% yield while conversion of artemisinin to either artemether or dihydroartemisinin has an 80% yield. We also factor some material loss in the tablet formulation and product packaging phases of the production process.

F. EVENTS

Introduction to eventing

An "event" is a future occurrence which will change the expected evolution of given behaviours and acts as a disruption to the baseline forecast. Events may include: changes

in funding, changes in treatment guidelines, new product launches, new formulation launches or specific disease awareness or education programmes. On-going trends which have already started, such as increasing access to RDTs in some countries or decrease in usage of oral artemisinin monotherapy drugs, are not considered as events and are included in the baseline projections instead.

The Consortium, with guidance from the Steering Committee, will profile a number of potential events that could impact artemisinin or RDT demand in the future. Only events affecting demand, as opposed to need or procurement, will be considered. To simplify the eventing process, some aspects of the global demand will not be directly evented, such as the split by products, the product split by strengths, the scale-up factors for parenteral and rectal artemisinin. These can be manually changed if a specific change is expected.

The eventing process is iterative by nature but will follow three key steps:

A PowerPoint-based ***event library*** will summarize all available information on the events and the eventing process to ensure full process transparency, including but not limited to event description, reason for inclusion or exclusion, forecast inputs and assumptions.

The consortium will leverage information, insights and opinions from UNITAID and the Steering Committee members to qualify and quantify the identified events. IMS will consult with in-house experts and/or with key Steering Committee stakeholders, as appropriate, to facilitate the eventing process.

Step 1: event selection

The selection of events will determine which events are active at each forecast cycle. While not all selected events necessarily have to be used in one forecast cycle, the IMS model will only support a maximum of ten events simultaneously. The decision on which events are selected will be taken by the Steering Committee for each forecast cycle. For each event included, full documentation of the inclusion or exclusion rationale will be included in the event library.

Step 2: event qualification

For each event selected by the Steering Committee, a short description of the occurrence will be drafted by IMS, in an effort to ensure a full understanding of the event nature, characteristics and likelihood. The regions, countries and channels the event will impact will also be clearly identified. Any past occurrence of the event, such as a previous occurrence in a different country, should also be captured, if applicable. Full documentation of the event qualification will be included in the event library.

Step 3: event quantification

Quantifying the event is a key aspect of the eventing process as it determines how the baseline forecast will change as a result of the occurrence of the event. It is first necessary to identify which aspect(s) of the artemisinin and RDTs demand will change, e.g., treatment rates, testing rates, treatment with AM etc., and then assess when and how the changes will take place.

<u>Locating the impact of the event</u>

Each layer of the demand flows can be evented, with the exception of the fever prevalence. Eventing will therefore focus on seven variables:

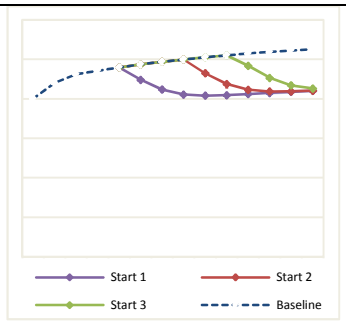
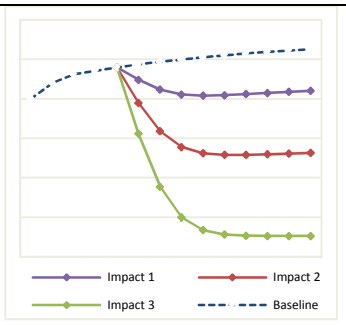
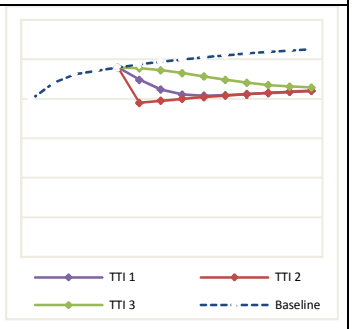
Demand flow layer	**By channel**	**By test results**
Treatment rates	**X**	

Testing rates	**X**	
Usage of RDTs	**X**	
Treatment rate with AM	**X**	**x**
Treatment rate with QA ACT	**X**	**x**
Treatment rate with non QA ACT	**X**	**x**
Treatment rate with non QA art. Mono	**X**	**x**

For a single event, it is therefore implied that a maximum 51 variables of the demand flow can be evented. As previously explained, events impacting the product split, the strength split or the scale-up of oral, parenteral or rectal artemisinin will be managed manually.

Quantifying the impact

The quantification of events is then defined by three key parameters as described in the table below.

Parameter	Start date	Impact	Time to impact
Description	The date at which the first noticeable change will be observed	The measure of how much the baseline is expected to change	A measure of how long the event will take to reach full impact
Format	Date, in month & year, from 2015 to 2020	Relative/absolute percentage change, (+) or (-)	Duration in year (integer)
Example	Jan-16, Nov-20	+5.0%, -85%	1 year, 10 years
Visualization			

Eventing parameters

The impact of an event can be twofold:

- A relative impact, in which the event changes the distribution across segments without changing the overall number of patients, tests or treatments
    - Example: increasing RDT usage at the expense of other testing methods, without changing the total number of tests
    - Example: increasing usage of QAACTs, at the expense of other treatment options, without changing the total number of treated patients
    - Unless otherwise specified, a relative increase or decrease will be proportionally mirrored on all the other segments within a given group
- An absolute impact, in which the event changes the overall number of patients, tests or treatments
    - Example: increasing usage of QAACTs for patients that would not otherwise have received an AM – the market is "grown"

To facilitate scenario building, all events can easily be switched on and off at the country level. The assumptions behind each event will be discussed and agreed with the Steering Committee, while IMS will facilitate these discussions to ensure the inputs fit the forecast model requirements.

Scenario building

A high case and a low case scenario can be generated to manage uncertainty around the occurrence or impact of selected events. While IMS will not conduct sensitivity analysis for all events, key uncertainties on impact, timing or occurrence can be included in a low or a high case.

Country groupings

Event assumptions will be applied individually by country or by group of countries. To simplify the overall eventing thought process and limit data entry, countries with smaller ACT demand will be grouped together in different cohorts and a single input will apply to all countries within the same group. While forecast outputs will still be available at the country level, this enables IMS to model events for 30 country/country groups at once instead of 88 separate countries.

Countries representing 85% of total ACT demand according to CHAI's baseline will be evented individually, and any event input can differ for each of these countries. A total of 20 countries will be evented individually:

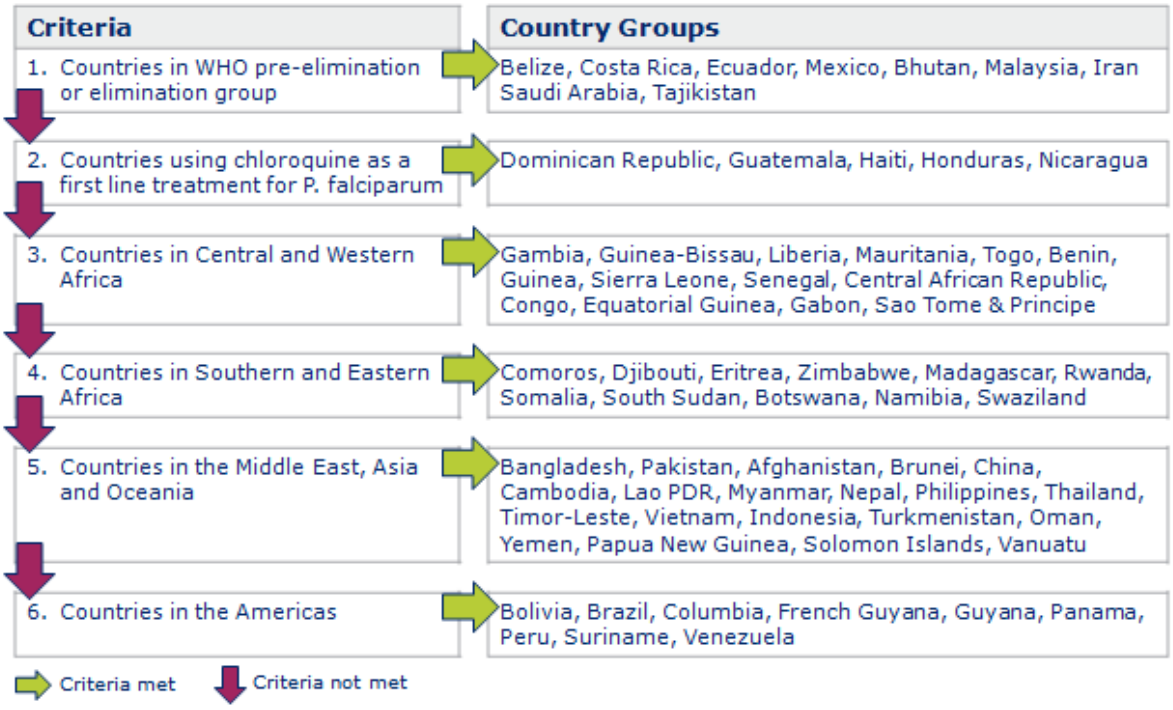
Angola, Burkina Faso, Burundi, Cameroon, Chad, Côte d'Ivoire, DRC, Ethiopia, Ghana, India, Kenya, Malawi, Mali, Mozambique, Niger, Nigeria, Sudan, Tanzania, Uganda, Zambia

The remaining 68 countries have been clustered into 6 "country groups". These groupings have been assigned by considering multiple criteria:

1. Countries in WHO pre-elimination or elimination group
2. Countries using chloroquine as a first line treatment for P. falciparum
3. Countries in Central and Western Africa
4. Countries in Southern and Eastern Africa
5. Countries in Middle East, Asia and Oceania
6. Countries in the Americas

These criteria have been applied sequentially to the 68 remaining countries. If a country satisfies multiple criteria then the group it is assigned to depends on the order the criteria are applied e.g. if a country is in pre-elimination phase and recommends chloroquine as a first line treatment choice for P. falciparum (Costa Rica) it will be placed in group 1 "Countries in WHO pre-elimination or elimination group" as this is the first criteria it meets.

Figure 7 Country Groupings for "Events"



The underlying assumption is that for a given event, countries will be expected to respond in a similar way and share the same start date, impact and time to impact. It should be remembered that no single country group makes up more than 5% of total ACT demand based on CHAI's need/demand model baseline. Any adjustments to the individual countries contained within these groups are therefore not expected to have a significant impact on the global demand forecast. Once events have been applied and calculated, outputs will be available at the individual country level.

Iteration of prevalence and fever cases

Once all events have been applied, any subsequent changes in ACT demand or testing rates will be used to recalibrate the malaria prevalence as per the relationship defined in need/demand model. IMS will apply these changes using CHAI-generated tables showing the impact of change in ACT share and testing rates on prevalence. IMS will then calculate the impact of a change in malaria prevalence on the number of fever cases. For example if in a given country events lead to a 10% reduction in malaria prevalence, and if likely malaria infections make up 12% of all fever cases, then a 1.2% reduction in the number of fever cases will be assumed.

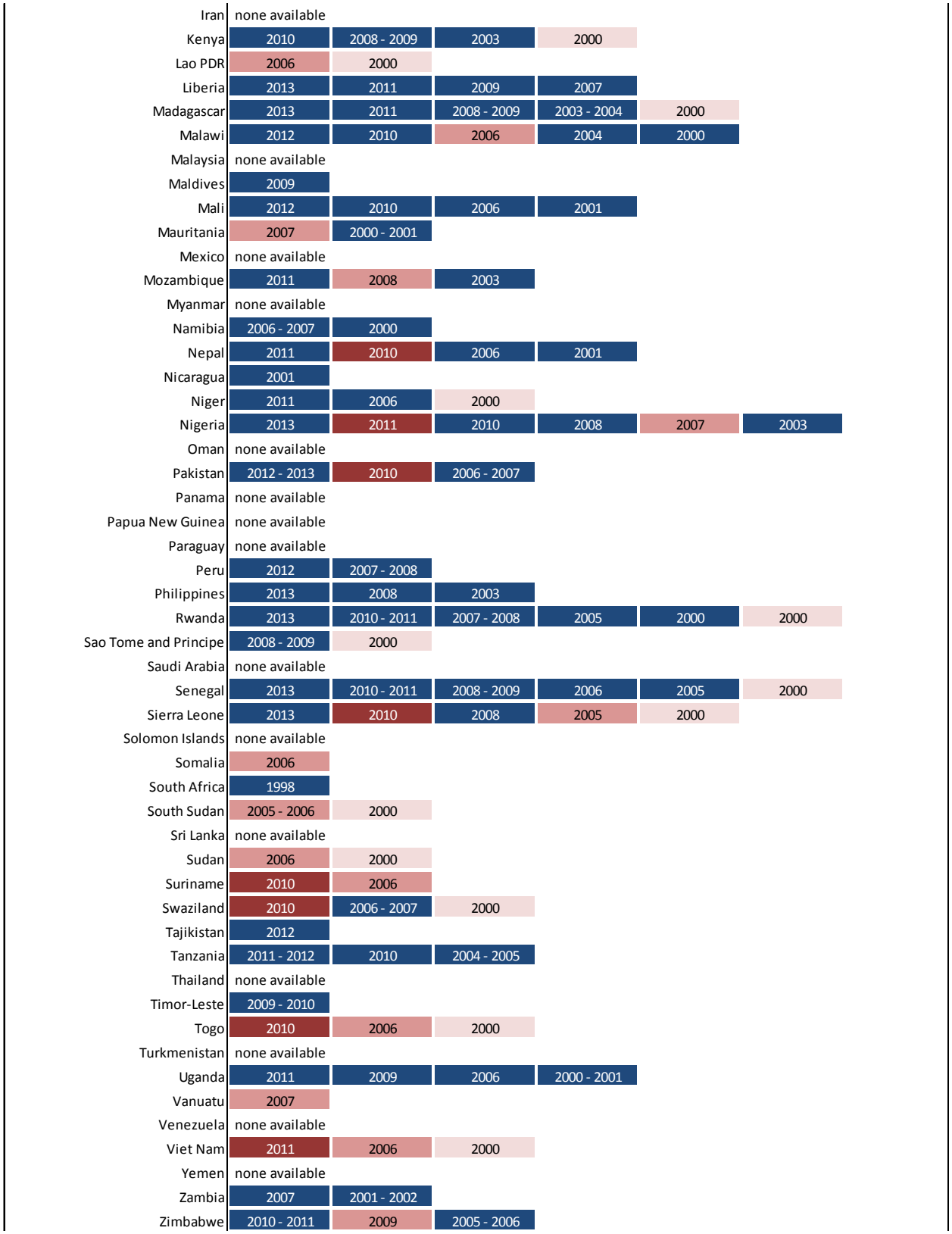
APPENDICES

Appendix 1 Household Survey Datasets Included in the CHAI Need/Demand model

Household Survey Color Key

	DHS/MIS	MICS4	MICS3	MICS2
Country A	2013	2011	2007	2001

Country	Survey Years *(most recent to least recent)*			
Afghanistan	none available			
Angola	2011	2006 - 2007	2001	
Australia	none available			
Bangladesh	2011	2007	2006	2004
Belize	none available			
Benin	2011 - 2012	2006	2001	
Bhutan	none available			
Bolivia	none available			
Botswana	2008			
Brazil	1996			
Brunei Darussalam	none available			
Burkina Faso	2010	2006	2003	
Burundi	2012	2010	2005	2000
Cambodia	2010	2005	2000	
Cameroon	2011	2006	2004	2000
Cape Verde	2005			
Central African Republic	2006	2000		
Chad	2004	2000		
China	none available			
Colombia	2010	2005		
Comoros	2012	2000		
Congo	2012	2005		
Costa Rica	none available			
Côte d'Ivoire	2011 - 2012	2006	2000	
Democratic Republic of the Congo	2013	2010	2007	2001
Djibouti	2006			
Dominican Republic	2013	2007	2002	
Ecuador	none available			
Equatorial Guinea	2000			
Eritrea	2002			
Ethiopia	2011	2005	2000	
French Guiana	none available			
Gabon	2012	2000		
Gambia	2005 - 2006	2000		
Ghana	2011	2008	2006	2003
Guatemala	1998 - 1999			
Guinea	2012	2005		
Guinea-Bissau	2006	2000		
Guyana	2009	2006 - 2007	2005	
Haiti	2000			
Honduras	2011 - 2012	2005 - 2006		
India	2005 - 2006			
Indonesia	2012	2007	2002 - 2003	


Iran none available
Kenya 2010 2008 - 2009 2003 2000
Lao PDR 2006 2000
Liberia 2013 2011 2009 2007
Madagascar 2013 2011 2008 - 2009 2003 - 2004 2000
Malawi 2012 2010 2006 2004 2000
Malaysia none available
Maldives 2009
Mali 2012 2010 2006 2001
Mauritania 2007 2000 - 2001
Mexico none available
Mozambique 2011 2008 2003
Myanmar none available
Namibia 2006 - 2007 2000
Nepal 2011 2010 2006 2001
Nicaragua 2001
Niger 2011 2006 2000
Nigeria 2013 2011 2010 2008 2007 2003
Oman none available
Pakistan 2012 - 2013 2010 2006 - 2007
Panama none available
Papua New Guinea none available
Paraguay none available
Peru 2012 2007 - 2008
Philippines 2013 2008 2003
Rwanda 2013 2010 - 2011 2007 - 2008 2005 2000 2000
Sao Tome and Principe 2008 - 2009 2000
Saudi Arabia none available
Senegal 2013 2010 - 2011 2008 - 2009 2006 2005 2000
Sierra Leone 2013 2010 2008 2005 2000
Solomon Islands none available
Somalia 2006
South Africa 1998
South Sudan 2005 - 2006 2000
Sri Lanka none available
Sudan 2006 2000
Suriname 2010 2006
Swaziland 2010 2006 - 2007 2000
Tajikistan 2012
Tanzania 2011 - 2012 2010 2004 - 2005
Thailand none available
Timor-Leste 2009 - 2010
Togo 2010 2006 2000
Turkmenistan none available
Uganda 2011 2009 2006 2000 - 2001
Vanuatu 2007
Venezuela none available
Viet Nam 2011 2006 2000
Yemen none available
Zambia 2007 2001 - 2002
Zimbabwe 2010 - 2011 2009 2005 - 2006

Appendix 2 Country Scope

The 88 countries in scope are: Afghanistan, Angola, Bangladesh, Belize, Benin, Bhutan, Bolivia, Botswana, Brazil, Brunei, Burkina Faso, Burundi, Cambodia, Cameroon, CAR, Chad, China, Colombia, Comoros, Congo, Costa Rica, Côte d'Ivoire, DRC, Djibouti, Dominican Rep., Ecuador, Eq. Guinea, Eritrea, Ethiopia, French Guiana, Gabon, Gambia, Ghana, Guatemala, Guinea-Bissau, Guinea, Guyana, Haiti, Honduras, India, Indonesia, Iran, Kenya, Lao PDR, Liberia, Madagascar, Malawi, Malaysia, Mali, Mauritania, Mexico, Mozambique, Myanmar, Namibia, Nepal, Nicaragua, Niger, Nigeria, Oman, Pakistan, Panama, Papua NG, Peru, Philippines, Rwanda, Sao Tome, Saudi Arabia, Senegal, Sierra Leone, Solomon, Somalia, South Sudan, Sudan, Suriname, Swaziland, Tajikistan, Tanzania, Thailand, Timor-Leste, Togo, Turkmenistan, Uganda, Vanuatu, Venezuela, Vietnam, Yemen, Zambia and Zimbabwe

Appendix 3 IMS Data Sources

Overview of outputs currently available in CHAIs Need/Demand model baseline

CHAI's Need/Demand Outputs	Description
Survey year	Year of data; survey data from the latest DHS and MICS report was used and then extrapolated for 2014
Continent	Continent of country
country	Country name
Sub-region	Sub-national data which may refer to district, province, state or other
fever04	The % of the total population aged 0-4 that have a fever, in a given two week period
fever57	The % of the total population aged 5-7 that have a fever, in a given two week period
fever8p	The % of the total population aged 8+ that have a fever, in a given two week period
pop04_2014	Population aged 0-4 in 2014
pop57_2014	Population aged 5-7 in 2014
pop8pl_2014	Population aged 8 and over in 2014

No. of FEVER	Number of fevers in total (adults and children)
No. of Likely malaria infections	Number of likely malaria infections amongst the febrile population (Note this doesn't model likely asymptomatic infections)
No. of SEEK.TREAT	Number of people (adults and children) that seek treatment in general
No. Seek.Treat.Public	Of those seeking treatment, number of people (adults and children) that seek treatment in the public sector
No.Seek.Treat.Private. Informal	Of those seeking treatment, number of people (adults and children) that seek treatment in the private informal sector
No.Seek.Treat.Private. Formal	Of those seeking treatment, number of people (adults and children) that seek treatment in the private informal sector
No. of TEST.PUBLIC	Number of people (adults and children) that get tested in the public sector with either an RDT or microscopy (among those with a fever)
No. Of TEST.PRIVATE. INFORMAL	Number of people (adults and children) that get tested in the private informal sector with either an RDT or microscopy (among those with a fever)
No.ofTEST.PRIVATE. FORMAL	Number of people (adults and children) that get tested in the private formal sector with either an RDT or microscopy (among those with a fever)
No. of TEST	Number of people (adults and children) that get tested in total (among those with a fever)
No. of AM.PUBLIC	The number of anti-malarials received by people who sought treatment in the public sector
No. Of AM.PRIVATE. INFORMAL	The number of anti-malarials received by people who sought treatment in the private informal sector
No. Of AM.PRIVATE. FORMAL	The number of anti-malarials received by people who sought treatment in the private formal sector
No. of AM	Number of anti-malarials in total in the market (public and private)
No. of ACT.PUBLIC	Number of ACTs in the public sector
No. of ACT.PRIVATE. INFORMAL	Number of ACTs in the private informal sector
No. Of ACT.PRIVATE. FORMAL	Number of ACTs in the private formal sector

No. of ACT	Number of ACTs in total in the market (public and private)
No. of AM.OT	Number of anti-malarials that are misused (overtreatment in public and private sector)
No. of AM.PUBLIC.OT	Number of anti-malarials that are misused (overtreatment in the public sector)
No. Of AM.PRIVATE. INFORMAL.OT	Number of anti-malarials that are misused (overtreatment in the private informal sector)
No. Of AM.PRIVATE. FORMAL.OT	Number of anti-malarials that are misused (overtreatment in the private formal sector)
No. of ACT.OT	Number of ACTs that are misused (overtreatment in the public and private sectors)
No. of ACT.PUBLIC.OT	Number of ACTs that are misused (overtreatment in the public sector)
No. Of ACT.PRIVATE. INFORMAL.OT	Number of ACTs that are misused (overtreatment in the private informal sector)
No. Of ACT.PRIVATE. FORMAL.OT	Number of ACTs that are misused (overtreatment in the private formal sector)

Description of IMS data assets available in <u>priority countries</u> and sampling methodologies

The following section will detail IMS data assets and sampling techniques in priority countries only as these countries make up the majority of ACT demand.

India Pharmaceutical Market

PUBLICATION CYCLE: Monthly

UNIVERSE SIZE:

Type	Name	Source	Universe	Audited Panel size	Market segment	Data collection frequency
Retail	Secondary stockist audit	Stockist sellout	22,624 Stockists	5,614 Stockists	81%	Monthly
Hospital	Hospital secondary audit	Stockist sellout			13%	Monthly
Combined	Total sales audit	Stockist sellout			100%	Monthly

DATA COLLECTION METHODOLOGY:

- A combination of "stratified" and "purposive" sampling techniques have been used to design a robust panel of stockists
- Stratified sampling over the regions ensures geographic coverage
- Purposive sampling ensures company coverage
- For a given region, stockists are selected to give the best mix of companies, ensuring a minimum of 20% coverage for top 200 companies
- The panel data is extrapolated to the market using projection factors which change monthly based on the sales input recorded from panel stockists

SPECIFIC MALARIA CONSIDERATIONS:

The sampling methodology may not fully capture anti malarial sales because:

- Distribution channels have better coverage in urban areas (whereas malaria is more prevalent in rural areas)
- The Indian Central government has a large "National Vector Borne Disease Control Program" under which it purchases anti malarial drugs directly from manufacturers
- State governments procure anti-malarials through tenders which are not covered in the IMS data

French West African Pharmaceutical Market

Countries with data available	
Côte d'Ivoire	Guinea
Cameroon	Benin

Gabon	Mali
Senegal	Burkina Faso
Congo	Togo

PUBLICATION CYCLE: Monthly or quarterly publication

UNIVERSE SIZE: Private pharmaceutical market covering 3095 pharmacies

DATA COLLECTION METHODOLOGY: Data is collected quarterly from wholesaler sales

- Sample size 22 wholesalers covering approximately 95% of market
- Projection factors are applied per country to scale up to the total market:

Côte d'Ivoire / 1.00

Cameroon / 1.03

Gabon / 1.00

Senegal / 1.00

Congo / 1.34

Guinea / 1.34

Benin / 1.37

Mali / 1.05

Burkina Faso / 1.01

Togo / 1.30

Country	Wholesalers	Pharmacies
Côte d'Ivoire	• CONTIEX • COPHARMED • BAA • LABOREX • MEX • DPCI	***700***
Cameroon	• CONTIEX • LABOREX • CAMPHARM • B2A • UCPHARM	***443***
Senegal	• CONTIEX • LABOREX • BAA • COPHASE • MEX	***600***

	• SODIPHARM	
Gabon	• CONTIEX • PHARMAGABON • B2A • COPHARGA	***149***
Congo	• CONTIEX • LABOREX • BAA • COPHARCO	***310***
Guinea	• CONTIEX • LABOREX	***250***
Benin	• CONTIEX • PROMOPHARMA • GAPOB	***140***
Mali	• CONTIEX • LABOREX • B2A • COPHARMA	***243***
Burkina Faso	• CONTIEX • LABOREX • B2A • COPHADIS • MEX • SOCOPHARM	***140***
Togo	• B2A • GTPHARM	***120***
Total FWA data	***22***	***3095***

Kenya Pharmaceutical Market

AUDIT OF: Wholesalers, Importers and Distributors

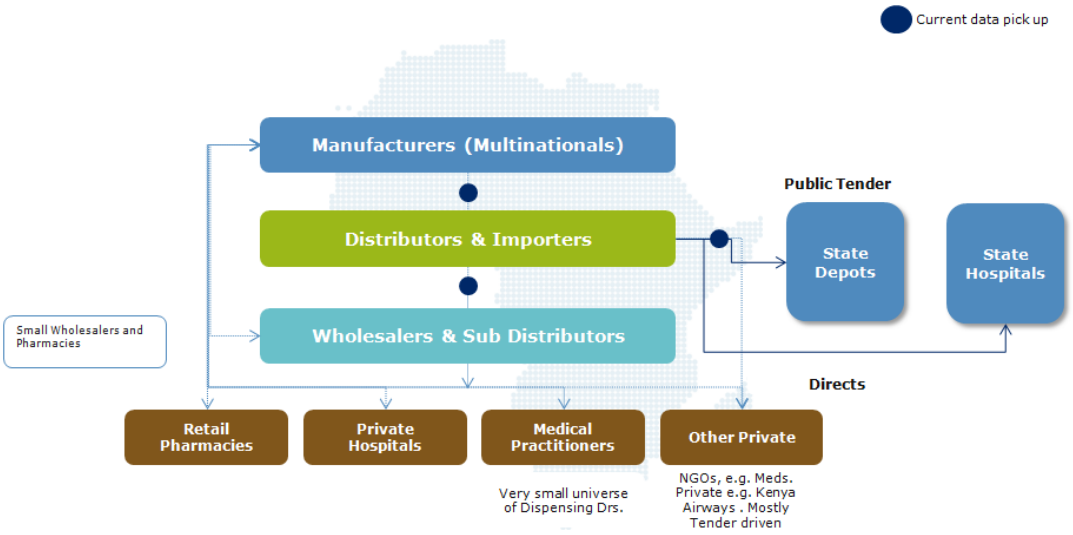
PUBLICATION CYCLE: Monthly

UNIVERSE SIZE: 10 wholesalers, importers, distributors

DATA COLLECTION METHODOLOGY: Wholesaler data collected on a monthly basis from 10 agents. IMS receives direct manufacturing data from 3 manufacturing companies (MNCs) for validation purposes.

No projection factors are applied.

REPRESENTATION: Public and private markets as represented by the selected panel. Estimate 70-80% MNC import coverage of pharmaceutical and para-pharmaceutical products.



Zambia Pharmaceutical Market

PUBLICATION CYCLE: Monthly

DATA COLLECTION METHODOLOGY: Zambia data is collected as a census, recording all products declared to the regulatory authority and delivered into the public stores i.e. data covers 100% of legal imports that are recorded by the Zambian authorities.

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