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S1. Supplementary Methods

S1.1 Calibration of Prevalence and Treatment Seeking Patterns

Treatment seeking data were obtained from the 2018 Malaria Indicator Survey (MIS)¹ and assigned to the fifteen MIS regions as listed in [Supp Table S1](#). These data were collected from December 11 2018 to January 31 2019 for children under five who had a fever in the preceding two weeks; children were counted as “treated” if advice or treatment was sought. The Kampala region did not receive enough survey responses for a reliable estimate, and the average treatment coverage of neighboring regions was used.

In order to account for seasonal fluctuations in *Anopheles* vector abundance, rainfall data were used as a proxy to adjust the daily transmission rate. Eleven years (2009-01-01 to 2019-12-31) of daily rainfall data within Uganda’s national borders from ERA5² were aggregated using Google Earth Engine. The daily means were then calculated, smoothed, and shifted forward by eleven days to account for the *Anopheles* lifecycle. This annual pattern was used to create an approximation of temporal variation in biting patterns as seen in [Supp Figure S1](#).

Following the collection of data on treatment seeking, drug choice, and rainfall patterns (along with the preparation of the population, district, and travel rasters for the model) we calibrated each pixel’s generic transmission parameter or biting parameter (β), which controls the transmission intensity of *P. falciparum* in the simulation. The calibration aims to match, for each pixel, the model’s 12-month average of *P. falciparum* prevalence in 2-10 year-olds (PfPR₂₋₁₀) to Malaria Atlas Project estimates of the same quantity for 2017³, as described previously⁴⁻⁶. Once complete, these MAP-informed pixel prevalences were updated to better match 2018-2019 PfPR₀₋₅₉ estimates (prevalence in children aged zero to 59 months) present in the 2018-2019 MIS (see [Supp Table S3](#)). However, this approach introduces some artifacts into the projected prevalence due to the Malaria Indicator Survey 2018-2019 survey district prevalence data being weighted higher, resulting in some spatial prevalence distributions that follow political boundaries.

S1.2 Calibration to Current Data on *pfkelch13* Allele Frequencies

A total of 83 *pfkelch13* allele frequencies, for alleles 469Y and 675V, were compiled from public literature⁷⁻¹¹ covering the period from 2015 to 2022 in 15 districts in Uganda ([Supp Table S4](#)). To

calibrate the model to these field data, simulations were run from 2004 to 2025, using the above calibrated prevalence and incidence values. Seven new model initialization parameters were added to reflect the following circumstances of 469Y and 675V emergence in the past:

- The district where 469Y first appeared
- The district where 675V first appeared
- The date of 469Y appearance
- The date of 675V appearance
- The initial allele frequency of 469Y (at appearance)
- The initial allele frequency of 675V (at appearance)
- The time at which mutation was activated in the model (after the model begins running in 2004, mutation is deactivated at least until equilibrium is reached)

Note that the term ‘appearance’ is intentionally vague, as we have no way of knowing when the first mutation occurred. In the simulation, we simply assume that one group of mutated parasites appears in a particular district at a particular time, with initial allele frequency x (which is fit below).

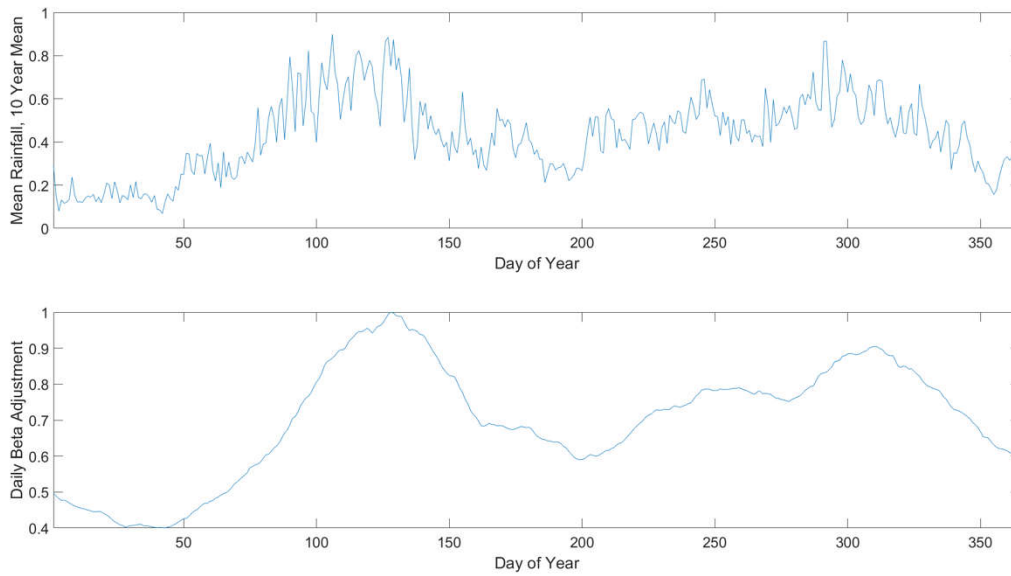
A total of 100 candidate parameter combinations were selected using Latin hypercube sampling to explore the relationships between the initial conditions and resulting allele frequencies during 2015-2022. For each parameter set, 30 model runs were executed with slight jittering to better capture the statistical variability between inputs and outputs, resulting in 3000 simulation runs. A machine learning approach, employing a traditional neural network built in PyTorch¹² was used to map the relationship between model inputs and the allele frequencies observed in 15 districts in Uganda. Two calibration approaches were applied:

1. **Data-to-Parameters mapping:** with this approach, the final calibrated neural network maps allele frequency data to the seven parameters listed above and the true allele frequency data are used to infer model initialization parameters.
2. **Parameters-to-Data mapping:** the final calibrated neural network, similar to a ‘model emulation’ tool¹³, is used to produce model outputs (allele frequencies) from input or initialization parameters (i.e. the seven parameters listed above). For this final calibrated neural network, we use an objective-function based search method to produce outputs close to the observed real-world data.

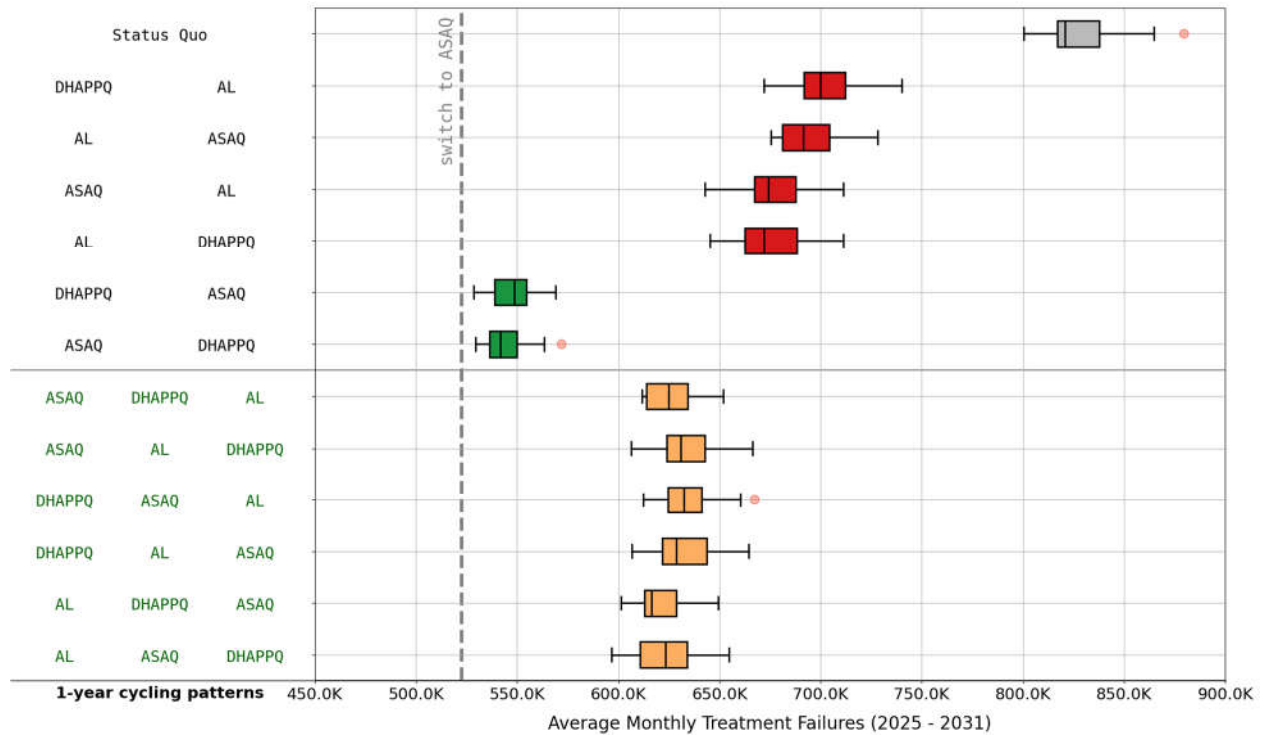
The "D-to-P" approach results in the development of an NN_{D-to-P} model that, once calibrated, takes allele frequency data as input and generates the corresponding model initialization parameters as output. One has to verify in this case that the model, when initialized with these parameters, produces the correct allele frequency output. In contrast, the P-to-D approach constructs an NN_{P-to-D} model that emulates the simulation process, allowing the neural network to be calibrated using an objective function centered on the true data (a feature not achievable with the NN_{D-to-P} approach). Building, calibrating, and training the NN_{P-to-D} model introduces an additional step where input parameter values are selected based on the best fit to the data. This fit was determined using three distinct objective functions, with absolute mean deviation between allele frequencies (83 pairs) serving as the primary objective function. A small penalization factor ($c \leq 1.0$) was applied to real-world allele frequencies that were lower than the model-predicted values, reflecting the likelihood that late arrival of an allele in a district is more probable than early arrival, due to the asymmetric variance associated with any waiting-time process.

The NN_{P-to-D} model was optimized using the Optuna Python library¹⁴. The process involved iterations from five random starting conditions (using Latin hypercube sampling boundaries), with comparisons of outputs for penalization factors $c = 0.1, 0.5$, and 1.0 ; this revealed no qualitative differences in the model fits as observed visually. The $c = 0.5$ penalty was chosen for the final calibrated NN_{P-to-D} model, and the inferred initialization parameters were: the 469Y allele was introduced on June 3, 2006, in Kumi district, with an initial frequency of 0.0534, while the 675V allele was introduced on December 10, 2006, in Soroti district, at a frequency of 0.000451. Mutation in the model was activated on October 27, 2012. This model was run and visualized to ensure that the projected allele frequencies ([Supp Figure S7](#)) and prevalence equilibrium matched real-world conditions between 2013 and 2022. Note that the initial appearance times are not meant to correspond to the true times that these allele frequencies were reached, as model simulations typically show an initial decrease after initial (artificial) appearance, followed by a standard expected sustained increase due to the action of natural selection. Mutation rates were calibrated as blood-stage asexual-parasite mutation events as described in previous modeling exercises^{15,16}.

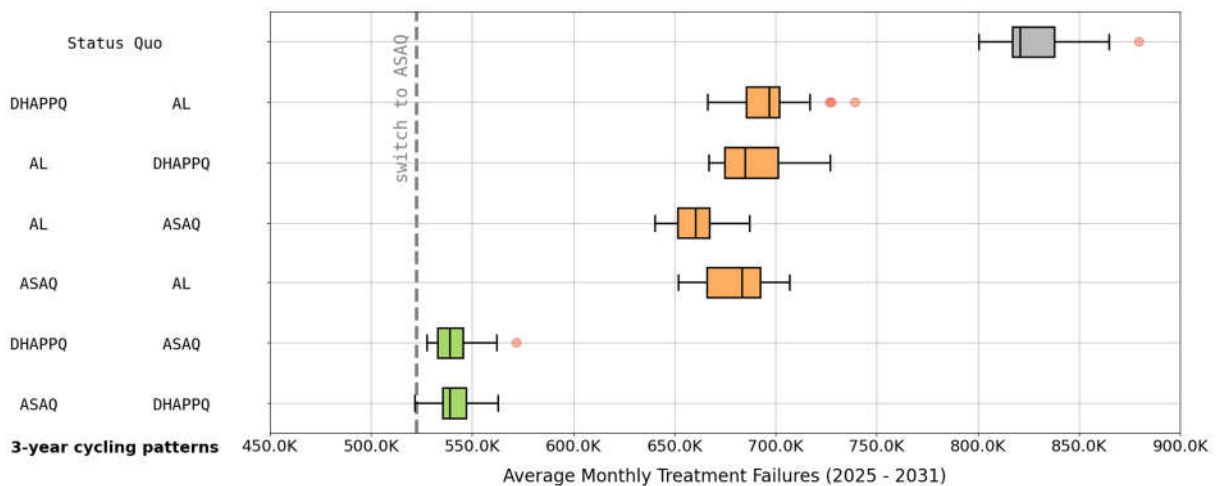
S2. Supplementary Figures



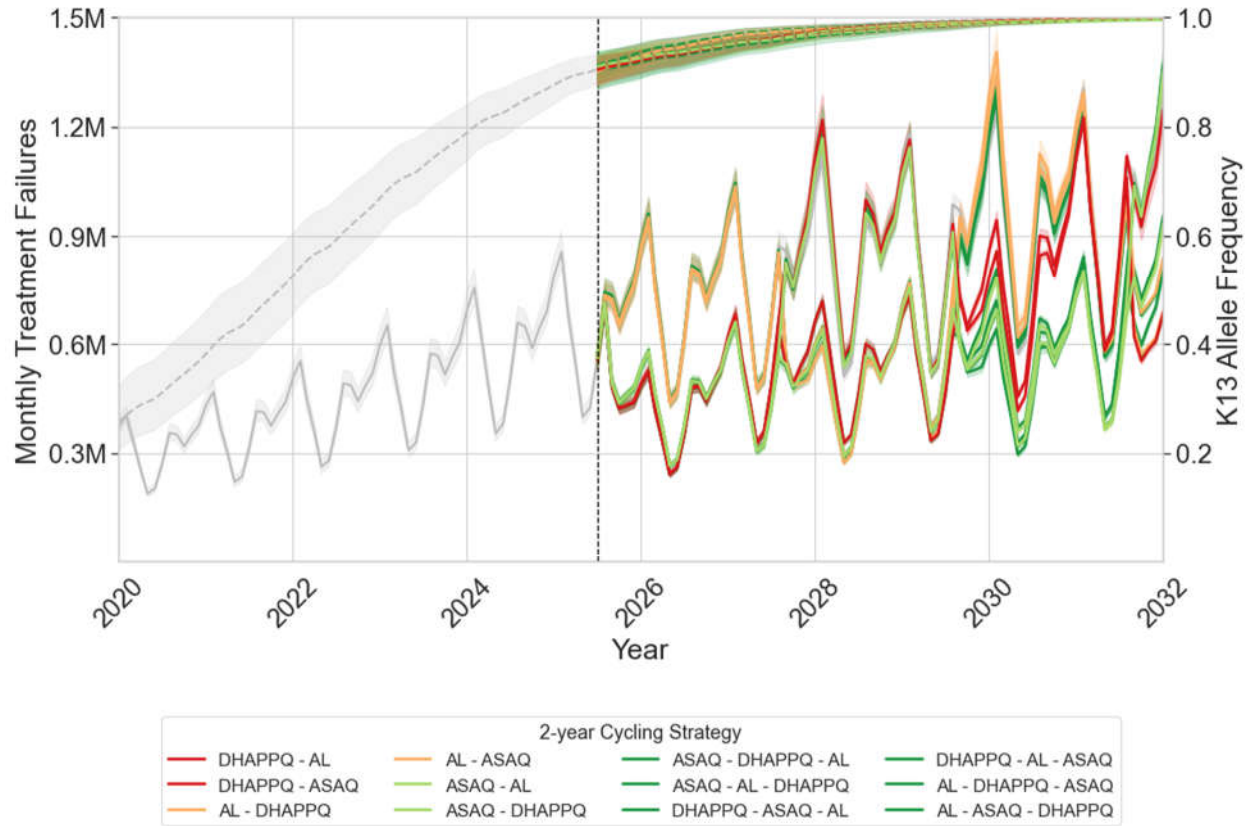
Supplementary Figure 1. Construction of the rainfall-derived seasonal transmission function used in the Uganda malaria simulation model. Top panel shows mean daily rainfall across Uganda, averaged over the period 2009–2019 from ERA5. Bottom panel shows daily scaling factor applied to the transmission rate parameter $\beta(t)$ representing seasonal variation in the *Anopheles* biting rate. This adjustment curve was smoothed and shifted forward by 11 days to reflect the delay between rainfall and peak mosquito abundance. The same within-year $\beta(t)$ profile was applied uniformly across all spatial locations in the model.



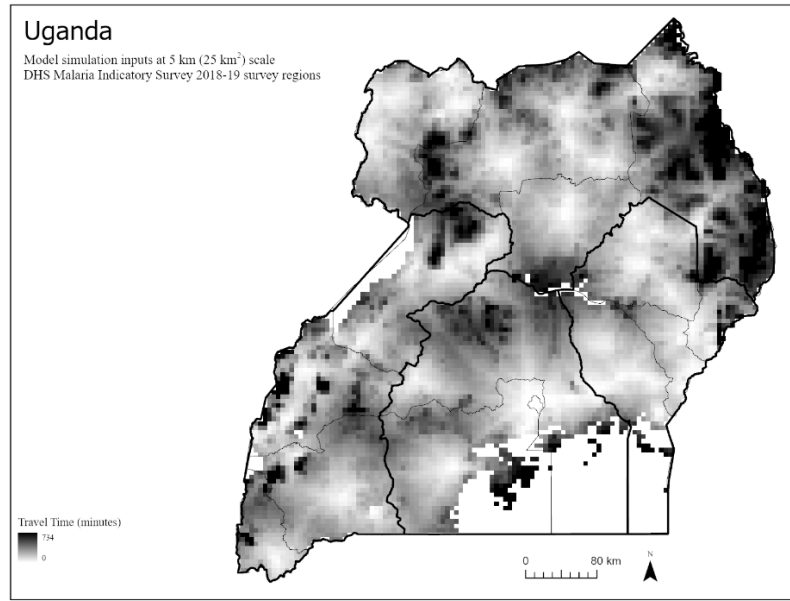
Supplementary Figure 2. Average Monthly Treatment Failures (2025 - 2031) under Different 1-Year Cycling Strategies. This figure replicates Figure 5 from the main text with 1-year cycling policies. The labels on the left show the order (left-to-right) of therapies used in each cycling regimen. Each boxplot summarizes N = 32 simulations. Boxplot centers are medians, box bounds show interquartile range, and whiskers show 1.5 IQR.



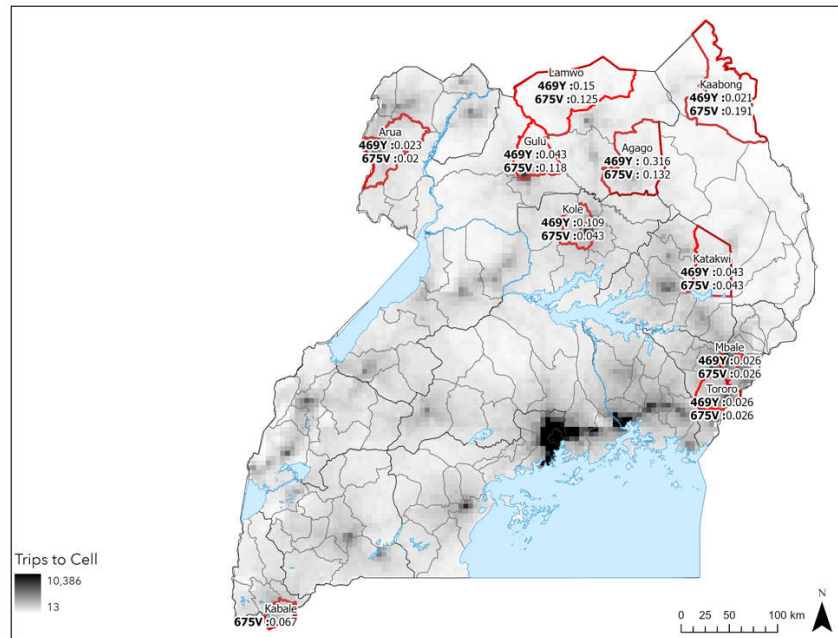
Supplementary Figure 3. Average Monthly Treatment Failures (2025 - 2031) under Different 3-Year Cycling Strategies. This figure replicates Figure 5 from the main text with 3-year cycling policies. The labels on the left show the order (left-to-right) of therapies used in each cycling regimen. Each boxplot summarizes N = 32 simulations. Boxplot centers are medians, box bounds show interquartile range, and whiskers show 1.5 IQR.



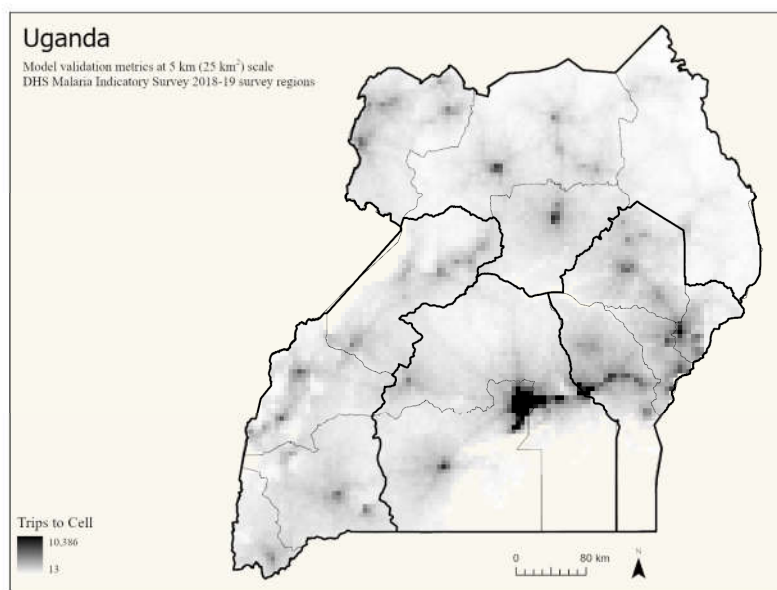
Supplementary Figure 4. Trends in malaria treatment failures and *pfkelch13* allele frequency (2020–2032) under different 2-year cycling strategies (2020–2031). Gray lines show the model burn-in and calibration prior to July 2025. Solid lines show monthly treatment failure counts (left axis) while dashed lines show the combined *pfkelch13* allele frequency (sum of frequencies for the 469Y and 675V alleles). The monthly treatment failure count includes all projected treatment failures for all antimalarials used in the general population. Shaded regions denote the 90% ranges across simulation outcomes (N = 32). Dark green lines represent cycling strategies involving all three therapies (AL, ASAQ, DHA-PPQ). Light green lines correspond to two-therapy cycling strategies starting with ASAQ. Orange lines represent two-therapy cycling strategies starting with AL. Red lines show two-therapy cycling strategies starting with DHA-PPQ. Shaded regions in both panels represent the 90% uncertainty range across simulations.



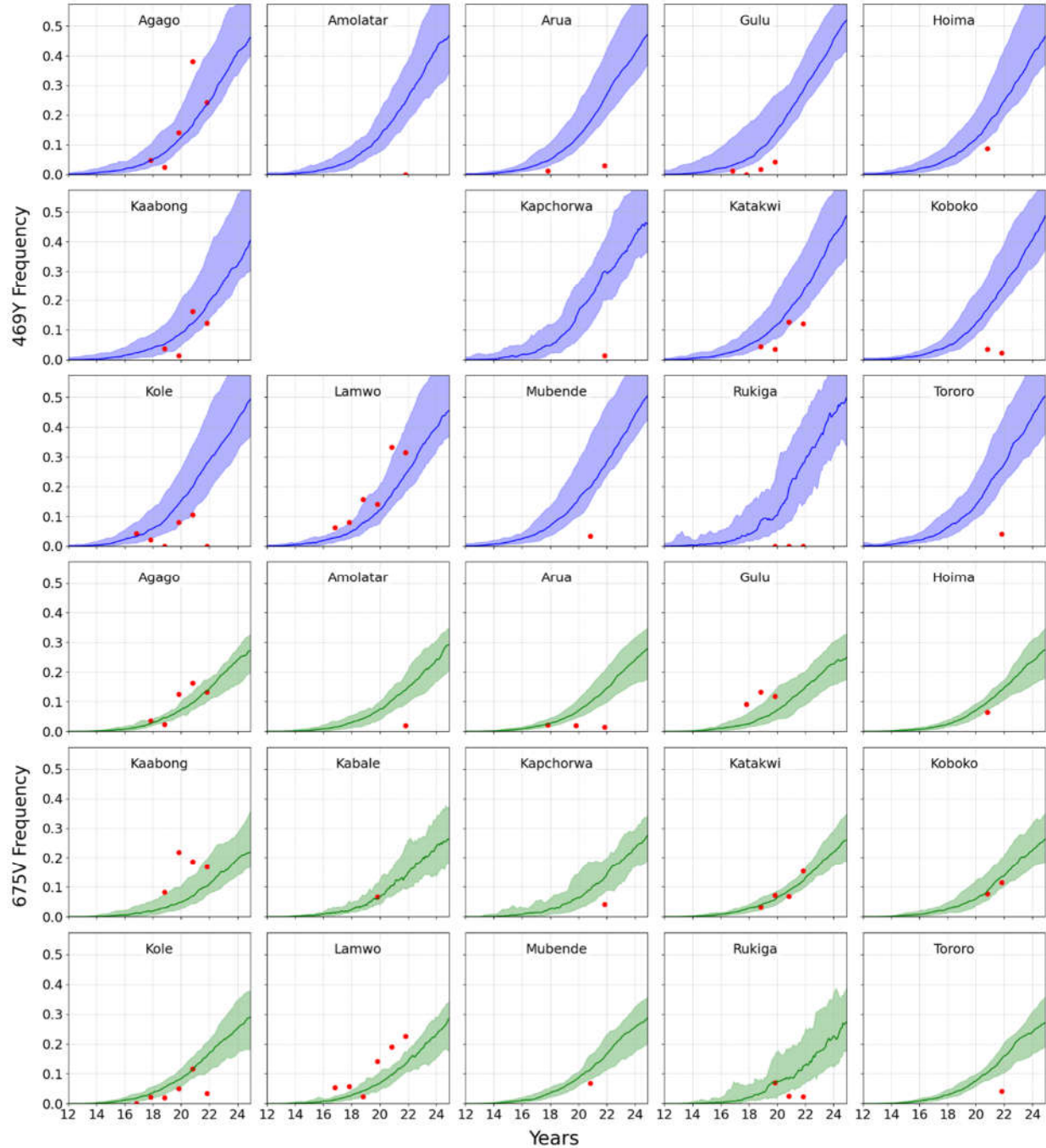
Supplementary Figure 5. Estimated travel time to the nearest city across Uganda, aggregated to 25 km² resolution. These values represent the travel friction surface used as input to a gravity-based human movement model. Higher travel time values (darker shades) indicate more isolated regions with lower accessibility to urban centers.



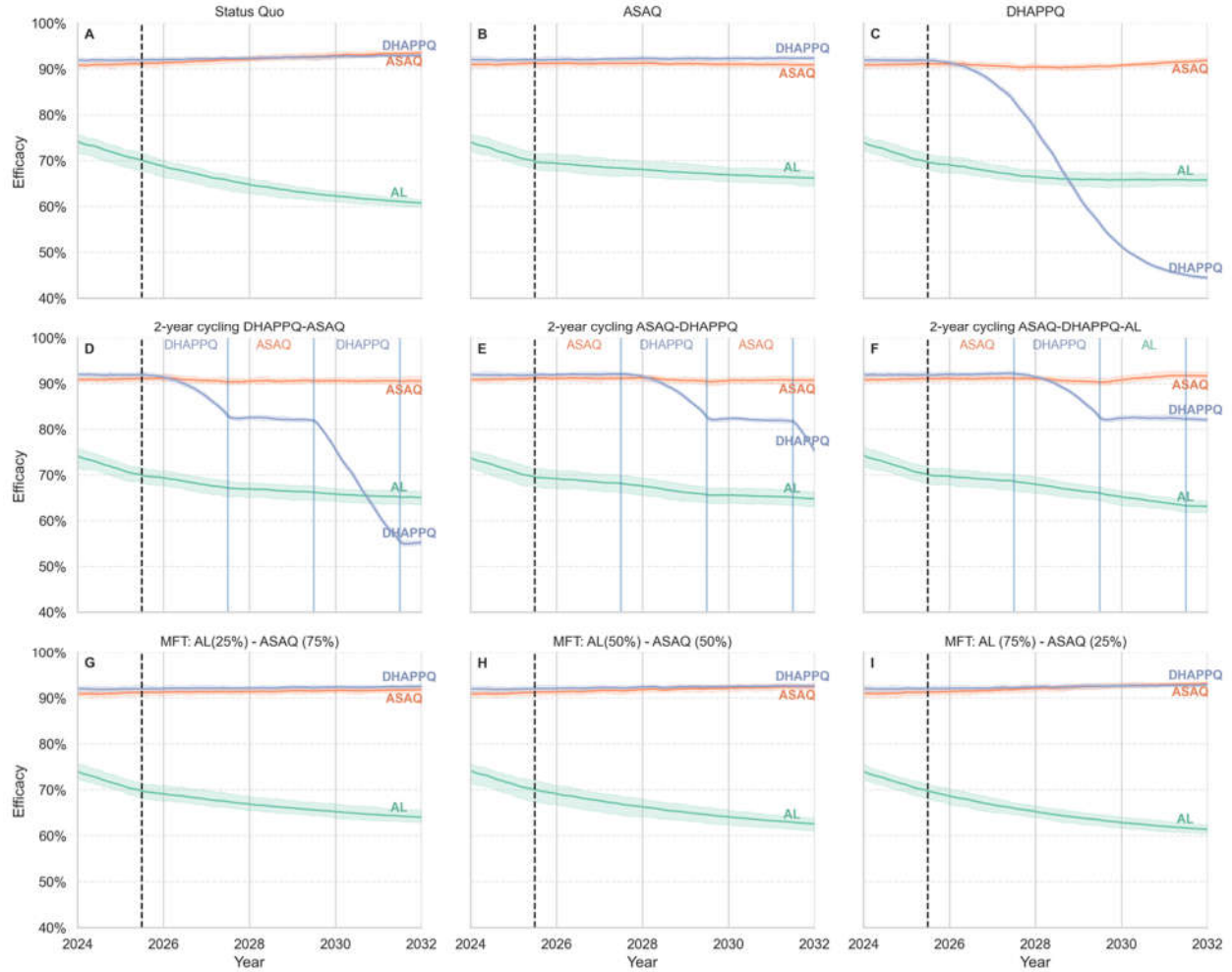
Supplementary Figure 6. Spatial overlay of observed pfkelch13 allele frequencies (469Y and 675V) and simulated travel density from the gravity model. Red boundaries indicate districts with field-verified presence of kelch variants. Background shading represents the number of simulated trips per pixel, highlighting connectivity to and from regions with known resistance.



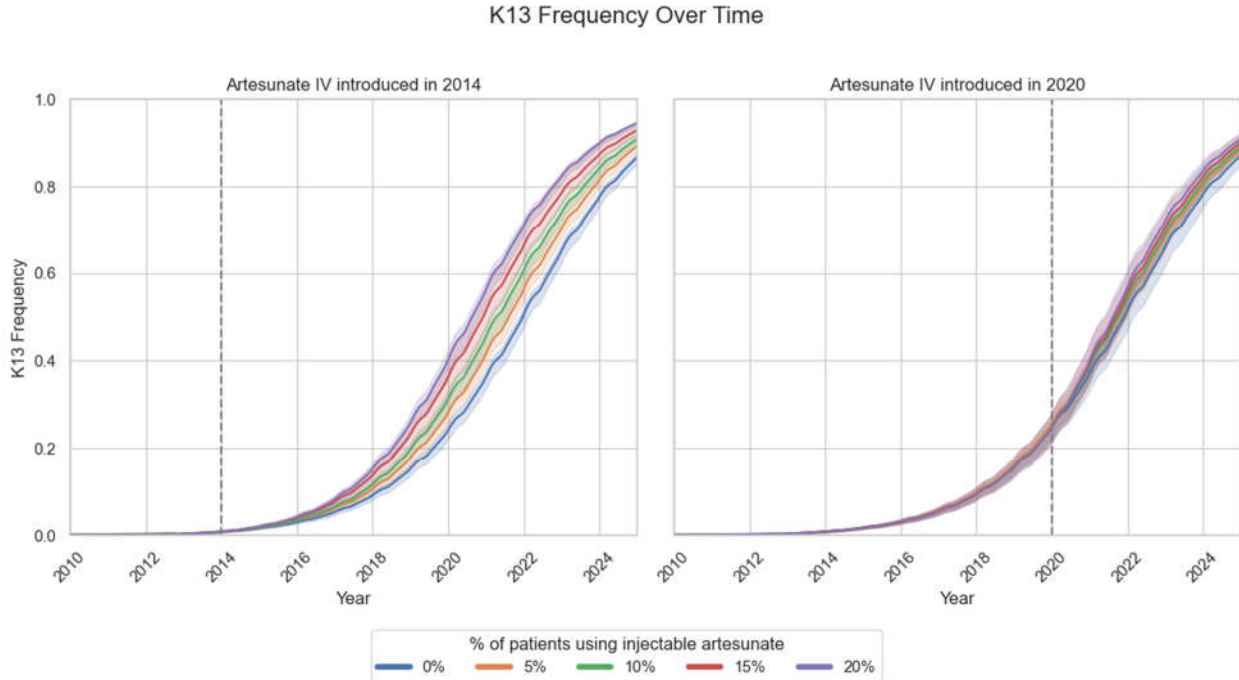
Supplementary Figure 7. Simulated travel density surface at 25 km² resolution, representing the cumulative number of trips arriving at each pixel across all model-runs. This surface was used for validation of the human movement model and to assess spatial connectivity across epidemiologically relevant districts.



Supplementary Figure 8. Calibration of *pfkelch13* 469Y and 675V allele frequencies (NN_{P-to-D} , $c = 0.5$) in 15 districts in Uganda. Each panel shows the simulated 469Y allele frequency (blue line) or 675V allele frequency over time, in one district, with the shaded area representing the interquartile range of the simulation outputs ($N = 32$). The red dots correspond to the observed data collected between 2015 and 2022. The model performs well in districts such as Kaabong, Katakwi, and Lamwo, where the predicted frequencies closely follow the observed data. In contrast, early predictions of allele emergence are evident in districts like Kole, Hoima, and Tororo, where the model anticipates a faster rise in frequency compared to the true data. Note that the one sample in Kagale district¹⁷ was sampled at the same health facility as samples from Rukiga district; around the time of sampling Kabale district was split into two districts (Kabale and the new district of Rukiga).



Supplementary Figure 9. Projected trends in ACT efficacies (2024–2032) under selected treatment strategies. Panels **A**, **B**, **C** in the top row show projected efficacy trajectories under the status quo and single-switch policies to ASAQ or DHA-PPQ. Panels **D**, **E**, and **F** in the middle row illustrate outcomes under three representative 2-year cycling strategies. Panels **G**, **H**, and **I** in the bottom row depict ACT-specific efficacy patterns under three distinct multiple first-line therapies (MFT) deployments. Each panel reflects median projected efficacies across $N = 32$ stochastic simulations, shaded regions in panels represent the 90% range across simulations. Note that DHA-PPQ efficacy drops quickly when selection pressure from DHA-PPQ is strong (panels **C** and **D**). ASAQ efficacy is projected to stay high under all evaluated strategies.



Supplementary Figure 10. Projected trajectories of *pfkelch13* mutant allele frequency (2010–2025) under hypothetical past introduction and usage rates of intravenous artesunate (IVAS). The left panel shows scenarios where IVAS is introduced in 2014, while the right panel considers introduction in 2020. Each line represents a different assumed proportion (0% to 20%) of patients choosing IVAS as first-line treatment for an uncomplicated falciparum malaria episode. Faster increases in kelch mutant frequency are observed with earlier IVAS introduction and higher IVAS usage rates, reflecting increased selection pressure. Vertical dashed lines indicate the year of IVAS introduction in each scenario. Shaded area represents the interquartile range of the simulation outputs (N = 32).

S3. Supplementary Tables

MIS Region	Treatment Coverage for children under 5
West Nile	86%
Acholi	87%
Karamoja	85%
Bunyoro	85%
Lango	95%
Teso	81%
Bugisu	85%
Tooro	79%
South Buganda	97%
Busoga	88%
Bukedi	81%
Kigezi	88%
Ankole	91%
North Buganda	89%
Kampala	insufficient response rate in survey

Supplementary Table 1. Treatment Coverage by MIS region. The Uganda 2018-2019 MIS contained data for fourteen of the fifteen MIS regions. The Kampala region recorded fewer than 25 responses, and the coverage estimate used in the simulation was 93%, which is the average of treatment coverages from bordering regions.

Strategy	Annual TF (median)	Monthly TF (median)	%Δ vs Status Quo	TF Rate 2025-26 (median)	TF Rate 2030-31 (median)
<i>Continued AL use (status quo)</i>	9.9M	820,898	0.00%	26.20%	33.10%
<i>Switch to ASAQ</i>	6.3M	522,456	-36.40%	19.20%	19.70%
<i>Switch to ASAQ</i>	8.7M	728,884	-11.20%	19.30%	37.60%
<i>2-year cycling: AL → ASAQ</i>	8.7M	722,369	-12.00%	26.00%	32.00%
<i>2-year cycling: AL → DHA-PPQ</i>	8.8M	732,470	-10.80%	26.30%	32.60%
<i>2-year cycling: ASAQ → AL</i>	7.4M	619,887	-24.50%	19.20%	20.10%
<i>2-year cycling: ASAQ → DHA-PPQ</i>	6.2M	520,568	-36.60%	19.10%	19.70%
<i>2-year cycling: DHA-PPQ → AL</i>	8.3M	691,259	-15.80%	19.20%	30.70%
<i>2-year cycling: DHA-PPQ → ASAQ</i>	7.0M	587,119	-28.50%	19.10%	30.20%
<i>2-year cycling: AL → ASAQ → DHA-PPQ</i>	7.3M	607,906	-25.90%	26.40%	21.60%
<i>2-year cycling: AL → DHA-PPQ → ASAQ</i>	7.4M	618,165	-24.70%	26.70%	20.40%
<i>2-year cycling: ASAQ → AL → DHA-PPQ</i>	7.5M	626,150	-23.70%	19.40%	21.70%
<i>2-year cycling: ASAQ → DHA-PPQ → AL</i>	7.5M	626,222	-23.70%	19.00%	30.90%
<i>2-year cycling: DHA-PPQ → AL → ASAQ</i>	7.5M	620,887	-24.40%	19.10%	20.00%
<i>2-year cycling: DHA-PPQ → ASAQ → AL</i>	7.5M	627,094	-23.60%	19.10%	30.90%
<i>MFT: 25% AL, 75% ASAQ</i>	7.1M	595,284	-27.50%	21.00%	22.80%
<i>MFT: 25% AL, 75% DHA-PPQ</i>	8.4M	696,822	-15.10%	20.90%	33.50%
<i>MFT: 50% AL, 50% ASAQ</i>	8.0M	667,406	-18.70%	22.60%	26.00%
<i>MFT: 50% AL, 50% DHA-PPQ</i>	8.4M	698,098	-15.00%	22.90%	30.10%
<i>MFT: 75% AL, 25% ASAQ</i>	9.0M	750,430	-8.60%	24.70%	29.70%
<i>MFT: 75% AL, 25% DHA-PPQ</i>	9.0M	748,395	-8.80%	24.70%	30.30%
<i>MFT: 25% ASAQ, 75% DHA-PPQ</i>	7.6M	630,079	-23.20%	19.30%	30.70%
<i>MFT: 50% ASAQ, 50% DHA-PPQ</i>	6.6M	550,783	-32.90%	19.00%	23.70%
<i>MFT: 75% ASAQ, 25% DHA-PPQ</i>	6.3M	521,649	-36.50%	19.20%	20.20%
<i>MFT: 33% AL, 33% ASAQ, 33% DHA-PPQ</i>	7.5M	624,462	-23.90%	21.50%	25.10%
<i>MFT: 5% AL, 47.5% ASAQ, 47.5% DHA-PPQ</i>	7.1M	592,199	-27.90%	20.70%	23.80%
<i>DHA-PPQ for 4 years, then ALAQ</i>	6.8M	568,566	-30.70%	19.20%	17.70%
<i>ASAQ for 4 years, then ALAQ</i>	6.0M	503,067	-38.70%	19.00%	17.80%
<i>AL for 4 years, then ALAQ</i>	8.5M	706,494	-13.90%	26.90%	19.20%
<i>2 years AL → 2 years ASAQ, then ALAQ</i>	7.2M	597,294	-27.20%	26.50%	18.70%
<i>2 years AL → 2 years DHA-PPQ, then ALAQ</i>	7.1M	595,683	-27.40%	26.40%	18.70%
<i>2 years ASAQ → 2 years AL, then ALAQ</i>	7.3M	609,280	-25.80%	19.20%	18.70%
<i>2 years ASAQ → 2 years DHA-PPQ, then ALAQ</i>	6.1M	508,574	-38.00%	19.30%	18.20%
<i>2 years DHA-PPQ → 2 years AL, then ALAQ</i>	7.3M	611,490	-25.50%	19.30%	18.60%
<i>2 years DHA-PPQ → 2 years ASAQ, then ALAQ</i>	6.1M	506,830	-38.30%	19.20%	18.00%
<i>Immediate ALAQ deployment</i>	5.7M	477,929	-41.80%	17.60%	18.20%
<i>3-year cycling: AL → ASAQ</i>	7.9M	660,325	-19.60%	26.40%	20.40%

3-year cycling: AL → DHA-PPQ	8.2M	684,893	-16.60%	26.70%	25.60%
3-year cycling: ASAQ → AL	8.2M	683,255	-16.80%	19.30%	31.70%
3-year cycling: ASAQ → DHA-PPQ	6.5M	538,964	-34.30%	19.20%	24.70%
3-year cycling: DHA-PPQ → AL	8.4M	696,892	-15.10%	19.10%	31.50%
3-year cycling: DHA-PPQ → ASAQ	6.5M	538,910	-34.40%	19.10%	19.50%
1-year cycling: AL → DHA-PPQ	8.1M	671,989	-18.10%	26.20%	22.60%
1-year cycling: AL → ASAQ	8.3M	691,637	-15.70%	26.20%	27.10%
1-year cycling: ASAQ → AL	8.1M	674,166	-17.90%	19.10%	29.60%
1-year cycling: ASAQ → DHA-PPQ	6.5M	541,889	-34.00%	19.20%	24.30%
1-year cycling: DHA-PPQ → AL	8.4M	699,887	-14.70%	19.10%	31.00%
1-year cycling: DHA-PPQ → ASAQ	6.6M	548,783	-33.10%	19.40%	21.10%
1-year cycling: AL → ASAQ → DHA-PPQ	7.5M	623,339	-24.10%	26.90%	21.60%
1-year cycling: AL → DHA-PPQ → ASAQ	7.4M	616,581	-24.90%	26.30%	20.30%
1-year cycling: ASAQ → AL → DHA-PPQ	7.6M	630,946	-23.10%	19.20%	24.00%
1-year cycling: ASAQ → DHA-PPQ → AL	7.5M	625,081	-23.90%	18.80%	29.60%
1-year cycling: DHA-PPQ → AL → ASAQ	7.5M	628,812	-23.40%	19.20%	22.40%
1-year cycling: DHA-PPQ → ASAQ → AL	7.6M	632,607	-22.90%	19.30%	29.50%

Supplementary Table 2. Summary of treatment outcomes and resistance indicators across evaluated antimalarial deployment strategies. This table reports key simulation outcomes for each treatment strategy, including annual and monthly treatment failures and treatment failure rates in early and late periods (2025–2026 and 2030–2031). Percentage changes are shown relative to the status quo (continued AL use) as a baseline comparator.

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