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group with the care givers of children who had severe malaria regarding their care pathways from a lower to a higher level of care. The purposive sample considered the following factors: the child's age, gender, and the distance to reference health care facilities. The healthcare providers and the group of stakeholders (pharmasists, village chiefs) have been purposefully selected to have a varied sample in relation to distance to health facilities to their location. The traditional practitioners will be selected to have a varied group as to kind of practices and location. Data is currently being collected and analyzed. An integrated presentation will be available by October 2025**.** Recommendations on how these findings will inform actual implementation of the SEMA-ReACT intervention will be made.

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SIMULATING MALARIA EVOLUTION AND IMPACT OF ANTIMALARIAL DRUG DEPLOYMENT IN BURKINA FASO USING A NEWLY CALIBRATED INDIVIDUAL-BASED MODEL

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With over 8 million annual cases reported throughout the entire country, *Plasmodium falciparum* malaria presents a serious health burden in Burkina Faso. As in every malaria-endemic country, this public health challenge requires sustained attention to reduce the number of deaths and curb possible emergence of drug resistance mutations. To help with decision making on drug-resistance preparation, we simulated malaria transmission and evolution across Burkina Faso using a previously validated individual-based mathematical simulation model. The model was calibrated using 2022 prevalence data from the Malaria Atlas Project, 2024 incidence data from the 75 health districts in Burkina Faso, known seasonal transmission patterns, and drug choice and coverage data from demographic health surveys. We evaluated multiple antimalarial drug deployment strategies, between 2025 and 2030, to evaluate which ones would have the largest preventive effect on delaying the arrival of artemisinin-resistant falciparum genotypes. We evaluated geographic strategies where different artemisinin combination therapies (ACTs) are distributed to different districts, multiple first-line therapy (MFT) approaches, and drug rotation approaches. Our results indicate that certain MFT and rotation strategies, when implemented with high deployment efficiency, have potential to reduce treatment failure rates by 10% to 40% compared to the status quo. Geographically stratified approaches have similar effects at reducing treatment failures but only if accompanied by rotations. These results highlight the importance of preparing for the arrival of artemisinin-resistant genotypes for countries where artemisinin resistance has not yet been detected.

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FALCIPAIN-2A MEDIATED RESISTANCE TO PEPTIDE-LIKE INHIBITORS IN *PLASMODIUM FALCIPARUM*

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Malaria, caused by *Plasmodium* parasites, remains a major global health issue, especially in tropical regions. The emergence of *P. falciparum* strains partially resistant to artemisinin underscores the need for new antimalarial agents. Peptidomimetic compounds have emerged as promising antimicrobial candidates, especially as protease inhibitors with antiplasmodial activity. Our work investigates the parasitological profile and resistance mechanisms of peptide-based inhibitors targeting *P. falciparum* asexual blood stages. The lead compound, Neq1153, showed a mean IC_{50} of 600 nM and a selectivity index of 350 against HepG2 cells. It is a slow-acting inhibitor with strong activity against rings and trophozoites, and showed 10-fold higher potency against Dd2 versus 3D7 parasites. However, it exhibited antagonism with artesunate and chloroquine. Phenotypic analyses suggest that Neq1153 interferes with hemoglobin digestion, potentially via interactions with vacuolar transporters PfCRT and PfMDR1. Notably, PfCRT mutations in Dd2 (T93S, F145I, I218F) and PfMDR1 mutations in NF54 (M841I+M924I) reduced potency by two-fold, while lower *pfmdr1* copy number in FCB parasites increased sensitivity. In contrast, increased *pfpm2/3* copy number reduced Neq1153 potency by 2- to 4-fold. *In vitro* evolution identified Falcipain-2a (FP2a) as a key resistance mediator, with copy number variations and S392R/S392I mutations arising under drug pressure. CRISPR/Cas9-edited parasites showed that only S392R in the Dd2 background conferred resistance comparable to that seen in Neq1153-selected parasites. These results highlight the complexity of resistance and the need for further studies on Neq1153's molecular interactions. Peptide-based inhibitors show promise as new antimalarials and offer insights into resistance mechanisms.

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MALARIA DRUG RESISTANCE MONITORING IN SENEGAL REVEALS DRAMATIC REGIONAL HETEROGENEITY WITH GENERAL INCREASES IN MARKERS ASSOCIATED WITH DECREASED SUSCEPTIBILITY TO PARTNER DRUGS LUMEFANTRINE AND AMODIAQUINE.

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Antimalarial drug resistance threatens malaria elimination efforts in Senegal. National surveillance for drug resistance allele and haplotype frequencies was done on 900 *Plasmodium falciparum* samples from febrile individuals at 12 health posts using MAD4HatTeR amplicon sequencing. No evidence for artemisinin resistant (ARTR) K13 mutations was found, but heterogeneity in allele and haplotype frequencies for Pfcrt, Pfmdr1, Pfdhfr, and Pfdhps were detected, consistent with increasing drug pressure. Most infections (55% [Confidence Interval, CI: 51.5%, 58.9%]) had the CVIET Pfcrt haplotype associated with increased amodiaquine (AQ) resistance, but this varied from 20% to 89.7% by region. for Pfmdr1, 51.4% (CI: 45.9%, 56.7%) of infections had the NFD haplotype, associated with decreased lumefantrine (LUM) susceptibility, that ranged from 14.3% to 93.8 %, depending on the region. The Pfdhfr IRN haplotype (N51I, C59R, and S108N) associated with pyrimethamine (P) resistance was near fixation in Senegal, but a decrease (78.9% [75.6%, 82.3%] was seen overall, characterized by reduced C59R frequency (80.9% [77.8%, 83.4%]), while N51I (96.6% [95.1%, 98.0%]) and S108N (98.1% [97.1%, 99.2%] remained near fixation. Pfdhps mutations associated with sulfadoxine (S) resistance increased: A437G (83.1% [80.0%, 86.2%]), S436A (42.7% [38.8%, 46.5%]), A613S/T (21.1% [17.8%, 24.6%]), A581G (16.9% [13.8%, 20.0%], I431V (16.7%, [13.7%, 19.8%]), and K540E (1.6% [0.6%, 2.3%]), but the ISGEAA haplotype associated with high SP resistance was rare (<1% across all samples). These results indicate the absence of ART K13 mutations, general increases in resistance-associated mutations (except relaxation of the Pfdhfr C59R), and dramatic regional differences in mutation frequency. We hypothesize these changes are due to differential population-level drug pressure including Seasonal Malaria Chemoprevention (SMC). Progressive selection of mutations associated with ART partner drugs (LUM and AQ) as well as SP (used in SMC) warrant ongoing surveillance for antimalarial resistance that threatens to undermine malaria elimination efforts in Senegal.