Supplemental Annex 1: Data management and analysis

Data entry and quality control

Data from paper questionnaires were routinely entered into a customized electronic data capture system (Voozanoo, Epiconcept, France). Data quality checks were conducted regularly to validate case and control eligibility, detect missing or inconsistent values, and correct erroneous entries.

Case and control inclusion

Analyses were restricted to participants who met enrolment criteria. All analyses except bacteriology were done for valid cases and controls who had at least one molecular result for blood or CSF. Follow-up analyses were limited to cases successfully contacted between 21 and 365 days after enrolment.

Molecular analyses

To minimize the risk of false positives from the fever chip, particularly for pathogens which could not be confirmed by individual PCR, biomolecular blood results were reported only for pathogens with at least 10 detections in cases or controls (Supplemental Table 2). This threshold reflects both a need for sufficient data for statistical comparisons and caution regarding the specificity of unconfirmed detections. Pathogens not meeting this threshold were excluded from the main analysis.

Confirmation PCR was performed on a subset of samples with positive or inconclusive fever chip results. Two measures were calculated:

1. **Proportion of confirmation PCR performed** = number of confirmation PCR tests ÷ total number of positive and inconclusive fever chip results.
2. **Confirmation rate** = number of positive confirmation PCRs ÷ total number of confirmation PCR tests performed.

Final biomolecular results combined fever chip, confirmation PCR, and, for EBV and HBV, imputed results (Supplemental Figure 1). In brief:

- Negative fever chip → final result negative.
- Positive/inconclusive fever chip with confirmation PCR → final result based on confirmation PCR outcome.
- Positive fever chip without confirmation PCR:
    - For EBV and HBV → final result determined by imputation.
    - For all other pathogens → final result recorded as positive.
- Inconclusive fever chip without confirmation PCR → recorded as missing.

For EBV and HBV, where detection rates exceeded 1% and sufficient PCR confirmations were available, missing confirmation PCR results were imputed to improve detection rate and odds ratio estimates. Separate logistic regression models for EBV and HBV were fitted on fever chip–positive samples with confirmation PCR to estimate covariate effects for imputation. Ten imputed datasets per pathogen were generated, then combined using Rubin's rules to yield averaged counts, detection rates, and odds ratios.

Unless otherwise specified, all reported results refer to blood and use the final result based on fever chip, confirmation PCR and imputation.

Imputation model specifications

Following the recommendations of Hughes et al. in *Accounting for missing data in statistical analyses: multiple imputation is not always the answer* (International Journal of Epidemiology, 2019), imputation models should include all variables from the primary analysis model (including the outcome), as well as variables that predict missingness and variables that predict the value of incomplete variables. In our context, the outcome was AFDUC/Control, and the main analysis model included: country, age group, hospital location, place of residence, HIV status, year of enrolment, month of enrolment, exposure to domestic or wild animals and codetection of other pathogens. Logistic regression was used to identify auxiliary variables that predicted either missingness or the value of the confirmation PCR result, which led to the inclusion of: (i) the number of pathogens with inconclusive fever chip results per participant, (ii) the year of fever chip testing, and (iii) sex.

Separate models were constructed for the imputation of missing EBV and HBV confirmation PCR results, as we aimed to impute these values based solely on estimates derived from EBV or HBV data respectively. Furthermore, the multivariable logistic regression models were fitted to data from cases and controls who tested positive for the pathogen on the fever chip and had confirmation PCR results. For EBV, the dataset comprised 691 positive EBV fever chip results, of whom 79 had missing confirmation PCR results requiring imputation. For HBV, the dataset comprised 226 HBV fever chip positives, of whom 22 had missing confirmation PCR result. For HBV, there were no missing confirmation PCR results in SA, and because HBV results and confirmation patterns differed by country, the HBV imputation model was restricted to data from BF and CI. To reduce the number of covariates, we summarised the test results for "codetection of other pathogens" into a single variable, representing the count of positive detections for all pathogens other than the target of the imputation model. Due to high collinearity between the covariates "year of enrolment" and "year of fever chip testing", the covariate "year of enrolment" was excluded from the final EBV imputation model. Similarly, for the HBV imputation model, "month of enrolment" and "year of enrolment" were excluded for the same reason.

The final imputation models were as follows:

- **EBV** (BF, CI, SA):
    - Outcome: EBV confirmation PCR result
    - Covariates: case/control status, country, age group, HIV status, hospital location, place of residence, month of enrolment, exposure to domestic or wild animals, number of positive detections for other pathogens, sex, number of inconclusive fever chip results for other pathogens, year of fever chip testing

- **HBV** (BF and CI only):
    - Outcome: HBV confirmation PCR result
    - Covariates: case/control status, country, age group, HIV status, hospital location, place of residence, exposure to domestic or wild animals, number of positive detections for other pathogens, sex, number of inconclusive fever chip results for other pathogens, year of fever chip testing

Statistical analyses

Baseline differences between cases and controls were assessed using Mann–Whitney U tests for continuous variables and Chi-squared or Fisher's exact tests for categorical variables.

Multivariable logistic regression was used to estimate adjusted odds ratios (aOR) for AdV, EV, EBV, HBV, and *P. falciparum* with case/control status as outcome. Adjustment sets were defined via a directed acyclic graph and included: country (BF, CI, SA), age group (<1, 1–4, 5–17, 18–44, 45+ years), hospital location (urban/rural; excluded in SA), residence (city/village), HIV status, year and month of enrolment, animal exposure (domestic/wild), and co-detection of other pathogens. Hospital location was excluded in SA models due to collinearity with residence. Regression estimates from imputed datasets were pooled following Rubin's rules.
Results of stratified and interaction (place of residence x pathogen of interest) models and sensitivity analyses are shown in Supplemental tables 3 to 9. Additional analyses included:

- Residence-specific regressions: applied to investigate whether pathogen detection differed by residence and performed separately for cases and controls, adjusting for age group, sex, year of enrolment, month of enrolment, and education; residence as exposure and the final result of the pathogen of interest as outcome.
- EBV–HIV relationship in SA: multivariable regression with EBV final result as outcome and HIV status as exposure, adjusted for age group and residence.
- *P. falciparum* and mortality: multivariable regression of deceased vs. surviving cases (exposure) in BF and CI and *P. falciparum* final result as outcome, adjusting for age group, sex, year of enrolment, month of enrolment, and residence.

A sensitivity analysis excluding all untreated malaria positive cases at enrolment did not significantly change the computed aOR for P. *falciparum* and other pathogens on the outcome AFDUC (Supplemental Table 8), therefore, untreated malaria positive cases were retained in the final analysis. We also used Cohen's kappa test to evaluate the concordance between malaria rapid test result at enrolment and fever chip result; and univariable and multivariable logistic regression models to assess the association between reported antimalarial pre-treatment and rapid test result at enrolment for cases, and *P. falciparum* fever chip positivity. Adjusted models included the covariates age group, sex, and residence.

Serological analyses

Serology was performed for a subset of cases with fever chip results. Borderline ELISA results were considered negative. Detection rates of DENV and CHIKV IgM were analysed descriptively by country and season. Multivariable logistic regressions assessed the effect of residence and follow-up status (deceased

vs. survived) on DENV and CHIKV-IgM positivity by country, adjusting for age group, sex, HIV status, year of enrolment and month of enrolment.

CSF analyses

A total of 120 cases had CSF results but no blood results. These were included in CSF-specific analyses but excluded from the biomolecular blood analyses.

Bacteriological analyses

All blood cultures data from valid cases with ongoing fever at enrolment were included in the analysis. The following organisms were considered contaminants: coagulase-negative *staphylococci*, *Staphylococcus epidermidis*, *Bacillus* spp., *Micrococcus* spp., and *Corynebacterium* spp. Contamination rates were compared between urban and rural hospitals using Chi-squared or Fisher's exact tests.