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# Cost-Effectiveness of Test-and-Treat Strategies to Reduce the Antibiotic Prescription Rate for Acute Febrile Illness in Primary Healthcare Clinics in Africa

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## Abstract

**Background** Inappropriate antibiotic use increases selective pressure, contributing to antimicrobial resistance. Point-of-care rapid diagnostic tests (RDTs) would be instrumental to better target antibiotic prescriptions, but widespread implementation of diagnostics for improved management of febrile illnesses is limited.

**Objective** Our study aims to contribute to evidence-based guidance to inform policymakers on investment decisions regarding interventions that foster more appropriate antibiotic prescriptions, as well as to address the evidence gap on the potential clinical and economic impact of RDTs on antibiotic prescription.

**Methods** A country-based cost-effectiveness model was developed for Burkina Faso, Ghana and Uganda. The decision tree model simulated seven test strategies for patients with febrile illness to assess the effect of different RDT combinations on antibiotic prescription rate (APR), costs and clinical outcomes. The incremental cost-effectiveness ratio (ICER) was expressed as the incremental cost per percentage point (ppt) reduction in APR.

**Results** For Burkina Faso and Uganda, testing all patients with a malaria RDT was dominant compared to standard-of-care (SoC) (which included malaria testing). Expanding the test panel with a C-reactive protein (CRP) test resulted in an ICER of \$ 0.03 and \$ 0.08 per ppt reduction in APR for Burkina Faso and Uganda, respectively. For Ghana, the pairwise comparison with SoC—including malaria and complete blood count testing—indicates that both testing with malaria RDT only and malaria RDT + CRP are dominant.

**Conclusion** The use of RDTs for patients with febrile illness could effectively reduce APR at minimal additional costs, provided diagnostic algorithms are adhered to. Complementing SoC with CRP testing may increase clinicians' confidence in prescribing decisions and is a favourable strategy.

## Key Points for Decision Makers

Complementing Standard-of-Care with C-reactive protein testing for patients with febrile illness in Africa could effectively reduce the antibiotic prescription rate (APR) at minimal additional costs.

The incremental cost per consultation for 1 percentage point reduction in APR provides an insightful alternative for the standard health-economic outcomes such as cost per quality-adjusted life-year (QALY) or per disability-adjusted life-year (DALY).

## 1 Introduction

Antimicrobial resistance (AMR) is a major global health threat, which increasingly undermines our ability to effectively control and treat infectious diseases [1]. The consequences of AMR can be severe, as it may increase the frequency, duration, morbidity and mortality rates of infectious diseases [1–3]. If AMR is allowed to spread unchecked, it will be detrimental in health and economic terms for societies worldwide [4], but especially for low- and middle-income countries (LMICs), where an additional 28 million individuals may be forced into extreme poverty due to increased out-of-pocket spending on life-saving treatment associated with AMR [5, 6]. Over-prescription by clinicians and the availability of over-the-counter (OTC) antibiotics are important causes

of inappropriate antibiotic consumption, thereby enhancing the selective pressure on microorganisms, which increases the growth of resistant microorganisms (i.e., selective pressure) that is contributing to AMR [2, 4, 7]. Hence, antibiotic stewardship—use of the right drug, at the right dosage, for the right indication—is considered a critical measure to rationalize antibiotic prescription, reduce unnecessary consumption, and contain AMR [8].

The availability and use of affordable, appropriate diagnostics, especially point-of-care (POC) rapid diagnostic tests (RDTs), would be instrumental to better target antibiotic prescriptions and inform patients on the cause of their symptoms, which potentially could reduce over-the-counter antibiotic use [4, 9, 10]. However, in practice, widespread implementation of diagnostics for improved infectious disease management is limited for various reasons. Firstly, only a few POC RDTs are tailored to LMICs—for example, in terms of prevalent pathogens and suitability to tropical conditions—and affordable [11, 12]. Secondly, available POC RDTs often have suboptimal specificity and sensitivity [13]. Finally, there is a lack of evidence on the clinical impact and cost-effectiveness of RDTs, especially in relation to the long-term effects of AMR, which extends beyond the current-day patients' quality of life [12, 14, 15]. Generic outcome measures such as the quality-adjusted life-year (QALY) or disability-adjusted life-year (DALY) are not consistently reported in health economic research papers on diagnostics for infectious diseases [14] and the valuation of health outcomes (i.e., QALYs or DALYs) extending beyond the cohort receiving treatment is challenging with prevailing methodologies employed in health economic analyses [16].

There is an urgent need for an improved understanding of the full cost and effects resulting from the implementation of diagnostic strategies that can inform future research and investment decisions by policymakers. The AMR Diagnostics Use Accelerator trial aimed to provide evidence on the usefulness of adopting a package of social and clinical interventions—consisting of POC RDTs, a clinical diagnostic algorithm for physicians, and targeted information for patients—on the clinical outcomes of patients presenting with acute fever to outpatient clinics in LMICs, as well as on antibiotic prescription [17]. The current study uses the results of the trial [18] to conduct a cost-effectiveness analysis to quantify the expected cost, clinical outcomes, and impact on antibiotic prescription and consumption resulting from the implementation of different (hypothetical) test strategies, compared to the current standard-of-care (SoC). Our study aims to contribute to evidence-based guidance of policymakers to inform investment decisions on interventions that foster more appropriate antibiotic prescriptions as well as to address

the evidence gap on the potential clinical and economic impact of RDTs on antibiotic prescription.

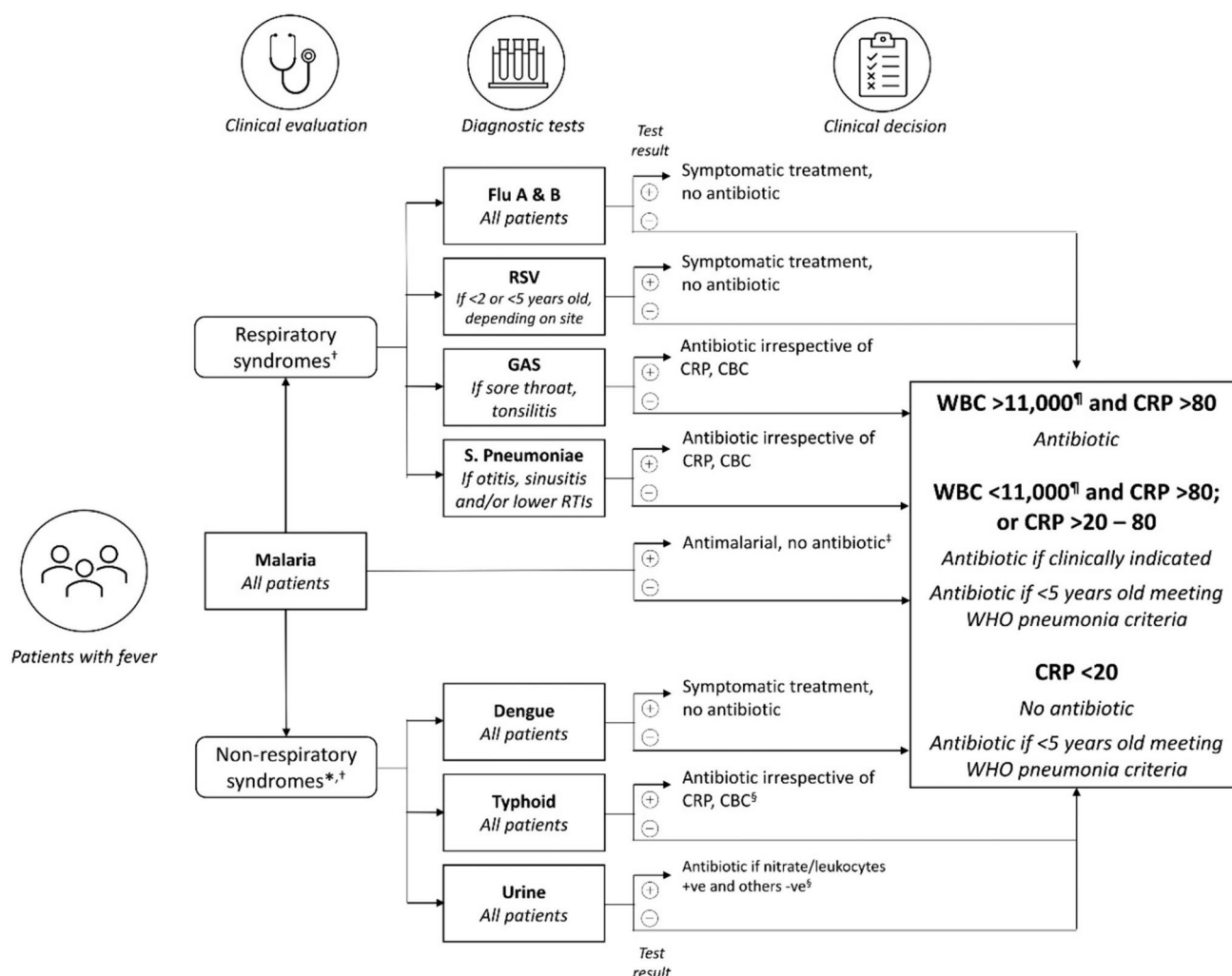
## 2 Materials and Methods

### 2.1 Accelerator Trial

Results from the Accelerator trial (NCT04081051), which have been published separately [18–21], were used to develop the country-based cost-effectiveness models applied to the three African countries where the trial took place—Burkina Faso, Ghana and Uganda. The intervention in the trial consisted of country-specific diagnostic algorithms, which were used by healthcare workers to determine whether to prescribe an antibiotic or not and are explained in detail elsewhere [19–21]. In short, the diagnostic algorithm included pathogen-specific and non-pathogen-specific POC RDTs including group A *Streptococcus* test, influenza test, malaria RDT, respiratory syncytial virus test, *Streptococcus pneumoniae* test, typhoid fever test, C-reactive protein (CRP) test, urine dipstick test and complete blood count (CBC) (see Fig. 1). The dengue test was added to the panel for Burkina Faso. Furthermore, communication messages about adherence to prescriptions were communicated by healthcare workers to study participants in the intervention arm. Clinical outcomes and antibiotic prescriptions were compared between the intervention arm and the control arm that followed diagnostic and treatment procedures routinely used in each country. As part of the trial, participants in both the intervention and control arms were followed for 7 days after the first visit to assess their health status and adherence to antibiotic prescription. For the analysis, the trial population was stratified in subcategories based on age and presenting signs and symptoms being respiratory or non-respiratory (see Online Supplementary Material (OSM) Appendix Table A1).

### 2.2 Test Strategies

The model simulated seven different test strategies. The first two strategies include the “standard-of-care” (SoC) and “trial-based” strategies, which were modelled alongside the Accelerator trial, based on the outcomes of the control and intervention arm, respectively. Five additional hypothetical test strategies were modelled to assess the maximum effect of different RDT combinations (pathogen-specific and non-pathogen-specific) on the antibiotic prescription rate, costs and clinical outcomes. The five hypothetical strategies were kept similar across the three countries, and include (i) malaria RDT only (country policy in line with World Health Organization (WHO) recommendations [22]); (ii) malaria RDT followed by a CRP test for malaria-negative



**Fig. 1** Fever clinical diagnostic algorithm, from Olliaro et al. [13]. *CBC* complete blood count, *CRP* C-reactive protein, *GAS* group A Streptococcus, *RSV* respiratory syncytial virus, *WBC* white blood cell count, *WHO* World Health Organization. <sup>\*</sup>Diagnostic panel depend-

ing on local endemicity. <sup>†</sup>Choice of tests at the discretion of local health practitioners. <sup>‡</sup>Unless a concomitant bacterial pathogen identified. <sup>§</sup>Start treatment followed by culture if needed. <sup>¶</sup>And neutrophils > 75% if WBC  $\geq 11,000$  and/or neutrophils >75% if WBC < 11,000

patients; (iii) malaria RDT followed by a complete blood count (CBC) test for malaria-negative patients; (iv) malaria RDT followed by a CBC and CRP test for malaria-negative patients; (v) malaria RDT followed by the full panel used in the intervention arm for malaria-negative patients. The hypothetical strategies (i–iv) were defined based on clinical relevance as indicated by the principle investigators of the Accelerator trial in the three countries, feasibility for implementation in clinical practice considering the cost of the individual RDTs, the number of RDTs that could be performed within a limited timeframe considering that one malaria RDT (+ CBC for Ghana) constitutes current SoC, and trial data availability per RDT (e.g., a substantial proportion of RDTs were conducted for a limited number of patients, which constrains generalisability). Strategy (v)

was selected to assess the hypothetical effect of the trial intervention.

### 2.3 Model Structure

A decision tree model was developed using R statistical software version 4.2.2 [23]. The general model structure was the same for all compared strategies (Fig. 2). The hypothetical cohort of 1,000 patients entering the model was differentiated clinically based on the presenting signs and symptoms being respiratory or non-respiratory. Subsequently, the result of the malaria RDT informed whether patients received treatment for malaria or continued for additional diagnostic tests and further clinical judgement. Based on additional diagnostic testing—altering per strategy—and clinical judgement, patients were prescribed treatment with





the probability of an SAE. The probability of prescribing antibiotics differed per strategy and was based on the clinical diagnostic algorithm that was informed by the test results of the respective strategy (see OSM Appendix Table A2 for a full overview of probabilities per country per strategy).

## 2.5 Costs

We took a healthcare perspective, therefore including only direct medical costs for the healthcare system. Costs for labour for healthcare personnel, tests and test analyzers are provided in Table 1. Half-year depreciation costs were considered for training and test analyzers with a 1-year and 5-year total depreciation time, respectively. An overview of the cost for therapeutics can be found in the OSM Appendix Table A3. Average drug costs and diagnostic test costs per consultation were estimated based on trial data. For the unfavourable outcome without SAE, additional costs were modelled as additional therapeutics. For the unfavourable outcome with an SAE, additional costs included cost for additional therapeutics and cost of hospitalization (assuming patients were discharged after two inpatient days [21]). All costs in local currency units were inflated using local inflation rates [24] and converted using official Purchasing Power Parity (PPP) conversion rates to reflect the cost in 2021 International dollars (\$), thereby eliminating price level differences across the three countries [25, 26].

## 2.6 Outcomes

The primary outcomes of the current analysis are the cost per consultation, antibiotic prescription rate (APR), and the incremental cost-effectiveness ratio (ICER) reflected as incremental cost per consultation for 1 percentage point (ppt) reduction in APR. The APR reflects the proportion of consultations in which antibiotics were prescribed (in line with WHO prescribing indicators [33]) and was the primary outcome measure of the Accelerator trial [13]. A reduction in the APR results in a reduction in the selective pressure that contributes to AMR [2, 4, 7]. Although it is uncertain what the exact relation is between APR and AMR, APR is considered an important surrogate outcome to quantify the effect of the test strategies [34]. The incremental difference in costs and APR between strategies results in the ICER, indicating the additional costs per consultation to reduce the APR with 1 ppt. No willingness-to-pay (WTP) threshold exists for the cost per ppt reduction in APR, hence no conclusions can be drawn with respect to the cost-effectiveness of the strategies. Instead, the analysis will enable a relative comparison of the cost-effectiveness between strategies for the three countries.

Secondary outcomes of the current analysis include the number of antibiotic regimens consumed, the number of

Defined Daily Doses (DDD) and antibiotic days-of-therapy. The number of antibiotic regimens consumed includes the total number of antibiotic regimens prescribed and the OTC regimens consumed (which were not prescribed by the healthcare professional). The DDD is a validated method to standardize the number of doses consumed and is developed by the WHO [35] (see OSM Appendix Table A4 for DDD per antibiotic). Since the DDD is impacted by weight- and age-based dosing, days-of-therapy was also included. Days-of-therapy is defined as the days of antibiotic therapy administered to a patient, independent of the dose [36]. Both the DDD and the days-of-therapy include the antibiotics prescribed and the antibiotics bought OTC. Only systemic (i.e., oral and injectable) antibiotics were included in the current analysis. The secondary antibiotic-related outcome measures are included to facilitate the utilization of the study results by future research.

In addition to the antibiotic-related outcome measures, DALYs were included to assess the short-term effect of the different interventions on clinical outcomes. DALYs were considered for the unfavourable outcome leaves of the decision tree. In case of an unfavourable outcome without SAE (i.e., the patient felt worse or the same at day 7), it was assumed that patients needed an additional 7-day cycle to get better, which is similar to new patients presenting at the clinic. To account for the additional disease burden, a disability weight of 0.001 DALY (0.051 DALY/52 weeks) was applied to these patients, which represented the disability weight for an acute, moderate episode of infectious diseases lasting 7 days [32]. In case of an unfavourable outcome with SAE (i.e., the patient had to visit the hospital), a disability weight of 0.0026 DALY (0.133 DALY/52 weeks) was applied, which represented the disability weight for an acute, severe episode of infectious disease lasting for 7 days [32].

## 2.7 Sensitivity and Scenario Analyses

In addition to the base-case analysis, we conducted a probabilistic sensitivity analysis (PSA) by fitting Beta (for probabilities), Gamma (for effects and costs) and Normal (for time) distributions to the variables based on trial data. If trial data were not available, parameters were varied by minus 20% and plus 20% of the mean, which was considered sufficient to assess the impact of parameter uncertainty on the outcomes. The results of 10,000 simulations are presented by a Bayesian 95% credible interval (CrI). The CrI can be interpreted as a 95% probability that the true (unknown) effect would lie within the interval, given the evidence provided [37].

Additional scenario analyses were conducted to assess the impact of the assumption that no antibiotics were prescribed for malaria-positive cases. This assumption can be considered as an optimistic base-case scenario given that

**Table 1** Overview of input variables used in the model

| Country independent cost                         |                        |            | Source     |  |
|--|------------------------|------------|------------|--|
|  |                        |            |            |  |
| Lab equipment                                    |                        |            |            | Purchase costs trial                           |
| CRP analyzer                                     | \$ 112.28              |            |            | Purchase costs trial                           |
| CBC analyzer                                     | \$ 254.49 <sup>a</sup> |            |            | Purchase costs trial                           |
|  |                        |            |            |  |
| Country-specific cost                            | Burkina Faso           | Ghana      | Uganda     |  |
|  |                        |            |            |  |
| Hourly salary                                    |                        |            |            |  |
| Nurse  | \$ 8.23                | \$ 3.20    | \$ 4.53    | Local PI                                       |
| Doctor   | \$ 17.00               | \$ 13.60   | \$ 10.10   | Local PI                                       |
| Lab technician                                   | \$ 8.37                | \$ 3.20    | \$ 4.53    | Local PI                                       |
| Hospitalization cost, one inpatient day          | \$ 51.14               | \$ 38.03   | \$ 124.83  | Burkina Faso: [27]; Ghana: [28]; Uganda: [29]  |
| Training cost <sup>b</sup>                       | \$ 265.00              | \$ 150.00  | \$ 135.00  | Local PI                                       |
|  |                        |            |            |  |
| Cost of tests                                    |                        |            |            |  |
| CRP  | \$ 2.86                | \$ 2.86    | \$ 2.86    | Purchase costs trial                           |
| CBC  | \$ 14.51               | \$ 10.68   | \$ 15.26   | Local PI                                       |
| Malaria RDT                                      | \$ 1.14                | \$ 2.14    | \$ 5.72    | Burkina Faso: [30]; Ghana and Uganda: local PI |
| Typhoid fever                                    | \$ 8.87                | \$ 8.87    | \$ 8.87    | Purchase costs trial                           |
| Group A Streptococcus test                       | \$ 1.37                | \$ 1.37    | \$ 1.37    | Purchase costs trial                           |
| Influenza test                                   | \$ 8.30                | \$ 8.30    | \$ 8.30    | Purchase costs trial                           |
| Respiratory syncytial virus test                 | \$ 7.15                | \$ 7.15    | \$ 7.15    | Purchase costs trial                           |
| <i>Streptococcus pneumoniae</i> test             | \$ 13.66               | \$ 13.66   | \$ 13.66   | Purchase costs trial                           |
| Dengue test                                      | \$ 1.60                | –          | –          | Purchase costs trial                           |
| Urine test                                       | \$ 0.03                | \$ 0.03    | \$ 0.03    | Purchase costs trial                           |
| HIV test   | –                      | –          | \$ 16.50   | [31]   |
| Blood film test                                  | –                      | –          | \$ 9.87    | [31]   |
| Urine microscopy test                            | –                      | –          | \$ 8.21    | [31]   |
| Stool microscopy test                            | –                      | –          | \$ 10.69   | [31]   |
| Widal test                                       | –                      | \$ 17.09   | \$ 48.83   | Ghana: local PI; Uganda: [31]                  |
| Hb test  | –                      | \$ 8.55    | \$ 14.01   | Ghana: local PI; Uganda: [31]                  |
|  |                        |            |            |  |
| Time spent per patient (in minutes) <sup>c</sup> |                        |            |            |  |
| Standard-of-care                                 |                        |            |            |  |
| Nurse  | 20                     | 0          | 0          | Local PI                                       |
| Doctor   | 0                      | 20         | 20         | Local PI                                       |
| Lab technician                                   | 0                      | 0          | 0          | Local PI                                       |
|  |                        |            |            |  |
| Alternative strategies, in minutes <sup>d</sup>  |                        |            |            |  |
| Nurse  | 45/32.5/20             | 0          | 0          | Local PI                                       |
| Doctor   | 0                      | 45/32.5/20 | 45/32.5/20 | Local PI                                       |

Table 1 (continued)

| Country-specific cost              | Burkina Faso | Ghana | Uganda | Local PI |
|------------------------------------|--------------|-------|--------|----------|
| Lab technician                     | 20           | 20    | 20     |          |
| Health effect                      |              |       |        |          |
| DALY, infectious disease, moderate | 0.051        |       |        | [32]     |
| DALY, infectious disease, Severe   | 0.133        |       |        | [32]     |

All costs are reported in International dollars

CBC complete blood count, CRP C-reactive protein, DALY disability-adjusted life-year, Hb haemoglobin, HIV human immunodeficiency virus, \$ International Dollar, PI Principal Investigator

<sup>a</sup>CBC test is part of Standard-of-Care in Ghana, hence it is assumed that CBC test equipment is already available.

<sup>b</sup>Training time calculation: five nurses trained for 8 h, two doctors trained for 8 h, and two lab technicians trained for 12 h

<sup>c</sup>In Burkina Faso, nurses of the health facilities were responsible for the management of patients. For all three countries, it was assumed that no lab-technicians were involved in SoC

<sup>d</sup>Required time per patient was based on number of tests performed. 20 min = malaria-only strategy; 32.5 min = malaria + CRP, malaria + CBC and malaria + CRP + CBC strategies; 45 min = malaria + all and trial-based strategies. Lab technician was only required in case of malaria + all and trial-based strategies due to large volume of tests

the trial results indicated that antibiotics were prescribed for malaria-positive cases. For the scenario analysis, the effect on the overall APR of different levels of antibiotic prescription for malaria-positive cases was assessed, considering a range of 0–60%.

Furthermore, a scenario analysis was conducted to assess the effect of implementing the strategies for patients with presenting signs and symptoms being respiratory or non-respiratory separately. Therefore, the model was run separately for patients with the presenting signs and symptoms being respiratory (respiratory scenario) and for patients with the presenting signs and symptoms being non-respiratory (non-respiratory scenario).

## 2.8 Assumptions

Individual patients could have made the decision not to adhere to the prescription of the healthcare professional by buying additional antibiotics OTC. The number of patients who bought OTC antibiotics that were not prescribed by the healthcare professional was based on trial data. Since the details on the costs, DDD and days-of-therapy per OTC antibiotic were not captured in the trial, these numbers were based on the average numbers resulting from the antibiotics prescribed during the trial—stratified per country and age group. Furthermore, the assumption was made that individuals below 5 years of age received liquid medicine unless the medication was not available in liquid form. To model the five hypothetical strategies, the following additional assumptions had to be made: the test and prescription algorithm was strictly followed by physicians; the test sequence started with a malaria test, only in case of a negative malaria test subsequent tests were done, which is a simplification of clinical practice; no antibiotics were prescribed in case of a positive malaria test; the adherence probabilities in the hypothetical strategies were assumed to be equal to the probabilities in the “trial-based” strategy; for the hypothetical strategies, undetected group A *Streptococcus*, *Streptococcus pneumoniae* and typhoid fever result in an unfavourable outcome in case the patient was not treated with antibiotics; otherwise reduced antibiotic prescription in the hypothetical strategies did not result in additional negative impact on the quality of life of patients beyond the results of the trial. Finally, it was assumed that all tests were performed at the same clinical encounter.

## 3 Results

### 3.1 Context

Based on the results of the intervention arm of the AMR Diagnostics Use Accelerator trial, Table 2 shows the



positivity rates, segregated per country per test. For the CRP and CBC test, the number of tests per sub-scale are reported. Table 2 indicates a high positivity rate for malaria and a relatively high percentage of patients with a CRP result > 80 for both Burkina Faso and Uganda. The results for Ghana are less distinct and demonstrate relatively low positivity rates across all tests. The malaria RDT was performed most frequently as part of SoC in Burkina Faso (100%) and Uganda (80.9%), in Ghana both malaria RDT (92.7%) and CBC tests (97.7%) were regularly performed as part of SoC (see OSM Appendix Table A5).

### 3.2 Outcomes

The total cost per consultation varies between strategies and between countries. The cost categories with the highest impact on the total cost are the test costs, labour cost and therapeutic costs (see Fig. 3). Due to a low number of unfavourable outcomes and low OTC consumption across the three countries, the associated costs only marginally impact the total costs. Similarly, the equipment costs and training costs constitute a fraction of the total cost per consultation. Regarding the five hypothetical strategies, the total cost of testing is dependent on the number of positive malaria tests as in these hypothetical scenarios, subsequent tests were only conducted if the initial malaria test yielded a negative test result. Consequently, the variations in test costs between the strategies in Burkina Faso are small as 646 patients out of the 856 tested positive for malaria (75.5%) (see Table 2). In contrast, the cost differences between strategies are more distinct for Uganda and Ghana due to the lower positivity rate for malaria. In Uganda, 500 out of 1,189 (42.1%) patients tested positive for malaria, while in Ghana 84 out of 738 (11.4%) patients had a positive malaria test. Labour and therapeutics costs are relatively constant across strategies making the cost of tests the main driver of the cost differences between strategies (see OSM Appendix Table A6 for a detailed overview).

The effect of the different strategies on APR varied per country (Fig. 4). Considering the 95% CrI, the “trial-based” strategy resulted in a significant decrease in the APR in Burkina Faso compared to the “SoC” strategy. However, in Ghana and Uganda, the APR in the “trial-based” strategy was not significantly different from the “SoC” strategy given the 95% CrI overlap (see Fig. 4). For the alternative strategies, a significant reduction in APR was observed compared to the “SoC” strategy for all three countries, except for the “malaria + CBC” strategy in Ghana. This could be explained by the fact that malaria and CBC testing was frequently performed in the SoC arm in Ghana. The comparison between the “malaria + all” strategy and the “trial-based” strategy provides insight into the effect the trial intervention could have in theory and the actual effect of the trial intervention,

respectively. Across all three countries, there is a substantial difference between these two strategies. A full overview of the impact of the different strategies on the number of antibiotics prescribed, DDD, days-of-therapy and DALY is provided in OSM Appendix Table A7. The impact of the different strategies on DALYs was negligible, which can be explained by the minor differences in the number of unfavourable outcomes between strategies and the low disability weight considered for an unfavourable outcome.

In Table 3, an overview of the incremental cost per consultation for a 1 ppt reduction in APR is provided. The ICER is calculated in a pairwise comparison with the “SoC” strategy and fully incremental. For Burkina Faso and Uganda, the “malaria” strategy resulted in a substantial reduction in APR and a marginal reduction in cost (non-significant) compared to the “SoC” strategy, making the “malaria” strategy dominant (i.e., less costly and results in better health outcomes than the comparator). Expanding the test panel to the “malaria + CRP” strategy could result in a further reduction in the APR, with a pairwise ICER of \$ 0.03 and \$ 0.08 for Burkina Faso and Uganda, respectively. For Ghana, the pairwise comparison with the “SoC” strategy—which includes both malaria and CBC testing—indicates that both the “malaria” strategy and “malaria + CRP” strategy result in a reduction in costs and a reduction in the APR, making these two strategies dominant versus the “SoC” strategy. When comparing the “SoC” strategy and the “malaria + CBC” strategy for Ghana, minor differences are found, which indicates that the full potential effect of the “SoC” strategy on APR is realized.

### 3.3 Probabilistic Sensitivity Analysis

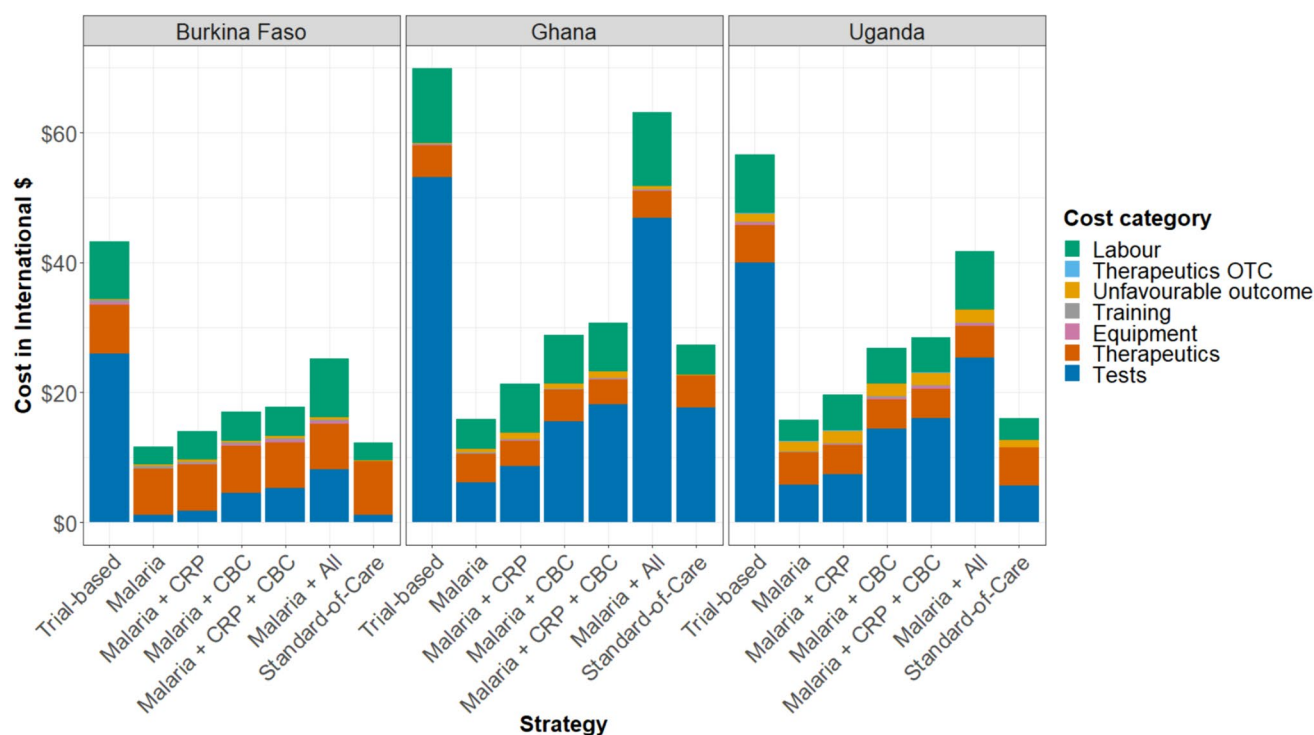
The results of the PSA are graphically presented in the cost-effectiveness planes (Fig. 5) with the “SoC” strategy as the comparator. The results of the PSA are in line with the deterministic outcomes and visualize the uncertainty of the deterministic outcomes that should be considered when interpreting the results of the current study. The spread of the scatterplots across countries and strategies is relatively low, which indicates that the results of the model can be considered as robust.

A cost-effectiveness acceptability curve (CEAC) was constructed to present the probability of each of the strategies being cost-effective at different levels of a hypothetical WTP, with a maximum WTP of \$ 20 per ppt reduction in APR, which represents an extreme and likely an improbable value. Nonetheless, this extreme value allows for the evaluation and understanding of the dynamics between the different strategies over a wide range of WTP thresholds. Across all three countries, the “malaria” strategy resulted in the highest probability of cost-effectiveness for a WTP ranging from \$ 0 to \$ 0.40 for Burkina Faso, \$ 0 to \$ 0.41 for Ghana,

**Table 2** Positivity rates per test per country for the tests in scope of the intervention

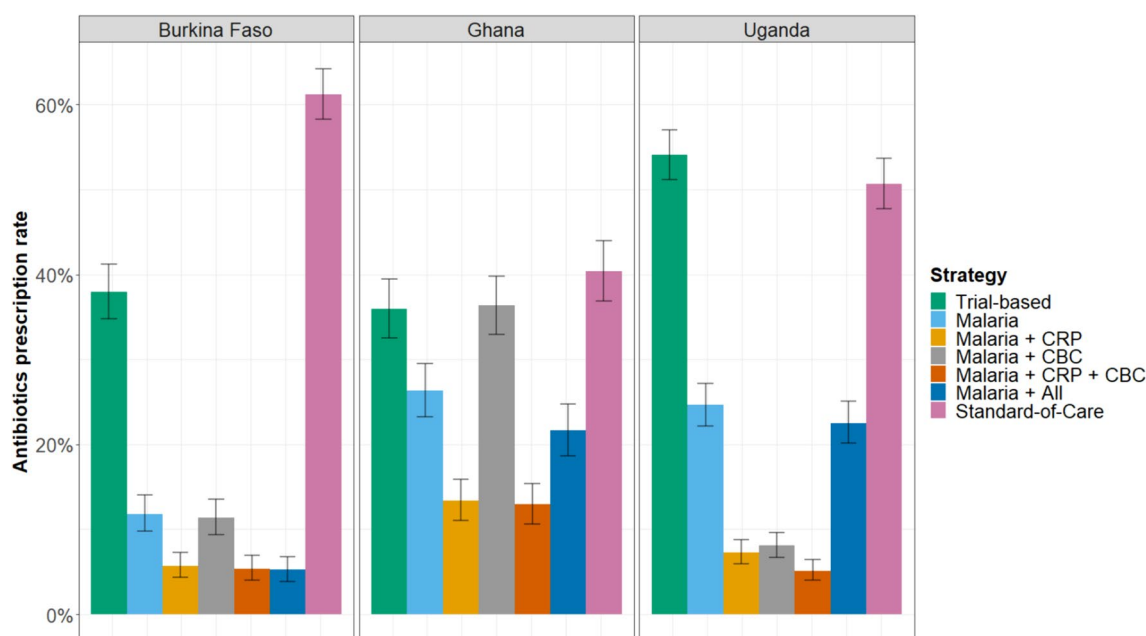
| Pathogen-specific                    | Burkina Faso                 |            | Ghana                        |            | Uganda                       |            |
|--------------------------------------|------------------------------|------------|------------------------------|------------|------------------------------|------------|
|                                      | <i>N</i> tested (% of total) | % positive | <i>N</i> tested (% of total) | % positive | <i>N</i> tested (% of total) | % positive |
| Group A <i>Streptococcus</i> test    | 36 (4)                       | 5.6        | 735 (97)                     | 4.8        | 285 (24)                     | 16.8       |
| Influenza test                       | 379 (44)                     | 6.1        | 734 (96)                     | 9.5        | 681 (57)                     | 5.7        |
| Malaria test                         | 856 (100)                    | 75.5       | 738 (97)                     | 11.4       | 1189 (100)                   | 42.1       |
| Respiratory syncytial virus test     | 136 (16)                     | 2.2        | 732 (96)                     | 2.9        | 141 (12)                     | 5.7        |
| <i>Streptococcus pneumoniae</i> test | 24 (3)                       | 12.5       | 398 (52)                     | 5.3        | 469 (39)                     | 10.2       |
| Typhoid fever test                   | 279 (33)                     | 2.9        | 736 (97)                     | 1.6        | 781 (66)                     | 11.8       |
| Dengue test                          | 53 (6)                       | 0          | –                            | –          | –                            | –          |
| Non-pathogen-specific                |                              |            |                              |            |                              |            |
| CRP test                             | 788 (92)                     |            | 730 (96)                     |            | 1188 (100)                   |            |
| < 20                                 |                              | 42.9       |                              | 83.2       |                              | 64.8       |
| 20–80                                |                              | 31.1       |                              | 13.6       |                              | 16.6       |
| > 80                                 |                              | 26.0       |                              | 3.3        |                              | 18.6       |
| Urine nitrite                        | 5 (1)                        | 0          | 393 (52)                     | 7.4        | 358 (30)                     | 4.8        |
| Urine esterase                       | 5 (1)                        | 0          | 393 (52)                     | 14.0       | 358 (30)                     | 54.5       |
| CBC test                             | 787 (92)                     |            | 738 (97)                     |            | 1188 (100)                   |            |
| WBC $\geq 11,000$                    |                              | 32.9       |                              | 56.8       |                              | 13.3       |
| Neutrophils $\geq 75\%$              |                              | 8.9        |                              | 12.9       |                              | 0.6        |

*CBC* complete blood count, *CRP* C-reactive protein, *RDT* rapid diagnostic test, *N* number of patients, *WBC* white blood cell count

**Fig. 3** Overview of costs per consultation per cost variable, reflected in International dollars. *CBC* complete blood count, *CRP* c-reactive protein, *OTC* over-the-counter

and \$ 0 to \$ 0.22 for Uganda. In case of a higher WTP, the “malaria + CRP” strategy becomes the strategy with the highest probability of being cost-effective across all three

countries. With a further increase of the WTP, the “malaria + CRP + CBC” strategy becomes the strategy with the highest probability of being cost-effective for Burkina Faso and



**Fig. 4** Effect of the intervention on antibiotic prescription rate, stratified by country and strategy. *CBC* complete blood count, *CRP* C-reactive protein

Uganda (see Fig. 6). While the CEAC results offer insights in the relative cost-effectiveness of the strategies, they also highlight the need for establishing a WTP threshold per ppt reduction in APR to translate these findings into actionable policy recommendations.

### 3.4 Scenario Analysis

The first scenario examines the impact of varying percentages (ranging from 0% to 60%) of malaria-positive patients receiving antibiotics. This range was considered to be representative of the percentages of malaria-positive cases receiving antibiotics in the “SoC” and “trial-based” strategies, which were as follows: 48% and 41.6% for Burkina Faso, 17.9% and 20.2% for Ghana, and 33.4% and 62.0% for Uganda, respectively. Across all three countries and all strategies, except for the “malaria + CBC” strategy in Ghana, there was a persistent reduction in APR compared to the “SoC” strategy over the entire range of 0% to 60% (see OSM Appendix Fig. A1). This finding suggests that the strategies’ effect on APR is not solely due to the potential reduction in APR resulting from not prescribing antibiotics to malaria-positive cases. It indicates that there is also an effect on APR in the malaria-negative group due to the additional tests performed or educational intervention introduced in the Accelerator trial, which further supports the finding of the main analysis that the test strategies could effectively reduce APR.

In the second scenario, the potential difference in the effect for patients with presenting signs and symptoms being respiratory (respiratory scenario) versus presenting signs and symptoms being non-respiratory (non-respiratory scenario) was assessed. The results indicate a higher APR across all strategies for the respiratory patient group in both Burkina Faso and Ghana. For Burkina Faso, the strategies resulted in a greater ppt reduction in APR compared to the “SoC” strategy in the respiratory patient population. On the contrary, for Ghana and Uganda, the strategies tended to be more effective in the non-respiratory patient population compared to the respiratory patient population (see OSM Appendix Table A8).

## 4 Discussion

A health economic analysis was conducted to quantify the expected cost, clinical outcomes, and impact on antibiotic prescription resulting from the implementation of a diagnostic strategy in Burkina Faso, Ghana and Uganda. The “trial-based” strategy resulted in a significant decrease in APR compared to the “SoC” strategy in Burkina Faso, whereas no significant decrease was found in Ghana and Uganda. Alternative diagnostic strategies, modelled as hypothetical cases, indicated that a significant reduction in the APR could be realized by the introduction of a diagnostic test strategy in all three countries. The “malaria” strategy resulted in cost savings but was also part of SoC

**Table 3** Incremental outcome, reported as deterministic outcome, including the 95% credible interval in brackets

| Strategy            | Cost (95% CrI)         | Antibiotic prescription rate (95% CrI), in % | ICER pairwise to SoC | ICER fully incremental |
|---------------------|------------------------|--|----------------------|------------------------|
| <b>Burkina Faso</b> |                        |  |                      |                        |
| Malaria             | \$ 11.60 (9.14–14.37)  | 11.8 (9.8–14.0)                              | Dominant             | –                      |
| SoC                 | \$ 12.24 (10.03–14.69) | 61.2 (58.2–64.0)                             | –                    | Dominated              |
| Malaria + CRP       | \$ 14.07 (11.18–17.25) | 5.7 (4.3–7.3)                                | \$ 0.03              | \$ 0.40                |
| Malaria + CBC       | \$ 17.03 (14.19–20.11) | 11.4 (9.4–13.6)                              | \$ 0.10              | Dominated              |
| Malaria + CRP + CBC | \$ 17.73 (14.85–20.94) | 5.4 (4.0–6.9)                                | \$ 0.10              | \$ 12.20               |
| Malaria + All       | \$ 25.16 (21.53–28.95) | 5.2 (3.9–6.8)                                | \$ 0.23              | \$ 37.15               |
| Trial-based         | \$ 43.24 (39.92–46.60) | 38.0 (34.8–41.2)                             | \$ 1.34              | Dominated              |
| <b>Ghana</b>        |                        |  |                      |                        |
| Malaria             | \$ 15.92 (13.23–18.92) | 26.4 (23.3–29.6)                             | Dominant             | –                      |
| Malaria + CRP       | \$ 21.25 (17.40–25.37) | 13.3 (11.0–15.9)                             | Dominant             | \$ 0.41                |
| SoC                 | \$ 27.32 (24.61–30.24) | 40.4 (36.9–43.8)                             | –                    | Dominated              |
| Malaria + CBC       | \$ 28.79 (25.12–32.66) | 36.3 (32.9–39.9)                             | \$ 0.36              | Dominated              |
| Malaria + CRP + CBC | \$ 30.67 (26.86–34.91) | 12.9 (10.6–15.4)                             | \$ 0.12              | \$ 23.55               |
| Malaria + All       | \$ 63.19 (58.45–68.08) | 21.6 (18.7–24.6)                             | \$ 1.91              | Dominated              |
| Trial-based         | \$ 69.90 (65.25–74.44) | 36.0 (32.5–39.5)                             | \$ 9.68              | Dominated              |
| <b>Uganda</b>       |                        |  |                      |                        |
| Malaria             | \$ 15.85 (13.29–18.77) | 24.6 (22.1–27.2)                             | Dominant             | –                      |
| SoC                 | \$ 15.99 (13.43–18.88) | 50.7 (47.7–53.6)                             | –                    | Dominated              |
| Malaria + CRP       | \$ 19.61 (16.37–23.12) | 7.3 (5.9–8.8)                                | \$ 0.08              | \$ 0.22                |
| Malaria + CBC       | \$ 26.82 (23.56–30.30) | 8.1 (6.7–9.7)                                | \$ 0.25              | Dominated              |
| Malaria + CRP + CBC | \$ 28.45 (25.12–32.15) | 5.1 (4.0–6.4)                                | \$ 0.27              | \$ 4.02                |
| Malaria + All       | \$ 41.77 (37.74–45.89) | 22.5 (20.1–25.0)                             | \$ 0.91              | Dominated              |
| Trial-based         | \$ 56.65 (52.82–60.60) | 54.1 (51.2–57.1)                             | Dominated            | Dominated              |

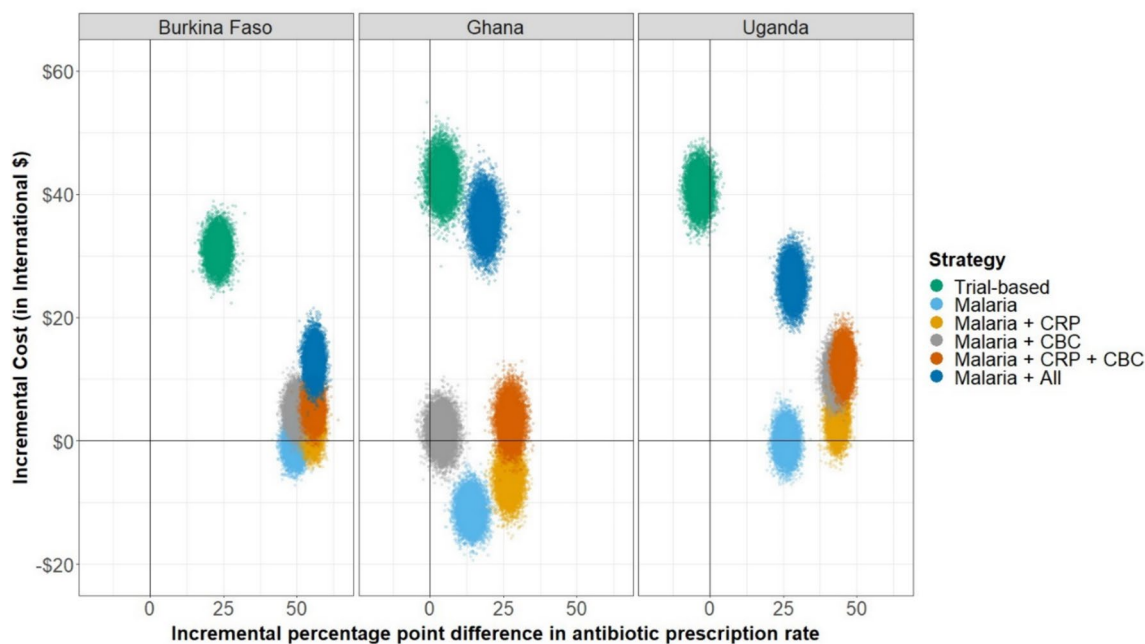
*CBC* complete blood count, *CrI* credible interval, *CRP* C-reactive protein, \$ International dollar, *ICER* incremental cost-effectiveness ratio, *SoC* Standard-of-Care

across all three countries and produced a less pronounced reduction in APR than other strategies. Initial testing with malaria and subsequent testing with a CRP test (for malaria-negative patients) resulted in a pairwise ICER ranging from \$ 0.03 to \$ 0.08 per consultation for 1 ppt reduction in APR versus the “SoC” strategy for Burkina Faso and Uganda, respectively, and was dominant (i.e., less costly and results in better health outcomes) versus the “SoC” strategy in Ghana.

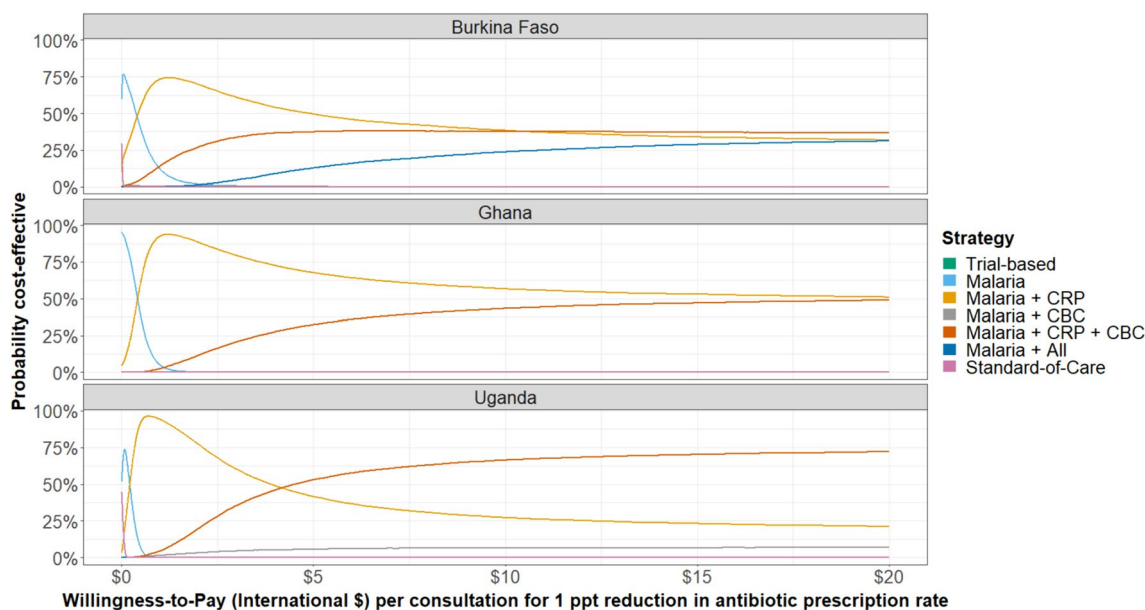
The results of the hypothetical strategies indicate the maximum effect the tests could have on APR given the assumption that the clinical test algorithm would be strictly followed. As a result, the findings are likely an overestimation of the actual result since in reality multiple factors influence the decision to prescribe antibiotics besides the test results, such as fear of adverse outcomes, lack of trust in POC test outcomes, patient expectations, prescriber’s awareness of AMR, and potential financial burden on patients due to test costs [12, 38]. Indeed, the observed difference in antibiotic prescriptions between the “trial-based” strategy and the “malaria + all” strategy indicate a substantial difference

between the actual and hypothetical strategies. The two strategies apply the same package of diagnostic tests, but the hypothetical “malaria + all” strategy resulted in a substantially larger ppt reduction in APR versus the “trial-based” strategy despite the training and education provided as part of the “trial-based” strategy. Based on the results of the scenario analysis, this difference can only partially be explained by the way malaria-positive patients would be treated in the hypothetical strategies and indicates the challenge of changing the status quo of presumptive antibiotic prescription by clinicians. Hence, the results of the current analysis should be considered optimistic if the implementation of the test strategy within clinical practice neglects the broader context of the decision to prescribe antibiotics. A systems approach is required to reduce inappropriate antibiotic prescriptions with diagnostic tests as a valuable tool to rationalize antibiotic prescription rather than the silver bullet.

The primary outcome of the present study is reported in the incremental cost per consultation for 1 ppt reduction in APR, which provides an insightful alternative for the standard health-economic outcomes such as incremental



**Fig. 5** Results of the probabilistic sensitivity analysis plotted over the cost-effectiveness plane with the “SoC” strategy as comparator. *CBC* complete blood count, *CRP* C-reactive protein



**Fig. 6** Cost-effectiveness acceptability curve. *CBC* complete blood count, *CRP* C-reactive protein, \$ International dollar, *ppt* percentage point

cost per DALY averted or cost per QALY gained. However, cost per 1 ppt reduction in APR is not a widely accepted standard outcome measure yet for interventions targeting antibiotic prescriptions [14, 39, 40]. No studies on antimicrobial stewardship programs in Ghana, Uganda or Burkina Faso have been identified that report the results in cost per ppt reduction in APR. Studies that do report

the cost per ppt reduction in APR (recalculated to International \$) range from \$ 0.07 for an antibiotic stewardship program among primary-care doctors in China [41] to \$ 1.59 for a combined primary-care intervention of general practitioner communication training and CRP testing for patients with respiratory tract infections in Europe [42] and \$ 3.56 for CRP testing in a primary-care setting for



patients with acute exacerbations of chronic obstructive pulmonary disease in England and Wales [43]. Since a WTP for a ppt reduction in APR is lacking, no conclusions can be drawn with respect to the absolute cost-effectiveness of these interventions. However, by reporting the results of the interventions in cost per ppt reduction in APR, comparisons can be made between interventions between countries. Not unexpectedly, interventions produce lower ICERs in LMICs (the present study and the study of Zhang et al. [41]) than high-income countries. However, AMR is a global threat that must be addressed concomitantly in all countries in ways that are proportionate to the wealth and purchasing power of their government and societies.

#### 4.1 Strengths and Limitations

The strength of the current study lies in the relative comparisons made across a range of test strategies and different countries. The relative comparisons provide valuable insights with respect to the most favourable test combination, which can support policy-makers in their decision on the allocation of scarce resources for maximum health benefit. Additionally, the between-country comparisons allowed us to identify parameters influencing cost-effectiveness (i.e., percentage of positive malaria cases), which is a strength of the study. The current analysis also comes with several limitations. To include hypothetical diagnostic strategies, we assumed a perfect diagnostic strategy implementation with healthcare providers strictly following the diagnostic algorithm in their decision as to whether to prescribe antibiotics or not. This is a simplification of reality and most certainly resulted in an overestimation of the effect of the strategies, but it does provide valuable insight in the potential of the alternative diagnostic strategies. Another limitation is related to the assumption that a reduction in antibiotic prescription does not negatively impact quality of life. Although this assumption is supported by previous studies [44, 45], it neglects malaria and bacteraemia co-infection, which could have resulted in negative health outcomes and requires antibiotic treatment [46, 47].

#### 5 Conclusion

The introduction of a diagnostic test panel for patients with acute febrile illness could result in a substantial reduction in the APR with a malaria test as the dominant strategy. Further reduction of the APR at minimal cost could be realized by the combination of a malaria test and a CRP test. The implementation of diagnostic tests for more appropriate antibiotic prescriptions is effective, but

requires a WTP per ppt reduction in the APR to decide on the most cost-effective strategy, and should be part of an integrated stewardship program to realize its full potential.

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**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Pim W.M. van Dorst with support from Simon van der Pol and Thea van Asselt. The first draft of the manuscript was written by Pim W.M. van Dorst and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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#### Declarations

**Potential conflicts of interest** Pim W.M. van Dorst, Piero Olliaro, Sabine Dittrich, Juvenal Nkeramahame, Simon van der Pol and Antoinette D.I. van Asselt have no reported conflicts of interest. Prof. Maarten Postma holds of stocks of Pharmacoeconomics Advice Groningen (Netherlands) and Health-Ecore (Zeist, Netherlands). Prof. Cornelis Boersma holds stocks of Health-Ecore (Zeist, Netherlands). All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the article have been disclosed.

**Ethics statement** The AMR Diagnostics Use Accelerator trial was registered with the US National Library of Medicine Clinical Trials database (identifier: NCT04081051). The overarching protocol was reviewed and approved by the Human Research Ethics Committee of the University of Oxford, United Kingdom. In addition, country-specific protocols were reviewed and approved by relevant regulatory authorities and national and/or institutional ethics committees in all participating countries.

**Consent to participate** Written informed consent was provided by all participating adults and official caregivers of participating children.

**Consent for publication** The study participants and official caregivers of participating children consented to their data being used for publication.

**Data availability** The data that support the findings of this study were provided by FIND, who received funding from the UK government for this study. Restrictions apply to the availability of these data and so are not publicly available. Data are available from the authors upon reasonable request and with permission of FIND.



**Code availability** The R model is available from the authors upon reasonable request and with permission of FIND.

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