








RESEARCH ARTICLE

REVISED Accounting for aetiology: can regional surveillance data alongside host biomarker-guided antibiotic therapy improve treatment of febrile illness in remote settings? [version 2; peer review: 2 approved]

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Abstract



Background: Across Southeast Asia, declining malaria incidence poses a challenge for healthcare providers, in how best to manage the vast majority of patients with febrile illnesses who have a negative malaria test. In rural regions, where the majority of the population reside, empirical treatment guidelines derived from central urban hospitals are often of limited relevance. In these settings, health workers with limited training deliver care, often without any laboratory diagnostic support. In this paper, we model the impact of point-of-care C-reactive protein testing to inform the decision to prescribe antibiotics and regional surveillance data to inform antibiotic selection, and then simulate the subsequent impact on mortality from febrile illnesses, rooted in the real-world context of rural Savannakhet province, southern Laos.

Methods: Our model simulates 100 scenarios with varying quarterly incidence of six key pathogens known to be prevalent in rural Laos. In the simulations, community health workers either prescribe antibiotics in-line with current practice as documented in health facilities in rural Laos, or with the aid of the two interventions. We provide cost-effectiveness estimates for each strategy alone and then for an integrated approach using both interventions.


Results: We find that each strategy is predicted to be highly cost-effective, and that the combined approach is predicted to result in the biggest reduction in mortality (averting a predicted 510 deaths per

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year in rural Savannakhet, a 28% reduction compared to standard practice) and is highly cost-effective, with an incremental cost-effectiveness ratio of just \$66 per disability-adjusted life year averted.

Conclusions: Substantial seasonal variation in the predicted optimal empirical antibiotic treatment for febrile illness highlights the benefits of up-to-date information on regional causes of fever. In this modelling analysis, an integrated system incorporating point-of-care host biomarker testing and regional surveillance data appears highly cost-effective, and may warrant piloting in a real-life setting.

Keywords

Febrile illness, aetiology, surveillance, biomarker, C-reactive protein, Southeast Asia, rural, cost-effectiveness

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REVISED Amendments from Version 1

This updated version of the manuscript has been created in response to the helpful comments we received from the reviewers (TH, RB). Detailed responses to their comments are available underneath their respective reviews. The main points of clarification were to highlight the challenges of inferring community epidemiology from hospital-level surveillance, and to emphasise that whilst multiplexed PCR platforms can contribute to patient care in resource-constrained regions, they cannot resolve all challenges associated with performing diagnostic microbiology in these settings. We are grateful to the reviewers for their thoughtful comments.

See referee reports

Introduction

There is a growing body of evidence that host biomarker tests, including commercially available low-cost point-of-care varieties, can help health workers identify patients with febrile illnesses who might benefit from antibiotic treatment^{1,2}. These tests have the potential to improve rational antibiotic prescribing, increasing the proportion of patients with bacterial infections that receive antibiotics, and diminishing overall drug pressure through fewer antibiotic prescriptions for patients with viral infections³.

However, these tests cannot inform the *selection* of an antibiotic. Thus, apart from the few diseases for which pathogen-specific point-of-care tests (POCTs) are available, for the overwhelming majority of patients with febrile illnesses, initial antimicrobial choice is empirical.

In low- and middle-income countries (LMICs) empirical treatment guidelines are often derived from sparse data collected at central urban hospitals, which may have little relevance to the rural settings where the majority of the population live. For example, in rural areas of Southeast Asia scrub typhus is a leading cause of hospitalisation, yet empirical management of fever in the community rarely includes an anti-Rickettsial antibiotic, even in areas where scrub typhus is known to be endemic⁴. Furthermore, seasonal, longitudinal and spatial heterogeneity pose additional challenges to providing locally relevant and up-to-date empirical treatment recommendations⁵. Finally, the emergence and spread of antimicrobial resistant (AMR) infections further complicates and constrains the selection of appropriate antibiotic treatment⁶.

Providing health workers with relevant data on the causes of febrile illness in their area would increase the probability that effective antibiotic therapy is selected and could improve patient outcomes. Until recently, acquiring such data was challenging, due to limited microbiological laboratory capacity in rural regions of most LMICs. However, new multiplex molecular testing platforms, including fully automated options that require no sample processing⁷, have been shown to be practical for use in resource-limited settings^{8,9}. Although these platforms cannot resolve all challenges associated with performing diagnostic microbiology in resource-constrained settings, they require less training and infrastructure than standard platforms. In conjunction with

appropriate support, placing these platforms in hospitals that currently lack the infrastructure to run fully-functioning microbiology laboratories could not only improve treatment of inpatients with suspected infections, but also improve care for the broader population, who seek care at peripheral clinics and community health posts within the catchment area of the regional hospital.

In this paper, we first explore the cost-effectiveness of such a system in terms of the costs and benefits for hospitalised patients with suspected infections. We then model the impact and cost-effectiveness this system could have in guiding empirical treatment in patients presenting to peripheral health facilities and community health posts in the geographical area served by the regional hospital. We compare current practice to the use of POC host biomarker-guided antibiotic therapy alone, the use of aetiological surveillance data alone and then an integrated system in which both approaches are combined. Our aim is to determine whether this approach warrants further investigation in a real-life setting, and not to provide a robust estimate of the potential magnitude of its impact. We use C-reactive protein (CRP) as an example host biomarker, as it is currently the most well characterised host biomarker in our region^{2,10}, and low-cost POCTs are already available on the market¹¹.

Modelling the cost-effectiveness of point-of-care multiplex polymerase chain reaction platforms for hospitalised patients

Multiplex polymerase chain reaction (PCR) platforms are increasingly available. They can test for dozens of target pathogens simultaneously, require limited training and infrastructure, and are deployable in resource-limited settings. Although sensitivity is inferior to traditional microbiological techniques, in hospitals that lack the infrastructure and laboratory capacity to reliably perform investigations such as blood cultures, these platforms can provide timely and potentially life-saving POC diagnoses to inform the management of severely ill, hospitalised patients.

A simple ‘back of the envelope’ calculation suggests that assuming a reduction of just one percentage point in case fatality rate (CFR) due to early diagnosis facilitating optimisation of empirical antimicrobial treatment, this could be a highly cost-effective strategy, even in the context of low-income countries (Table 1). This excludes further potential cost-savings in terms of antibiotic use averted, including both their direct purchase costs and the subsequent, and often higher costs of AMR associated with their use¹².

Modelling the impact of dynamic empirical treatment recommendations and point-of-care C-reactive protein guided antibiotic therapy

There is, however, a potential additional benefit of such a system – providing regional and timely data on causes of fever that can then be used to improve empirical treatment decisions for patients elsewhere in the region, who are unable to attend the hospital themselves. It is well recognised that compliance with recommendation for referral in many LMICs is low, due to geographical, financial and social constraints¹³, and that this is particularly problematic for common childhood illnesses, such as paediatric pneumonia¹⁴.

Table 1. Cost-effectiveness of a point-of-care multiplex PCR diagnostic platform in the management of hospitalised patients with suspected infections.

	Units	Unit cost	Total cost	Notes
One-step multiplex PCR device	0.2	\$35,000	\$7,000	Assume 5-year useful life
Server and peripheral equipment	0.2	\$5,000	\$1,000	
Laptop	0.2	\$1,200	\$240	
Laboratory technician	12	\$1,000	\$12,000	
Total annual capital and labour costs			\$20,240 ^a	
Samples per annum	1825 ^b			Assume 5 samples/day ¹⁵
Capital and labour cost per sample			\$11 ^c	a/b
Multiplex panel (one per sample)	1	\$155	\$155 ^d	
Other consumables	1	\$5	\$5 ^e	
Total cost per sample			\$171	c+d+e
Three scenarios for CFR without PCR			5%, 7%, 10%	
Three scenarios for CFR with PCR			4%, 5%, 7%	
DALYs per death			50	WHO age-adjusted life expectancy, based on a median age of 21 in hospitalised inpatients from a fever study in rural Laos ¹⁶
Cost/DALY in three comparative scenarios			\$342, \$171, \$114	

DALY, disability adjusted life year.

Data could be distributed to community health workers (CHWs) through smartphones equipped with electronic decision-support tools, that provide pragmatic guidance as to optimal antibiotic selection, given POC CRP test results or simple-to-elicited clinical symptoms indicative of a bacterial infection¹⁷, and accounting for background information on causes of fever from the regional hospital multiplex PCR platform.

Methods

Model development

We developed a model in R, simulating the impact and cost-effectiveness of such an integrated system in the context of 1,500 villages, each with a CHW in rural Savannakhet province, southern Laos¹⁶. We first simulate the outcomes of febrile illness due to common infections in this population in the absence of treatment. We then estimate their outcomes if CHWs were supplied with antibiotics to dispense based on clinical judgement, and then evaluate the potential impact of POC CRP-guided antibiotic therapy and/or the use of regional surveillance data on causes of fever to guide antibiotic prescribing. Our model assumes the following:

- A population of 880,000 people served by CHWs in Savannakhet province, based on census figures from the Lao Statistics Bureau at the Ministry of Planning and Investment¹⁸: 1,000,000 people in the province of whom approximately 120,000 live in the provincial capital;
- An overall incidence of febrile illness of 0.33 per person per annum, distributed by quarter to reflect seasonality,

and based on regional estimates for the burden of febrile illness¹⁹;

- That 36.6% of these fevers are cases of dengue (8.7%), scrub typhus (6.8%), influenza (6.4%), Japanese encephalitis (6.2%), leptospirosis (6.1%), or bacteraemia (2.4%), based on a cause of fever study in rural Laos, and including only confirmed mono-infections that had a prevalence of 5% or above¹⁶;
- Interventions only affect outcomes in patients with these known pathogens. The other 63.4% of simulated patients with unknown causes of fever receive no benefit from the interventions, although the costs of the interventions are applied to their management;
- Patients with malaria (1.1% in the original study) are excluded from the simulation as these would be managed based on a positive rapid diagnostic test (RDT) for malaria;
- The model runs 100 simulated scenarios with a stochastically determined incidence of the above diseases, drawn from gamma distributions with means shown in Table 2, reflecting the uncertainty and heterogeneity in their incidence;
- Viral infections convey a CFR of 0.1% irrespective of receiving an antibiotic^{20,21};
- CFRs for scrub typhus in the absence of a tetracycline are 6%²², for leptospirosis it is 2.2% in the absence of either

Table 2. Model parameters.

Disease	Proportion	CFR when untreated	Effective antibiotic	Standard practice (No treatment, beta-lactam, tetracycline)	Probability CRP high
Dengue	8.7%	0.1%	-	41%, 41%, 18%	12%
Scrub typhus	7.9%	6%	Tetracycline	34%, 39%, 26%	70%
Influenza	6.3%	0.1%	-	64%, 32%, 4%	20%
JEV	6.2%	0.1%	-	27%, 63%, 10%	42%
Leptospirosis	6.1%	2.2%	Tetracycline or beta-lactam	34%, 39%, 26%	81%
Bacteraemia	2.4%	15%	Beta-lactam	43%, 33%, 23%	84%
Unconfirmed	62.4%	0.5%	-	49%, 38%, 13%	36%
Notes/sources	16	20–25, 26	16		2

a tetracycline or a beta-lactam²³, and for bacteraemia in the absence of a beta-lactam the CFR would be 15%^{24,25};

- Deaths are associated with a loss of life of 50 years as described in Table 1, conservatively based on World Health Organization (WHO) age-adjusted life tables²⁶;
- To classify an intervention as cost-effective we compare its incremental cost-effectiveness ratio (ICER) per disability-adjusted life year (DALY) averted to a conservative willingness to pay (WTP) threshold of \$1230, half the Laos Gross Domestic Product (GDP) per capita²⁷;
- Healthcare workers in the field must choose between providing no treatment, a beta-lactam, or a tetracycline antibiotic. In the absence of CRP-testing or the surveillance data, their prescribing practices are conservatively assumed to resemble those of more highly-trained healthcare workers in the fever study from Laos¹⁶, detailed in Table 2, whereby for example 26% of patients with scrub typhus received a tetracycline;
- POC CRP tests with a threshold of 40mg/L to guide the decision to prescribe (CRP \geq 40mg/l) or withhold (CRP < 40mg/l) antibiotics, have a sensitivity and a specificity as detailed by pathogen in Table 2, based on data from prospective studies conducted in Cambodia, Laos and Thailand²;
- An incremental cost of \$2 per POC CRP test;
- The costs of establishing a multiplex PCR platform for regional surveillance is \$42,200 with an expected useful life for the equipment of 5 years, and a cost of reagents and consumables per specimen of \$160 (as detailed in Table 1);
- We assume that a subset of 1/50 samples from patients with febrile illnesses in the community would be collected for multiplex PCR testing to inform the regional estimates for causes of fever (i.e. we conservatively assume that all costs incurred are above and beyond those that

would be incurred if the platform was installed for use in hospitalised patients and regional estimates obtained from the diagnoses in these patients).

Using these assumptions and parameter estimates we compare the population mortality rates and costs for the following strategies, as compared with a hypothetical situation of no treatment:

- 1) Standard prescribing practices based on those documented at rural health facilities in Laos¹⁴
- 2) POC CRP-guided antibiotic therapy, with decision to prescribe antibiotics determined by a POC CRP-test with the above assumed test characteristics, and subsequent antibiotic selection in proportion to that in standard practice
- 3) The decision on whether to prescribe an antibiotic equates to that in standard practice, but the selection of antibiotic is based on the regional surveillance data, using an algorithm that selects the antibiotic with the best expected value in terms of health gains given the known incidence of infections in the region at that point in time (i.e. $\min \sum [incidence[i] * CFR[i] * (1 - efficacy[a])]$, where [i] relates to each of the pathogens in that quarter and iteration of the simulation and [a] is each of the two antibiotics). The model allows for the fact that the random selection of samples from 1/50 patients might not be a true reflection of the actual distribution of pathogens in the broader population, in which case the recommended empirical treatment will not be optimal
- 4) A combination of both approaches, in which decision to prescribe antibiotic is determined by the POC CRP test and subsequent selection of antibiotic determined by the above regional surveillance data algorithm.

This is repeated in 100 simulations to capture the heterogeneity in causes of fever. The mean expected mortality under each of the four strategies is then compared with a hypothetical situation of no treatment.

Cost-effectiveness estimation

The total mortality for the population of 880,000 is converted to DALYs. The four strategies are then compared against a hypothetical situation of no treatment, and ranked in order of effectiveness. The incremental costs and gains are then used to estimate the ICER per DALY averted, from least effective to most effective, to identify strategies that are strongly dominated (i.e. both more costly and less effective than other options). This process is repeated to identify strategies that are weakly dominated (i.e. there are more effective strategies with lower ICERs). The ICERs for the remaining strategies are then re-estimated and plotted as a cost-effectiveness frontier on the cost-effectiveness plane. We also plot cost-effectiveness acceptability curves, showing the proportion of iterations in which each strategy was identified as most cost-effective at varying levels of WTP per DALY averted.

Results

Predicted number of deaths

In the absence of any treatment, the model predicts 2701 deaths per year in the rural population of Savannakhet (equivalent to a mortality rate of 307 deaths per 100,000 person-years) due to the six pathogens. Current antibiotic prescribing practice would avert 863 of these deaths. The use of CRP-guided antibiotic therapy, without the surveillance data, would avert an

additional 325 deaths due to identification of a greater proportion of patients with bacterial infections whom may benefit from antibiotic treatment. Use of the regional surveillance data alone would have a lower impact than CRP-guided antibiotic therapy alone, reducing mortality by an additional 192 deaths compared with current prescribing practice. The combined regional surveillance data and CRP-guided antibiotic strategy was predicted to avert most deaths, achieving reductions of 510 deaths compared with current practice, or 1373 deaths compared with the hypothetical situation of no treatment. The distribution of these deaths over the entire year are shown in Table 3 and by quarter are shown in Figure 1.

Table 3. Predicted number of deaths in rural Savannakhet under each strategy.

Strategy	Predicted deaths in rural Savannakhet, n (95% CI)
No treatment	2,700 (2,590-2,820)
Standard practice	1,840 (1,760-1,930)
Surveillance-guided treatment	1,650 (1,580-1,720)
CRP-guided treatment	1,510 (1,440-1,590)
CRP- and surveillance-guided treatment	1,330 (1,270-1,390)

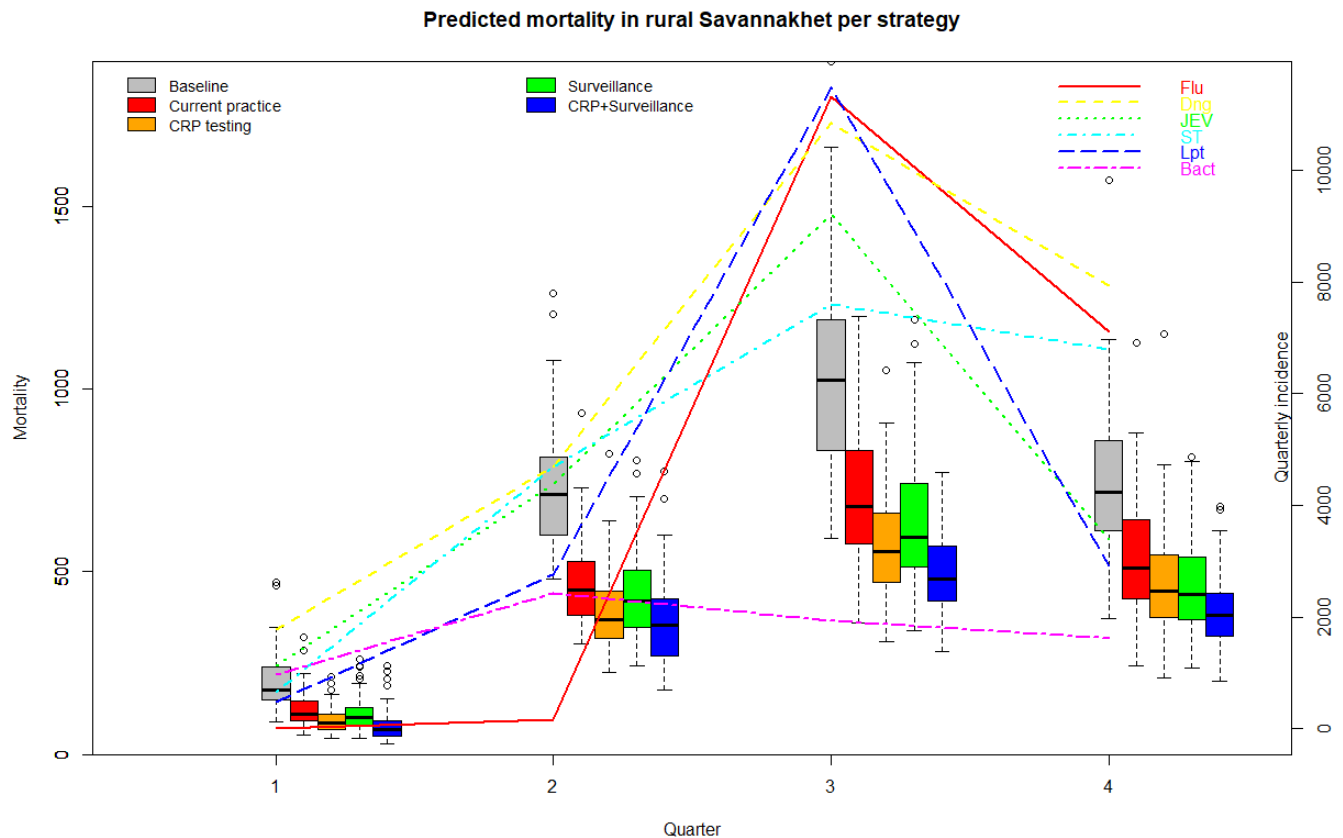


Figure 1. Predicted mortality under each treatment strategy and predicted incidence of the six pathogens, by quarter.

Predicted treatment choices

The overall proportion of patients prescribed an antibiotic was 15 percentage points lower in the two strategies that included CRP-guided antibiotic therapy than those without, at 44% as compared with 59%. The proportion of 100 simulated scenarios in which either a beta-lactam or a tetracycline would be recommended by the surveillance system, broken down by each quarter, is shown in Table 4. There is much variability in the optimal treatment choice between and within the four quarters over the 100 simulated scenarios, illustrating the importance of up-to-date surveillance data.

Predicted costs and cost-effectiveness

The incremental costs of deploying the CRP tests as compared with standard practice were estimated at \$505,000,

less than half the estimated incremental cost of the regional surveillance system, which was \$1,162,000. Given these costs and benefits, the ICER per DALY averted for the CRP-guided antibiotic therapy strategy alone compared with current practice was \$32, while the ICER per DALY averted for the regional surveillance system alone compared with current practice was \$121, therefore individually they can both be considered very cost-effective.

In a multi-way comparison the use of the regional surveillance data alone was excluded due to being strongly dominated by the CRP-guided antibiotic therapy strategy; the ICER of the combined strategy of CRP-guided antibiotic therapy and regional surveillance data as compared with CRP-guided antibiotic therapy alone was \$66, therefore highly cost-effective. The simulated costs and benefits of each strategy across the 100 simulations and the cost-effectiveness frontier are shown in Figure 2.

Table 4. Percentage of the time that either a beta-lactam or a tetracycline would be recommended by the surveillance system, in each quarter.

Drug	Quarter 1	Quarter 2	Quarter 3	Quarter 4
Beta-lactam	98%	75%	24%	9%
Tetracycline	2%	25%	76%	91%

The cost-effectiveness acceptability curves for the four strategies is shown in Figure 3. This indicates that at a WTP of over \$30 per DALY averted there is a greater than 50% probability of the CRP-guided antibiotic therapy strategy being most cost-effective, while the combined strategy is most likely to be cost-effective at a WTP value of over \$200 per DALY averted, and

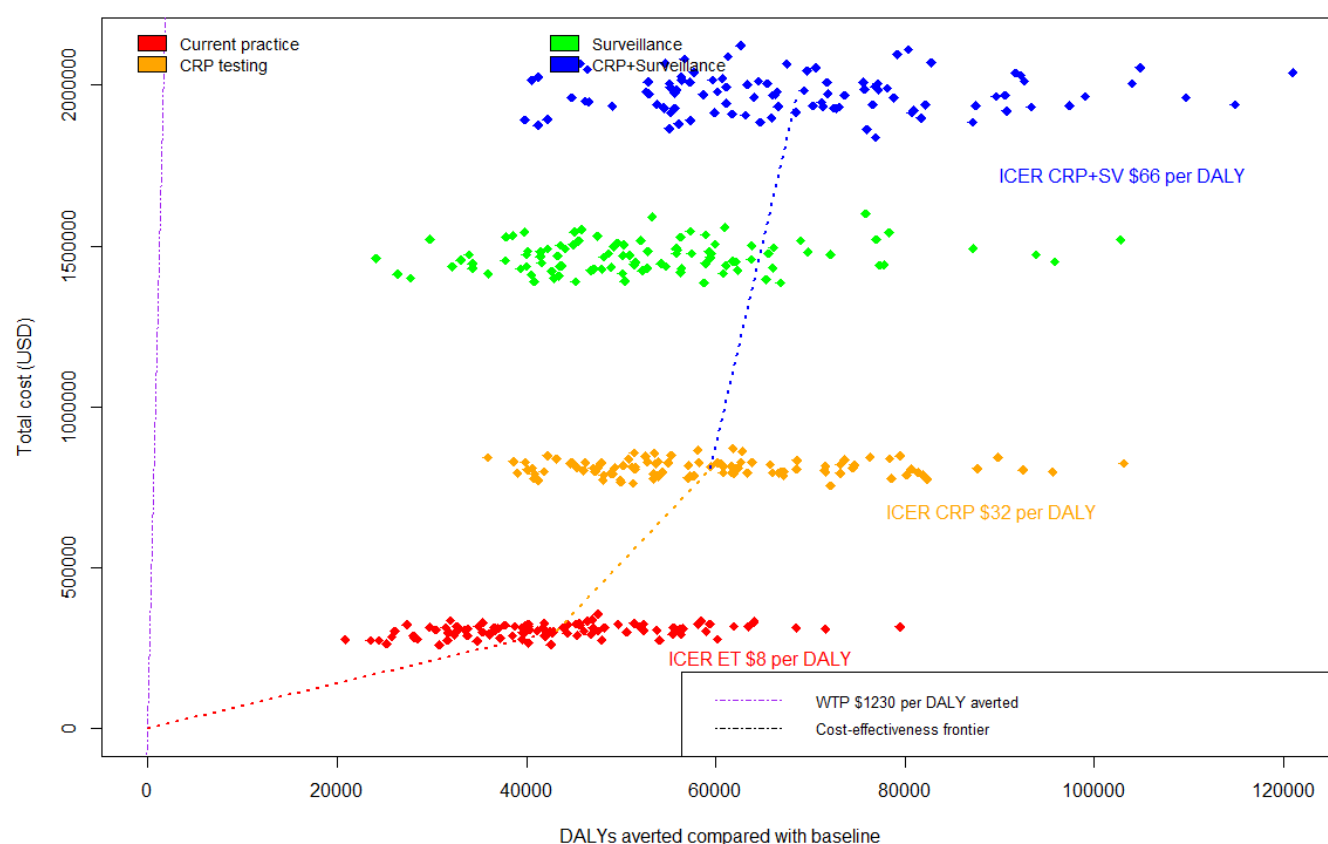


Figure 2. The simulated costs and benefits of the four alternative strategies.

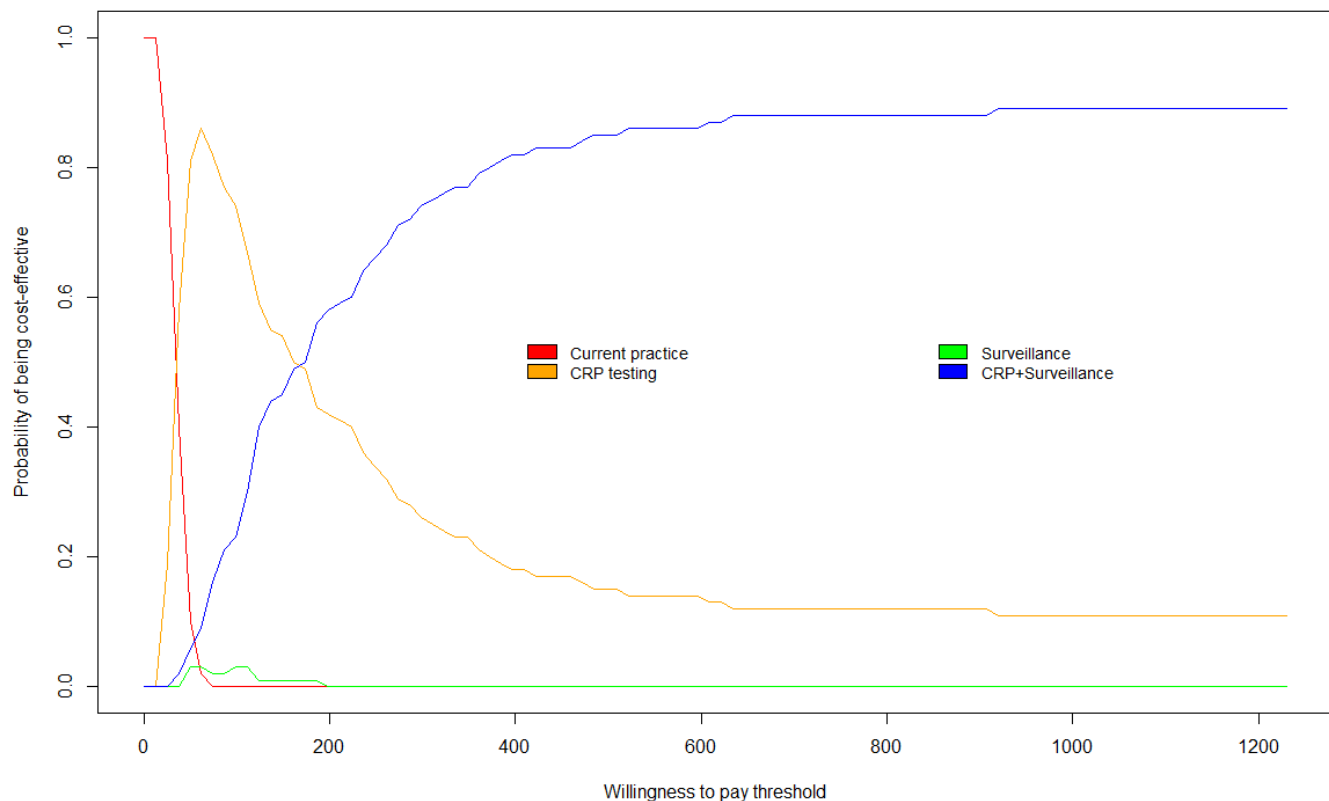


Figure 3. Cost-effectiveness acceptability curves for the four strategies.

this approaches 100% at a WTP threshold of \$600, well below the conservative threshold of \$1230 per DALY averted, half of the Laos GDP per capita.

Discussion

After decades of presumptive antimalarial treatment for patients with febrile illness in endemic settings, the decline in malaria transmission and the widespread availability of malaria RDTs poses a challenge to healthcare providers in how best to manage the vast majority of patients with febrile illnesses who have a negative malaria test.

This study models the impact and cost-effectiveness of introducing host biomarker testing to guide the decision to prescribe antibiotics, and regional surveillance data to guide the selection of antibiotic when they are thought to be required. In isolation, both CRP-guided antibiotic therapy and the use of regional surveillance data were cost-effective, although CRP-guided antibiotic therapy was both less costly and more effective than the surveillance system. The combination of the two interventions was the most cost-effective option, delivering the largest reductions in mortality (28% as compared with current practice), with an ICER of just \$66 per DALY averted.

To capture any variation in results in response to spatial and longitudinal heterogeneity in causes of fever, we ran the model over

100 simulated scenarios with different pathogen incidences. In all these scenarios the relative gains and cost-effectiveness estimates were largely consistent, with the combined strategy being the most effective, and both CRP-guided antibiotic therapy and surveillance data alone being more effective than current practice in 100% of scenarios, and the CRP-guided treatment being more effective than surveillance strategy alone in 77% of scenarios.

Our estimate is deliberately conservative. As previously stated our aim was to determine whether this approach warrants further investigation in a real-life setting, and not to provide a robust estimate of the potential magnitude of its impact. In fever studies from the region (and elsewhere), a pathogen is detected in only a minority of patients¹⁶. Given the known limitations in sensitivity of all currently available diagnostics, it is likely that some patients in whom the cause of fever remains unknown have a bacterial infection that may benefit from treatment with antibiotics. Indeed CRP levels in patients without a known cause for their infection are on average higher than those with an identified viral infection². In this modelling simulation, the majority of patients were not assigned a specific pathogen, and we assumed no health benefits conveyed by antibiotics (prescribed empirically or with the guidance of CRP-testing) in these patients. It is likely therefore that the results are an underestimate of the potential health gains associated with this approach.

In addition, by calculating DALYs, we considered only benefit conveyed by preventing years of life lost in the small number of deaths, but not from any reduction in the duration of time that patients were ill and potentially unable to work or attend school. Furthermore, we did not include the cost benefits of a 15% reduction in antibiotic prescription rates, neither in terms of direct purchasing costs nor avoidance of AMR. Including these benefits would increase the cost-effectiveness of both strategies that utilise CRP-guided antibiotic therapy.

Our study benefits from being rooted in the real-world context of Savannakhet province, with the majority of model assumptions informed by prospectively collected regional data. However, we recognise a number of limitations. The performance characteristics of POC CRP tests with a threshold of 40 mg/l are informed by prospective studies conducted by our research unit, predominantly recruiting outpatients with non-severe illnesses. We are aware of the limitations of using CRP-testing to guide antimicrobial therapy in all patients with febrile illness, particularly with regards lack of sensitivity in patients with severe illnesses²⁹. We recognise the need for a robust assessment of illness severity to precede any potential use of POC CRP-guided antibiotic therapy, if the approach we have explored in this paper is to be piloted in a real-life setting.

We assume that appropriate treatment (for example, a beta-lactam for bacteraemia), is 100% effective. Similarly, we assume that inappropriate treatment (for example, a tetracycline for bacteraemia) has no effect on patient outcome. This 'all or nothing' approach is simplistic and does not account for inter-patient heterogeneity, for example idiosyncratic bioavailability of antibiotics or patient comorbidities, adjunctive therapies in addition to antibiotics (for example, referral to higher-level care) and other host factors that may contribute to pathogenesis and response to treatment. Nor does it account for the need to provide intravenous antibiotic treatment, for example in those unable to take oral medications or in patients with melioidosis or multi-drug resistant infections where oral treatment options may not be available.

A further simplification is the inclusion of only two classes of antibiotics—beta-lactams and tetracyclines. This was a deliberate decision, taken to simulate the probable scenario that a limited-skill CHW can only be expected to reliably dispense one or two different antibiotics. In the original Laos fever study¹⁴ beta-lactams and tetracyclines made up 81% of all prescriptions. Firstly, we assumed that each patient received only one class of antibiotic. Secondly, we conservatively allocated the remaining 19% of prescriptions to the beta-lactam group; scrub typhus (tetracycline-sensitive) was more prevalent than bacteraemia (beta-lactam-sensitive) in this simulated cohort, hence this approach will have reduced our cost-effectiveness estimates, compared with the alternative of allocating some or all the additional 19% of prescriptions to the tetracycline group.

Empirical treatment recommendations are determined by the simulated relative proportions of different bacterial pathogens, amongst patients in whom a cause of fever is determined. Only pathogens that were diagnosed (and by definition, tested for) in the original Laos fever study are included in our model. Hence the spectrum of simulated pathogens is necessarily determined

by the comprehensiveness of the original diagnostic panel. It is therefore conceivable that a more comprehensive diagnostic panel could alter the proportional incidence of particular pathogens (potentially including additional pathogens). For example, a high prevalence of Streptococcal disease, not specifically tested for in the original fever study, amongst patients with acute respiratory infections, the most common presenting syndrome in patients with febrile illness, could make selection of a beta-lactam antibiotic always the optimal choice. This would make the contribution of a regional surveillance system, in terms of guiding empirical antibiotic therapy, redundant. Whilst we do not feel that this scenario is likely, a prospective study with an exhaustive aetiological diagnostic panel would be required to conclusively reject this possibility.

In addition, the accuracy of our simulated pathogen spectrum is limited by the fact that influenza testing only occurred during one of the three 'flu seasons', and at only one of the two hospitals in the original study. We decided not to extrapolate these results to the whole study period. Doing so would have increased the relative proportion of influenza cases and improved our cost-effectiveness estimates by virtue of the fact that more patients would have been assigned a simulated diagnosis of influenza, the lowest CFR in the model (0.1%) and fewer patients assigned diagnoses of scrub typhus, leptospirosis, bacteraemia or unknown, all of which have higher CFRs. It should be noted that whilst our CFRs are informed by the available literature, they will inevitably be affected by ascertainment bias of patients with more severe disease, and will therefore, in general, be overestimates.

In our model empirical treatment recommendations are updated on a quarterly basis in response to the results of diagnostic investigations performed on random samples taken from patients with febrile illness attending CHWs. We allow for the fact that the number of samples taken in the community might not be sufficiently large to consistently represent the actual distribution of detected pathogens in the broader population. This could of course be improved with a higher sampling frequency (at a higher cost). The model, however, did not account for imperfect sensitivities of the multiplex molecular testing platform, and the degree to which the sampling distribution represents the true population distribution of pathogens will be influenced by the sensitivity of the diagnostic investigations. It is likely that samples from remote areas would be restricted to small volume dried blood specimens, and hence diagnostic yield may be low. Further work is required to better understand the utility of the approach proposed here and whether sampling from patients with febrile illnesses attending rural clinics may provide more accurate representation of community fever aetiology, by virtue of the fact that larger sample volumes may improve diagnostic yield.

Standard prescribing practices are assumed to reflect that in the original Laos fever study, which recruited both inpatients and outpatients. It is feasible that the cohort of patients that attend hospital may not be reflective of those that consult a CHW: patients with more severe disease may choose to seek care at a hospital whilst patients with fulminant disease may be underrepresented as they may die before reaching a health

facility. This highlights an inherent challenge of using health facility-based presentations to infer community-level epidemiology. As outlined above, whilst population-based surveillance (for example, collecting samples directly from patients presenting to CHWs) appears attractive, further work is required to determine operational feasibility and the impact that low volume dried blood specimens may have on diagnostic yield.

Assuming equivalence in prescribing practices for patients presenting to CHWs and those presenting to hospital in the original study, may have overestimated antibiotic prescription rates amongst CHWs in the simulated standard practice scenarios. However, we believe it is reasonable to assume that, without guidance, CHWs would indeed prescribe at higher rates than their higher-trained counterparts. In addition, CHW prescriptions based on clinical judgement are likely to be less well targeted against the underlying pathogen. We have not accounted for this in our model and doing so would improve the cost-effectiveness of the surveillance system, compared to standard practice.

The estimated fever incidence of 0.33 episodes per person per annum is taken from a multi-country (Indonesia, Malaysia, Philippines and Thailand) observational cohort study¹⁹ in children aged 2 to 14 years, which used a robust definition of fever (documented axillary temperature of $\geq 38^{\circ}\text{C}$). It is possible that this estimate may not reflect the burden of febrile illness in Savannakhet province. However, the estimate is broadly consistent with fever incidence from CHW programmes in Southeast Asia, with whom our research unit collaborate.

Finally, an inherent assumption in the proposition of an integrated regional surveillance system like the one we discuss in this paper, is that adequate pathogen-specific POCTs are not yet available for common circulating pathogens. In our context, a RDT for scrub typhus has great potential to improve patient management. Whilst a regional surveillance system can indicate in which geographical areas a tetracycline should be first-line treatment for febrile illness, a scrub typhus RDT could indicate which individual patients would be most likely to benefit from this treatment. Current scrub typhus RDTs are affected by high background seroprevalence in endemic areas³⁰. If an affordable

antigen-based scrub typhus RDT with acceptable reliability and validity is developed, a surveillance system like the one we propose, could help guide in which areas and in which seasons it might most usefully be deployed.

Conclusions

Treatment of febrile illness, and specifically the decision on whether and which antibiotics are warranted is challenging even for experienced clinicians. In rural areas of LMICs where front-line healthcare workers have limited training and no laboratory support, antibiotic targeting is understandably poor. Tools to improve this are, however, available and deploying them could reduce an avoidable burden of illness and overuse of antibiotics.

A previous modelling analysis undertaken by our group found CRP-guided antibiotic therapy alone to be cost-effective in the management of non-malarial febrile illness in rural Laos³. Here we took a very different modelling approach to consider CRP-guided antibiotic therapy alongside the use of regional surveillance data on causes of fever to provide dynamic empirical treatment recommendations for patients with febrile illness. In this modelling analysis this approach appears highly cost-effective, and may warrant piloting in a real-life setting.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Software availability

The model code is available for download: DOI: <https://doi.org/10.5281/zenodo.2206939>³¹.

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Summary:

The submitted manuscript describes the simulated impact and cost-effectiveness of various strategies, including the use of point-of-care biomarker testing and regional surveillance data - as derived from the implementation of forwardly-deployed multiplex PCR - to guide antibiotic therapy in a resource-limited setting. Data informing the model are derived from previous work in SE Asia by this well-established research group. This issue, namely the accurate and timely diagnosis and treatment of non-malarial febrile illness, is incredibly important to advancing many of the Sustainable Development Goals, and the approach the authors have taken is an important preliminary step in developing effective and feasible interventions.

The manuscript is well organized, clearly written, and highly readable. In particular, I would commend the authors for the detailed and transparent description of the assumptions and methods underpinning the simulations. The included tables and figures are appropriate and well-designed. The results of the study are compelling and certainly suggest that additional prospective studies are warranted. The finding that CRP-guided antibiotic prescribing led to a decrease in deaths due to the identification of a greater proportion of patients with bacterial infections was especially notable, as much of the existing literature emphasizes the potential for biomarkers to reduce unnecessary antibiotic use. This is an important, albeit simulated, finding.

Overall, I have few criticisms and/or comments, which I have outlined below:

Major Comments:

1. The cost inputs for the implementation of a multiplex PCR infrastructure (Table 1) do not account for the analysis of surveillance data on a quarterly basis. I assume that this would require basic epidemiological analysis skillsets that, based on my experience in East Africa, are often not available at district-level hospitals. Even when there is a health information

manager at the district level, these individuals are often overburdened with routine reporting requirements. I am somewhat skeptical that this type of work could be conducted on a quarterly basis without an increase in human resources. Similarly, there are no inputs to reflect the cost of dissemination, which I assume would be done through meetings with CHWs or software updates to mHealth platforms. I do not think this negates the principle study findings, but I suspect there is more complexity and cost to the proposed interventions than accounted for in the analysis.

2. The assumption of case fatality rates for all viral diseases seems particularly low to me, especially for pediatric dengue and influenza, which are assumed to be highly incident in the model cohort. Such a low rate may be reasonable for viral pathogens that cause many upper respiratory infections (i.e. rhinovirus, coronavirus), but less so for dengue and influenza.
3. It would be interesting to see different analyses for children and adults as one would expect differences in (i) the incidence of febrile illness, (i) epidemiology of disease, and (iii) case fatality rates.

Minor Comments:

Modeling the cost-effectiveness...

- 1st Paragraph: While multiplex PCR platforms require less training and infrastructure than standard platforms, they are not without their own issues such as routine maintenance and problem-solving. Depending on the platform, heat and/or dust can be adversely impact performance. Of course, problems with power-interruptions and the weak logistical supply chains remain.

Modeling the impact...

- 2nd Paragraph: Perhaps worth referencing Keitel *et al.* (2017)¹ that adopted a similar approach using an electronic clinical decision algorithm (Note – I am not affiliated with the authors of this study in any way).

Methods

- While the burden of malaria is quite low in this study, there remains the issue of asymptomatic parasitemia, which may or may not be detected by RDT and may or may not be contributing to the febrile illness. I don't think this needs to be addressed here, but worthwhile considering given that some individuals with a positive malaria RDT may not receive required antibiotics. See recent manuscript by Dalrymple *et al.* (2019)².

Results

- Is there any data on routine vital statistics from the study area that could be used to validate the estimate of 2,701 deaths per year and the prevention of 863 deaths with current practice?

Discussion:

- While tetracyclines are generally well-tolerated, they are often not used in pregnant women and young children. I am not familiar with recommended alternative regimens for scrub typhus (if any) and whether there would be any expected increase in adverse events associated with increased prescription of this class of antibiotics.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: P. falciparum malaria in East Africa; pediatric fever management; rapid diagnostic tests; dengue; epidemiology; implementation science.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Jul 2019

Arjun Chandna

We thank the reviewer for their comprehensive comments on our manuscript and we are pleased that the reviewer recognises the need for strategies to improve care for patients with non-malarial febrile illnesses. Below we respond to the reviewer's specific comments.

We agree that a basic epidemiological skillset would be required to analyse the quarterly data and determine whether and how empirical treatment guidelines should be updated. We did not account for these costs nor the costs for disseminating results and implementing updates to treatment guidelines, but a sensitivity analysis exploring the impact of higher costs for the surveillance system indicates that these have a negligible impact (for brevity we opted not to include this in the manuscript, although interested

readers can explore these and other parameter estimates using the published code). As the reviewer describes, with advances in information and communication technologies it is feasible that these activities (the data analysis and dissemination) could be centralised, with results being delivered to mHealth platforms. A need would still remain for trained personnel at each health facility with whom central staff could liaise and to act as a focal point for local health workers. This human interaction is crucial to foster trust and achieve behaviour change. We acknowledge that including these additional costs would improve the accuracy of our cost-effectiveness estimates, but as the reviewer mentions, their omission is unlikely to alter the principle findings.

It is challenging to determine accurate case fatality rates (CFR) for febrile illnesses, especially for viral infections, as a substantial proportion are asymptomatic or of insufficient severity to trigger care seeking, particularly to central levels of the health system, where surveillance activities are often conducted (and estimates for CFRs calculated). Our CFRs for viral infections are based on the available literature: a CFR of between 0.05 to 0.09% for H1N1 influenza in New York City, established using active surveillance (i.e. telephone surveys); and the World Health Organization's estimate of 0.2 to ~1.0% for the CFR for dengue in Southeast Asia, using passive surveillance (i.e. only patients severe enough to present to a level of healthcare where diagnostic tests are present contribute to the denominator). Hence overall, we believe our estimate to be conservative, and the actual CFRs for illnesses due to these pathogens presenting at the community health worker level are likely to be substantially lower. Notwithstanding, motivated by the reviewer's comments, we ran a sensitivity analysis using an exceedingly high CFR for viral infections of 1% and while this resulted in much higher overall mortality in the simulated cohort, this had no impact on the cost-effectiveness of both host biomarker- and surveillance-guided strategies (alone or in combination) as these are determined by the appropriate use of antibiotics in patients with bacterial infections, with no impact on mortality in patients with viral infections. If more accurate data on CFRs were available our model could easily be re-run, although we suspect the principle findings would remain unchanged.

We agree that it would be interesting to perform different analyses for children and adults but currently we do not have the data with which to do this.

We have updated the manuscript to clarify that whilst multiplexed PCR platforms require less training and infrastructure than standard platforms, they cannot resolve all challenges associated with performing diagnostic microbiology in resource-constrained settings.

We are aware of the important study by Keitel and colleagues that incorporates clinical signs and point-of-care tests to improve management of febrile illness in resource-limited settings. Whilst, to our knowledge, they did not explore the dynamic incorporation of aetiological surveillance data as we describe here, both their group and ours are currently undertaking prospective studies to explore the utility of this approach.

Asymptomatic parasitaemia is unlikely to be responsible for a substantial number of positive malaria RDTs in our low-prevalence setting, and we agree with the reviewer that this issue need not be addressed here.

Unfortunately, we are not aware of any reliable granular data from the Savannakhet region that could be used to validate our mortality projections.

Short courses of tetracyclines are regularly used to treat paediatric scrub typhus in our settings, without an increase in adverse events. As the reviewer eludes to, tetracyclines are contraindicated in pregnancy, and although the evidence base is limited alternative treatments for scrub typhus in pregnant women, for example azithromycin, may be preferable. However, incorporating this into our model is beyond the scope of the current analysis.

Competing Interests: No competing interests were disclosed.

Reviewer Report 15 February 2019

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Chandna and colleagues have compared the performance of surveillance-guided and biomarker-guided antibiotic therapy, both separately and combined, in computer model simulations. A strength of this exercise, is that the authors parameterized the model using estimates based on data collected largely from the Savannakhet region, where the simulation is set. They simulated performance both in terms of DALYS averted and cost-savings per DALY. The authors also thoroughly described the potential limitations of the model, addressing many of my concerns as a reviewer.

On page 8 they stated that "our aim is only to determine whether this approach warrants further investigation in a real-life setting, and not provide a robust estimate of potential magnitude of its impact", which succinctly describes the elegance of this exercise and others like it. It would have been even better had this aim been stated in the abstract and in the introduction, so that readers can properly contextualize the methods and results sections.

While a well-conducted, well-explained study, there was one element that I thought was a potential drawback that ought to be addressed in the discussion. The authors used local hospital presentations to represent population-based epidemiology and (in the simulation) improve upon standard of care. They then concluded that antibiotic prescribing based on regional surveillance can improve upon standard of care. There are two issues with this:

1) Hospital presentations do not represent cases in the general population, tending to be

comprised of more serious cases that have been referred up the clinical chain, minus fulminant cases that die before they can present in hospital.

2) Being conducted in one region, they cannot say that their regional epidemiology differs from region to region. Rather, it may simply be the case that the standard of care is wrong and should be altered everywhere to match more closely to their findings from Savannakhet.

The authors have been so thorough with their caveats that I suspect the above may have been addressed in a tangential way that I did in fact miss. However, I do think the discussion section ought to explore the utility of population-based surveillance for informing community-delivered care. Population-based surveillance can both determine regional variation, and population (not hospital) incidence of infections causing febrile illness.

Two such initiatives are the Child Health and Mortality Prevention Surveillance (CHAMPS) program, which uses pathology-based methods to accurately determine cause of death among children in demographic surveillance sites, and the Countrywide Mortality Surveillance for Action (COMSA) platform, a sample registration system that is designed to draw inference from CHAMPS. Paired with disease mapping initiatives such as those run from my institution, we may be able to provide enough locally-specific inference to inform efforts such as the ones simulated by Chandna and colleagues.

To conclude, this study appears to be methodologically sound, well-reasoned, clearly-presented and well-written. In addition, it is a wonderful example of value that can be added to previously collected primary data through the use of simulation. It is a valuable addition to the literature as the global health community grapples with what it means to provide "precision public health", or healthcare that is matched to locally-specific estimates.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, mortality surveillance, disease mapping, policy translation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Jul 2019

Arjun Chandna

We thank the reviewer for taking the time to read our manuscript so carefully. We are pleased that the reviewer recognises the potential merits of simulation, and how it might be leveraged to guide future research exploring alternative approaches to “precision public health”. We are equally pleased that the reviewer recognises our efforts to describe the limitations of our approach, as we firmly believe that this degree of transparency is essential in order for readers to contextualise results. Below we respond to the reviewer’s specific comments.

We have emphasised that our primary aim was to explore whether the combined approach of host biomarker- and surveillance-guided antibiotic therapy warrants further exploration by including this statement in the Introduction (as well as in the Discussion). We have not included it in the Abstract in the interests of brevity.

We agree that there is an inherent difficulty of extrapolating community epidemiology from health facility-based presentations. As the reviewer eludes to, we had acknowledged this in a tangential way, with regards to the likely difference in prescribing practices for patients presenting to hospital (who likely have more severe disease). In response to the reviewer’s comments we have made this more explicit, and in addition we have taken the opportunity to highlight some of the challenges of population-based surveillance in resource-limited settings, with regards to operational feasibility and low volume dried blood specimens.

We agree that we cannot comment on regional heterogeneity in fever aetiology from this study, and it is possible that the standard of care for community fever management throughout Laos should be altered to reflect our simulated findings from Savannakhet. However, as far as we are aware, we had not drawn this conclusion and therefore have not altered the manuscript to clarify this. Of note, predicted benefits of accounting for regional heterogeneity in fever aetiology in Laos has previously been described (White *et al.*, PLoS ONE, 2012, DOI: 10.1371/journal.pone.0044545).

Competing Interests: No competing interests were disclosed.