Defining the burden of febrile illness in rural South and Southeast Asia: an open letter to announce the launch of the Rural Febrile Illness project.

Journal Item

OPEN LETTER

Defining the burden of febrile illness in rural South and Southeast Asia: an open letter to announce the launch of the Rural Febrile Illness project [version 1; peer review: 3 approved]

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Abstract

In rural areas of South and Southeast Asia malaria is declining but febrile illnesses still account for substantial morbidity and mortality. Village health workers (VHWs) are often the first point of contact with the formal health system, and for patients with febrile illnesses they can provide early diagnosis and treatment of malaria. However, for the majority of febrile patients, VHWs lack the training, support and resources to provide further care. Consequently, treatable bacterial illnesses are missed, antibiotics are overused and poorly targeted, and patient attendance wanes along with declining malaria.

This *Open Letter* announces the start of a new initiative, the Rural Febrile Illness (RFI) project, the first in a series of projects to be implemented as part of the South and Southeast Asian Community-based Trials Network (SEACTN) research programme. This multi-country, multi-site project will begin in Bangladesh, Cambodia, Lao PDR, and Myanmar and will define the epidemiological baseline of febrile illness in five remote and underserved areas of Asia where malaria endemicity is declining and access to health services is limited. The RFI project aims to determine the incidence, causes and outcomes of febrile illness; understand the opportunities, barriers and appetite for adjustment of the role of VHWs to include management of non-malarial febrile illnesses; and establish a network of community healthcare providers and facilities capable of implementing interventions designed to triage, diagnose and treat patients presenting with febrile illnesses within these communities in the future.

Keywords

Community Health Workers, Etiology, Fever, Primary Health Care, Rural Health, Southeastern Asia, Telemedicine, Western Asia, Village Health Workers

This article is included in the Mahidol Oxford Tropical Medicine Research Unit (MORU) gateway.

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Introduction

The majority of individuals in South and Southeast Asia live in rural areas, often characterised by high levels of poverty and restricted access to healthcare[1–3]. Data on causes of disease in these areas to prioritise interventions for scale up are limited. Despite this, there are indications that diseases of an infectious aetiology, 'febrile illnesses', account for substantial morbidity and mortality[4,5].

Malaria is the quintessential febrile illness. For decades, empiric antimalarials were recommended for patients presenting with fever[6], reflective of the burden associated with this fatal but treatable illness. In many parts of Asia, village health workers (VHWs) were introduced to improve access to treatment. Rapid declines in malaria incidence have subsequently been observed[7]. As a result, today fever seldom means malaria[8], and the exact cause of the illness often remains unknown, as does optimal management and what becomes of these individuals[9].

Falling malaria incidence highlights the inadequacies and fragilities of this vertical approach to healthcare. VHWs receive limited training, support and remuneration, and once malaria has been ruled out, often cannot provide further testing or treatment for their patients. Consequently, treatable bacterial infections are missed[10,11], and antibiotics, if available, are overused and poorly targeted[11–13]. Furthermore, the current inability to address non-malarial fever adversely affects uptake of malaria testing: patients have little to gain from having malaria ruled out in areas where it is already rare, but no other care offered for their illness[14,15]. This hampers eradication efforts and risks resurgence of drug-resistant malaria[16,17]. Encouragingly, it has been shown that the trend of decreasing patient attendance (and malaria testing) can be reversed when the remit of the VHW is extended to other basic healthcare provision[14].

This *Open Letter* announces the start of the Rural Febrile Illness (RFI) project, the first project in the South and Southeast Asian Community-based Trials Network (SEACTN) research programme[18]. The RFI project will begin in Bangladesh, Cambodia, Lao PDR and Myanmar and aims to define the epidemiological baseline of febrile illness in remote and underserved areas of Asia where malaria endemicity has declined and access to health services is limited. The primary objective of the RFI project is to determine the incidence, causes and outcomes of febrile illness in the rural communities residing within the project areas. The longer-term objective of SEACTN is to establish a network of community healthcare providers and facilities, capable of implementing interventions designed to triage, diagnose and treat patients presenting with febrile illnesses and other causes of ill health within these communities in the future.

Project overview

The RFI project is a multi-country, multi-site initiative comprised of a number of prospective observational studies. The project is divided into three key Work Packages (WP) with parallel supporting activities (Table 1). Detailed protocols for individual components of the RFI project are available at www.seactn.org.

Work Package A (WP-A)

In collaboration with VHWs we will develop and deploy electronic data collection tools to capture the incidence, presenting syndromes and outcomes of febrile illness amongst individuals presenting to the most peripheral level of the health system. In Lao PDR, community healthcare providers working at primary health centres (PHCs) rather than VHWs will implement the project, as utilisation of VHWs is currently low in this area[2].

Data collected from VHWs and PHCs will be complemented by parallel health status and health seeking behaviour surveys, verbal autopsies, and village and health facility mapping projects, designed to gain a comprehensive understanding of the burden of febrile illness and access to care in the areas served by these health facilities and providers. We will also perform targeted aetiological investigations in a subset of patients presenting to WP-A providers and facilities.

Work Package B (WP-B)

WP-B activities will be concentrated around two higher-level health facilities (health clinics and/or hospitals) in each of the sites in Bangladesh, Laos PDR and Myanmar, located within (or nearby) the same geographical area as the VHWs and PHCs selected for WP-A. More extensive aetiological investigations, as well as assays of host biomarkers, will be performed in patients with febrile illnesses attending these facilities.

Work Package C (WP-C)

In WP-C we will draw on the data collected in WP-A and WP-B to create temporally- and spatially-explicit electronic decision-support tools (eDSTs), designed to assist community health workers (both VHWs and healthcare providers at PHCs) in their assessment, triage and treatment of patients presenting with febrile illnesses in rural and remote areas. The data from WP-A and WP-B will also be used to identify the most high-impact and cost-effective point-of-care tests (POCTs) that could be included within the eDSTs, as well as appropriate delivery mechanisms. Subsequent deployment and health system integration will be informed by stakeholder analyses in the same settings to better understand the opportunities, barriers and appetite for adjustment of the role of VHWs and other community healthcare providers to include management of non-malarial causes of febrile illness.

Study sites and implementing partners

Strong, long-standing partnerships have been leveraged to plan and implement this multi-disciplinary project, across at least

Table 1. Key objectives of the RFI project.

Overall	
1	Determine the incidence, causes and outcomes of febrile illness in five rural areas of Bangladesh, Cambodia, Lao PDR and Myanmar
2	Establish a network of community healthcare providers and facilities, capable of implementing interventions designed to triage, diagnose and treat patients presenting with febrile illnesses within these communities in the future
Work Package A	
1	Develop electronic data collection tools for patients presenting to village health workers and primary health centres with febrile illnesses in the study areas
2	Determine the incidence and outcomes of febrile illnesses amongst patients presenting to village health workers and primary health centres in the study areas
3	Describe and understand health status and health-seeking behaviour for febrile illnesses in the study areas
4	Describe common causes of mortality and events immediately preceding death in the study areas
5	Map the geographic location, accessibility, treatment availability and workforce capacity of health facilities within and nearby the study areas
Work Package B	
1	Describe the causes and outcomes of febrile illnesses amongst patients presenting to sentinel rural health facilities in the study areas
2	Determine the diagnostic performance of host biomarkers to distinguish bacterial from viral infections amongst patients presenting with febrile illnesses
3	Determine the prognostic performance of host biomarkers to identify patients with febrile illnesses at risk of severe outcomes
Work Package C	
1	Complete stakeholder analyses to identify the opportunities, barriers and appetite for adjustment of the role of community healthcare providers to include management of non-malarial causes of febrile illness
2	Model the cost-effectiveness of different combinations of interventions to improve the management of febrile illness in the study areas
3	Develop and pilot electronic decision-support tools and point-of-care tests that can assist community healthcare providers in their assessment, triage and treatment of patients with febrile illnesses

620 villages in five rural regions of Bangladesh, Cambodia, Lao PDR and Myanmar (Figure 1).

In Bangladesh the project will be implemented in partnership with BRAC, one of the largest non-governmental development organisations in the world. As of September 2020, 130 villages have been selected and local health facilities (Upazila Health Complexes and District Hospitals) identified in Cox's Bazar and Bandarban districts.

The project in Cambodia will be a collaboration with the National Center for Parasitology, Entomology and Malaria Control (CNM), the Provincial Health Departments of Battambang and Pailin provinces, and Action for Health Development (AHEAD), a civil society organisation working to improve health in rural communities. The study will take place in western Cambodia in 120 villages from Pailin and Battambang provinces.

Two study sites are planned in Myanmar. In Northern Kachin state, 89 villages and two health clinics (Himalaya Clinic I and II), have been selected across three townships (Puta-O, Machanbaw and Nawngmun), where Medical Action Myanmar (MAM), a non-governmental healthcare organisation, operates a network of VHWs and rural health clinics. The second site is in Kayin state, where the Shoklo Malaria Research Unit (SMRU) supervises a large community health worker programme focused on malaria elimination. Overall, 130 villages and two health clinics (Wang Pha and Mawker Thai) across the townships of Hlaingbwe, Myawaddy and Kawkareik are planned for selection.

In southern Lao PDR, 28 PHCs (serving 160 villages) within three districts (Atsaphangthong, Thaphalanxay and Phin), as well as Atsaphangthong district hospital and Savannakhet provincial hospital have been selected. The project will be conducted in partnership with Savannakhet Provincial Health Office (SPHO).

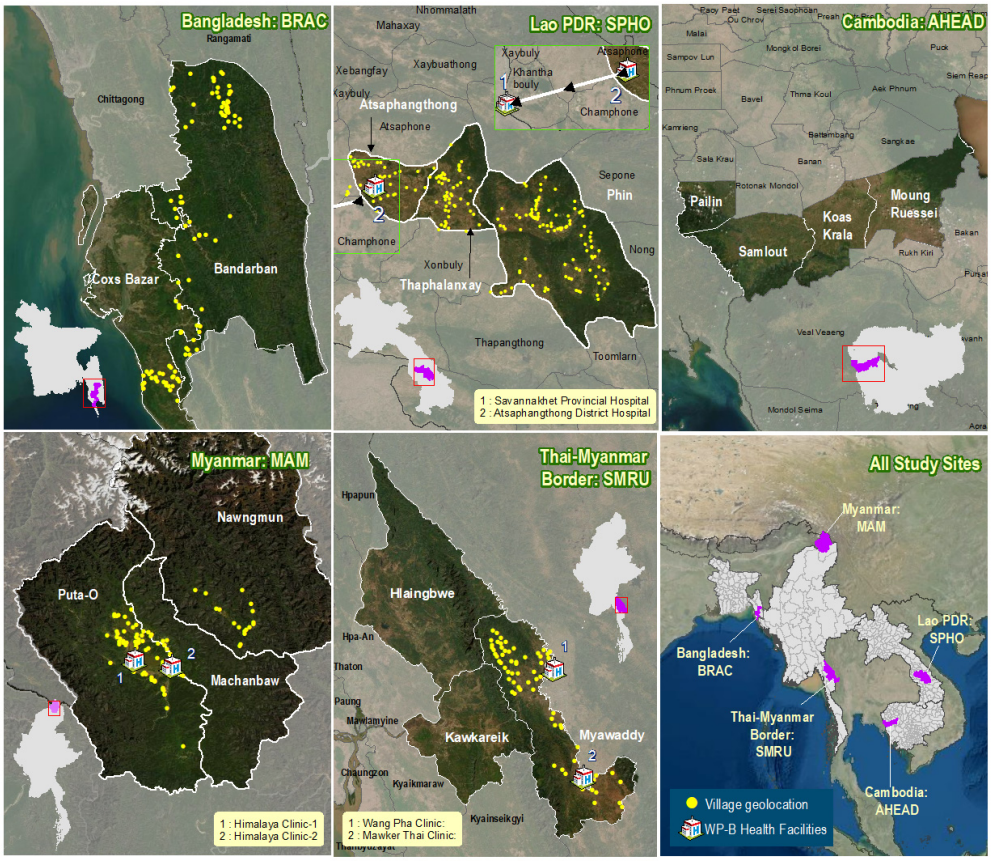

Figure 1. Study areas with selected villages and health facilities. AHEAD, Action for Health Development; MAM, Medial Action Myanmar; SMRU, Shoklo Malaria Research Unit; SPHO, Savannakhet Provincial Health Office; WP-B, Work Package B. Due to access difficulties related to the ongoing COVID-19 pandemic, participating villages in the townships of Hlaingbwe and Kawkareik (Thai-Myanmar border region) and WP-B health facilities in Bangladesh are yet to be finalised. WP-B activities are currently not planned in Cambodia and village selection is underway.

WP-A

Electronic data collection tools

Electronic data collection forms are being developed using the CommCare platform (Cambridge, MA, USA) and loaded on to mobile Android tablets. The tablets, accompanied by solar chargers where necessary, will be distributed to all VHWs (PHCs in Lao PDR) in SEACTN villages. Their feedback will inform iteration of the data collection forms following a human-centred design approach[19]. Once finalised, the tablets will be used to capture data from patients with febrile illnesses who attend the VHWs and PHCs (see below).

Data will be securely uploaded in real-time. In areas without mobile internet uploads will occur periodically during visits by the local implementing partner (BRAC, AHEAD, MAM, SMRU or SPHO). The aim is to develop a data stream from source to web-based interface with near real-time geospatial mapping of the incidence and outcomes of febrile illness. A detailed Data Management Plan is available on request from the Mahidol-Oxford Tropical Medicine Research Unit (MORU) Data Access Committee.

Digital health education materials

Training materials are being developed in partnership with DigitalMedic and serve three primary purposes:

- To sensitise communities to the project aims and objectives (see below);
- To support in-person training of the VHWs and PHC workers, focussing on ensuring accurate syndromic classification of febrile illnesses, reliable collection of clinical data and biological samples, and confidence in operating the electronic data collection tool;
- To improve patient understanding of the health problems the project aims to address.

Community engagement activities

Prior to the initiation of the study the local implementing partner will meet with villagers, village leaders and relevant local authorities to explain the project rationale, aims and planned activities, using digital educational material as outlined

above. Community consent will be sought for the collection of basic demographic and syndromic data (using the same electronic data collection tool) from all patients attending VHWs and PHCs (both febrile and non-febrile patients) to better understand the health needs of the community and inform future directions of the SEACTN.

Determining the incidence and outcomes of febrile illnesses in patients presenting to village health workers and primary health centres

All patients who attend the VHW (or PHC in Lao PDR) will be screened, and those with a febrile illness who provide consent will be enrolled. Enrolment will be consecutive and is planned for 18 months. Based on current attendances we estimate that we will capture approximately 100,000 febrile illness episodes across the five study sites.

The VHW (or PHC worker) will use the electronic data collection tool to record a limited set of clinical data and the result of the malaria rapid diagnostic test (mRDT). No changes to patient management will occur as a result of the study, except that the health worker will be prompted to consider referral and/or inform the operations team of the implementing partner if any danger signs are elicited, subject to the specific context at each site[20–22]. The participant will be followed-up by the VHW 28 days later to determine the outcome of their illness.

In participants outside the neonatal age range a capillary blood sample (finger- or heel-prick) will be collected at the same time as the mRDT and stored as a dried blood spot (DBS) on filter paper. In a subset of participants (at least 20,000 illness episodes) a convalescent DBS will be collected at the one-month follow-up. Targeted molecular and serological investigations (Table 2) will be performed on an initial set of 10,000 illness

Table 2. Aetiological investigations to be performed in the RFI project, including specimen type, target pathogen, diagnostic platform and laboratory location[24–26]. *Dengue NS1 testing will be performed on the acute (D0) sample only. **Blood cultures will be performed in-country at a quality-assured laboratory close to the WP-B health facility. RDT, rapid diagnostic test; JE, Japanese Encephalitis; NPS, nasopharyngeal swab.

Setting	Specimen	Target pathogen	Laboratory location and diagnostic platform		
			MORU PCR (Day 0)	MORU Paired serology (Day 0 and Day 28)	On site (Day 0)
WP-A: VHWs and PHCs	Capillary blood	*Plasmodium* spp.			RDT
		Dengue	✓	NS1* and IgM	
		Chikungunya	✓	IgM	
		Pan-Alphavirus	✓		
		Pan-Flavivirus	✓	Zika and JE IgM	
		Orientia tsutsugamushi		IgM	
		Rickettsia typhi		IgM	
		Rickettsia spp.		IgM	
		Leptospira spp.		IgM	
WP-B: Rural health facilities	Capillary blood	*Plasmodium* spp.			RDT or microscopy
	Venous blood	Dengue	✓	NS1* and IgM	
		Chikungunya	✓	IgM	
		Pan-Alphavirus	✓		
		Pan-Flavivirus	✓	Zika and JE IgM	
		Orientia tsutsugamushi	✓	IgM	
		Rickettsia spp.	✓	IgM	
		Leptospira spp.	✓	IgM	
		16S rRNA (eubacteria)	✓		
		Bacterial bloodstream infections			Blood culture**
	NPS	Respiratory pathogens	✓		

episodes to determine the aetiology of the febrile illness, with remaining samples stored for future targeted analyses.

Health-seeking behaviour surveys

We will conduct health status and health-seeking behaviour surveys to understand pathways to care for individuals with febrile illnesses. A better appreciation of how care for acute illness is currently sought in these settings will enable us to determine the overall burden of febrile illness in the study areas, and identify the best options for potential intervention in the future.

Community-level data, such as estimated vaccine coverage, availability of water, sanitation and hygiene (WASH) facilities, and assessments of indoor air quality, will be gathered to help contextualise the project's findings.

Verbal autopsies

Little information exists on the febrile (and non-febrile) causes of mortality in the study areas[23]. In collaboration with researchers from the University of Toronto, we have adapted the World Health Organization's (WHO) Verbal Autopsy (VA) tool to conduct electronic VA questionnaires for all deaths that occur in SEACTN villages in Bangladesh, Cambodia, Lao PDR and the North Kachin site in Myanmar[27]. Understanding the common causes of mortality and the circumstances that surround death will enable us to identify targets for interventions that can be implemented and evaluated within the SEACTN programme in the future.

Village and health facility mapping

A thorough understanding of local healthcare infrastructure is essential to direct referrals to higher-level care appropriately. Villages, transport networks and health facilities in the study areas will be mapped using field collection and satellite imagery, and detailed profiles created of the study villages including population statistics, communication and transport systems, health services and campaigns, physical environment and socioeconomic metrics. WHO's AccessMod 5 software will be used to estimate travel time from the study villages to health facilities and potential gaps in local service provision identified. In addition to informing how future interventions can be deployed within the SEACTN, we will provide this information to health system planners and policy makers to help identify where new health facilities could be provided and existing services strengthened to achieve highest impact.

WP-B

Determining the aetiologies of febrile illnesses in patients attending rural health facilities

To gain a comprehensive understanding of the causes of febrile illness in the region, we will recruit a cohort of patients attending two sentinel health facilities within four of the project areas. The information from these cohorts will be combined with the aetiological data from WP-A, where we are limited to collecting low-volume DBS specimens from a subset of participants (the remote locations preclude collection of samples from all villages and prevent maintenance of a cold chain).

All patients aged > 28 days who attend the health facilities with a febrile illness will be screened, and those who provide consent will be enrolled. Six hundred participants (inpatients and outpatients) will be enrolled in each age stratum (> 28 days to < 5 years; ≥ 5 years to < 15 years; ≥ 15 years), across both health facilities within a single project area (i.e. 1,800 participants in each area). Recruitment is planned for a minimum 12 continuous months at each site to ensure seasonality is adequately captured.

Baseline data will be recorded including demographics, anthropometrics, presenting syndrome, vital signs, clinical signs, duration of illness and any care sought for the illness thus far. In Bangladesh, Lao PDR and the Kayin state site in Myanmar blood cultures will be collected and the results provided to the treating clinical teams.

Venous blood samples and nasopharyngeal swabs will be collected and transported to MORU's central laboratories in Bangkok, where molecular and serological aetiological investigations (Table 2) will be performed. Novel molecular techniques such as target enrichment sequencing will also be validated against existing molecular diagnostics and used to investigate a broader range of pathogens than can be detected by the pathogen-specific tests[28]. Additional investigations for participants with specific syndromes (for example, urine, pus, throat swab and/or cerebrospinal fluid culture) will be considered, subject to feasibility at each of the facilities.

Admitted participants will be followed-up daily during their admission. All participants will be followed-up on day 2 (in person or via telephone) and asked to return to the health facility 28 days after enrolment to determine the outcome of their illness. A venous blood sample will be collected at this time for convalescent serological testing.

Identification of clinical features and host biomarkers that distinguish bacterial from viral infections in febrile patients

The venous blood samples collected from patients attending the rural health facilities will also be used to quantitatively measure host biomarkers that reflect immune activation and endothelial dysfunction. We will use this information, together with the baseline clinical data and results of the aetiological investigations, to construct diagnostic algorithms that can distinguish bacterial from viral infections[29–32]. Host biomarkers feasible for measurement using POCTs, will be prioritised, so that the algorithms could be used to guide antimicrobial prescribing in resource-limited primary care settings.

Development of prognostic clinical prediction models for febrile patients at risk of severe outcomes

We will also use the host biomarker data, in conjunction with the baseline clinical and day 2 and 28 outcome data, to derive prognostic algorithms (clinical prediction models) to identify patients at risk of severe outcomes, which could be used to guide referral decisions from community healthcare settings to higher-level care[33–38]. The baseline clinical data, host biomarker panels and outcome definitions have been harmonised with a

parallel study (NCT04285021) to facilitate data sharing and external validation of the prediction models.

WP-C

Stakeholder mapping and analyses

Throughout the RFI project, key stakeholders will be engaged and interviewed on the topic of expanding the remit of VHWs and/or other community healthcare providers to include management of non-malarial febrile illnesses. Stakeholders will include policy makers and managers within the Ministries of Health of the respective countries; representatives of international and national donor organisations; individuals and organisations responsible for the implementation and supervision of VHW and other community-based health programmes; and VHWs and community members.

During the interviews, information and views will be collected about operational challenges, opportunities and policy bottlenecks concerning the expansion of VHW programmes, with particular attention to the key issues of health system integration, capacity, and sustainability. After an initial set of interviews with seed informants, selected after a stakeholder mapping exercise, additional interviewees will be identified through snowball sampling. Collected material will be analysed thematically, while interim outputs such as matrix tables or position maps will be constructed to better understand the role and interest of different categories of stakeholders, their resources, and their level of support to the expansion of VHW programmes. Findings will also inform participatory development of the eDSTs (see below).

Economic evaluation of interventions that could be deployed in the SEACTN to improve the management of febrile illness

We will draw on the data and findings from WP-A and WP-B to develop economic models to assess the cost-effectiveness of different (combinations of) interventions to improve the management of febrile illness, that could be trialled in subsequent projects within the SEACTN. Analyses will be conducted on standalone interventions such as the implementation of POCTs[39], as well as multi-layered approaches integrating regional data on causes of illness within eDSTs, alongside POCTs[40]. The outputs of the cost-effectiveness analyses will also be provided to relevant governmental and non-governmental actors to support the planning and scale-up of national programmes.

Development of eDSTs for use by rural community healthcare providers

The results from these modelling assessments and the data from WP-A and WP-B, will be used to design bespoke, spatially-explicit eDSTs that can assist community healthcare providers in their assessment, triage and treatment of patients with febrile illnesses (Figure 2).

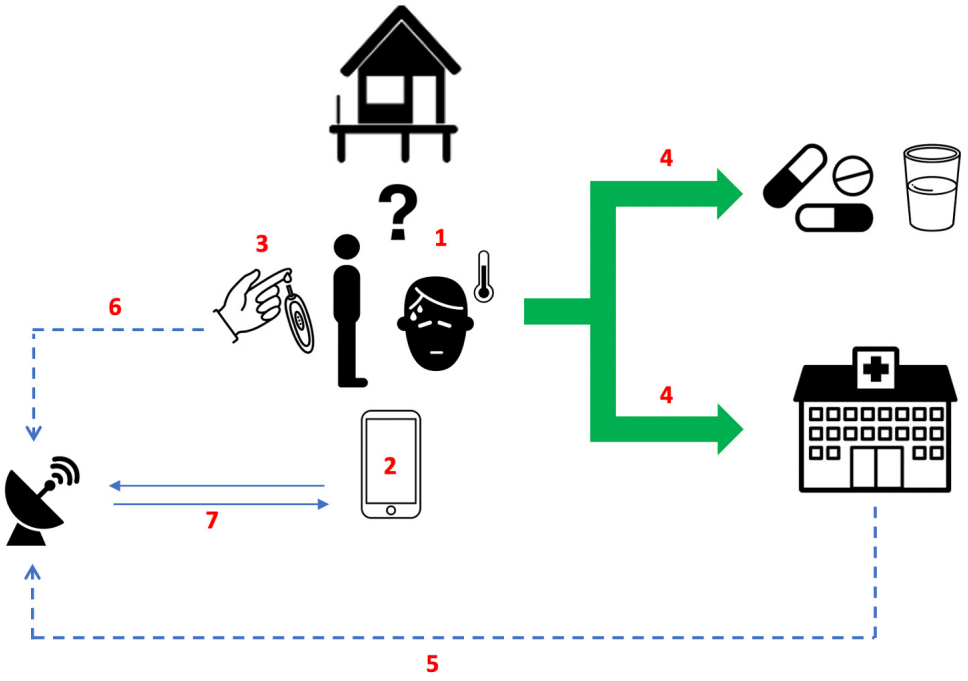

Figure 2. Overview of the long-term ambition for the management of febrile illnesses within SEACTN. (1) Patient with febrile illness presents to village health worker (VHW). (2) Simple clinical algorithm pre-loaded on mobile device helps VHW assess patient. (3) VHW performs point-of-care test (POCT) if recommended by algorithm. (4) VHW decides between community-based treatment or referral for higher-level care. (5) Regional health facilities (sentinel nodes) periodically provide data from patients attending with febrile illnesses (including patients referred by VHWs working within SEACTN). (6) Proportion of samples collected from febrile patients at the time POCTs are performed, stored on filter paper and transported to reference laboratories. (7) Data from (5) and (6) integrated with data from (2) to periodically update clinical algorithms to reflect seasonal and longitudinal changes in febrile illness landscape.

The eDSTs will be loaded on to the mobile tablets that the VHWs and PHC workers are already familiar with using for data collection. Interactive training modules will be developed (in partnership with DigitalMedic), and will include educational content on the common causes of febrile illness in the region, as well as instructional information on how to use the new eDSTs and any relevant POCTs. User feedback will be sought and the eDSTs iterated using a human-centred design process[19]. Once finalised the eDSTs will be put forward for evaluation in future projects to be conducted within the SEACTN.

Dissemination of findings

Interim findings from relevant aspects of the project (for example, aggregate results of the aetiological investigations for febrile illness and the VA study) will be periodically summarised and fed back to the local communities via village leaders and local authorities. This will allow important information to be actioned in a time-sensitive manner, whilst preserving the confidentiality of individual participants.

The final results generated from this study will be disseminated to key stakeholders (identified during the stakeholder mapping exercises) and the study communities (via the same community engagement forums used to launch the project) in both English and local languages. The results will also be shared with the scientific community via peer-reviewed publications and conference presentations.

Limitations

Studying febrile illness at the most peripheral level of a health system provides a unique opportunity to influence the course of a patient's illness at their first contact with formal health services. This is particularly important in settings where regulation of facilities, providers and treatments is often lacking or inadequately enforced. However, working at this level of the health system also poses certain challenges.

We are limited to collecting low-volume DBS specimens from patients attending VHWs and PHC workers. The aetiological yield of these specimens may be low. However, they are feasible for collection in large numbers, and without attempts to understand the causes of fever in rural areas of the region, meaningful improvements in the management of febrile illness will likely remain elusive. To mitigate this risk, we will recruit cohorts of patients attending sentinel health facilities within these areas (WP-B), where collection of a wider range of specimens will permit more extensive aetiological investigations. Furthermore, the yield from the DBS specimens will be monitored and reviewed by the RFI Study Management Group. Depending on the results, DBS assaying may be expanded or replaced with an alternate strategy.

Expansion of the role of VHWs is both feasible and impactful[14]. However there is a limit to the number of roles that these skilled yet lay-people can be expected to fulfil, without adequate recognition, supervision and remuneration[41]. Stakeholder engagement, planned throughout the RFI project, will be crucial to understand the feasibility of long-term adjustments to the VHW role.

Conclusion

The RFI project aims to better understand and quantify the burden of febrile illness, the aetiological causes and the manner in which it affects people living in some of the most underserved areas of South and Southeast Asia, all on a scale which has not been attempted before. We will collect information to better understand and predict the outcomes of patients with febrile illnesses based on a multitude of factors, which will form the basis for interventions within the SEACTN in the future.

The foundational infrastructure established by the RFI project will include a network of upskilled and supported community healthcare providers, user-friendly electronic data collection tools, functioning biological specimen collection, transport and diagnostic pipelines, and robust data management systems for near real-time geospatial mapping of the incidence and outcomes of patients with febrile illness. SEACTN will be well positioned to support ongoing surveillance of febrile illnesses in the region, enabling earlier detection of disease outbreaks and the regular updating of treatment algorithms in response to seasonal and longitudinal changes in the regional febrile illness landscape.

Data availability

No data are associated with this article.

Acknowledgements

The authors are grateful for the support from the local authorities in participating countries and to our partners and collaborators. We thank the SEACTN Expert Review Group for helpful advice on the design of the project.

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Open Peer Review

Current Peer Review Status: ✔ ✔ ✔

Version 1

Reviewer Report 30 April 2021

https://doi.org/10.21956/wellcomeopenres.18033.r43501

✔ **Emily Ciccone**
Division of Infectious Diseases, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

This open letter describes plans for a large, multi-country project focused on describing the etiology and improving the management of febrile illness in rural areas of South and Southeast Asia. This ambitious work is incredibly important as the widespread availability of malaria testing and treatment has led to a decline in malaria incidence, leaving most febrile illnesses undifferentiated. This diagnostic uncertainty leads to inappropriate and inadequate treatment, including the overuse of antibiotics, which drives antimicrobial resistance, a major threat to global public health.

In this article, the authors clearly outline their objectives and plans for implementation of the initiative, and the maps in Figure 1 distinctly show the varied locations of the included study sites. I also appreciated their acknowledgment of the challenges of working in rural areas with VHW providers, and think that there was sufficient explanation and justification of their plans. The continual reassessment of the feasibility of expanding the VHW role through stakeholder engagement itself will provide interesting information that will shape the evolution of such programs in response to the changing epidemiology of the conditions that VHW treat.

A few minor comments related to each Work Package are as follows:

WP-A

1. Please clarify the patient population that will be included. As the VHWs will be the primary providers that are included in the study, I assume the patient population will be children under 5 years of age, but would recommend clearly stating the target study population and if there are any differences in the age groups that will be enrolled at each site.

2. How will follow-up assessments be done? In other words, will they be in-person visits or phone calls? I assume in-person for at least a portion as convalescent DBS are being collected, but some clarification here would be useful.

3. How was 28 days chosen for the follow-up interval? This seems to be quite long for acute febrile illnesses. A brief justification of how this interval was chosen would be helpful.

4. Will the health-seeking behaviour surveys be conducted for all participants in WP-A or a subset? If a subset, how with the sampling be done?

WP-B

1. Again, a bit more clarification about age group would be helpful here - will any adults be enrolled or does the >/= 15 age group only extend up to 18 years of age?

2. Would be interested in more detail regarding the host biomarker testing. Specifically, which tests are planned? Will the results of POCT be available to providers in real time?

WP-C

1. I found Figure 2 to be a bit confusing, particularly the group of icons in the center. Perhaps it would be helpful to include a few more arrows demonstrating the progression of the initial assessment (presentation --> mobile algorithm --> POCT --> location of care decision).

A few stylistic/grammatical things to consider are as follows:

- Could delete word "residing" in last paragraph of the introduction as communities themselves don't res
- Spell out BRAC when it is first mentioned in the Study sites and implementing partners section.
- Should be "local facilities have been identified" in same paragraph
- Remove the parentheses around "combinations of" in the paragraph about economic evaluation of interventions in WP-C section.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am an early career physician scientist primarily focused on improving the management of pediatric febrile illness in sub-Saharan Africa (specifically Uganda and Malawi). My current projects study the use of rapid diagnostics, including biomarker and pathogen-specific testing, at peripheral health centers with limited laboratory capacity and by VHWs to improve antibiotic stewardship among children with acute respiratory illness.

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.

Reviewer Report 23 April 2021

https://doi.org/10.21956/wellcomeopenres.18033.r43499

Teresa B. Kortz
Department of Pediatrics, University of California, San Francisco (UCSF), San Francisco, CA, USA

Overall, a clear, well-written letter. This is an important topic and the proposed initiative has the potential to positively impact child health.

I may have missed it, but how is this being funded and what is the timeline?

Abstract
- Clear, no comments.

Introduction
- Suggest describing village health workers some more. For example, who are they, what role do they play, how do they improve access to treatment...
- Are the declines in malaria incidence related to VHWs? That is how I interpreted the second paragraph.

Project overview
- What is the proposed timeline for this project and the various work packages?

Study sites and implementing partners
- Was there a site selection process and if so, what was it? Was there an effort to recruit a certain type or number of community?

- How is "febrile illness" defined for the sake of study inclusion?
- Which "host biomarkers feasible for measurement using POCTs, will be prioritised"?

Dissemination/Limitations/Conclusion

- No specific comments.

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: sepsis, severe febrile illness, pediatric critical care in resource-variable settings, host prognostic biomarkers, fever etiology, resource utilization

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.

Reviewer Report 20 April 2021

https://doi.org/10.21956/wellcomeopenres.18033.r43297

Samuel Akech
Health Services Unit, KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya

The open letter communicates about a series of planned studies in several study sites in Asia to define aetiology of febrile illnesses, develop and implement point of care tests (POCTs) to differentiate bacterial versus viral infections, develop electronic decision support (eDST), and

implement the POCTs and eDSTs using community health workers (village health workers and primary health care workers) for referral and treatment. In this letter, the authors have summarised linked pieces of research projects that are grouped into 3 work packages with several specific objectives. It is therefore expected that sufficient detail would be missing in a project that has several components. However, the ultimate success of this project as described would a successful implementation of the eDST, POCTs, and referral/treatment by the Community Health Workers (CHWs).

Comments:
A brief description of training and capabilities of CHWs in the study settings will assist readers to gain insights into prospects of successful implementation. What other tasks do the CHWs already have? Will therefore be detailed implementation science conducted to understand implementation challenges for the project and is there a conceptual framework for the project implementation? It would be good to briefly mention how the implementation is expected to work at the level of CHWs who are quite central. Are the CHWs remunerated, what is their motivation, how much are researchers working with policy makers in the study countries-some insights will be good. Are the village health workers collecting heel/thumb prick samples? Is this something that they are permitted to do in this setting-this could be briefly explained.

Are there examples of treatments that CHWs would be allowed to give based on results of POCTs? If POCTs suggests a bacterial infection, it may be harmful to give an antibiotic and send the patient home since causes of a positive bacterial test could be varied e.g., UTI, sepsis, intra-abdominal infections (especially in adults), and it is difficult to imagine an antibiotic that can be given by CHWs that would cover all potential causes without need for a referral. In such cases, eDST would be configured to trigger a referral or no referral.

It would seem more logical if aetiological study and development of POCTs were done at earlier phases and then promising POCTs implemented plus eDST using CHWs. Can a diagram for sequence of activities be included?;

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Malaria, sepsis, clinical trials, paediatrics, epidemiology, severe childhood illness

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.