

# Febrile illness: a unified approach to protocol design for multicentered studies

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Les Pensières Center for Global Health

**Understanding the relative importance of different  
causes of illness among adults and children with  
fever attending health care services at Cambodia**

Chou Monidarin, UHS-LRM Cambodia

# Introduction

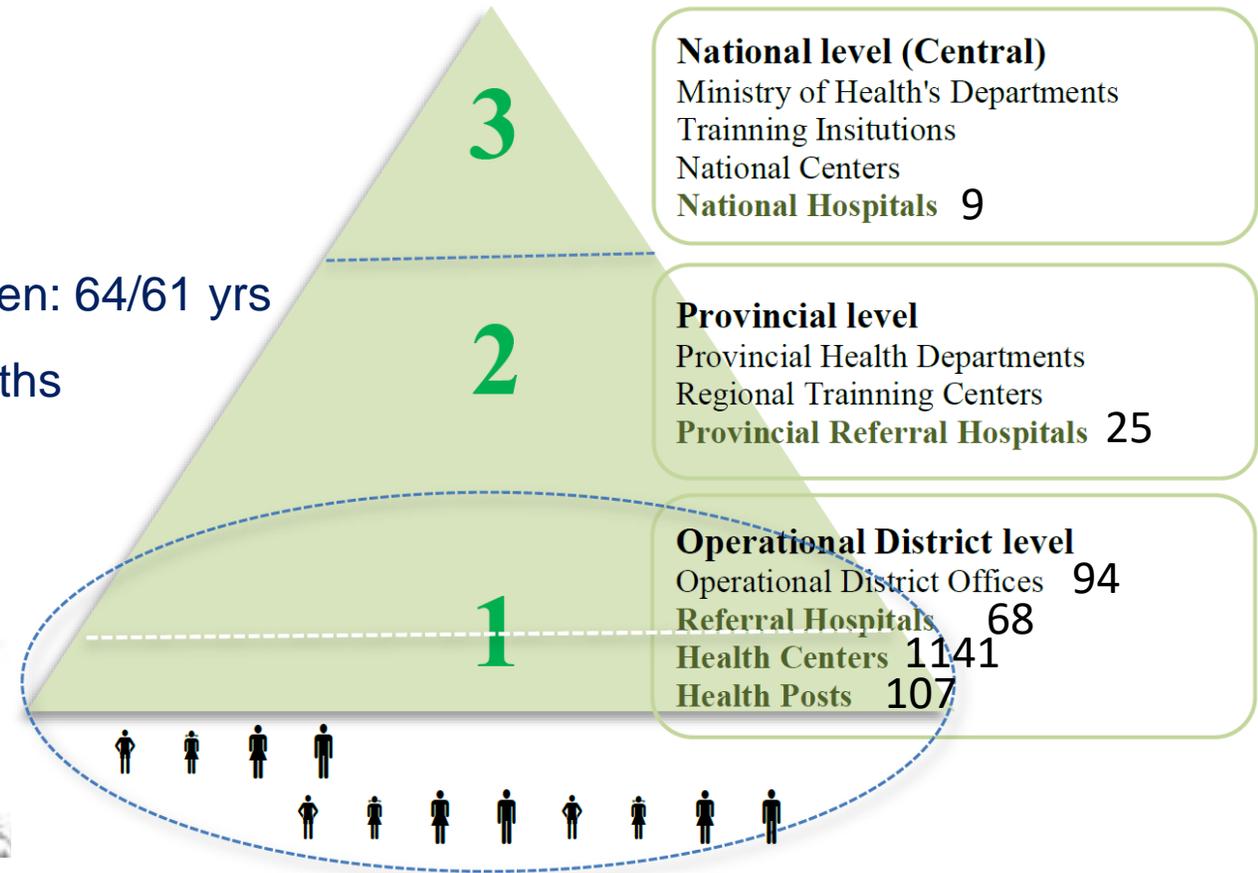
## The Cambodia profile and level of Health System

Population: 14,406,000 (2013)

GDP per capita income: \$2,360

Life expectancy at birth women/men: 64/61 yrs

Under 5 mortality: 45/1000 live births



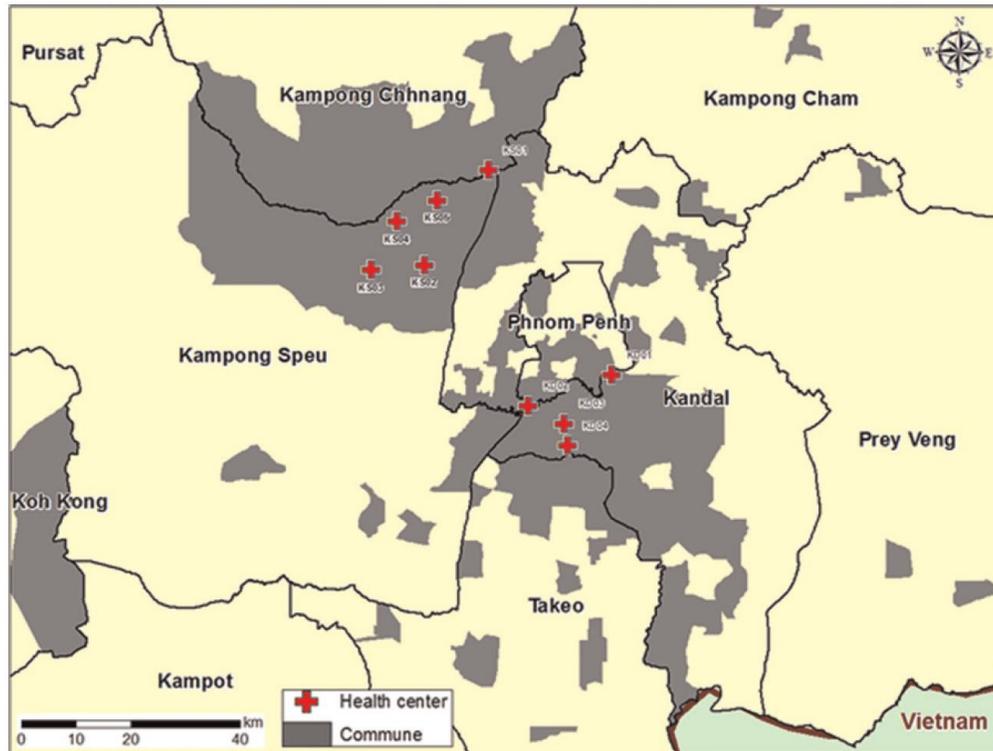
# Introduction (2)

- The definition of fever within medical literature varies widely, it is defined as simply an elevation of body temperature
- Fever is the main clinical symptom of various infectious diseases.
- Limited resources and the great diversity of acute febrile illness etiologies challenge diagnosis, treatment, and public health responses to endemic and epidemic diseases.
- There is few published information on the causes of fever in Cambodian

# Data from previous publication

## Infectious Etiologies of Acute Febrile Illness among Patients Seeking Health Care in South-Central Cambodia

Matthew R. Kasper,\* Patrick J. Blair, Sok Touch, Buth Sokhal, Chadwick Y. Yasuda, Maya Williams, Allen L. Richards, Timothy H. Burgess, Thomas F. Wierzba, and Shannon D. Putnam



Among the 9,997 patients, the etiologies were identified in 38.0% of patients

- 19.9% (1,983) patient were positive for influenza.
- Dengue virus were in 883 cases (8.9%).
- Malaria was identified among 7.2% (716) of patients,
- Acute leptospirosis was serologically identified in 20.8% of study subjects.

# A Prospective Study on Febrile Illness Requiring Hospitalization Conducted at Angkor Hospital for Children

OPEN ACCESS Freely available online



## A Prospective Study of the Causes of Febrile Illness Requiring Hospitalization in Children in Cambodia

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### Abstract

**Background:** Febrile illnesses are pre-eminent contributors to morbidity and mortality among children in South-East Asia but the causes are poorly understood. We determined the causes of fever in children hospitalised in Siem Reap province, Cambodia.

**Methods and Findings:** A one-year prospective study of febrile children admitted to Angkor Hospital for Children, Siem Reap. Demographic, clinical, laboratory and outcome data were comprehensively analysed. Between October 12<sup>th</sup> 2009 and October 12<sup>th</sup> 2010 there were 1225 episodes of febrile illness in 1180 children. Median (IQR) age was 2.0 (0.8–6.4) years, with 850 (69%) episodes in children <5 years. Common microbiological diagnoses were dengue virus (16.2%), scrub typhus (7.8%), and Japanese encephalitis virus (5.8%). 76 (6.3%) episodes had culture-proven bloodstream infection, including *Salmonella enterica* serovar Typhi (22 isolates, 1.8%), *Streptococcus pneumoniae* (13, 1.1%), *Escherichia coli* (8, 0.7%), *Haemophilus influenzae* (7, 0.6%), *Staphylococcus aureus* (6, 0.5%) and *Burkholderia pseudomallei* (6, 0.5%). There were 69 deaths (5.6%), including those due to clinically diagnosed pneumonia (19), dengue virus (5), and melioidosis (4). 10 of 69 (14.5%) deaths were associated with culture-proven bloodstream infection in logistic regression analyses (odds ratio for mortality 3.4, 95% CI 1.6–6.9). Antimicrobial resistance was prevalent, particularly in *S. enterica* Typhi, (where 90% of isolates were resistant to ciprofloxacin, and 86% were multi-drug resistant). Comorbid undernutrition was present in 44% of episodes and a major risk factor for acute mortality (OR 2.1, 95% CI 1.1–4.2), as were HIV infection and cardiac disease.

**Conclusion:** We identified a microbiological cause of fever in almost 50% of episodes in this large study of community-acquired febrile illness in hospitalized children in Cambodia. The range of pathogens, antimicrobial susceptibility, and comorbidities associated with mortality described will be of use in the development of rational guidelines for infectious disease treatment and control in Cambodia and South-East Asia.

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### Introduction

Febrile illness in children is a common cause of admission to hospital globally, with significant associated morbidity and mortality [1]. In developing countries this is frequently compounded by low rates of immunisation, untreated comorbidities, and late presentations [2]. Febrile illnesses are caused by diverse pathogens, presenting with non-specific symptoms to healthcare facilities with limited diagnostic capacity [3,4]. Clinical manage-

ment guidelines for acute febrile illness are available [5,6], but rarely supported by knowledge of the locally prevalent causative agents.

The Kingdom of Cambodia lies in South-East Asia and has a mortality rate in children aged <5 years of 54/1000 live births [7]. This has halved over the last decade but remains one of the highest in the region. The prevalence of undernutrition in children <5 years of age (less than 2 SD of weight for age) is 28% [7]. There is

In 1180 children of febrile children with Median of age was 2.0 (0.8–6.4)

- laboratory identified that microbiological cause in almost 50% of febrile illness
- The Common microbiological diagnoses were reported: dengue virus (16.2%), scrub typhus (7.8%), and Japanese encephalitis virus (5.8%).

(Kheng Chheng et al, PLoS ONE 8(4): e60634, 2013)

# Acute Undifferentiated Febrile Illness in Rural Cambodia: A 3-Year Prospective Observational Study

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From January 2008 to December 2010, 1193 febrile patients and 282 non-febrile individuals from 3 health centers in eastern and western Cambodia

At least one pathogen was identified in 73.3% (874/1193) of febrile patient samples

Frequent pathogens :

*P. vivax* (33.4%), *P. falciparum* (26.5%), *Leptospira* (9.4%), Influenza viruses (8.9%), Dengue viruses (6.3%), *O. tsutsugamushi* (3.9%), *Rickettsia* (0.2%), and *P. knowlesi* (0.1%).

*Mueller TC et al, PLoS ONE 9(4): e95868, 2014.*

A data from Takeo provincial hospital:  
 CPA3, 250 beds, IPD/OPD : 1400/5300 per month

Cases / Year	2017		2016		2015	
	# Cases < 5 y	# Cases > 5 y	# Cases < 5 y	# Cases > 5 y	# Cases < 5 y	# Cases > 5 y
<b>Acute undifferentiated fever (acute fever without any localizing signs)</b>	NA	NA	NA	NA	NA	NA
<b>Acute differentiated fever (acute fever with symptoms)</b>	329	499	270	517	237	495
Fever with rash	NA	NA	NA	NA	NA	NA
Fever with ARDS: Acute onset fever with respiratory distress in the form of SpO2 <90% at room air or frank ARDS with PaO2/FiO2 ratio <200.	307	343	226	398	189	264
Fever with respiratory symptoms (upper or lower respiratory tract) other than ARDS	0	57	23	7	22	18
Febrile encephalopathy / Acute encephalitic syndrome	10	57	10	88	14	104
Fever with other focus	12	42	11	24	12	109
Chronic Fever of Unknown Origin-(FOU)						
Totals	<b>329</b>	<b>499</b>	<b>270</b>	<b>517</b>	<b>237</b>	<b>495</b>

# Conclusion & Perspectives

- Many case of febrile symptom were not able to identify etiology
- Improve the laboratory capacity for reliable and rapid diagnostics to identify the cause of fever is important
- National surveillance system on febrile illness is needed
- Need to assesses the impact of health and economic burden of acute febrile unidentified cause



Thank You