

# PhD defence Kanika Koirala

## Epidemiology of persistent febrile illnesses in Eastern Nepal

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### Supervisor

- late Prof. Dr. Marleen Boelaert (ITM)
- Prof. Dr. François Chappuis (UNIGE, Switzerland)
- Prof. Dr. Suman Rijal (BPKIHS, Nepal)

### Summary

Introduction:

Persistent febrile illness (PFI), defined as fever lasting over 7 days, is a neglected field of clinical research in low- and middle-income countries (LMICs), in contrast with acute undifferentiated fever (AUF). PFI is a broader and more practical definition than the classical fever of unknown origin (FUO). Determining the differential diagnosis of PFI in the rural tropics, including Nepal, is difficult due to the lack of available diagnostic tools and laboratory resources. This leads to failure to establish a confirmatory diagnosis, resulting in inadequate clinical management of patients including the improper use of antibiotics, a main driver of microbial antibiotic resistance. In addition, the wide use of antibiotics in the community decreases the yield of bacterial culture, a key tool to diagnose systemic bacterial infections.

This PhD study was carried out as a nested study within the framework of the Neglected Infectious Diseases DIAGNosis (NIDIAG) study, which investigated the etiologies of PFI cases admitted to hospitals in four LMICs, i.e. Cambodia, Democratic Republic of Congo (DRC), Nepal and Sudan, with a focus on potentially severe and treatable conditions: amoebic liver abscess, brucellosis, enteric fever, leptospirosis, malaria, rickettsial diseases, tuberculosis, visceral leishmaniasis, human African trypanosomiasis and HIV/AIDS (NIDIAG's target conditions). In this thesis, we present a systematic review of the literature on the causes of PFI in Nepal, then report the results of the NIDIAG study arm conducted in eastern Nepal and the extent and risk factors of antibiotic use pre- and post-hospital admission in Nepal and the three other countries.

Methods:

To achieve the objective of generating evidence on the causes for prevalent PFI in Nepal, we first performed a systematic literature review to describe published data on the burden of NIDIAG target conditions in Nepal. We then implemented a prospective diagnostic study in a tertiary teaching hospital (B. P. Koirala Institute of Health Sciences, or BPKIHS) and a secondary health care facility (Dhankuta District Hospital) in eastern Nepal. Consecutive patients > 5 years with > 7 days fever without a confirmed diagnosis were enrolled. A standard set of diagnostic tests were conducted on-site and in national and international reference laboratories to determine the infectious etiology of PFI, and clinical or laboratory features associated with visceral leishmaniasis (VL) were searched for. We nested a cross-sectional study in the overall NIDIAG persistent fever study describing the prevalence of antibiotic intake and the type of antibiotics before and after study inclusion in the six health care facilities in

Nepal, Cambodia, DRC and Sudan.

#### Results:

A total of 3,218 articles were extracted through the systematic search of standard literature databases, and 73 studies were included in the systematic review. As there were no published articles dedicated on PFI in Nepal, we focused on the epidemiological, diagnostic and treatment (including antibiotic bacterial resistance) data on individual NIDIAG target conditions occurring or likely to occur in Nepal.

Malaria and VL are endemic in the Terai lowlands with a decreasing incidence trend, while tuberculosis remains a major public health problem in the whole country. Leptospirosis, rickettsiosis and brucellosis constitute a sizeable proportion of diagnoses identified in studies conducted on AUF but are overlooked in clinical practice due to the lack of available field diagnostic tools. In contrast, enteric fever tends to be over-diagnosed, due to the lack of specificity of diagnostic tests available at the primary and secondary care level. Of note is that the large majority of diagnostic studies conducted on AUF concerned the Kathmandu valley.

In the prospective observational study, a total of 425 patients with febrile episodes of > 7 days were enrolled at BPKIHS between March 2013 and September 2014. Of these, 251 (59.1%) were male and the participants' mean age was 34 years (SD 19; range: 5-86 years). Two hundred and thirteen patients (50.1%) were enrolled during the dry season. A final diagnosis was reached in 225 (52.9%) patients, while diagnosis remained undefined in 200 (47.1%) patients. The diagnosis of any target condition was made in 129 (31.2%) patients, the most frequent being VL (n=52; 12.5%), followed by rickettsiosis (n=22; 5.3%), tuberculosis (n=21; 5%), leptospirosis (n=21; 5.0 %) and enteric fever (n=5; 1.2%). Four cases of borreliosis were confirmed by RT-PCR for the first time in Nepal, but the *Borrelia* species could not be identified. No cases of malaria or brucellosis were diagnosed. Eleven (2.6%) patients had a confirmed diagnosis of more than one target condition. The main nontarget conditions were upper respiratory tract infections (n=30; 7.2%), urinary tract infections (n=26; 6.3%), and pneumonia (n=12; 2.9%). Clinical and laboratory parameters significantly associated with VL were anemia (positive likelihood ratio (LR+): 4.0), hepatomegaly (LR+: 4.0), splenomegaly (LR+: 7.6) and leucopenia (LR+: 8.7).

In Cambodia, DRC, Nepal and Sudan the use of one or more antibiotics prior to consultation or admission for PFI was reported in 428 (22.1%) of 1,939 participants enrolled in the NIDIAG study. The highest rate was found in Nepal (207/583: 35.5%), with multiple antibiotics used in 96 patients (46.8%). Antibiotic use prior to study inclusion was more frequent in children and adolescents than in adults (adjusted risk ratio (aRR) 1.44; 95%CI 1.15-1.77), but threefold less in those over 65 years old (aRR 0.37; 95%CI 0.20-0.61). We found no clinical symptoms or signs to be strongly associated with antibiotic use prior to study inclusion. 49.5% of pre-inclusion antibiotic courses were discontinued and not replaced at the time of study inclusion, ranging from 29.3% (Sudan) to 68% (in Nepal).

#### Conclusions:

The differential diagnosis of persistent fever in Nepal is highly variable and includes both pathogen-specific (e.g. VL, tuberculosis) and non-pathogen specific conditions (e.g. pneumonia). We propose a diagnostic approach that include clinical and laboratory features to guide first-line treatment for the management of patients with PFI in Eastern Nepal. Improved diagnosis should lead to a better management of antibiotic use, as overuse is rampant in Eastern Nepal and more generally in LMICs.

#### Public defence:

The defence will be **30 minutes** long, followed by **60 minutes of discussion** with the jury exclusively. During the defence, the attendees from the public are not permitted to participate in the discussion. However, once the defence has finished and the jury president announces the end of the defence, the floor will be open to the public.

#### Deliberations:

After the defence, the thesis jury will deliberate behind closed "doors", under the supervision of the jury president. The thesis jury grants the thesis with or without honours.

## Downloads

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