

# PhD defence Laura Kuijpers

## Enteric fever in Cambodia: A multi-disciplinary study.

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Dit is de omschrijving

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### Summary:

Enteric fever is a systemic infection mainly caused by the bacteria *Salmonella Typhi* and *Salmonella Paratyphi A*. Humans are the only host and transmission occurs through food and water contaminated by stool from patients or chronic carriers. It is a major cause of morbidity and mortality in low resource settings. The disease is endemic in Cambodia and during 2013–2015 an outbreak of *Salmonella Paratyphi A* infections occurred in Phnom Penh, the capital city. For this doctoral thesis, a multi-disciplinary approach was adopted to study enteric fever in Cambodia.

First, whole-genome sequencing with genetic comparison and establishment of phylogenetic relationships was used for the retrospective investigation of the *Salmonella Paratyphi A* outbreak. The outbreak isolates clustered together in one clade which has been isolated in Cambodia since at least 1999. Historical isolates, isolates from sporadic cases, and isolates from another *Salmonella Paratyphi A* outbreak in China revealed different clusters. The Cambodian isolates were pan-susceptible. The results imply that human or environmental factors rather than bacterial factors played a key role in the recent emergence of *Salmonella Paratyphi A*.

Next, the clinical and microbiological characteristics of *Salmonella Paratyphi A* versus *Salmonella Typhi* infections were compared. A retrospective review of the clinical charts of 254 blood culture confirmed enteric fever patients who presented at the Sihanouk Hospital Center of HOPE in Phnom Penh was conducted. Antibiotic susceptibility testing was performed and the genomes of a selection of isolates were sequenced. Presenting symptoms of both serotypes were found to be similar. Higher rates of inflammatory markers in *Salmonella Typhi* infections suggests more severe disease. Of the *Salmonella Typhi* isolates, 42.9% displayed multidrug resistance, compared to none of the *Salmonella Paratyphi A* isolates. Decreased ciprofloxacin susceptibility (DCS) was observed for nearly all *Salmonella Typhi* isolates versus a minority of *Salmonella Paratyphi A* isolates. From 2015 onwards however, DCS increased rapidly for *Salmonella Paratyphi A*. This is worrying as ciprofloxacin is the current first line treatment.

Diagnosing enteric fever remains challenging. Blood culture is used as the reference method but has a low sensitivity and takes days until diagnosis. Rapid diagnostic tests (RDTs) that can detect *Salmonella* antigens might shorten the time to diagnosis. We evaluated the performance of RDTs when used on blood culture broth in different steps. The two-best performing RDTs were applied to 413 stored grown blood culture broths from Cambodia and the Democratic Republic of the Congo. The 2 RDTs showed a good sensitivity and specificity for the detection of *Salmonella Typhi* but both tests failed to detect *Salmonella Paratyphi A*, which limits their use in Cambodia.

The main mechanism of *Salmonella Typhi* and *Salmonella Paratyphi A* transmission is fecal shedding of the bacteria. The current standard for tracing carriers is stool culture. This is challenging for *Salmonella Paratyphi A* as it does not produce hydrogen sulfide (H<sub>2</sub>S), which makes colonies of other *Salmonella* serotypes stand out based on colony color. *Salmonella Paratyphi A* may resemble other common gut bacteria, and this results in time-consuming additional testing. Chromogenic media were shown to detect *Salmonella Paratyphi A* in low concentrations of stool and resulted in few false positive results. This suggests that chromogenic media may be used for the detection of *Salmonella Paratyphi A* carriage.

Last, to understand facilitators of disease transmission and ineffective treatment, in-depth interviews were conducted among both lay-persons and healthcare providers in Phnom Penh. Results showed that lay people did not link the disease to the bacterial contamination of foods. Patients visited a

range of health care providers like drug sellers, who provided a cocktail of pills including antibiotics without confirmation of the diagnosis. Future efforts aimed at disrupting transmission and improving treatment need to address health illiteracy and should take into consideration the pluralism of the Cambodian health care system.