# Non-Typhoidal *Salmonella* Infections Unmask the Challenges in Pediatric Febrile Illness Care in DR Congo

*PhD Thesis Presented on December 20, 2023, at KU Leuven, Leuven, Belgium*

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## Keywords

Non-typhoidal *Salmonella* ; bloodstream infection ; antimicrobial resistance.

Severe febrile illness resulting from malaria or bacterial infections, such as pneumonia or invasive *Salmonella* infections, account for more than a third of global under-five mortality cases (1). Particularly in children in sub-Saharan Africa, non-typhi *Salmonella* (NTS) frequently cause bloodstream infections that are ten times more fatal than severe malaria infections (2–4). The high NTS burden in children in sub-Saharan Africa is attributed to highly invasive sub-Saharan African NTS strains and to frequent comorbidities that compromise the immune response such as Plasmodium falciparum malaria, anemia, malnutrition and HIV (5). The diagnostic uncertainty and barriers to treatment of invasive NTS infections further increase mortality (5).

I was fortunate to conduct my PhD research in DR Congo in collaboration with Belgian (Institute of Tropical Medicine Antwerp, KU Leuven), national (Institute of National Biomedical Research Kinshasa, Hôpital St. Luc Kisantu, DR Congo) and international (International Vaccine Institute) partners. I investigated the challenges to manage invasive NTS infections in children under-five and evaluated potential solutions, many of which can be generalized to other causes of severe febrile illness.

## Prevention is better than cure: how to contain NTS infections?

Based on sentinel blood culture surveillance data from 2007 onwards, I revealed the increasing occurrence of NTS bloodstream infections in DR Congo (6). Three quarters of bloodstream infections in children under-five admitted to a district hospital in Kisantu were caused by NTS (6). Most NTS were extensively drug resistant due to concurrent ampicillin, cotrimoxazole, chloramphenicol, third generation cephalosporin and fluoroquinolone or azithromycin resistance (6 and unpublished data). Vaccines are being developed to prevent these invasive, highly resistant NTS infections, but must target multiple serotypes to be effective. I demonstrated that, although most NTS were serotype Typhimurium and Enteritidis, a Typhimurium serovariant which lost the vaccine-targeted O5-antigen had emerged (variant Copenhagen) (6).

Interestingly, NTS bloodstream infections mainly occurred during the rainy season. Based on longitudinal analysis of the surveillance data, satellite-based estimates of rainfall data and malaria statistics, I demonstrated that both the seasonal increase in *P. falciparum* malaria and rainfall by itself account for the seasonal NTS dynamics (7). This stresses the importance of malaria control to reduce the NTS burden, but also suggests water borne NTS transmission and thus the importance of clean water and sanitation measures.

## The need for speed: how to improve prehospital care?

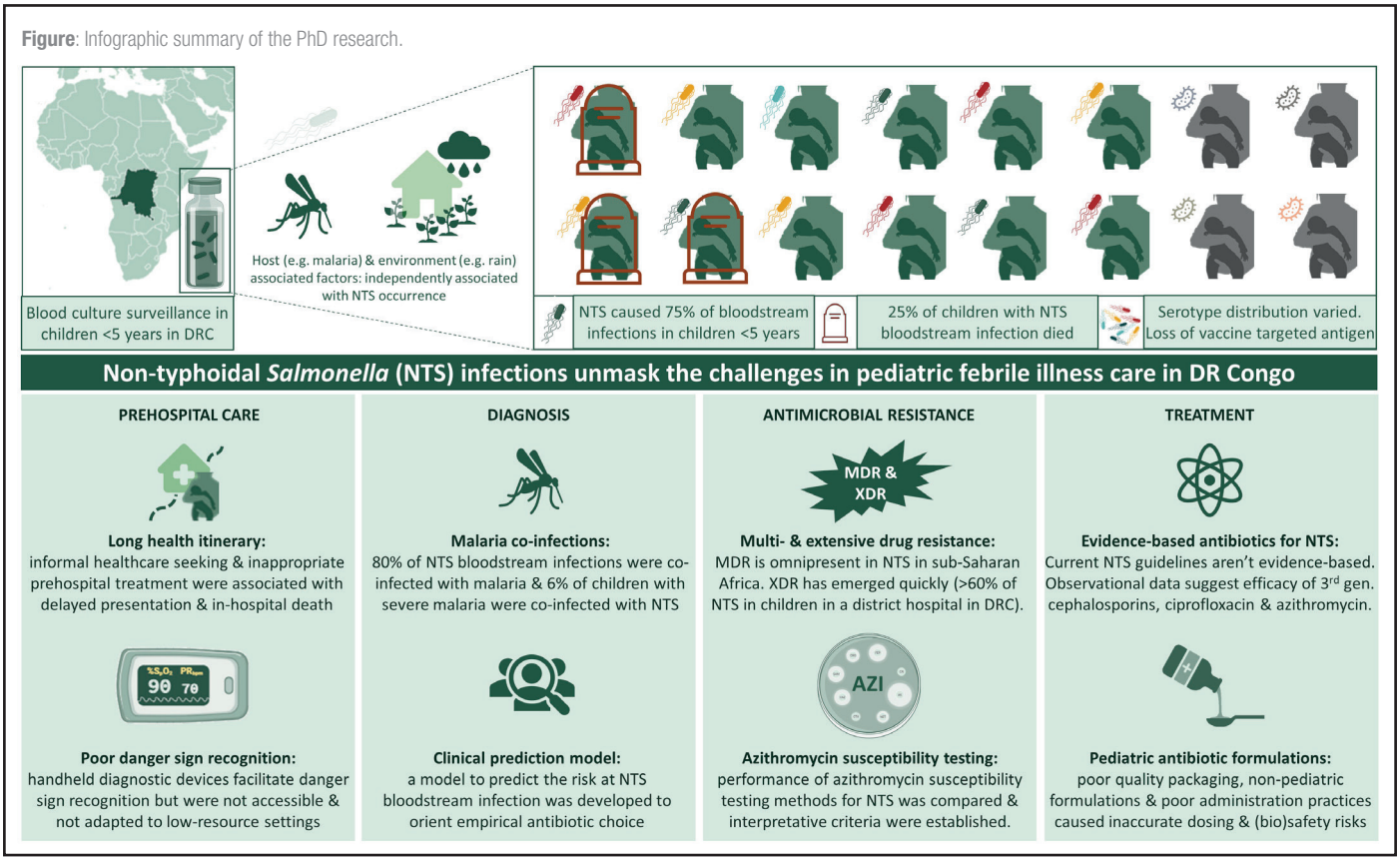
Over an 18-month period, 2682 children admitted to Kisantu hospital with severe febrile illness were enrolled in prospective observational cohort studies (unpublished data). Sadly, 7% (185/2682) of them died (unpublished data). From the subset of children with NTS bloodstream infection, 24% (80/333) died, which is very high, particularly when compared to a case fatality of 3% (37/1277) in children with severe P. falciparum malaria (8 and unpublished data). Irrespective of severe febrile illness etiology, death mostly occurred during the first 2 days of hospital admission and was associated with delayed presentation (8). Both death and delayed presentation were associated with informal prehospital health care seeking and inappropriate prehospital management (8).

Recognition of clinical danger signs is essential for timely hospital referral, but frontline healthcare workers often have limited clinical training and expertise in low-resource settings. Handheld diagnostic devices can help them to recognize danger signs, such as high fever, rapid breathing, severe anemia or hypoglycemia. However, we observed difficulties with device selection, procurement and shipment, adoption and maintenance of a tympanic thermometer, a multimodal oximeter with automated respiratory rate measurement, a hemoglobinometer and a glucometer. We therefore described the end-users' needs that must be considered to improve access to affordable, well performing, robust and user-friendly devices adapted to low-resource settings (9,10).

## Finding a way out of the maze: how to improve hospital care?

Early diagnosis and prompt appropriate treatment are essential to improve survival. Unfortunately, NTS bloodstream infection have a high diagnostic uncertainty. Eighty percent (265/333) of children with NTS bloodstream infection were co-infected with *P. falciparum* malaria and no pathognomonic clinical signs and symptoms could be identified in my research (unpublished data). Vice versa, As a result, blood cultures are required for diagnostic confirmation, but access to blood cultures in sub-Saharan Africa is limited and the time from sampling to final results

**Figure**: Infographic summary of the PhD research.




(identification & antibiotic susceptibility testing) is 3-5 days. Two-thirds (189/313) of NTS isolated during the prospective studies in Kisantu had extensive drug resistance due to concurrent non-susceptibility to ampicillin, cotrimoxazole, chloramphenicol, third generation cephalosporins and fluoroquinolones (unpublished data). Due to the combination of diagnostic uncertainty and high antibiotic resistance, NTS are often not covered by empirical antibiotics (mostly intravenous third generation cephalosporins). Therefore, I developed a clinical prediction model for settings where NTS are often resistant to standard-of-care empirical antibiotics. which can be used to modify empirical antibiotic choices based on the predicted NTS risk (unpublished data). Clinicians can use this model to decide to modify a child's empirical antibiotic treatment based on the predicted NTS risk.

In a systematic review and meta-analysis, I revealed that, despite the rapidly increasing antibiotic resistance in NTS, antibiotic treatment recommendations for invasive NTS infections are merely extrapolated from typhoid fever or based on expert consensus, as good-quality data on the efficacy of antibiotics to treat invasive NTS infections are missing (11). The review also revealed that, while azithromycin is often recommended to treat NTS, azithromycin susceptibility testing is not done because there are no recommendations on how to test and interpret it. In a multi-laboratory study with bio-banked NTS isolates from five surveillance collections I established that disk diffusion performed well to test azithromycin susceptibility in field settings and determined the epidemiological cut-off to interpret azithromycin susceptibility in invasive NTS infections (12).

Finally, I compared the survival of children with NTS bloodstream infection enrolled in one of the prospective observational studies in Kisantu based on the administered antibiotic treatment. Children with NTS bloodstream infection who received susceptibility-matched third generation cephalosporins, ciprofloxacin or azithromycin (n = 142) had a significantly better survival than children who only received susceptibility-mismatched antibiotics (n = 77, hazard ratio = 0.16 [0.30-0.09]) (unpublished data). These observational data provide the first evidence on the efficacy of third generation cephalosporins, fluoroquinolones and azithromycin to treat NTS bloodstream infections in children under-five in sub-Saharan Africa. Last but not least, I described how poor quality and non-pediatric antibiotic formulations and poor prescription and administration practices cause inaccurate antibiotic dosing and (bio) safety risks and require local, national and supranational action (13).

The insights on azithromycin susceptibility testing and antibiotic treatment of NTS generated as part of this PhD research were integrated in the European antibiotic susceptibility testing guidance and antibiotic treatment guidelines from the World Health Organization, respectively (14, 15). The observations regarding poor access to and quality of pediatric formulations, have triggered national regulatory action in DR Congo.

In conclusion, this PhD thesis reports the high burden of NTS bloodstream infections in children under-five in DR Congo. The control, diagnosis and treatment of NTS bloodstream infections is very challenging. To prevent NTS infections, future research should focus on a better understanding of environmental transmission, NTS vaccine development and the potential impact of the new malaria vaccines (RTS,S/AS01 and R21/Matrix-M). Formalizing, training and monitoring the primary healthcare sector, improved detection of clinical danger signs with "tropicalized" handheld diagnostic devices, and increasing access to blood culture diagnostics can accelerate NTS diagnosis. Finally, promptness and appropriateness of NTS treatment must be improved by strengthening the evidence on antibiotic treatment (drug, duration, oral switch) with clinical trial data and integrating these data in user-friendly treatment algorithms, by facilitating adoption of antibiotic susceptibility testing in field settings and reference laboratories, by improving access to good quality and age-appropriate antibiotic formulations and administration devices (including infusion devices), and by improving early supportive management.

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