

Letter to the editor

New genomics studies to understand the link between nontyphoidal *Salmonella* bacteremia and gastroenteritis in Africa

Robert S. Onsare^{1,2,3}, Calman A. MacLennan^{3,4}

¹ Centre for Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya

² Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

³ Novartis Vaccines Institute for Global Health, Siena, Italy

⁴ MRC Centre for Immune Regulation, School of Immunity and Infection, College of Medicine and Dental Sciences, University of Birmingham, Birmingham, United Kingdom

Key words: nontyphoidal *Salmonella*; bacteremia; diarrhea; whole genome sequencing; genomics

J Infect Dev Ctries 2014; 8(2):252-253. doi:10.3855/jidc.4377

(Received 03 November 2013 – Accepted 29 January 2014)

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Dear Editor – Nontyphoidal *Salmonellae* (NTS) are attracting increasing attention as a cause of invasive disease among African children and HIV-infected individuals [1-4]. However, these invasive (hence iNTS) infections continue to cause confusion, partly because of the contrasting clinical presentations of NTS disease in high- and low-income countries [4]. NTS in US and Europe normally cause self-limiting gastroenteritis [5]. In sub-Saharan Africa, they cause bacteremia [2] with symptoms of gastroenteritis in under half of patients [1]. Case fatality rates for NTS bacteremia are 20-25%, multidrug resistance is increasing, and no vaccine is available [1,4].

Understanding iNTS disease in Africa is hindered by our limited knowledge of diarrheal NTS and its relationship to invasive disease. Better characterisation of African diarrheagenic isolates and comparison with invasive ones would help us understand whether the same strains are responsible for both clinical presentations or whether invasive disease is the consequence of different, potentially more virulent clades of NTS. This would also provide valuable insight into routes of transmission. Since healthcare resources and services in the continent have to be prioritised for the treatment of the most critically-ill patients, more is known about iNTS disease than NTS diarrhea. Microbiological facilities are limited, so few data exist on contemporaneous presence of NTS in stool and blood. Where blood culturing occurs, stool cultures are rare, and vice versa. This does not

preclude *Salmonella* in blood of patients with NTS diarrhea nor NTS in the gastrointestinal tract of those with iNTS disease.

S. Typhimurium and Enteritidis, are responsible for most iNTS cases in Africa [1,2] and confusingly around 50% of NTS gastroenteritis in the US [5]. It is unclear why iNTS is so common in Africa. Possible explanations include differences in immunity, virulence, hygiene and transmission [4]. Recent whole genome sequencing (WGS) studies demonstrate that invasive African *S. Typhimurium* is genetically distinct [6], belonging to a new MLST type, ST313. This is characterized by marked genome degradation [7] and has spread throughout the continent [3]. Studies on the genotype/phenotype relationship of ST313, and the genomes of invasive African *S. Enteritidis*, are awaited.

The Global Enteric Multicenter Study provides important insights into diarrhea etiology in developing countries [8]. Of the four African sites, NTS only significantly associated with diarrhea in Kenya, possibly because of high levels of NTS in control subjects elsewhere. Of concern, a diarrhea study from Western Kenya found NTS in stool significantly associated with mortality. Most isolates were serovar *Typhimurium* or Enteritidis [9]. Neither study investigated bacteremia nor genotype, so it is unknown whether *S. Typhimurium* were ST313. In a Nairobi study comparing invasive and gastrointestinal NTS

isolates from hospitalized children, *S. Typhimurium* and Enteritidis again accounted for most isolates [10]. Pulsed-field gel electrophoresis (PFGE) detected no difference between invasive and gastrointestinal isolates. However, PFGE has limited ability to discriminate genetic differences compared with WGS.

Understanding the relationship between African invasive and diarrheagenic NTS disease requires new studies that recruit patients with bacteremia and gastroenteritis, investigate the presence of NTS in blood and stool of all participants, and use WGS to characterize isolates. Another approach to the genetic characterisation and discrimination of NTS isolates is transcriptomics [11]. Transcriptomics is complementary to WGS and can lead towards improved insight into how genetic differences relate to function. There is currently little evidence to support zoonotic transmission of NTS in Africa [12] and parallel studies to identify any environmental reservoirs of NTS are needed. Until such studies happen, understanding the pathogenesis and transmission of African NTS disease, and our ability to develop new interventions to improve clinical management, will remain limited.

Acknowledgements

This work was supported by a European Union FP7 Industry and Academia Partnerships and Pathways award, GENDRIVAX (Genome-driven vaccine development for bacterial infections). This is a collaboration between the Novartis Vaccines Institute for Global Health, Kenyan Medical Research Institute, Wellcome Trust Sanger Institute and Swiss Tropical and Public Health Institute [grant number 251522].

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Corresponding author

Professor Calman A. MacLennan
 Novartis Vaccines Institute for Global Health,
 Via Fiorentina 1, 53100 Siena, Italy.
 T +39 0577 539240
 F +39 0577 243352
 Email: calman.maclennan@novartis.com

Conflict of interests: CAM is an employee of the Novartis Vaccines Institute for Global Health and the recipient of a clinical research fellowship from GlaxoSmithKline.