iNTS burden in sub-Saharan African children: an African view

Simon Kariuki¹, Martina Oneko¹, Samuel Kariuki², Calman A. MacLennan³, Brian Greenwood⁴, Mary J. Hamel⁵ on behalf of Clinical Trials Partnership Committee (CTPC)

¹KEMRI-CDC, Kisumu, Kenya; ²KEMRI-CMR, Nairobi, Kenya, ³Wellcome Trust, Sanger Institute, Hinxton, Cambridge, UK; ⁴London School of Tropical Medicine and Hygiene, London, UK; ⁵Centers for Disease Control and Prevention, Atlanta, GA, USA
Background

- Invasive nontyphoidal Salmonella disease is a leading cause of bloodstream infection in sub-Saharan Africa
- Associated with high case-fatality rate – 20-25%
- Due to challenges in diagnosis and widespread antibiotic resistance there is need for new interventions e.g. vaccines
- However, there is paucity of data on incidence and public health impact of iNTS disease in sub-Saharan Africa
- Systematically microbiology data collected during the multi-site RTS,S/AS01 malaria vaccine 3 trial presents an excellent opportunity to describe the burden of iNTS disease in Africa
Objectives of the analysis

- Describe the incidence of nontyphoidal Salmonella disease and typhoid fever in children in sub-Saharan Africa

- Genetically characterize the Salmonella isolates associated with iNTS
RTS,S malaria vaccine trial

- Randomized, controlled, double-blind trial
- 11 sites in 7 African countries with different malaria transmission intensities
- From July 2009 to December 2013 infants aged 6-12 weeks and children 5-17 months were randomized to receive RTS,S/AS01 or a comparator vaccine
- Infants followed up for a median of 38 months
- Children followed up for a median of 48 months
Methods

• All hospitalized children were evaluated using a standardized algorithm that included:
  – Blood-culture
  – Blood smear for malaria diagnosis by microscopy

• Microbiology methods
  – Standard microbiology methods for blood and CSF culture using automated BactecTM incubators and pediatric bottles
  – Positive cultures were sub-cultured using standard methods
  – A culture was considered positive if a definite pathogen was isolated or if a bacterium that could be either a pathogen or a contaminant was isolated within 48 hours of incubation
  – Salmonella species were confirmed serologically by slide and tube agglutination tests using specific O and H antisera
Results – Study population

- From July 2009 through December 2013, a total of 15,459 children were enrolled in the trial (8922 in the older and 6537 in the younger age category).

- Baseline characteristics were similar in the two study groups but differed by site (IPTi, IRS coverage and moderate anemia).

IPTi- Intermittent Protective Therapy-infants
IRS- Indoor residual spray
Isolated organisms per site

- Bagamoyo
- Kilifi
- Lambarene
- Manhica
- Lilongwe
- Nanoro
- Agogo
- Korogwe
- Kombewa
- Kintampo
- Siaya

Legend:
- Other
- Meningococcus
- Hemophilus
- Pneumococcus
- Salmonella
Salmonella and malaria incidence in infants

Incidence of Malaria

Incidence of Salmonella

Salmonella incidence per 1000 yrs

Malaria incidence per person yrs at risk
Salmonella and malaria incidence in children

Salmonella incidence per 1000 yrs

Malaria incidence per person yrs at risk
Summary

- There is high incidence of iNTS disease in sub-Saharan Africa
- There is an association between iNTS disease and malaria transmission
- These data provide estimates of iNTS bacteremia incidence in children across different sites in Africa
- The data will be useful in guiding evaluation and implementation of interventions to reduce the high burden of iNTS disease in Africa
Next steps

- Define incidence of Salmonella bacteremia according to age, demographics and clinical outcome
- Determine the case fatality rate, among children with iNTS and typhoid fever
- Investigate risk factors for resistant and severe forms of iNTS
- Characterize the isolated Salmonellae at the serovar level and genetic level by whole genome sequencing
Investigators by study site

Albert Schweitzer Hospital, Lambaréné, Gabon, and Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany:
- Selidji Todagbe Agnandji, Bertrand Lell, José Francisco Fernandes, Béatrice Peggy Abossolo, Anita Lumeka Kabwende, Ayola Akim Adegnika, Benjamin Mordmüller, Saadou Issifou, Peter Gottfried Kremser, Marguerite Massinga Loembe;

Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique and Barcelona Centre for International Health Research (CRESIB)-Universitat de Barcelona, Hospital Clinic, Barcelona, Spain:

Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso and Institute of Tropical Medicine, Antwerp, Belgium:
- Halidou Tinto, Umberto D'Alessandro, Hermann Sorgho, Innocent Valea, Jean Bosco Ouédraogo, Palpouguini Lompo, Salou Diallo, Ousmane Traore, Armand Bassetto, Edgard Dao

KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya:
- Mary J. Hamel, Simon Kariuki, Martina Oneko, Chris Odero, Kephas Otieno, Norbert Awino, Vincent Muturini-Koi, Kayla F. Laserson, Laurence Slutsker, Jackton Omoto

KEMRI–Walter Reed Project, Kombewa, Kenya:
- Walter Otieno, Lucas Otieno, Nekoye Otysula, Stacey Gondi, Allan Otieno, Bernhard Ogotu, Jew Ochola, Irene Onyango, Janet Oyieko;

KEMRI–Wellcome Trust Research Program, Kilifi, Kenya:
- Patricia Njuguna, Roma Chilengi, Pauline Akoo, Christine Kerubo, Charity Maingi, Ally Olotu, Philip Bejon, Kevin Marsh, Gabriel Mwabingu, Jesse Gitaka;

Kintampo Health Research Center, Kintampo, Ghana and London School of Hygiene and Tropical Medicine, London, UK:
- Seth Owusu-Agyei, Kwaku Poku Asante, Owusu Boahen, David Dosoo, George Adjei, Daniel Chandramohan, Brian Greenwood, Elisha Adeniji, Abena Kunadu Yawson, Kingsley Kayan;

National Institute for Medical Research, Korogwe, Tanzania, University of Copenhagen, Copenhagen, Danemark and London School of Hygiene and Tropical Medicine, London, UK:
- John Lusingu, Samwel Gesase, Anangisye Malabeja, Omari Abdul, Coline Mahende, Edwin Liheluza, Martha Lemnge, Thor G. Theander, Chris Drakeley, Joyce Mbwana;

School of Medical Sciences, Kumasi, Ghana:
- Daniel Ansong, Tsiri Agbenyega, Samuel Adjei, Harry Owusu Boateng, Theresa Rettig, John Bawa, Justice Sylverken, David Sambian, Anima Sarfo, Alex Agyekum;

University of North Carolina Project, Lilongwe, Malawi:
- Francis Martinson, Irving Hoffman, Tisungane Mvalo, Portia Kamthunzi, Rutendo Nkomo, Tapiwa Tembo, Gerald Tegha , Mercy Tsidy, Jane Kilembe, Chimwemwe Chawinga;

GlaxoSmithKline Vaccines, Wavre, Belgium:
- W. Ripley Ballou, Joe Cohen, Yolanda Guerra, Erik Jongert, Didier Lapierre, Amanda Leach, Marc Lievens, Opokua Ofori-Anyinam, Aurélië Olivier, Johan Vekemans, and PATH Malaria Vaccine Initiative, Washington, D.C.:
  - David Kaslow, Didier Lebouleux, Barbara Savarese, David Schellenberg.