The impact of cryptosporidiosis is not limited to the diarrhoeal episode alone but has been associated with long term sequelae, with several studies suggesting that both asymptomatic and symptomatic cryptosporidial infections have a significant adverse effect on nutritional status, cognitive development, increased overall diarrhoeal burden and mortality in children.

Although there are studies showing high cryptosporidial disease burden in developing countries, resulting in immediate and prolonged morbidity, the epidemiology of cryptosporidial infections in humans is not clearly understood. Moreover, there is a dearth of longitudinal data on the course of infection in the absence of overt diarrheal disease. A clear understanding of the natural history of cryptosporidiosis and correlates of protection are essential in developing effective, efficient and sustainable disease control and preventive measures. In intensive active surveillance of a cohort of children from birth till three years of age to study the natural history of cryptosporidiosis in a semi-urban slum area in southern India, we have shown early childhood exposure and a high rate of asymptomatic infection. The proportion of re-infected children was high and clustering was observed in children for both infection and diarrhoea. Protection against cryptosporidial infection increased with the order of infection but was only 69% after four infections. *C. hominis* was the predominant *Cryptosporidium* species, and there was no evidence of species-specific protection. Clustering of infection is suggestive of host susceptibility. Multiple re-infections conferred some degree of protection against subsequent infection.

These studies demonstrate the power of harnessing the synergistic benefits of a birth cohort study design in a community setting and efficient molecular approaches to detect cryptosporidial infections, to enhance understanding of a common but under-recognised pathogen.

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Type: Invited Presentation

Final Abstract Number: 24.004
Session: Pediatric Diarrhea in Low Income Countries: Rotavirus and Beyond
Date: Friday, March 4, 2016
Time: 15:45-17:45
Room: Hall 2

Molecular diagnostics and the aetiology of diarrhea in low-income countries

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Abstract: Studies of childhood diarrhea in developing countries have traditionally employed a wide range of diagnostic modalities including culture, microscopy, and enzyme immunoassay. Molecular diagnostics offer a substantial increase in sensitivity, however they also increase the background rate of pathogen detection. A quantitative analytic approach can help identify the subset of clinically significant molecular detections. In this symposium talk, we will present estimates of of pathogen-specific attributable fractions of diarrhea from ongoing re-analyses of two multisite studies of childhood diarrhea (GEMS and MAL-ED). Compared to prior burden estimates from these studies, this approach reveals a substantial increase in the burden of diarrhea due to pathogens for which conventional diagnostics were not sufficiently sensitive, in particular *Shigella*, ST-ETEC, and adenovirus 40/41. Burden estimates for other pathogens, including rotavirus and *Cryptosporidium*, were not significantly changed. After rotavirus, *Shigella* was associated with the highest burden of moderate-to-severe non-bloody diarrhea, which suggests that current guidelines limiting the role of antibiotics to bloody diarrhea in children in these settings need to be re-evaluated. These findings also have significant implications for the prioritization of pathogen-specific interventions aimed at reducing the burden of diarrheal disease in children in these settings.

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Room: Hall 5

Dengue, Chikungunya and Zika Virus: Global emergence

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Abstract: (no abstract received from presenter)

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Room: Hall 5

Pathogenesis of severe dengue infection

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Abstract: The pathogenesis of severe dengue (SD) is thought to be due to the complex interplay between the virus, host genes and the host immune response. As vascular leak, which is the hall mark of SD, occurs following the resolution of the viraemia, it was thought that an inappropriate immune response to the virus, was the main cause of SD. However, recent data shows that dengue NS1 alone activates monocytes through the TLR4 receptor, inducing inflammatory cytokine production and that NS1 was involved in vascular leak in acute dengue. We too have found that dengue NS1 stimulates IL-10 production from monocytes, which in turn could lead to suppression of dengue virus specific T cell responses and thereby contribute to disease severity. In our studies, which have investigated the kinetics of changes in inflammatory mediators, the degree of viraemia and the onset and extent of vascular leak, have shown that inflammatory mediators are significantly elevated in patients with SD, around day 4 to 5 of illness. Levels of both IL-10 and IL-17 and other cytokines were significantly elevated in patients with SD when compared to milder dengue, before the onset of vascular leak.

Our previous studies had shown that platelet activating factor (PAF) was an important mediator of vascular leak. We found that although the dengue virus (DENV) or dengue immune serum did not induce PAF production by monocytes, lipopolysaccharide (LPS) acted synergistically with the DEN, in the production of PAF. Since LPS levels in serum have been found to be significantly elevated in SD, LPS could further contribute to disease pathogenesis and vascular leak.

Mast cells are an important source of PAF and have shown to be important in disease pathogenesis in dengue mice models. We found that mediators such as tryptase and secretory phospholipase, which are produced exclusively by mast cells, are significantly elevated in patients with DHF, during early infection. Therefore, in summary, the events that lead to severe dengue appear to occur before the onset of vascular leak and the role of mast cells and viral proteins in the pathogenesis of SD should be further investigated.

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Room: Hall 5

Management of severe dengue

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Abstract: Dengue is an important human arboviral disease caused by infection of four antigenically related strains of dengue virus (DENV 1-4) belonging to the Flaviviridae family. Despite extensive worldwide efforts, it remains a major public health concern with 55% of the world's population estimated to be at risk for dengue. Infection by any of the four dengue serotypes can cause a wide spectrum of disease manifestations that ranges from mild, self-limiting febrile dengue fever to severe, life-threatening disease. The pathophysiological hallmark that determines disease severity is the degree of plasma leakage, bleeding and single or mutli-organ involvement. In recent years, there were several clinical trials using re-purposed pharmaceutical agents to treat dengue, however none has shown significant usefulness for its recommendation for routine use. Lacking the anti-viral agents, management of dengue is largely supportive in nature. Ability to recognise infection early and early signs of disease progression remain key in instituting early and appropriate interventions, preventing disease progression or late presentation of disease where treatment options are limited and outcomes are poor. Patients with severe dengue should be admitted to a hospital with access to intensive care facilities. Judicious intravenous fluid replacement is critical to balance the 2 stages between plasma leakage and fluid reabsorption during recovery phase. Dengue is a dynamic disease particularly so during the critical phase where plasma volume changes rapidly, close and frequent monitoring of hematocrit is critical to guide fluid replacement. Concealed bleeding may pose a clinical challenge and in instance blood transfusion may be needed. Dengue mortality can be reduced with system priming to recognise the disease and systematic treatment approach.

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Zika virus: What you need to know

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Room: Hall 6

Leptospirosis

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Abstract: Leptospirosis is present worldwide and is especially important in developing countries, where sanitation is precarious. Sporadic cases are linked to contact with urine-contaminated water. In tropical countries, urban outbreaks can occur after floods in rainy season. Mild non-lethal anicteric forms comprise most cases and can be easily confused with flu, dengue fever, other mild viral illnesses and *P. vivax* malaria. About 5 to 10% of cases develop severe sepsis-like disease or meningitis during outbreaks. The serious illness form, also known as Weil's Disease, courses with jaundice, shock, renal failure, coagulopathy and other organ dysfunctions, leading to prolonged hospitalization in intensive care facilities and death, with high healthcare costs. Differential diagnosis includes bacterial sepsis, hepatitis, yellow fever, Hantavirus disease, *P. falciparum* malaria and other severe febrile illnesses. Highly sensitive and specific rapid diagnosis tests are commercially lacking. Antibodies or antigen detection by enzyme-linked assays and nucleic acid detection by PCR in blood or other body fluids are promising. Mechanisms of disease are little known, but evidence points out to systemic inflammatory response syndrome-like pathophysiology in severe cases. Spirochete cell wall proteins, lipopolysaccharide, enzymes like phospholipase and other bacterial toxic products produce tissue damage and activate inflammatory response locally and systemically, through toll-like receptors on antigen-presenting cells, triggering cytokine secretion by innate and adaptive immune cells, resulting in inflammatory and immune responses. Some patients evolve with shock, coagulopathy, organ failure and death. Which regulatory mechanism leads to severe disease is not exactly known. Lethality varies widely in severe cases, reaching 50% in some reports, depending of diagnosis and treatment institution speed, level of care and other factors.