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SAVE THE DATE
3rd Annual Global Health and Infectious Disease Conference
April 10, 2015

2014 CGHID CONFERENCE
March 28, 2014

2nd Annual Global Health and Infectious Disease Conference
Maternal and Child Health and Infectious Diseases at the Human–Animal Interface

Center for Global Health and Infectious Disease (CGHID)
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<td>7:30 am</td>
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<tr>
<td>8:00 am</td>
<td>Welcome&lt;br/&gt;Larry J. Shapiro, MD&lt;br/&gt;Washington University&lt;br/&gt;Overview of the Center for Global Health and Infectious Disease&lt;br/&gt;William G. Powderly, MD&lt;br/&gt;Washington University&lt;br/&gt;Introduction of Speakers&lt;br/&gt;Stephen M. Beverley, PhD&lt;br/&gt;Washington University</td>
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<tr>
<td>8:20 am</td>
<td>A Solution Pathway to the Global Epidemic of Preterm Birth&lt;br/&gt;Craig E. Rubens, MD, PhD&lt;br/&gt;Global Alliance to Prevent Prematurity and Stillbirth at Seattle Children's and University of Washington School of Medicine</td>
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<td>8:55 am</td>
<td>From Microbiome to Mechanism: Roles of the Vaginal Microbiota in Women's Health&lt;br/&gt;Amanda L. Lewis, PhD&lt;br/&gt;Washington University</td>
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<td>9:30 am</td>
<td>Break</td>
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<td>Introduction of Speakers&lt;br/&gt;Graham A. Colditz, MD, DrPH&lt;br/&gt;Washington University</td>
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<td>10:05 am</td>
<td>Immunomodulating Effects of Helminth Infections during Pregnancy: The Entebbe Mother and Baby Study&lt;br/&gt;Alison M. Elliott, MBBS, MD, DTH&amp;H, FRCP&lt;br/&gt;London School of Hygiene &amp; Tropical Medicine, Medical Research Council/Uganda Virus Research Institute</td>
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<tr>
<td>10:40 am</td>
<td>New Treatments for Malaria&lt;br/&gt;Audrey R. Odom, MD, PhD&lt;br/&gt;Washington University</td>
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from the observation that chronic murine enteric norovirus infection triggers enteric disease phenotypes only in the presence of mutations in a specific Crohn’s disease susceptibility gene ATG16L1 (Nature 456:259; Cell 141:1135). This ‘virus-plus-susceptibility gene’ interaction generates abnormalities in epithelial Paneth cell granule secretion and responses to intestinal injury. Atg16L1 is an autophagy (Atg) gene, and additional Atg genes also participate in secretion of granule contents by goblet cells and osteoclasts (Developmental Cell 21:966, EMBO In Press). Remarkably, intestinal bacteria are required for chronic enteric norovirus infection, again demonstrating the intimacy of relationships between intestinal microbes and viruses. Given the importance of these interactions between the virome and the host, we have sought to define the total human and mouse virome using metagenomic analysis, leading to the discovery of a novel murine astrovirus (J. Virol. 86:12262), and at least 32 novel viruses associated with AIDS in macaques (Cell 151:253). These viruses may contribute to AIDS enteropathy. Recent work has identified an enteric virome signature in human inflammatory bowel disease, and a larger-than-expected enteric human virome. These findings indicate that the matrix of genetic interactions between the host and the virome determine normal immune status and disease susceptibility.

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<td>Edward J. Pearce, PhD</td>
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<td>Skewed Cytokine Response to</td>
<td>Candida albicans Vaginal Colonization: Implications for Pregnancy and Global</td>
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<td>Candida albicans Vaginal</td>
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<td>Colonization:</td>
<td>Margaret K. Hostetter, MD</td>
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<td>Implications for Pregnancy</td>
<td>Cincinnati Children’s Hospital Medical Center</td>
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<td>The Virome in Health and</td>
<td>Herbert W. Virgin IV, MD</td>
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<td>Disease Phenotypes</td>
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<td>3:15 pm</td>
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<td>Introduction of Speakers</td>
<td>Victoria J. Fraser, MD</td>
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<td>3:40 pm</td>
<td>Emerging Microbial Threats:</td>
<td>James M. Hughes, MD</td>
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<td>Emerging Microbial Threats: Issues, Challenges, and Opportunities at the</td>
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<td>Opportunities at the</td>
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<td>Human-Animal-Ecosystem</td>
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<td>Interface</td>
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<td>4:15 pm</td>
<td>The Role of Zoological Parks</td>
<td>Sharon L. Deem, DVM, PhD, Dipl ACZM</td>
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<td>in One Health</td>
<td>Saint Louis Zoo</td>
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<td>4:50 pm</td>
<td>Concluding Remarks</td>
<td>William G. Powderly, MD</td>
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Solution Pathway to the Global Epidemic of Preterm Birth

Although important gains have been made in child survival over the past two decades, reduction in neonatal mortality (i.e., deaths in the first month of life) has lagged substantially. Neonatal deaths now account for 44% of all under-5 deaths worldwide. Preterm birth is the leading cause of neonatal death, the second leading cause of all under-5 mortality, and a leading cause of severe childhood disability. It is also associated with significant maternal morbidity and mortality. Over 15 million preterm births occur annually in the developed and developing world. Despite this high global burden and its impact, little is known about how to prevent preterm birth and, in low-income and middle-income countries, how best to scale up strategies that are practical and affordable. Finding solutions to the complex problem of preterm birth will not come easily, but will need an expanded strategic agenda. Time and again, results have shown that investment in science yields health solutions. Now is a crucial time to affect such advancements for preterm birth. Dr. Rubens’ lecture will address this worldwide epidemic, current scientific knowledge, what is needed, and recent innovative efforts to address preterm birth prevention and management on a global scale.

The Virome in Health and Disease Phenotypes

It is unclear why inflammatory diseases occur in only a few people carrying disease risk alleles. In addition, a large number of immune/inflammatory diseases, including inflammatory bowel disease and asthma are increasing in incidence, perhaps due to changes in our physiology wrought by alterations in the microbial communities that live on or in us. This has led us to put forward the concept that the virome can set the level of the ‘normal’ immune system and, further, can interact with allelic variants in the host to cause variations in normal immune function and variable penetrance of disease (reviewed in Cell 138:30; Cell 147:44). Data in support of these concepts includes the observation that chronic herpesvirus infection symbiotically protects against bacterial infection by setting the level of innate immunity and changing host transcription in an organ-specific manner (Nature 447:326, Blood 115:4377, J. Virol. In Press). Interestingly, chronic herpesvirus infection is, in turn, regulated by infection with enteric helminths, one of the most common types of infections worldwide. Co-infection with enteric helminths can reactivate latent herpesvirus infection by stimulating release of IL-4 which activates key viral promoters in a STAT-6-dependent manner. Further support for the concept that chronic viruses can alter physiology in important ways comes...
properties. Bacterial vaginosis (BV) is an “imbalance” of the vaginal microbiota linked with increased risks of sexually transmitted infection, urinary tract infection, and infection-associated preterm birth. However, despite thousands of reports describing the BV-associated microbiota and its risks, the mechanisms underlying these risks are only beginning to emerge. This talk will describe the first successful attempt to apply Koch’s postulates to BV, demonstrating that a single bacterium, Gardnerella vaginalis, is sufficient to cause many of the clinical features of BV in a murine model. Mucus degradation has long been hypothesized to play a major role in reducing host defenses in BV. Here we demonstrate parallel processes in human specimens and the animal model, leading to mucus damage and a reduction in the barrier function of mucus. Ongoing efforts are employing outcomes-based clinical studies together with our experimental models to fully investigate the significance of mucus barrier degradation and its translational potential as a target for preventing maternal and infant morbidity and mortality.

Audrey R. Odom, MD, PhD, is assistant professor of pediatrics and molecular microbiology at Washington University’s School of Medicine. Her research focuses on identifying new therapies to treat malaria.

New Treatments for Malaria

Severe malaria due to Plasmodium falciparum remains a serious global health problem. A major challenge to malaria control is widespread and developing resistance of the parasite to existing antimalarial therapies. There is an urgent need for development of new antimalarial agents. Growth and development of Plasmodium falciparum parasites requires a specialized group of cellular compounds, known as isoprenoids. The parasite makes isoprenoids through a unique metabolic pathway, the MEP pathway. This pathway is shared by other important pathogens such as Mycobacterium tuberculosis, but not present in humans. We have targeted one MEP pathway enzyme, IspD, for small molecule inhibition. Through a combination of virtual and physical high-throughput screening approaches, as well as medicinal chemistry optimization, we have developed a new series of selective, drug-like compounds as new antimalarial leads.

Craig E. Rubens, MD, PhD, is co-founder and executive director of Global Alliance to Prevent Prematurity and Stillbirth (GAPPs) at Seattle Children’s, and professor of pediatrics and global health at University of Washington School of Medicine. An internationally recognized infectious disease expert, Craig leads GAPPs’ work in program development and strategic partnerships that leverage cross-disciplinary science to accelerate a discovery-to-delivery pipeline for improving maternal and newborn care and ultimately preventing prematurity and stillbirth. Dr. Rubens’ long-term research interests include infectious diseases afflicting pregnant women, newborns, and children around the world, specifically the mechanisms of infection during pregnancy and the early newborn period that result in poor pregnancy and newborn health outcomes like preterm birth and stillbirth.

Sharon L. Deem, DVM, PhD, Dipl ACZM, is a wildlife veterinarian and the director of the Saint Louis Zoo Institute for Conservation Medicine. She has conducted conservation and research projects in 30 countries around the world. Her research has included, among many others, a health-monitoring program for gorillas in central Africa, health assessments of sea turtles in Africa and the Americas, veterinary support for a maned wolf ecological study in Bolivia, health care of working elephants in Myanmar, and avian health studies in the Galapagos Islands, Ecuador. Her interests in wildlife veterinary medicine focus on the spread of disease between domestic animals and wildlife and the health impact of environmental changes and human contact on wild species.

The Role of Zoological Parks in One Health

The One Health concept, an initiative that aims to merge animal and human health science to benefit both, has rapidly gained international attention and acceptance in recent years. Zoological park staff members are integral players on One Health teams. Accredited zoos today are much more than simple “arks” of protection for threatened and endangered wildlife, with staff that provide health care and conduct health studies on animals, and increasingly on humans, both within zoo walls (ex situ) and in the wild (in situ). Six significant roles for zoo personnel in this emerging field of One Health include (1) studies on diseases of conservation concern; (2) health care for the sustainability of biodiversity; (3) zoo animals as sentinels of disease across taxa, including humans; (4) disease surveillance at the interface of wildlife, domestic animals, and humans; (5) comparative medicine; and (6) exploration of the diversity of life at both the macro and micro scales. The zoological staff footprint extends across the entire planet and provides an underutilized, but growing, resource in efforts to ensure the health of non-human species, humans, and ecosystems globally.

Alison M. Elliott, MBBS, MD, DTH1&H, FRCP, is Professor in the Department of Clinical Research at the London School of Hygiene & Tropical Medicine, UK, and Head of the Co-infection Studies Programme at the Medical Research Council/Uganda Virus Research Institute (MRC/UVRI), Uganda. Since 1997 she has been based in Uganda at the Uganda Virus Research Institute. Her current interests focus on the interactions between co-infections, the effects of helminth infection on immune responses to vaccines, and infectious and allergic disease incidence in children in Uganda, as well as research-capacity building in Africa.

Immunomodulating Effects of Helminth Infections During Pregnancy: The Entebbe Mother & Baby Study

Populations in tropical, resource-poor countries are still highly exposed to a wide range of infectious diseases, including helminth infections. This may be regarded as
the normal condition for a mammalian host. People who grow up in such a setting exhibit immunological differences compared to people from resource-rich, temperate settings, including differences in immune response to vaccines, and differences in susceptibility to immunologically mediated diseases such as asthma, allergy and autoimmunity. The Entebbe Mother and Baby Study is a birth cohort in Uganda. It was established to investigate the effects of maternal and early childhood worm infections and their treatment on outcomes in infancy and childhood. Children in the cohort are now aged about nine years old. Lessons from the cohort will be discussed in this talk.

Margaret K. Hostetter, MD, is the Albert B. Sabin Professor of Pediatrics Albert B. Sabin Professor and Director of the Division of Infectious Diseases at Cincinnati Children’s Hospital Medical Center. She is a board-certified specialist in pediatric infectious diseases whose research focuses on the yeast *Candida albicans*, a cause of vaginal colonization in pregnant women and of potentially fatal bloodstream infections in premature infants and other immunocompromised hosts. She is a member of the Institute of Medicine of the National Academy of Sciences.

**Skewed Cytokine Response to Candida albicans Vaginal Colonization: Implications for Pregnancy and Global Health**

*C. albicans* colonization of pregnant women rises from 30% (US) to >60% (India, Africa). Because vaginal antifungal suppositories reduced the incidence of preterm birth by 25-40% in clinical trials, we hypothesized that untreated *C. albicans* during pregnancy favors Th17 cells at the expense of Tregs.

E6/E7 vaginal epithelial monolayers and full thickness EpiVaginal™ tissue were colonized with 10⁶ *C. albicans* strains for 24 hrs at 37°C. Cytokine release was measured by ELISA and by flow cytometry.

Colonization by 10⁶ wild type *C. albicans* increased the release of Th17-inducing IL-1β, TNF-α, IL-17A, IL-6, IL-8, IL-22 and IL-23 in both vaginal epithelial models (p<0.01), while impairing production of Treg-promoting mediators including CCL20, TGFβ, and human β-defensin 2 (p<0.019). Release of Th17-inducing cytokines from EpiVaginal™ tissue was 20-100 fold greater than from E6/E7 monolayers. Cleavage of IL-1β was detected on Western blot. Mutant analysis implicated *C. albicans* Int1, proteins of the candidal prostaglandin synthesis pathway (Ole2, Fet3), and enzymes of surface mannosylation (Pmr1, Mnn4) in IL-1β release. Treatment of colonized vaginal epithelial cells with heparin (500 or 1000 u/ml) decreased Th17-inducing cytokines IL-1β, IL-6, and IL-23 (p<0.001) and increased Treg-promoting mediators CCL20 and human β-defensin 2 (p<0.004).

Similar studies are now underway in pregnant rhesus macaques. If cytokine skewing is confirmed in vivo, clinical trials will be performed to evaluate Th17/Treg balance in colonized pregnant women in Bangladesh and Zambia.

**James M. Hughes**, MD, is professor of medicine and public health at Emory University. His areas of interest include emerging infectious disease; antimicrobial resistance; vectorborne and zoonotic diseases; strategies for improving adolescent immunization coverage; and policies and practices for preventing, rapidly detecting, and responding to emerging diseases.

**Emerging Microbial Threats: Issues, Challenges, and Opportunities at the Human-Animal-Ecosystem Interface**

Emerging infectious diseases pose challenges for the clinicians, veterinarians, microbiologists, researchers, public health professionals, and policymakers in the United States and around the world. No country is free of the risk of disease emergence, and two-thirds to three-quarters of recent emerging events have involved vectorborne or zoonotic diseases, with the majority of those originating in wildlife. Examples from the past 20 years include hantavirus pulmonary syndrome, Nipah virus encephalitis, West Nile encephalitis, SARS, monkeypox, H5N1 influenza, pandemic H1N1 influenza, MERS, and H7N9 influenza. Health workers (e.g., physicians, veterinarians, microbiologists, public health officials, pathologists, entomologists, wildlife biologists, ecologists) have played important roles in the initial recognition of many of these events. This presentation will review factors contributing to disease emergence, discuss some recent illustrative examples, describe challenges in zoonotic disease detection and response, and review current efforts to strengthen global capacity for early detection, response, and control of emerging diseases.

**Lora L. Iannotti**, PhD, is an assistant professor at the Brown School at Washington University. Her research focuses on undernutrition among young children living in developing countries, and more specifically, on micronutrient deficiencies related to poverty and infectious disease. In two project sites in Haiti and East Africa she is studying the combined effects of interventions designed to prevent undernutrition, improve water and sanitation, and foster economic development.

**Amanda L. Lewis**, PhD, is assistant professor of molecular microbiology in Washington University’s School of Medicine. Research in the Lewis lab focuses on understanding the roles played by members of the vaginal microbiota in adverse health outcomes suffered by women, particularly in the perinatal period. Multidisciplinary approaches blend biochemical and genetic tools with animal models, clinical specimens, and small molecules to define how individual bacterial pathogens interact with the urogenital mucosa; and moreover, to elucidate the role of vaginal ecology in shaping processes of pathogenesis.

**From Microbiome to Mechanism: Roles of the Vaginal Microbiota in Women’s Health**

Urogenital infection is a major cause of global morbidity and mortality for women and infants. A woman’s risk of adverse health events due to genitourinary infection appears to be determined in part by whether her vaginal microbiota has ‘healthy’ or ‘unhealthy’