“Paenibacillus infection with frequent viral coinfection contributes to postinfectious hydrocephalus in Ugandan infants.”
Science Translational Medicine 12, eaba0565 (2020).

An international team investigated the origin of the severe brain infections afflicting thousands of Ugandan infants in the neonatal period, and often resulting in hydrocephalus in the survivors. Fluid from the brain taken at surgery led to the recovery of a novel strain of a highly virulent bacteria, shown on the tree of life of related organisms. These infection cases, shown as red dots on the map, are concentrated within a region in Eastern Uganda characterized by wetlands and swamps on the north and south banks of Lake Kyoga that the Nile river flows into and out of. Map adapted and based on OCHA/ReliefWeb (UN Office for the Coordination of Humanitarian Affairs) and used as permitted by the agency.

An international team has completed a 5-year project involving teams of scientists across Africa, Europe, and the US, resulting in a major breakthrough in understanding a previously mysterious lethal childhood disease.

Severe systemic bacterial infection in the neonatal period, neonatal sepsis, accounts for an estimated 680,000-750,000 neonatal deaths per year worldwide – more than childhood deaths from malaria and HIV combined. The most common brain disorder in childhood is hydrocephalus, which creates the most common need for neurosurgery in early childhood. The largest single cause of hydrocephalus in the world is as a sequelae of neonatal sepsis, accounting for an estimated 160,000 yearly cases of postinfectious hydrocephalus in infancy (Karimy et al 2020). The microbial agents responsible for this enormous loss of human life, from both neonatal sepsis and postinfectious hydrocephalus, have been poorly characterized – a worldwide Microbial Dark Matter problem (Sinnar and Schiff, 2020).

We have been applying next-generation molecular methods to improve the identification of causal agents in Africa and Southeast Asia. Both neonatal sepsis and postinfectious hydrocephalus occur disproportionately in the developing world, and most of the hydrocephalic cases will die in childhood.
without adequate treatment (Kulkarni et al 2017), substantially compounding the effective mortality due to neonatal sepsis and its tremendous burdens on societies.

Over a 5 year study in Uganda, supported by the US National Institutes of Health, using advanced genomic techniques we uncovered some of the major bacterial and viral underpinnings of these infections (Paulson et al 2020).

We discovered in the brains of African infants a new highly virulent strain of bacteria, a Paenibacillus, upon a background of a virus, cytomegalovirus, that often harms the brains of infants. Our work is a transdisciplinary fusion of cutting-edge genomics, computational analysis, microbiology, infectious disease, brain imaging, metabolomics, and pathology. We have shown that our strategy, a pan-genomic approach to pathogen discovery in syndromic infectious disease, has the power to reveal microbial causality in literally millions of cases of neonatal sepsis and postinfectious hydrocephalus that occur each year world-wide. The impact of our findings can lead to the saving of hundreds of thousands of lives each year.

We took a powerful approach to the pervasive problem of reproducibility of genomic organism detection on samples from normally sterile body fluids – these are called low-biomass samples. We collected samples from each patient in two different ways, and submitted the separate samples to two different university scientific laboratories, where the samples were analyzed with independent methods. The initial link between hydrocephalus and Paenibacillus was made through high throughput sequencing and PCR analyses at the Center for Infection and Immunity in the Mailman School of Public Health at Columbia University. Working collaboratively, we developed a comprehensive understanding of the cause through rigorous statistical convergence in reproducibility, verification of the viral presence with optimized polymerase chain reactions (PCR), recovered the new strain of bacteria with assembly of its genome, and replicated its unusual virulence in mice.

We are now developing the point-of-care tests required to identify and treat these infections. And we are developing predictive models that will enable us to utilize our detailed surveillance of over a thousand of these infants, combined with environmental variables from satellite rainfall measurements (many of these infections are linked to rainfall), to predict optimal point-of-care treatment. We call this Predictive Personalized Public Health or P3H. It is a novel way to control infectious disease, and since it can be valuable for the Coronavirus epidemic, we are turning our full attention to developing strategies that can be universally helpful to health care systems as we all struggle against the current pandemic (Ebeigbe et al, 2020; Sauer et al, 2020). At all of the sites we study overseas, both in Uganda and Vietnam, the Coronavirus will now be added to the list of worrisome pathogens that we need to be alert to in our efforts to improve the care and survival of the neonates that become ill from serious infections.

The Centers involved in this research included scientists and physicians from:
- The Institute for Personalized Medicine at Penn State College of Medicine (Director, James R. Broach), Center for Neural Engineering, and Penn State Departments of Biochemistry, Neurosurgery, Engineering Science and Mechanics, Physics, Mechanical Engineering, Biology, Medicine, Public Health Sciences, Pathology, Division of Pediatric Infectious Diseases, and Comparative Medicine.
- Genentech (Principal Statistical Scientist, Joseph N. Paulson)
- The Center for Immunity and Infection at the Mailman School of Public Health at Columbia University (W. Ian Lipkin, Brent L. Williams, Nischay Mishra)
• The CURE Children’s Hospital of Uganda (Edith Mbabazi-Kabachelor, Director of Research), Mbale, Uganda
• Harvard University (Boston Children’s Hospital, T. H. Chan School of Public Health)
• National Center for Biotechnology Information, US National Institutes of Health
• MetaGenoPolis, Université Paris-Saclay, INRAE, Jouy-en-Josas, France
• Mbarara University of Science and Technology, Mbarara, Uganda
• Washington University in St Louis
• University of Liverpool, UK
• Mbale Regional Referral Hospital and Busitema University, Mbale, Uganda

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