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Concept Note: The Neonatal Septisome

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New Perspective to an Old Problem

We have uncovered a world-wide burden from the sequelae of neonatal infections which has not been recognized by the global health community. The reasons are complex, and revolve around the recent introduction of technical pediatric neurosurgery in developing countries, along with the stigmata and shortened life spans of severely damaged children. One of us (BCW) has accumulated the world's largest experience in the treatment of children with hydrocephalus in the developing world, and the other (SJS) is leading efforts to define and model the microbiome that underlies this situation. Our attention to these brain damaged infants has refocused our attention on the relatively stagnant state of our approach to neonatal infections in the developing world. With several clinical trials underway in Uganda, and a strong network of colleagues throughout East Africa, we are in a unique position to leverage our experience and network of colleagues to have a transformational impact on this situation.

Economic Burden of Disease

The World Health Organization estimates that 1.6 million neonates die world-wide of infection each year, and almost half of these cases of neonatal sepsis (NS) occur in sub-Saharan Africa (SSA). There are about 100,000 postinfectious hydrocephalus (PIH) cases per year in SSA, generated from a pool of 1,000,000-2,000,000 million cases of NS. As developing countries acquire the technical capability of pediatric neurosurgery, large numbers of children previously left untreated swamp new facilities. The most common condition overwhelming the most established centers, in Uganda and Kenya, is PIH. This experience is similar to those of colleagues we have trained to treat hydrocephalus in Vietnam, Nepal, Zambia, Nigeria, Ghana, Ethiopia, and Tanzania. The brains of children with PIH are devastated, with new estimates in SSA of human capital lost of $1.2-1.4 billion, and the values of statistical lives lost of $26-48 billion per year, from our colleagues at the Department of Global Health and Social Medicine at Harvard. The potential economic benefits from a modest 10-20% reduction of such cases would be extraordinary, and solid medical investigation would lead to prevention of the majority of these cases.

Present Situation

PIH and other severe sequelae are generated from inadequately treated NS. If we knew the organisms that caused NS, we could both design inexpensive point-of-treatment diagnostics to optimize therapy, and institute public health preventative strategies to decrease the incidence of NS. But we don't know the agents – we only know the minority that we can culture, and these appear to vary substantially by site. Most studies of NS in developing countries are conclusive in one result: that the organisms are not the common ones seen in industrialized countries where peripartum testing and responsive antibiotics have made NS relatively rare. In East Africa, climate effects drive the case incidence of PIH, and recent genomic evidence demonstrated that rainfall changes the microorganism spectrum underlying PIH as well. Our findings suggest that much environmental PIH has a link to domestic farm animals in rural African settings, and we suspect that the ubiquitous issues of water supply quality and neonatal home environment will be obvious but difficult components to address in the near term.

We wish to dramatically affect this situation in the near term with a 4-pronged approach: 1) define and predict the neonatal *Septisome*, 2) optimize treatment of NS in a sustainable fashion to reduce serious sequelae such as brain damage, 3) institute cost-effective rational public health and vaccination strategies for prevention of NS, and 4) develop a template for instituting 1-3 in other developing countries.

Stage I – The Neonatal Septisome

The first step is to define the viral and bacterial agents associated with NS - the neonatal Septisome. Since this needs to be done in a context specific fashion throughout the developing world, we propose to move high-throughput sequencing to the point-of-diagnostics using the emerging generation of inexpensive desk-top sequencers. Our strong partner in this endeavor is **Gregory T. Lucier, CEO of Life Technologies**, which manufactures the Ion Torrent sequencer. We will back this up initially with US based sequencing (underway at the J. Craig Venter Institute). But we make a clear distinction between the slower time-scale of organism discovery using high-throughput sequencing, and the urgent time-scale of treating individual cases of NS.

The neonatal Septisome is literally a living entity that changes with time and varies by geographical locale – it is a spatiotemporal dynamic biological system that we can at best sparsely measure. We will therefore adapt the effective strategy used in numerical weather prediction and probabilistic robotics – a model-based predictive control observer. We will fuse this model with real-time (scale of weeks to months) Septisome and climate satellite sensing data. This will give us the next generation of therapeutics for NS - predictive real-time therapy of antibiotics and antivirals. We must answer the question: On a given day, when a sick infant arrives with NS, what antimicrobials are immediately instituted to lessen the damage to the infant? Such urgent therapy is required whether or not the organisms causing that particular infant's infection are identified. Reality must be predicted and reconstructed when it cannot be directly and immediately sensed.

Stage II – Optimize Treatment of Neonatal Sepsis

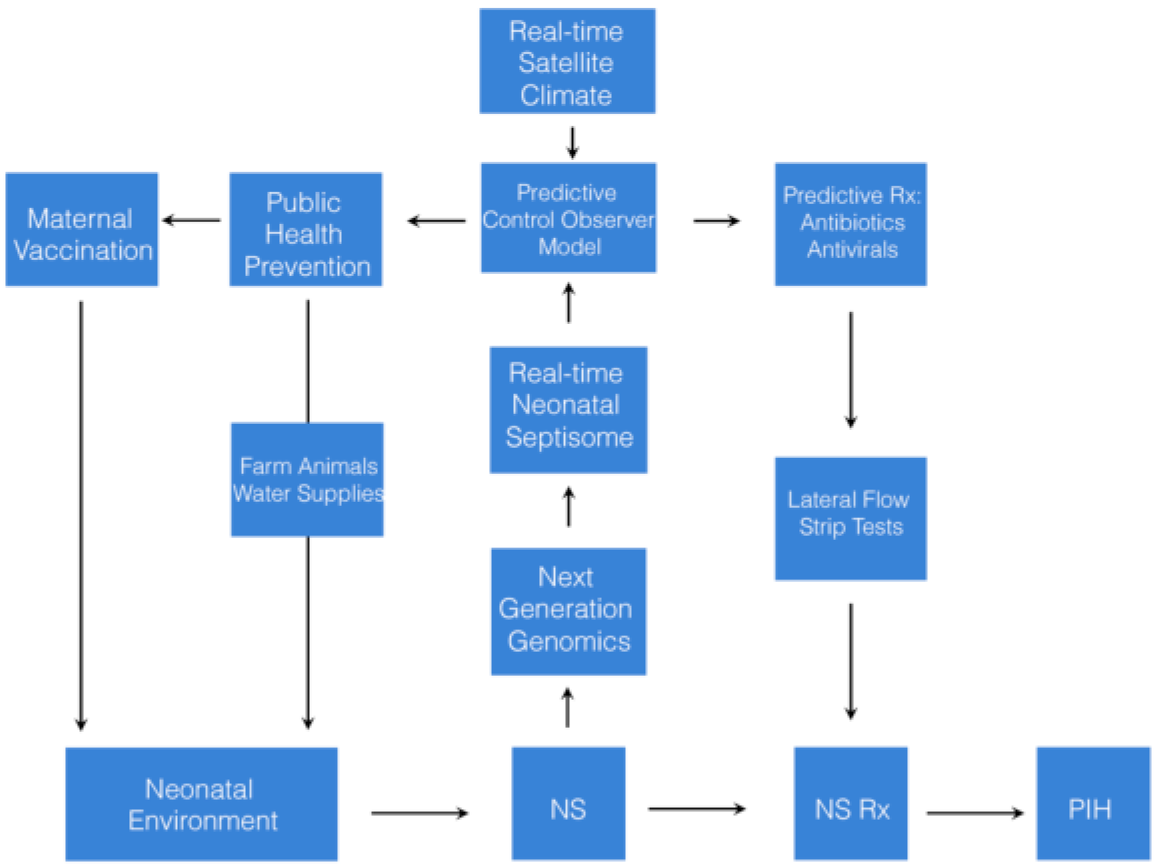
Once we have defined the neonatal Septisome, we can develop inexpensive lateral flow strip tests for urgent point-of-diagnostics in NS. At this point, the need for high-throughput sequencing drops to a low optimal rate for surveillance. This optimal rate is determined, as in all control robotics, by the tracking error rate - the gap between what you predict and what you measure.

Stage III – Public Health Prevention and Vaccination

Once we have defined the neonatal Septisome for a given region, an immediate consequence is that it will guide the rational development of public health strategies to reduce the exposure to the agents responsible for NS, such as water supply improvement or animal husbandry practice changes. Such changes will face all of the monetary, inertial, and cultural barriers that force the kinetics of such improvements to be much slower than the needs that millions of sick neonates dictate. We can therefore consider whether a novel strategy of maternal vaccination to the most likely pathogenic bacteria or viruses might be highly cost-effective in protecting infants for their first months of life. Once we have the first definitions of the Septisome in hand, we wish to immediately investigate whether such maternal vaccination strategies are feasible in animal models, and if so, whether human trials of such an approach might hold promise of an important and cost-effective neonatal safety net.

Stage IV – Sustainable Template for Other Countries

The lessons learned from instituting Stages I-III in one country should be packaged into a template for other developing countries. Each new country needs a site for organism discovery, and needs to learn to collect available satellite climate data. Our predictive model will be open source, but a core group of people at each site have to learn to use such a model. The inexpensive lateral flow diagnostics will be customized for each country, and often vary by season. The standard for setting up a country for these skills should be that they are sufficiently expert to assume the role of the instructors to new sites. Our metric for success should be that the infrastructure for these 4 stages will itself become sustainable.



Flow chart for sustainable reduction of the incidence and aftereffects (such as postinfectious hydrocephalus, PIH) of neonatal sepsis (NS). We define the *Neonatal Septisome*, and create a predictive model that includes measurements of both the spectrum of the microorganisms that cause NS, as well as ongoing climate effects. The model guides optimal therapy for NS (NS Rx), directs inexpensive lateral flow strip test components, as well as guides public health and potential future maternal vaccination strategies.