

A conversation with Dr. Pinaki Panigrahi, March 8, 2018

Participants

- Dr. Pinaki Panigrahi – Professor, Department of Epidemiology, University of Nebraska Medical Center (UNMC); Director, Center for Global Health and Development, UNMC
- Christian Smith – Research Analyst, GiveWell

Note: These notes were compiled by GiveWell and give an overview of the major points made by Dr. Pinaki Panigrahi.

Summary

GiveWell spoke with Dr. Panigrahi of the University of Nebraska Medical Center (UNMC) as part of its investigation into synbiotics for the prevention of neonatal sepsis. Conversation topics included the prevention of neonatal sepsis and child stunting using synbiotics as well as future trials of synbiotics.

Prevention of neonatal sepsis and child stunting using synbiotics

Background

Probiotics have increasingly been used in an attempt to reduce morbidity and mortality. While the jury is still out on the most appropriate probiotics for different use cases, many neonatal intensive care units in the U.S. and other western countries have started administering probiotics.

Probiotics should not be thought of as one-size-fits-all solutions. Rather, probiotics have the most potential when a particular strain is administered due to a rationale for why the strain may be effective in addressing the pathogenesis of a specific disease in a particular population.

A recent trial (<https://doi.org/10.1016/j.jpeds.2017.11.055>) of a commonly used probiotic, *Lactobacillus rhamnosus*, provides an example of the potential dangers of probiotics. This trial failed to find a protective effect from the probiotic and suggested that the probiotic may have been responsible for increasing the incidence of necrotizing enterocolitis and sepsis to some extent.

Synbiotics are preparations that contain both a probiotic and a prebiotic.

Scale of neonatal sepsis and child stunting

Neonatal sepsis is responsible for approximately one million deaths annually. The case fatality rate for neonatal sepsis tends to be high in developing nations, but varies substantially between different pathogens that can cause sepsis.

Dr. Panigrahi believes that the larger issue in child health is stunting, which annually affects approximately 165 to 180 million children under the age of five. Stunting can

impair cognitive development in children, resulting in significant consequences for both individual health and global economic growth.

Randomized controlled trial (RCT) of synbiotics for prevention of neonatal sepsis

Results from population-based surveillance studies on neonatal sepsis in rural India and south Asian countries suggest in that late-onset sepsis (occurring after three days of life) is much more prevalent than earlier thought. While early-onset sepsis is generally the result of improper cutting of the umbilical cord, late-onset sepsis may have a variety of causes. Dr. Panigrahi and his colleagues determined that late-onset sepsis was being caused by the translocation of bacteria from the intestine to the bloodstream.

From 2007 to 2012, Dr. Panigrahi and his colleagues conducted a large-scale RCT of synbiotics for the prevention of neonatal sepsis in rural India (<https://doi.org/10.1038/nature23480>). Effort was made to achieve a diverse sample of infants from coastal, tribal, and other areas. The synbiotic used for the trial contained *Lactobacillus plantarum*, which was selected from 280 candidate bacterial strains.

Process

Neonates were treated with the synbiotic between the second and fourth day of life. This timeframe was chosen because at two to four days of life, an infant's gut is still naïve and therefore more likely to permit bacterial colonization.

Treatment was provided in the form of capsules that could be split open and mixed with a liquid solution for the infant to swallow. The only challenge with synbiotic treatment is that synbiotics must be kept refrigerated to retain potency. However, probiotics can remain at room temperature for approximately six months before losing significant potency.

Cost

The synbiotic capsules costed approximately \$1 per week of treatment.

Findings

The RCT found that synbiotic treatment significantly reduced neonatal sepsis (which, as defined by the WHO, includes many different forms of infection). The treatment also significantly reduced respiratory tract infections.

Potential of synbiotics for prevention of child stunting

Undernutrition and food insecurity may not be fundamental in the pathogenesis of childhood stunting. Enteropathy and enteric dysfunction resulting in chronic intestinal inflammation is now considered to play a significant role in the pathogenesis of stunting. Dr. Panigrahi believes these conditions could be prevented by treating infants with synbiotics.

Future trials of synbiotics

Dr. Panigrahi would like to conduct further RCTs of synbiotics to determine whether synbiotic treatment would be effective for:

- **Different settings** – Future RCTs could be conducted in African countries or other areas of India. Dr. Panigrahi and his colleagues have begun the process of determining potential sites for future trials, although the final determinations will depend upon national-level government officials, policymakers, and funding agencies.
- **Vulnerable infants** – Dr. Panigrahi believes that future trials should include smaller and premature infants. The effect of synbiotics on smaller and premature infants may be similar to or greater than the effect on normal birthweight and full-term infants. The target population of the original RCT in rural India excluded vulnerable infants, which may have resulted in a smaller impact on sepsis.
- **Reduction of stunting** – Dr. Panigrahi believes that treatment intensity should be increased in order for future trials to have a significant impact on child stunting. A reasonable treatment regimen may be a one-week course of synbiotics every month during a child's first two years of life.

While Dr. Panigrahi expects future trials to occur in low-resource settings, he hopes that findings from these trials will be useful for understanding better ways to use synbiotics in a wide range of settings.

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