Identification of Metagenomic Determinants of Disease Severity in Children from the Pneumonia Etiology Research for Child Health(PERCH) Study

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Abstract

The Pneumonia Etiology Research for Child Health (PERCH) study is a multi-country case-control study that focuses on the causes of pneumonia among children under 5 years of age hospitalized in seven diverse countries. The study seeks to discern the specific microbial pathogens and associated contextual factors precipitating the progression of pneumonia to a degree warranting hospital intervention.The study involves a comprehensive comparison between children who experienced very severe pneumonia and those with milder cases. In this project we will utilize metagenomics to profile the microbial communities in the upper respiratory tract of various samples collected from three of the seven countries: The Gambia, South Africa, and Mali. In these countries, the DNA extracted from each child's microbiome sample will be sequenced. This project seeks to decipher the genetic makeup of the microbial populations present in these samples. By integrating metagenomic data, the study seeks to unravel the underlying microbiological factors contributing to pneumonia severity. The ultimate goal is to leverage this knowledge for devising enhanced strategies to aid these children, ultimately fostering improved health outcomes among children in these specific regions.

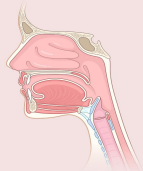
Research Aim

Very Severe Pneumonia
- Very severe pneumonia was defined as cough or difficulty breathing and at least one of the following signs: central cyanosis, difficulty breastfeeding or drinking, vomiting everything, convulsions, lethargy, unconsciousness, or head nodding.

Severe Pneumonia
- Severe pneumonia was defined as cough or difficulty breathing with lower chest wall indrawing

Non-Pneumonia
- Community controls and an additional (HIV)-infected control group at high HIV-prevalence sites matched at random on age and enrollment date of cases.

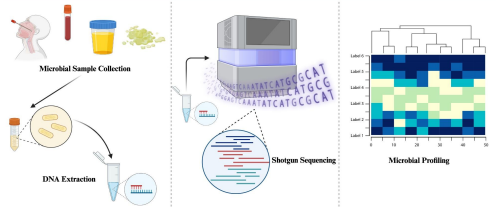
Upper Respiratory Tract



Research Aim: Shotgun metagenomic analysis of the upper respiratory tract of children with pneumonia and healthy controls.

Laboratory Methods

1. Sample Collection
2. Metagenome Sequencing
3. Data Analysis



Sample Size

Very Severe Pneumonia
N = 100

Severe Pneumonia
N = 100

Community Control
N = 100

Figure 1. PERCH Sampling Scheme. N corresponds to individual samples.

Expected Outcomes

- **Establish Comprehensive Microbiome Profiles**
  Create detailed upper respiratory tract microbiome profiles in children with severe and very severe pneumonia, alongside healthy controls.
- **Baseline for Assessment**
  Construct essential baseline data to evaluate and understand the impact and efficacy of immune profiling assays.
- **Insight into Microbial Dynamics**
  Gain understanding of complex interactions between microorganisms in the upper respiratory tract and the immune system, particularly in severe pneumonia cases.
- **Discerning Influential Patterns**
  Differentiate significant microbiome patterns between pneumonia-affected children and healthy controls, revealing pivotal factors influencing pneumonia severity.

Future Directions

- **Enhanced Etiology Detection:** Improve pneumonia cause identification, including viral-bacterial co-infections and culture-negative cases for targeted treatments.
- **PERCH Samples Insights:** Uncover microbial and immunological contributors to severe pneumonia in young LMIC children using PERCH samples.
- **Metagenomic Sequencing:** Use sequencing to pinpoint microbes, vital for precise treatments and reducing antibiotic resistance.
- **Correlation and Severity:** Investigate links between microbes, autoantibodies, and severity for potential improved therapies, though further mechanistic studies needed.
- **Path to Funding:** Successful outcomes can lead to external funding, expanding PERCH cohort analysis and gaining comprehensive pneumonia insights.

Broader Impacts

- **Holistic Approach:** The PERCH study reshapes pneumonia strategies by addressing prevention, diagnosis, and treatment comprehensively.
- **Effective Vaccination:** PERCH drives vaccine development against leading pneumonia causes, including viral agents like RSV and influenza strains.
- **Precision Diagnostics:** Findings lead to advanced tools that aid clinicians in pinpointing pneumonia causes, enabling tailored treatment for children.
- **Reduced Antibiotic Reliance:** PERCH results emphasize viral causes, prompting treatment adjustments that decrease antibiotic dependence, curbing antimicrobial resistance risks.
- **Global Impact:** PERCH's insights revolutionize pneumonia management, improving child health outcomes worldwide.

Acknowledgements

I deeply thank my invaluable supporters: My PI, Daniel P. Beiting and the Beiting Lab for mentorship, Bill and Melinda Gates Foundation for foundational contributions, University Research Foundation 2023 and PennCHOP Microbiome Program for vital resources, and University of Pennsylvania and FERBS Program for significant financial backing.

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