Carrie L. Byington, MD

Research

Pneumonia is the number one cause of death in children worldwide. As a pediatric scientist, my research focuses on bacterial and viral pathogens of the respiratory tract that may result in pneumonia. A major focus of our research team is the understanding of the diagnosis, epidemiology, and evolution of respiratory pathogens in an effort to improve child health.

In 2015, the support of the Benning Society allowed the completion of a year-long observational study of viruses in families. The Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) used the FilmArray platform (BioFire Diagnostics, Salt Lake City, UT) that our research group helped develop to 1) describe the viral etiology of respiratory illness by prospectively collecting weekly symptom diaries and nasal swabs from families for one year, 2) analyze data by reported symptoms, virus, age, and family composition, and 3) evaluate the duration of virus detection. The major findings of this study include the detection of respiratory viruses in children younger than 5 years in 50% of weeks, identification of the most common viruses detected with and without symptoms, and the duration of detection by sensitive PCR technology (Figures 1 and 2). These findings are immediately applicable to the clinical setting and will be used by medical providers to interpret the relevance of positive viral diagnostic tests, particularly in children. In the longer term, we will use Benning funds to further analyze the data, with co-investigators in the Department of Mathematics, to determine patterns of viral transmission within households in an effort to identify opportunities to interrupt this transmission.

Through collaboration made possible by the Benning Society, my research group is working with Dr. Mark Yandell, a Benning Chair holder and Dr. EJ Osborn, a TL1 post-doctoral fellow supported by the Utah Center for Clinical and Translational Science to examine the whole genomes of invasive pneumococcal isolates that we have archives over 20 years to identify pneumococcal virulence genes in order to identify new targets for prevention through universal immunization and treatments. We have focused initially on pediatric pneumococcal parapneumonic empyema (PPE). To examine the genetic underpinnings of PPE, and determine whether PPE is characterized by a shared genetic basis across different serotypes, we performed whole-genome sequencing of 214 invasive S. pneumoniae isolates from Utah children collected pre and post PCV licensure (1996-2000 and 2001-2013 respectively). We used a reference mapping approach against a number of S. pneumoniae genomes (R6, Spn23F and INV104B). To find variants associated with PPE, we used a probabilistic Fst approach to measure genetic differentiation at marker sites between PPE and non-PPE causing strains.

We identified a total of 5.9-7.8 x 10^4 SNPs and 2.5-2.6 x 10^5 putative structural variants (minor allele frequency > 5%). We identified genetic differentiation at a number of regions throughout the S. pneumoniae genome, some of which correspond with previously identified and putative virulence factors such as zmpB, cphF, and pspA. Other peaks correspond to novel putative PPE virulence genes such as ABC-MSP. Both point mutations and larger structural variants were associated with PPE. To ensure that differential strain enrichment did not confound our results, we...
performed similar genetic analyses within single serotypes (1, 3, 7F, and 19A) to control for strain background variation, and found similar levels of increased genetic differentiation at regions identified with the full collection of strains. Our work highlights genomic regions in \textit{S. pneumoniae} that are associated with PPE and presents new candidate genes for functional screens in PPE disease models. Given the significant morbidity and mortality associated with PPE, identification of genetic variants enriched in PPE isolates can be evaluated as potential new targets for disease prevention and treatment.

\textbf{Research Service Project: The Pediatric Molecular Infectious Diseases Laboratory and Pathogen Archive}

Our team has been collecting respiratory samples for bacterial and viral pathogens since 1996. With the Benning Fund resources, we have been able to establish and support a new molecular laboratory and pathogen archive. The molecular laboratory has allowed us to better define the respiratory pathogens isolated from children allowing us to perform non-culture based serotyping and to prepare nucleic acid for genetic sequencing to enrich the scientific quality these clinical specimens. The pathogen archive includes some of the best-characterized specimens in the US. The \textit{Streptococcus pneumoniae} archive with over 500 IPD isolates is one of the largest in the nation. The laboratory is supporting the genetic sequencing of all invasive pneumococcal isolates and will result in a searchable database for comparative genomics. The archive of viral specimens includes over 5000 samples collected from a year-long NIH-sponsored study of families in which nasal swabs and symptom diaries were collected each week-they Utah Better Identification of Germs-Longitudinal Viral Epidemiology (Utah BIG-LoVE) study. Finally, we have an archive of thousands of specimens from the largest pneumonia investigation ever conducted in the US, the CDC-sponsored EPIC study.

The archive is available to investigators on the University of Utah campus and beyond. Investigators in the SOM Departments of Biochemistry, Internal Medicine, Pediatrics, Pathology and the University of Utah Departments of Biology and Mathematics have used the archive. In addition to these efforts, I am the Director of the Utah Center for Clinical and Translational Science and Associate Vice President for Faculty and Academic Affairs for the Health Sciences. In these roles, I lead many of the institutional efforts around faculty development and mentoring for investigators. The Clinical and Translational Scholars program has trained 86 junior faculty members at the University of Utah and has resulted in rates of 92% for extramural funding at program graduation and 98% faculty retention at 7 years.4

\textbf{Biographical Summary}

\textit{Education and Professional Experience:} Undergraduate in Biology at Texas A&M (1981-85); MD Baylor College of Medicine (1985-89); Pediatric Internship and Residency Baylor College of Medicine (1989-92); Postdoctoral Fellowship in Pediatric Infectious Diseases in Laboratory of Nina Agabian, PhD at University of California, San Francisco (1993-1995); Faculty Member Department of Pediatrics (1995-present).

\textit{Current Professional Service:} Associate Vice President for Faculty and Academic Affairs for the Health Sciences; Vice Dean for Faculty, School of Medicine; Director of the Utah Center for Clinical and Translational Science; Chair, American Academy of Pediatrics, Committee on Infectious Diseases.

\textit{Honors and Awards:} Golden Anniversary Prize in Clinical Investigation 2004; Gary C. Schoenwolf Mentorship Award 2011; Linda Amos Service to Women Award 2012; Association of American Medical Colleges Award for Innovation in Research and Research Education 2014; Fellow American Academy of Pediatrics and Infectious Diseases Society of America.

\textbf{References}


