167. A *Bordetella pertussis* Human Challenge Model Induces Immunizing Colonization in the Absence of Symptoms

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Background. *Bordetella pertussis* is one of the leading causes of vaccine preventable death and morbidity globally. Over the last 20 years, pertussis has resurged worldwide, even in territories with high immunization coverage. To improve vaccine strategies, a greater understanding of human *B. pertussis* infection and immunity is required. This study aims to develop a safe controlled human *B. pertussis* infection model and to define natural immune responses against wild-type *B. pertussis* in order to facilitate the development of bioassays and next-generation pertussis vaccines.

Methods. In this first-in-human controlled infection model, healthy volunteers aged 18–45 years with an anti-pertussis toxin (PT) IgG level of <20 IU/mL were inoculated intranasally with *B. pertussis* strain B1917. Safety, colonization, and shedding were monitored over a 17-day inpatient period. Colonization was assessed by culture and qPCR of nasal washes and nasopharyngeal swabs. Azithromycin eradication therapy was commenced on day 14. The dose of inoculum was escalated to optimize colonization rate, expressed as the percentage of volunteers colonized at any sampling point between day 3 and 14. The immunological response is being assessed at various time points over 1 year.

Results. 24 volunteers were challenged in groups of 4–5. The dose was gradually escalated from 10^3 colony forming units (cfu) to 10^5 cfu. Colonization rate ranged from 0% (dose 10^3 cfu) to 80% (10^5 cfu). Amongst this initial cohort, no significant safety concerns or symptoms attributed to *B. pertussis* disease were reported. Eradication was achieved by 48 hours in 100% of colonized volunteers. At least 4-fold rise in anti-PT IgG by day 28 in comparison to baseline was observed in 5 out of 8 volunteers who had >1,000 cfu/mL viable *B. pertussis* in the nasal wash and in one volunteer without detectable colonization. Nasal wash cultures were more sensitive in detecting colonization than nasopharyngeal swab cultures. No shedding of *B. pertussis* was detected in systematically collected environmental samples.

Conclusion. This is the first study to demonstrate safe deliberate induction of *B. pertussis* colonization. It shows that asymptomatic *B. pertussis* colonization occurs and causes a systemic immune response. The model that we have developed will be a valuable tool to further investigate *B. pertussis* colonization and vaccine development.

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168. Intradermal Immunization Drives Humoral and Cellular Immunity to the Lung and Protects Against Acute *P. aeruginosa* Pneumonia

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Background. *Pseudomonas aeruginosa* is a leading cause of hospital-associated pneumonia, with 6,700 multidrug-resistant infections in the US annually. Evidence suggests that antibodies and CD4 Th1 and Th17 responses contribute to protection against *P. aeruginosa* infection. Recent work suggests that intradermal (ID) immunization with a vaccine adjuvanted with a double mutant of *E. coli* heat-labile toxin (dmLT) can direct protective immune responses to mucosal tissues such as the lungs. We sought to determine whether ID immunization with *P. aeruginosa* outer membrane proteins (OMPs) with dmLT could drive migration of CD4+ T cells and antibodies to the lungs and protect against *P. aeruginosa* pneumonia.

Methods. We immunized C57Bl/6 mice with 1 μg of OMPs with 1 μg dmLT. Control mice received OMPs or saline. Antibody and T-cell responses were assessed by ELISA and flow cytometry, respectively. We then evaluated the protective efficacy of the vaccine in a lethal acute pneumonia model. Immunized mice were challenged with 7×10^6 CFU of *P. aeruginosa* via oropharyngeal aspiration into the lungs. Finally, we examined whether memory CD4+ T cells was essential for protection by depleting immunized mice of vaccine-induced memory CD4+ T cells.

Results. Mice immunized with OMPs and dmLT had a significantly greater concentration of anti-pseudomonal IgG in the serum and lungs and a significantly greater proportion of CD4+ T cells in the lung producing IFN-γ or IL-17A than mice immunized with OMPs alone or saline. ID immunization provided significant protection against *P. aeruginosa* pneumonia, with 78% of immunized mice surviving compared with 100% mortality in saline immunized controls. Memory CD4+ T-cell–depleted mice displayed reduced survival (40%) compared with nondepleted mice (80%), confirming that memory CD4 T+ cells contribute to OMP-dmLT vaccine-mediated protection.

Conclusion. These results demonstrate that ID vaccination against *P. aeruginosa* protects against acute lethal *P. aeruginosa* pneumonia by stimulating antigen-specific IgG and Th1- and Th17-type CD4+ memory T cells in the pulmonary milieu. ID immunization with dmLT may reduce the global morbidity and mortality caused by multidrug-resistant respiratory pathogens.

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854. The Impact of the CMS SEP-1 Core Measure on Antimicrobial Utilization: a Multicenter Interrupted Time-Series (ITS) Analysis

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Background. Hospitals began reporting the SEP-1 Core Measure to CMS in October 1, 2015, to promote the use of best practices for patients with sepsis. The impact of SEP-1 on overall antimicrobial utilization (AU), a potential unintended consequence, is unclear.

Methods. We performed an ITS analysis to evaluate changes in antimicrobial utilization after SEP-1 implementation. AU was measured as days of therapy (DOT)/1,000 days present (dp) for all adult inpatients who spent more than 24 hours in 18 hospitals in the southeastern United States. The 12-month period from October 1, 2014 to September 30, 2015 was defined as the "pre" period. After a 1-month wash-in, the 12-month period from November 1, 2015 to October 31, 2016 was defined as the "post" period. AU was aggregated by hospital by month for inpatient units. Total AU and NHSN AU categories were analyzed separately. ITS was modeled using a segmented regression analysis through a GEE model with negative binomial distribution and log link.

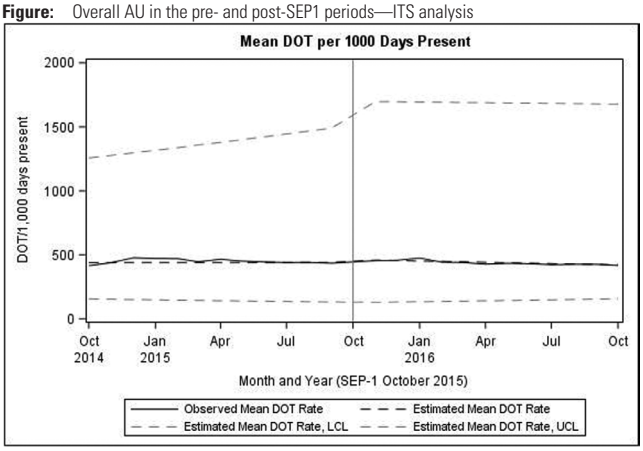
Results. A total of 362,460 patients had 688,583 DOT pre-SEP1 (mean 1.9 DOT/admission), and 291,884 patients had 530,382 DOT post-SEP1 (mean 1.8 DOT/admission). The diagnosis of sepsis (3.1%) and median length of stay (3, IQR 2–4) were unchanged after SEP-1. Utilization of combined vancomycin and piperacillin–tazobactam (P-T) increased 17% at SEP-1 implementation but this increase was not statistically significant (Table). Overall AU, anti-MRSA agents, and anti-pseudomonal agents were unchanged after SEP-1 (figure, table).

Conclusion. Implementation of the CMS SEP-1 measure did not lead to higher rates of AU in our cohort of hospitals, although this study did not assess adherence to SEP-1. Further research is needed to improve the use of antimicrobial therapy in hospitalized patients with suspected sepsis.

Table: Rate ratios of AU (DOT/1,000 dp) in the pre- and post-SEP-1 periods

Measure	Pre-SEP-1 initial rate trend (95% CI; *P*-value)	Change in rate at implementation (95% CI; *P*-value)	Post-SEP-1 change in rate trend (95% CI; *P*-value)
Overall	1.00 (0.99–1.02); 0.98	1.05 (0.98–1.12); 0.17	0.99 (0.97–1.02); 0.53
Anti-MRSA	0.99 (0.97–1.01); 0.34	1.09 (0.93–1.28); 0.30	1.00 (0.97–1.04); 0.80
Anti-pseudomonal	1.00 (0.98–1.02); 0.78	1.05 (0.95–1.15); 0.33	0.99 (0.96–1.02); 0.48
Vancomycin + P-T	0.98 (0.95–1.01); 0.29	1.17 (0.96–1.41); 0.12	1.03 (0.98–1.08); 0.31

Figure: Overall AU in the pre- and post-SEP1 periods—ITS analysis



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