multidimensional scaling (NDMS) ordination shows high interpatient dissimilarity (Bray–Curtis) for most samples, the post-ABX intrapatient dissimilarity varies by ABX. The AZ group exhibited chronic alterations in taxa dissimilarity and the CF group had increases in dissimilarity directly post-ABX. The CF+AZ group displayed both acute and persistent perturbations (Figure 1). Although there was no significant change in ARG richness post-ABX, there was a significant increase in overall ARG abundance across all samples ($P < 0.003$). Within each ABX, there were unique changes in ARG abundance, and groups with CF had increases in ARG abundance (Figure 2).

Conclusion. ABX used to treat CAP can cause acute microbiome disruptions, as evidenced by decreased microbiome species diversity and richness, and an increase in ARG abundance post-ABX. The duration of this impact is variable. To prevent microbiome disruptions, measures to prevent inappropriate ABX use via ABX stewardship are necessary.

Figure 1. NDMS ordination plots of species composition for patient samples show drug specific increases in acute and chronic dissimilarity.
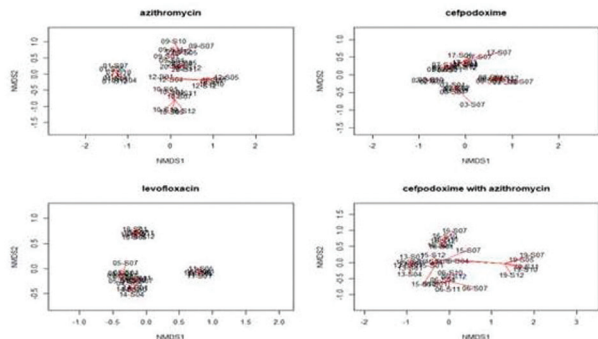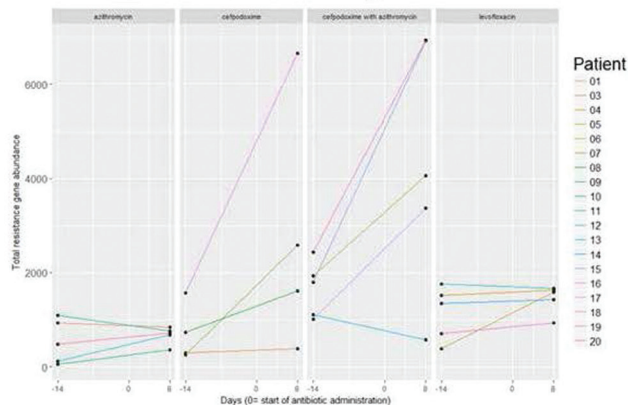

Figure 1. Plot of first two NDMS axes of metagenomic sample species abundance dissimilarity measured by Bray-Curtis.

Figure 2. ARG abundance (RPKM) pre (0) and post (1.00) antibiotic for each patient

Resistance Gene Abundance Changes After Antibiotics

Gene counts for resistance genes in Reads Per Kilobase of transcript, per Million mapped reads (RPKM) for each patient (ID).

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1774. Ridinilazole (RDZ) for *Clostridium difficile* infection (CDI): Correlation of *In Vitro* Spectrum of Activity with Human Gut Microbiome Profiles from a Phase 2 Clinical Trial

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Background. Recurrence of CDI (rCDI) is associated with perturbation of the gut microbiome during treatment with vancomycin (VAN) or metronidazole (MTZ). RDZ is a novel, targeted spectrum antibacterial under investigation to treat CDI and reduce rCDI. Here correlation of *in vitro* spectrum of activity with preservation of the human gut microbiome and clinical outcomes is presented.

Methods. Susceptibility testing was to CLSI standards with VAN, MTZ, and fidaxomicin (FDX) comparators. The Phase 2 clinical trial was a double-blind, randomized study of 100 patients assigned 1:1 to 10 days RDZ 200 mg BID or VAN 125 mg QID treatment. Primary endpoint was sustained clinical response (SCR), defined as cure at end of therapy (EOT), and no rCDI for the next 30 days. Relative effects of RDZ and VAN on the gut microbiome were examined by sequencing 16S rDNA amplicons from stool collected at baseline, days 5, 10, 25, and end of study. Bioinformatic analyses were performed in QIIME.

Results. RDZ *C. difficile* ($N = 50$) MIC range was 0.125–0.25 μg/mL. *Clostridium* spp. showed varied RDZ susceptibility; *C. innocuum* MIC_{90} 1 μg/mL, *C. ramosum* and *C. perfringens* MIC_{90} >512 μg/mL. VAN showed potent to moderate growth inhibition of all *Clostridium* spp. (MIC range 1–16 μg/mL). Limited RDZ activity was observed for Gram-positive anaerobes, including *Bifidobacteria*, *Eggerthella*, *Finegoldia*, and *Peptostreptococcus* (MIC_{90} >512, >512, 64, and 64 μg/mL) compared with VAN (MIC_{90} 1, 4, 0.5, and 0.5 μg/mL). *Bacteroides fragilis* MIC_{90} for RDZ and VAN were >512 and 64 μg/mL, respectively. These *in vitro* data correlate closely with human microbiome profiles. RDZ reduced *C. difficile* to below detection with other reductions in abundancy observed in only 2 families from the *Clostridia*. VAN at EOT resulted in significant losses, often below detection, in 4 Firmicutes families, Actinobacteria, and Bacteroidetes and a 25-fold increase in Proteobacteria abundance. The preservation of the microbiome by RDZ likely accounted for reduced rCDI compared with VAN with RDZ shown to be superior on SCR to VAN with rates of 66.7% and 42.4%, respectively (pre-specified 90% CI 3.1, 39.1).

Conclusion. These data demonstrate strong translation of *in vitro* spectrum to human gut microbiome preservation during therapy and support further clinical development of RDZ.

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1775. Microbiome-Based Classifiers Accurately Differentiate Infectious Diarrhea From Functional Gastrointestinal Disorders and Provide Population-Scale Confidence Measures of Fecal Microbiota Restoration in Recurrent *C. Difficile* Infection

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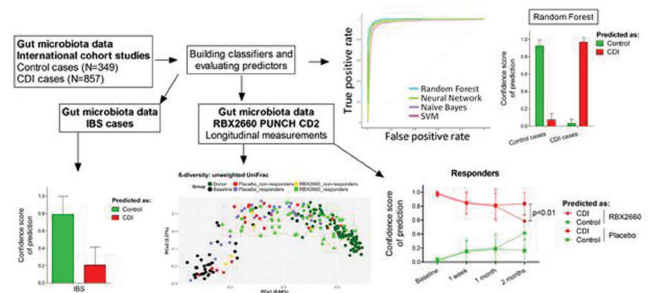*Saturday, October 6, 2018: 10:30 AM*

Background. Fecal microbiota therapy is being actively pursued as treatment for recurrent *C. difficile* infection (rCDI), as well as for other GI disease indications associated with dysbiosis, for example, irritable bowel syndrome (IBS). RBX2660 is a microbiota-based drug designed to restore a healthier microbiome and has demonstrated clinical efficacy for preventing rCDI. Despite this and other treatment successes, our understanding of functional microbiota reconstitution at the population scale is still evolving, as is the ability to distinguish IBS from CDI recurrence. Herein we describe development of a Random Forest classifier for CDI diagnosis, and we evaluate microbiome restoration in participants of the Phase 2 trial of RBX2660.

Methods. Fecal 16S rDNA sequences from 2,129 subjects enrolled in diverse multi-center cohorts were analyzed (1,235 adults and 447 children with CDI, AAD, IBS, or controls). Technical variations due to different DNA extraction, primer region coverage, and sequencing platforms were addressed using closed-reference OTU picking with UCLUST. The RDP classifier and SILVA database assigned taxonomy for each OTU sequence. Stratified random sampling with 50 repeated tests of microbiota training sets was performed for supervised learning. Microbiota signatures of patients in the RBX2660 PUNCH CD2 trial were then assessed using classifiers built to predict CDI treatment outcomes and IBS misdiagnosis.

Results. Random Forest built the best classifiers accurately predicting 97.7% of CDI cases, and confidently distinguished CDI from IBS patients based on their microbiome signatures (figure). RBX2660 treatment significantly restored microbiota community composition in rCDI cases compared with placebo controls.

Conclusion. Random Forest classifiers built on a population-scale study of microbiota composition in patients with GI disease provide a highly accurate predictor of CDI cases versus potential IBS misdiagnosis in adults and children. RBX2660 significantly reduced disease classification scores in rCDI patients with a healthy-like microbiota reconstitution markedly accelerating after 30 days of treatment.

2553. Individual Patient-Level Data Meta-Analysis of Live Attenuated and Inactivated Influenza Vaccine Effectiveness Among US Children, 2013–2014 Through 2015–2016

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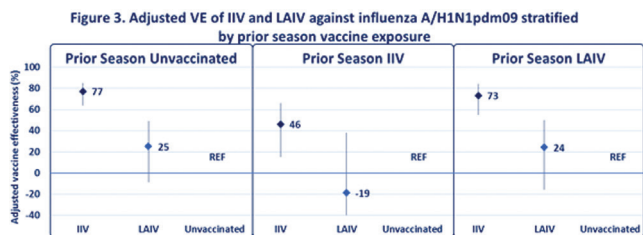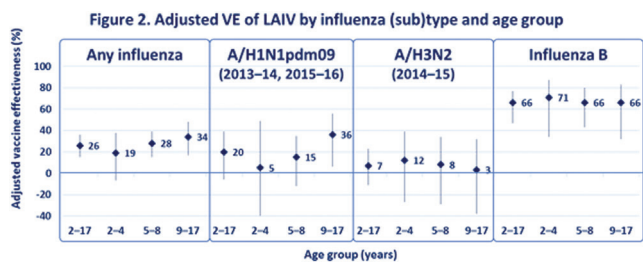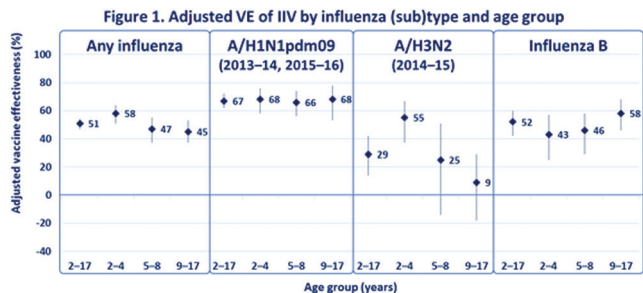
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Background. Quadrivalent live attenuated influenza vaccine (LAIV4) was not recommended for use in the United States for the 2016–2017 and 2017–2018 influenza seasons based on US observational studies of vaccine effectiveness (VE) from 2013–2014 to 2015–2016. We pooled individual patient data on children aged 2–17 years enrolled in 5 US studies during these 3 influenza seasons to further investigate VE by vaccine type.

Methods. Analyses included 17,173 children enrolled in the US Department of Defense Global Laboratory-based Influenza Surveillance Program, US Influenza Vaccine Effectiveness Network, Influenza Incidence Surveillance Project, Influenza Clinical Investigation for Children, and a Louisiana State University study. Participants' specimens were tested for influenza by reverse transcription-polymerase chain reaction (RT-PCR), culture, or a combination of rapid antigen testing and RT-PCR. VE was calculated by comparing odds of vaccination with either inactivated influenza vaccine (IIV) or LAIV4 among influenza-positive cases to test-negative controls and calculated as $100 \times (1 - \text{odds ratio})$ in logistic regression models with age, calendar time, influenza season, and study site (random effect). Patients were stratified by prior season vaccination status in a subanalysis.

Results. Overall, 38% of patients ($N = 6,558$) were vaccinated in the current season, of whom 30% ($N = 1,979$) received LAIV4. Pooled VE of IIV against any influenza virus was 51% (95% CI: 47, 54) versus 26% (95% CI: 15, 36) for LAIV4. Point estimates for pooled VE against any influenza by age group ranged from 45% to 58% for IIV and 19% to 34% for LAIV4 during the 3 seasons (Figures 1 and 2). Pooled VE against influenza A(H1N1)pdm09 was 67% (95% CI: 62, 72) for IIV versus 20% (95% CI: −6, 39) for LAIV4. Pooled VE against influenza A(H3N2) was 29% (95% CI: 14, 42) for IIV versus 7% (95% CI: −11, 23) for LAIV4, and VE against influenza B was 52% (95% CI: 42, 60) for IIV and 66% (95% CI: 47, 77) for LAIV4. VE against influenza A(H1N1)pdm09 was lower for LAIV4 versus IIV across all strata of prior season vaccination (Figure 3).

Conclusion. Consistent with individual studies, our pooled analyses found that LAIV4 effectiveness was reduced for all age groups against influenza A(H1N1)pdm09 compared with IIV. This result did not vary based on prior vaccination status.

Figure 1. Adjusted VE of IIV by influenza (sub)type and age group

Figure 2. Adjusted VE of LAIV by influenza (sub)type and age group

Figure 3. Adjusted VE of IIV and LAIV against influenza A/H1N1pdm09 stratified by prior season vaccine exposure

2554. Safety and Immunogenicity of NasoVAX, a Novel Intranasal Influenza Vaccine

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Background. NasoVAX is a replication-deficient adenovirus-based vaccine designed to express influenza hemagglutinin in nasal epithelial cells when given as a nasal spray. In preclinical studies, NasoVAX was associated with divergent strain protection. Prior preclinical and clinical studies with the vector demonstrated lack of impact from baseline adenovirus immunity.

Methods. Sixty healthy adults were randomized to an A/California 2009-based monovalent NasoVAX formulation at doses of 10^9, 10^{10}, or 10^{11} viral particles or saline placebo, all given as a 0.25 mL nasal spray in each nostril. Subjects were followed for safety, including solicited local and systemic side effects. Immune measures included hemagglutination inhibition (HAI) and neutralizing antibody (MN) at days 1, 15, 29, 90, and 180, and γ-interferon ELISpot at day 1 and 8. A parallel cohort of 20 similar subjects were dosed with Fluzone® injectable influenza vaccine containing an A/California 2009 component and had assessments at the same timepoints. The laboratory was blind to treatment assignment for these comparator samples.

Results. NasoVAX was well tolerated with no serious adverse events and no fever. Solicited symptoms such as nasal congestion, sore throat, and headache did not increase with dose and were not statistically different than placebo. Available immune response data are shown below.

Group	NasoVAX (10^9 vp)	NasoVAX (10^{10} vp)	NasoVAX (10^{11} vp)	Fluzone®	Placebo
Seroprotection Rate at Day 29 (≥1:40 HAI)	80%	100%	100%	95%	53%
(95% CIs)	(51.9%, 95.7%)	(78.2%, 100.0%)	(78.2%, 100.0%)	(75.1%, 99.9%)	(26.6%, 78.7%)
MN Responder Rate at Day 29 (2-fold rise)	40%	47%	73%	70%	0%
(95% CIs)	(16.3%, 67.7%)	(21.3%, 73.4%)	(44.9%, 92.2%)	(45.7%, 88.1%)	(0.0%, 21.8%)
Median ELISpot Day 8 SFC/10^6 PBMC	58.0	12.0	307.5	55.5	0.0
(95% CIs)	(5.31, 110.69)	(0.0, 60.36)	(2.15, 612.78)	(4.12, 106.87)	(0.0, 38.49)

Conclusion. NasoVAX intranasal influenza vaccine was well tolerated and elicited comparable antibody responses and nearly 6-fold higher cellular immune responses than a licensed injectable vaccine.

2555. Predicting Risk of Breakthrough Invasive Pneumococcal Disease in Children After 13-Valent Pneumococcal Conjugate Vaccination

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Background. Thirteen-valent-pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the childhood immunization schedule in Massachusetts beginning in April 2010. We evaluated the predictors of vaccine-type (VT) invasive pneumococcal infection (IPD) occurrence despite vaccination.

Methods. Cases of IPD in children <18 years of age were detected through an enhanced surveillance system in MA since 2001. All cases and *Streptococcus pneumoniae* (SP) isolates are submitted to Department of Public Health (MDPH) and parents/physicians are interviewed for confirmation of demographic and clinical data. All available isolates are serotyped by Quellung reaction. Children who received any dose of PCV7 were excluded from this study. We used 4-layer, feed-forward, neural network with back-propagation learning algorithm, random forest algorithm with 150 classification trees, and extreme gradient boosting (XGBoost) algorithm based on boosted trees with over than 200 iterations to make prediction about risk of nonvaccine serotype (NVST) causing IPD.

Results. Overall, 144 IPD cases have been identified between April 1, 2010, and March 31, 2017, and 27 (19%) were VT IPD. Compared with children with complete PCV13 vaccination, IPD among those with incomplete immunization was more likely