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Session: 99. Vaccines I - Influenza and RSV
Thursday, October 3, 2019: 3:30 PM

Background. Annual national estimates of influenza vaccine effectiveness (VE) typically measure protection against outpatient medically attended influenza illness. We assessed influenza VE in preventing laboratory-confirmed influenza hospitalization in children across two influenza A(H3N2)-predominant seasons.

Methods. Children < 18 years hospitalized with acute respiratory illness were enrolled at 7 pediatric hospitals in the New Vaccine Surveillance Network. We included subjects ≥6 months with ≤10 days of symptoms enrolled during the 2016–2017 and 2017–2018 seasons (date of first through last influenza-positive case for each site). Combined mid-turbinate and throat swabs were tested using molecular assays. We estimated age-stratified VE from a test-negative design using logistic regression to compare the odds of vaccination among cases positive for influenza with controls testing negative, adjusting for age, enrollment month, site, underlying comorbidities, and race/ethnicity. Full/partial vaccination was defined using ACIP criteria. We verified vaccine receipt from state immunization registries and/or provider records.

Results. Among 3441 children with complete preliminary data, in 2016–2017, 156/1,710 (9%) tested positive for influenza: 91 (58%) with influenza A(H3N2), 5 (3%) with A(H1N1), and 60 (38%) with B viruses. In 2017–2018, 193/1,731 (11%) tested positive: 87 (45%) with influenza A(H3N2), 47 (24%) with A(H1N1), and 58 (30%) with B. VE for all vaccinated children (full and partial) against any influenza was 48% (95% confidence interval, 26%–63%) in 2016–2017 and 45% (24%–60%) in 2017–2018. Combining seasons, VE for fully and partially vaccinated children against any influenza type was 46% (32%–58%); by virus, VE was 30% (4%–49%) for influenza A(H3N2), 71% (46%–85%) for A(H1N1), and 57% (36%–70%) for B viruses. There was no statistically significant difference in VE by age or full/partial vaccination status for any virus (table).

Conclusion. Vaccination in the 2016–2017 and 2017–2018 seasons nearly halved the risk of children being hospitalized with influenza. These findings support the use of vaccination to prevent severe illness in children. Our study highlights the need for a better understanding of the lower VE against influenza A(H3N2) viruses.

Table. Preliminary vaccine effectiveness estimates, by vaccination status and by age group, for 2016-17 and 2017-18 combined seasons.

	A(H3N2)	A(H1N1)	B	All Viruses
By vaccination status				
Any (fully and partial)	30% (4%-49%)	71% (46%-85%)	57% (36%-70%)	46% (32%-58%)
Fully vaccinated	25% (-5%-46%)	73% (45%-87%)	56% (33%-71%)	45% (28%-57%)
Partially vaccinated	41% (-4%-67%)	62% (2%-85%)	53% (7%-76%)	48% (21%-66%)
Any vaccination (full and partial), by age group				
6 mos – 8 yrs	38% (11%-57%)	76% (52%-88%)	63% (42%-76%)	54% (40%-65%)
9 – 17 yrs	23% (-38%-58%)	54% (-35%-84%)	50% (-4%-76%)	37% (-1%-61%)

Disclosures. **All Authors:** No reported Disclosures.

900. Effect of Influenza Vaccine Priming on Current Season Vaccine Effectiveness among Children and Adolescents, US Flu VE Network 2014–2015 Through 2017–2018

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Session: 99. Vaccines I - Influenza and RSV
Thursday, October 3, 2019: 3:45 PM

Background. Studies have demonstrated that optimal protection against childhood influenza requires two "priming" doses of influenza vaccine in the first season of vaccination. Two doses of influenza vaccine are recommended for US children aged 6 months-8 years who received ≤1 dose in prior seasons. We examined risk of influenza among children fully or partially vaccinated during study seasons and vaccine effectiveness (VE) by the number of priming doses.

Methods. Analyses included children aged 6 months-17 years enrolled during outpatient visits for acute illness for ≤7 days with cough in the US Influenza Vaccine Effectiveness Network during 2014–2015 through 2017–2018. Participants' respiratory specimens were tested for influenza by rRT-PCR. Vaccination histories back to birth year were obtained from electronic immunization records. VE was calculated by comparing vaccination odds among influenza-positive cases to test-negative controls, as 100 × (1 – odds ratio) adjusted for season, site, age, high-risk status, and calendar time.

Results. Of 7,583 children, 6,362 (84%) had received ≥1 dose in their lifetime. Among vaccinated children, 90% were primed prior to the enrollment season, and 80% were primed prior to age 2 years. Most (55%) received two priming doses in their first season. Among children recommended to receive two priming doses in the enrollment season, receipt of two doses vs. one was associated with a lower risk of influenza illness (aOR: 0.60; 95% CL: 0.36, 1.00). VE of ≥1 dose in the enrollment season against any influenza among unprimed children was 53% (95% CL: 36, 66). VE of ≥1 dose in the enrollment season was similar among children primed with one dose in their first season (46%; 95% CL: 34, 55) and among those primed with two doses (46%; 95% CL: 35, 55). Overall results were similar when stratified by age and for A/H3N2 viruses, which predominated during study years.

Conclusion. Among the US children recommended to receive two priming doses of vaccine in the enrollment season, receipt of two doses provided optimal protection. VE in seasons after the priming did not differ by the number of priming doses. Results were driven by predominance of A/H3N2 viruses and may not be similar for A/H1N1pdm09 or B viruses. Current US influenza vaccine recommendations for children are effective and appropriate.

Disclosures. **All Authors:** No reported Disclosures.

901. MEDI8897 Prevents Serious RSV Disease in Healthy Preterm Infants

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Session: 99. Vaccines I - Influenza and RSV
Thursday, October 3, 2019: 4:00 PM

Background. RSV is the principal cause of lower respiratory tract infection (LRTI) among infants, and a significant unmet need exists for RSV prevention in healthy infants. We have developed a highly potent, extended half-life monoclonal antibody (mAb), to protect infants for an entire RSV season using a single IM dose. Here we report the efficacy, safety, pharmacokinetics, and anti-drug antibody (ADA) responses for MEDI8897 in palivizumab-ineligible preterm infants born between 29 and 35 weeks gestation.

Methods. A total of 1,453 Infants were randomized 2:1 to receive a single 50 mg IM injection of MEDI8897 (n = 969) or placebo (n = 484) and followed for 360 days. Enrollment occurred just prior to the 2016 and 2017 RSV seasons in 23 northern and southern hemisphere countries. Blood was collected periodically. Infants with a medically attended (MA) LRTI (outpatient or inpatient) had nasal swabs obtained for central RSV testing by RT-PCR. Predefined clinical criteria were used for the case definition.

Results. A total of 1,417 (97.5%) subjects completed the 150-day efficacy follow-up period and 1,367 (94.1%) completed the study. In the MEDI8897 group, a 70.1% (95% CI: 52.3%, 81.2%; $P < 0.0001$) reduction in the incidence of medically attended RSV LRTI and a 78.4% (95% CI: 51.9%, 90.3%; $P = 0.0002$) reduction in the incidence of RSV LRTI hospitalization was achieved. These efficacy results were consistent when analyzed by hemisphere, RSV subtype, and subject demographics. Similar proportions of adverse events (86.8% placebo; 86.2% MEDI8897) and serious adverse events (16.9% placebo; 11.2% MEDI8897) were reported in study subjects. There were no significant hypersensitivity reactions with similar proportions reported for both groups (0.6% placebo; 0.5% MEDI8897). The incidence of ADA detected any time post baseline was low (3.8% placebo; 5.6% MEDI8897) with no impact on PK or safety. The occurrence of non-RSV LRTIs was similar for both groups indicating no replacement by other pathogens.

Conclusion. In this large randomized study of RSV prophylaxis in healthy preterm infants, MEDI8897 immunoprophylaxis provided a significant reduction in RSV MA-LRTI and hospitalization. These results have promising implications for the future of RSV prophylaxis for all infants.

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Disclosures. **All Authors:** No reported Disclosures.

902. A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of a Single Immunization of Ad26.RSV.preF against RSV Infection in a Viral Challenge Model in Healthy Adults

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Session: 99. Vaccines I - Influenza and RSV
Thursday, October 3, 2019: 4:15 PM

Background. Despite the high disease burden of RSV in older adults and children, there is currently no approved vaccine. Ad26.RSV.preF, an experimental RSV vaccine, has demonstrated immunogenicity and tolerability in first-in-human clinical studies. The aim of this study was to assess the potential of the Ad26.RSV.preF vaccine to protect against RSV infection and disease in an established RSV human challenge model, used for the first time to evaluate a vaccine.

Methods. We conducted a randomized, double-blind, placebo-controlled, human challenge study (NCT03334695). Healthy adults received 1×10^{11} vp Ad26.RSV.preF vaccine (active) or placebo (pbo) intramuscularly. After 28 days, volunteers were challenged intranasally with a low-passage clinical strain of RSV-A (0.8 mL of Memphis 37b) and then quarantined for 12 days. Nasal washes were collected twice daily throughout quarantine, starting 2 days post-challenge (viral load [VL] by qRT-PCR and quantitative cultures). Disease severity was recorded thrice daily using symptom diary cards.

Results. Fifty-three volunteers (active, $n = 27$; pbo, $n = 26$) were challenged with RSV-A. Quantitative viral assessments were consistently lower in active than pbo. The primary endpoint of the study was met: the area under the curve (AUC) for RSV VL over time (via qRT-PCR) was significantly lower in active pbo ($P = 0.012$). Median peak VL was lower for active (0 $\log_{10}$ copies/mL) than pbo (5.4 $\log_{10}$ copies/mL). Median AUC for RSV VL over time (quantitative culture) was lower for active than pbo (0 vs. 109, $P = 0.002$). Disease severity was lower for active than pbo, with a median AUC total symptom score of 35 (active) vs. 167 (pbo) ($P = 0.002$). Overall, RSV infection (defined by qRT-PCR alone or combined with symptoms) and disease severity over time were lower in active vs. pbo.

Conclusion. RSV infections, VL, and RSV disease severity were consistently lower in healthy adults receiving Ad26.RSV.preF vs. placebo, demonstrating promising protection from RSV infection and disease. This was the first time that antiviral prevention was observed against RSV after active immunization. Ad26.RSV.preF warrants further evaluation in field trials for efficacy against natural RSV infections in populations considered at risk of severe RSV disease.

Disclosures. **All Authors:** No reported Disclosures.

903. Resensitization to β-Lactams in Enterococci Depends on Penicillin-Binding Protein (PBP) Mislocalization and Is Mediated by a Single Protein That Modulates Cell Membrane (CM) Adaptation to Daptomycin (DAP)

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Session: 100. IDSA Featured Oral Abstract
Thursday, October 3, 2019: 5:05 PM

Background. DAP disrupts bacterial CM by binding to septal anionic phospholipids (APLs). LiaX, an effector of the LiaFSR stress system, modulates DAP-R by diverting APLs away from the septum. Enterococci are intrinsically resistant to β-lactams due to the presence of PBPs (e.g., PBP5) with low affinity to these drugs. However, emergence of DAP-R leads to increased susceptibility to β-lactams, a phenomenon designated as the see-saw effect. Here, we dissect the molecular mechanism of this phenomenon.

Methods. We studied a clinical strain pair of DAP-S (S613) and DAP-R (R712) *E. faecalis* strains recovered from a patient before and after DAP therapy. We generated deletions of *liaX* and PBPs (*ponA* and *pbp5*) in DAP-susceptible (DAP-S) *E. faecalis* OG1RF and JH2-2. APLs and membrane structures were visualized with NAO and/or FM4-64. PBPs and LiaX localization were evaluated with bocillin-FL or immunofluorescence. *PBP* transcripts and PBP5 protein levels were measured by qRT-PCR or immunoblotting, respectively. β-Lactam binding affinity of PBPs was assessed by SDS-PAGE of bocillin-FL stained membranes and a LiaX–PBP5 interaction was evaluated by the bacterial two-hybrid (BACTH) system. MICs were determined via *E*-test.

Results. Deletion of *liaX* led to DAP-R and redistribution of APL microdomains (nonseptal foci with CM aberrations; Figure 1A) in all strains, with a marked decrease in ceftriaxone (CRO) MICs. Only PBP5 was essential for β-lactam resistance but not for DAP-R. DAP-R was associated with mislocalization of PBPs to the sites of CM aberrations (Figure 2). Notably, LiaX and PBP5 were localized to the septum in DAP-S strains but redistributed away from septal areas upon development of DAP-R (Figure 3). An interaction of LiaX and PBP5 was confirmed by the BACTH system. Mislocalized PBPs, most notably PonA and PBP5, had increased affinity for β-lactams in all DAP-R strains. The increased affinity of PBPs to β-lactams was not associated with increased transcripts or PBP5 levels.

Conclusion. LiaX regulates CM adaptation and cell wall synthesis via membrane remodeling and direct interactions with key PBPs. Changes in LiaX that cause DAP-R results in mislocalization of PBPs to nonseptal areas and likely increases access of β-lactam to the active site, explaining the see-saw effect.

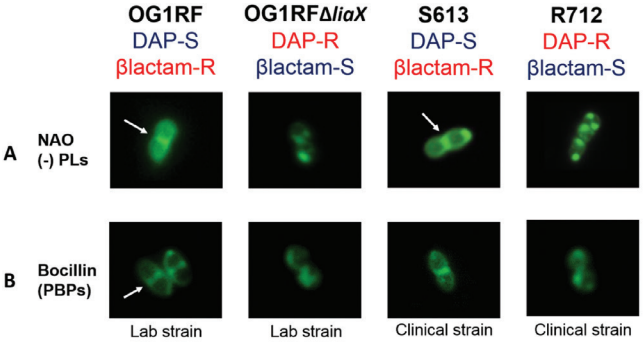

Figure 1: Representative images showing cell membrane remodeling and penicillin-binding protein (PBP) mislocalization occurs in daptomycin-resistant (DAP-R) lab and clinical strains.
A. 10-N-nonyl-acridine orange staining of anionic membrane phospholipids (PLs) localize at division septum (white) in daptomycin-sensitive strains and are redistributed in DAP-R strains. **B.** Bocillin-FL staining of cell wall synthesis proteins, PBPs, mislocalize away from the septum in DAP-R strains.

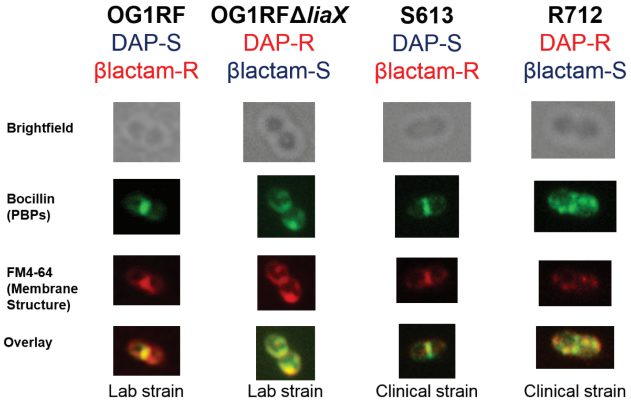

Figure 2: Representative images showing bocillin-FL stained penicillin-binding proteins (PBPs) localize to the septum in daptomycin-sensitive strains but mislocalize in daptomycin-resistant strains to nonseptal aberrant phospholipid microdomains and membrane deformities (stained with FM4-64).

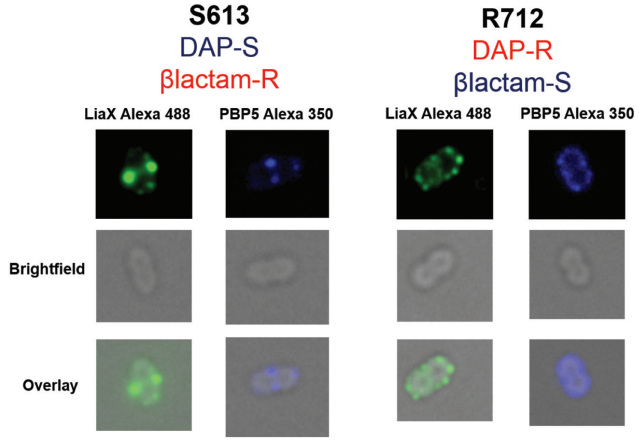

Figure 2: Representative images of clinical strains showing LiaX (Alexa 488 secondary) and PBP5 (Alexa 350 secondary) both localize to the division septum in a daptomycin-susceptible strain and mislocalize in a daptomycin-resistant strain.

Disclosures. **All Authors:** No reported Disclosures.