<6 months of age. We used these baseline estimates, an efficacy of 79% for both products, uptake of 60% for the maternal vaccine (based on uptake of maternal tetanus/diphtheria/pertussis vaccine) or 70% for the monoclonal antibody (based on uptake of hepatitis B vaccine birth dose) and assumed a duration of protection of infants between 3 and 5 months to assess immunization impact. With the immunization strategies analyzed, we estimated between 14,591 and 30,336 hospitalizations, 20,621 and 79,020 ED visits, and 58,670 and 228,840 outpatient visits associated with RSVi could be prevented each year.

Conclusion. Immunization products under development have the potential to substantially reduce MA-RSVi. This model will be used to assess the benefits of different immunization strategies developed to protect infants against RSVi. The model is flexible and can be updated as more data become available.

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2558. Predicting β-Lactam Resistance Using Whole Genome Sequencing (WGS) in *Klebsiella pneumoniae*: The Challenge of β-Lactam Inhibitors

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Background. Antimicrobial susceptibility testing (AST) is the major driver in designing effective therapy. As multiple resistance determinants can demonstrate the same phenotype (e.g., inhibitor resistant [IR], extended spectrum [ES], and carbapenem hydrolyzing [CH] β-lactamases), critical information provided from AST for therapy, stewardship, and infection control is currently lacking. WGS provides more comprehensive genetic data, explaining phenotype, and provides insight into clonality. Efforts are in development that apply novel statistical methods (e.g., PRIMERS I-IV) and machine learning (*Sci Reports*, 2108, 8, 421) to interpret results accurately and anticipate AST. Using a collection of clinical strains that spanned a 3.5-year period, we tested how well the detection of problematic IR, ES, and CH *bla* resistance genes predicted phenotype.

Methods. Fourty-one isolates were chosen for AST from a collection of 1,777 WGS *K. pneumoniae*. Isolates chosen possessed the following β-lactamases: (9 isolates) NDM; (3) NDM and OXA-48; (5) KPC-8 or KPC-14; (24) with a very complex β-lactamase background (all possessed an inhibitor resistant TEM (IRT), SHV ESBL, +/− CTX-M, and/or +/− KPC). AST was performed using CLSI methods for piperacillin/tazobactam (PIP/TAZO), ceftazidime (CAZ), aztreonam (ATM), ceftazidime/avibactam (CAZ/AVI), CAZ/AVI/ATM, and ceftolozane/tazobactam (TOL/TAZO) by disk diffusion assay.

Results. Presented below.

Prediction: NDM + isolates will be CAZ/AVI and TOL/TAZO resistant. Addition of ATM will restore susceptibility to CAZ/AVI.	
beta-lactamase detected	Result
bla_{NDM-1}	9/9 isolates R to CAZ/AVI, PIP/TAZO (8/9), and TOL/TAZO; 9/9 S to CAZ/AVI + ATM
bla_{NDM-1} & bla_{OXA-48}	3/3 isolates R to CAZ/AVI, PIP/TAZO, and TOL/TAZO; 3/3 S to CAZ/AVI + ATM
Prediction: bla_{KPC-R} confers resistance to CAZ/AVI.	
bla_{KPC-8} (V240G) or bla_{KPC-14}	5/5 isolates S to CAZ/AVI (but zone size diminished) 5/5 R to TOL/TAZO and PIP/TAZO*
Prediction: Complex beta-lactamase background (IR, ESBL +/- KPC) test susceptible to CAZ/AVI.	
CTX-M-15, TEM-76 (S130G), & SHV-27 (G156D)	3/3 isolates S to CAZ/AVI and TOL/TAZO
CTX-M-15, TEM-76 (S130G), & SHV-12 (L35Q/G238S/E240K)	1/1 isolate S to CAZ/AVI and R to PIP/TAZO and TOL/TAZO
CTX-M-15, TEM-30 (R244S), & SHV-5 (G238S/E240K) or SHV-27	7/7 isolates S to CAZ/AVI, PIP/TAZO (6/7), and TOL/TAZO
CTX-M-15, TEM-33 (M69L), & SHV-27	1/1 isolate S to CAZ/AVI, PIP/TAZO, and TOL/TAZO
TEM-79 (R244G), SHV-5, SHV-12, or SHV-27, & KPC-2	11/11 isolates S to CAZ/AVI and R to PIP/TAZO and TOL/TAZO*
TEM-30 (R244S), SHV-12, CTX-M-15, & KPC-2	1/1 isolates S to CAZ/AVI and R to PIP/TAZO, TOL/TAZO*
	*R due to KPC

Conclusion. In all cases, bla_{NDM-1} and $bla_{NDM-1/OXA-48}$ containing isolates were resistant to CAZ/AVI; the addition of ATM fully restored susceptibility to CAZ/AVI. Surprisingly, clinical *K. pneumoniae* isolates bearing KPC-8 (V240G) and KPC-14 did not test fully resistant to CAZ/AVI, suggesting a more complex mechanism than the D179Y variant of KPC-3. Lastly, despite the complexity of the β-lactamase background, CAZ/AVI retained potency. Interestingly, TOL/TAZO maintained efficacy in these same complex backgrounds in the absence of NDM, KPC, and SHV-12. As previously shown in PRIMERS I-II, PIP/TAZO resistance was not observed in the majority of isolates as was predicted by the genotype. WGS in *K. pneumoniae* to predict AST results and potentially guide clinical decisions is improved for novel combinations like CAZ/AVI.

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2559. Incidence and Clinical Impact of Discordant Genotypic and Phenotypic Categorization of Methicillin Susceptibility in *Staphylococcus aureus* Bacteremia

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Background. Methicillin-susceptible/methicillin-resistant *Staphylococcus aureus* (MSSA/MRSA) can be directly identified from positive blood culture bottles using molecular methods. This provides faster results than traditional phenotypic testing, but discrepancies between the two are occasionally found. We sought to determine the incidence and clinical impact of such discrepancies.

Methods. Positive blood culture bottles are routinely tested in the hospital clinical laboratory for *mecA* via Xpert MRSA/SA BC (PCR), and antimicrobial susceptibility testing (AST) via MicroScan PC33 is performed on recovered *S. aureus* isolates; discrepancies between PCR and AST are resolved by repeat and supplemental (Kirby-Bauer) testing. A retrospective review of medical and laboratory data from January 2015 to December 2017 was performed on all patients that had discordant PCR and AST results.

Results. Approximately 1,200 PCR assays were performed from January 2015 to December 2017, and there were 5 (0.4%) cases with discordant AST Results. Four cases were classified as MSSA by PCR but MRSA by AST, and 1 case was classified as MRSA by PCR but MSSA by AST. For the former group, antimicrobial therapy was changed in 2 patients to cover MRSA and 1 patient was readmitted, while the remaining 2 patients were already being treated for MRSA; for the latter case, this patient was treated for MRSA during the initial hospitalization, but was readmitted with disseminated MSSA and subsequently deceased. Based on genetic targets identified by PCR and cefoxitin and oxacillin AST, discrepancies were likely due to borderline oxacillin resistance (BORSA) (n = 1), presence of an SCC*mec* variant not detected by PCR (n = 1), or undetermined (n = 3).

Conclusion. Rapid identification of MRSA bacteremia via PCR provides actionable information to direct empiric treatment. While highly accurate, PCR results are infrequently not corroborated by AST. This rare possibility should be considered when modifying therapy based on initial PCR results, and there should be close communication between the clinical team and laboratory for these challenging cases.

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2560. Multispecies Outbreak of KPC-2 Producing *Enterobacteriaceae* in a Chilean Pediatric Hospital

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Background. Carbapenem-resistant *Enterobacteriaceae* (CRE) are a critical global health problem. We detected a surge of CRE cases in a pediatric hospital in Chile, a country with a low endemicity of KPC-producing organisms. Herein, we describe the molecular epidemiology of this outbreak.

Methods. CRE isolates from clinical specimens and surveillance rectal swabs (obtained using chromID CARBA SMART agar, BioMerieux) of pediatric patients were collected from July 2015 to January 2017. Species identity was confirmed by MALDI-TOF. Carbapenemase genes (bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, and $bla_{OXA-48-like}$) were detected by multiplex PCR, followed by amplification and sequencing of the bla_{KPC} allele. Conjugation experiments were conducted with representative species as donors and sodium azide-resistant *E. coli* J53 as recipient. PCR-based plasmid typing (PBRT Diatheva kit) was then performed on donors and recipients. For *K. pneumoniae*, genetic relatedness was investigated by PFGE, multilocus sequence typing and *wzi* typing.

Results. Sixty-one CRE clinical and surveillance isolates were obtained from 49 patients aged 17 days to 16 years. bla_{KPC-2} was present in 57/62 isolates; no other carbapenemases were found. For 11 patients, multiple cultures were obtained; 4/11

had more than one KPC-harboring species. KPC-harboring isolates displayed ertapenem MICs ranging from 1 to >8 mg/L. Preliminary analyses suggest that bla_{KPC-2} is contained within a nonclassical Tn4401 structure (lacking the upstream promoter). Mating experiments indicate that bla_{KPC-2} is carried by a conjugative IncN backbone plasmid. Interestingly, *K. pneumoniae* isolates were nonclonal by PFGE and belonged to multiple STs unrelated to CG258 (ST34, ST36, among others) and different *wzi* types (37, 154, among others).

Species	KPC-2 infection	KPC-2 surveillance	KPC (-)	No. isolates recovered
Klebsiella pneumoniae	12	27	1	40
Escherichia coli	2	2	0	4
Citrobacter freundii	0	3	1	4
Enterobacter cloacae	0	1	2	3
Enterobacter kobei	3	3	0	6
Klebsiella oxytoca	1	2	0	3
Raoultella ornithinolytica	0	0	1	1
Total	18	38	5	61
	56			

Conclusion. We report a multispecies outbreak of KPC-2 producing CRE in children mainly driven by horizontal dissemination of a promiscuous IncN plasmid. The nonclonal, multispecies nature of this outbreak provides insights into the complex dynamics of KPC dissemination in countries like Chile, where the clonal spread of highly successful clones like CG258 is not the predominant dissemination vehicle, and instead HGT-related spread could be playing a more important role.

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2561. Using Whole Genome Sequencing to Assess the Emergence of Antibiotic Resistance During Treatment of *Enterococcus faecium* and *Enterococcus faecalis* Bacteremia at Mount Sinai Hospital

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Background. Multidrug-resistant Enterococci are a major cause of nosocomial infections, yet our understanding of how resistance emerges during antibiotic treatment remains incomplete. We performed whole- and complete-genome sequencing of all paired isolates from 11 *Enterococcus faecium* and 10 *Enterococcus faecalis* cases that acquired resistance during hospitalization at Mount Sinai Hospital. Comparative and phylogenetic genomic analyses identified novel mechanisms of resistance and heteroresistance.

Methods. 2.5 years of electronic health records were analyzed to identify cases of bacteremia that acquired resistance to at least 1 of the 8 antibiotics. Core genome phylogenetic analyses of paired susceptible and resistant isolates was performed to confirm persistent single clone infections. Long read sequencing data, with Illumina error correction, were used to assemble and align complete genomes. Population analysis profile (PAP) assays were performed to assess the prevalence of heteroresistance.

Results. Among the 102 persistent enterococcal bacteremia cases, 57 isolates from 21 cases (20.6%) cases experienced a gain in resistance. Phylogenetic analyses confirmed that 80% of cases had single clone blood infections, with maximum of 138 days separating paired isolates. Known genetic determinants were responsible for emerging linezolid (LIN), vancomycin (VAN), and gentamicin synergy resistance in almost all cases. In 2 instances, emerging daptomycin (DAP) resistance was not accounted for by known resistance determinants. Notably, PAP assays revealed that LIN-, VAN-, and DAP-resistant subclones were present in only a subset of bacteria in clinical isolates. Longitudinal pairwise analyses of complete genomes revealed novel candidate SNPs for DAP resistance, both located in genes involving cell wall metabolism and maintenance, as well as multiplasmid recombination events that led to VAN heteroresistance.

Conclusion. Our study demonstrates the high prevalence of emerging antibiotic resistance during treatment. We find previously unreported single and structural genomic events that contribute rapid adaptation to antibiotic treatment.

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2562. Re-Appraisal of Aminoglycoside (AG) Susceptibility Testing Breakpoints Based on the Application of Pharmacokinetics–Pharmacodynamics (PK-PD) and Contemporary Microbiology Surveillance Data

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Background. Resistance to AGs and numerous other classes continues to emerge. To ensure that susceptibility is accurately characterized and that clinicians have reliable data to select effective agents, appropriate *in vitro* susceptibility testing interpretive criteria (susceptible breakpoints [BKPTs]) are crucial to ensure optimal patient care. Recently, USCAST, the USA voice to EUCAST/EMA, evaluated the BKPTs for the 3 most commonly used AGs, gentamicin, tobramycin, and amikacin [Bhavnani et al., IDWeek 2016; P-1977]. As a result of consultation from interested parties, which included evaluating AG dosing regimens provided in the US-FDA product package inserts and simulated patients with varying creatinine clearance, these BKPTS were reassessed.

Methods. Data sources considered included longitudinal US reference MIC distributions using *in vitro* surveillance data collected over 18 years, QC performance (MIC, disk diffusion), population pharmacokinetics (PK), and *in vivo* PK-PD models. Using population PK models, PK-PD targets for efficacy and Monte Carlo simulation, percent probabilities of PK-PD target attainment by MIC after administration of traditional and extended interval AG dosing regimens were evaluated among simulated patients. Epidemiological cut-off and PK-PD BKPTs were considered when recommending BKPTs for AG–pathogen pairs.

Results. An example of PK-PD target attainment analysis output is provided in Figure 1 and a subset of recommended AG BKPTs for 3 pathogens is shown in Table 1. Updated USCAST BKPTs, which were based on the application of population PK and PK-PD models, simulation techniques, and contemporary MIC distribution statistics, are generally lower than those of EUCAST/EMA, USA-FDA, and CLSI. Adequate PK-PD target attainment was not achieved for some AG-pathogen pairs, even when high-dose AG dosing regimens and PK-PD targets for stasis were evaluated (e.g., gentamicin vs. *P. aeruginosa*; amikacin vs. *S. aureus*).

Conclusion. These revised AG BKPT recommendations, which will be made freely available to EUCAST, USA-FDA, and CLSI, will be finalized after considering comments from additional interested stakeholders. This process will be followed in an effort to bring harmonization to global BKPTs for AGs.

Figure 1. Percent probabilities of PK-PD target attainment by MIC value for tobramycin dosing regimens using total-drug plasma PK-PD targets for Enterobacteriaceae based on pooled data from a murine thigh-infection model among simulated patients with normal renal function

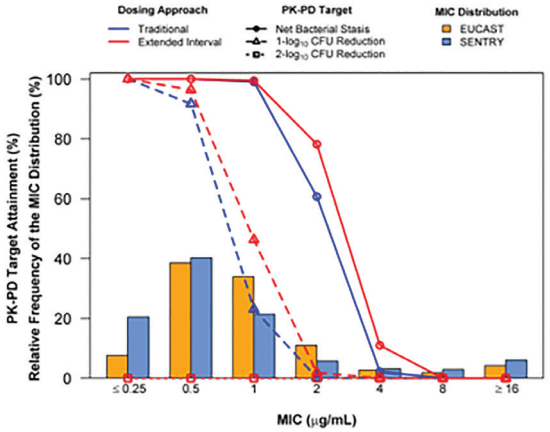

Table 1. Summary of candidate USCAST aminoglycosides *in vitro* test interpretive BKPT criteria and those of other BKPT organizations

Pathogen/aminoglycoside	MIC breakpoints in μg/mL by criteria organization Susceptible/Resistant[a]			
	CLSI	USA-FDA	EUCAST	USCAST[e]
Enterobacteriaceae				
Amikacin	≤16 / ≥64	≤16 / ≥64[b]	≤8 / >16	≤4 / ≥8
Gentamicin	≤4 / ≥16	≤4 / ≥16[c]	≤2 / >4	≤2 / ≥4
Gentamicin - pneumonia	≤4 / ≥16	≤4 / ≥16[c]	≤2 / >4	≤1 / ≥4
Tobramycin	≤4 / ≥16	≤4 / ≥16[d]	≤2 / >4	≤ 2 / ≥4
Tobramycin - pneumonia	≤4 / ≥16	≤4 / ≥16[d]	≤2 / >4	≤ 1 / ≥4
Pseudomonas spp.				
Amikacin	≤16 / ≥64	≤16 / ≥ 64[b]	≤8 / >16	≤2 /≥ 8
Tobramycin	≤4 / ≥16	≤4 / ≥16[d]	≤4 / >4	≤1 / ≥2
Staphylococci				
Gentamicin	≤4 / ≥16	≤4 / ≥16[c]	≤1 / >1	≤ 1 / ≥2

a. CLSI M100-S28 (2018) interpretive criteria.
b. Amikacin package insert (Teva Parenteral Medicines, Inc.).
c. Gentamicin package insert (Fresenius Kabi USA, LLC.).
d. Tobramycin package insert (Akorn, Inc.).
e. Based primarily on the assessment of high dose, extended interval regimens and the assumption of combination therapy.

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