2764. Generation of a Balanced, Tetravalent Dengue Vaccine Based on Contemporary Strains Using a Computational, Synthetic Biology-Based Platform

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Background: The WHO estimates that there may be 50 million cases of dengue virus (DENV) infection worldwide every year. There is no safe vaccine against DENV licensed in the United States. The development of a balanced and effective anti-DENV vaccine is vital to preventing morbidity and mortality. Codagenix used its proprietary *SAVE* (Synthetic Attenuated Virus Engineering) platform to generate and test a live attenuated, tetravalent vaccine against DENV.

Methods: Codagenix used *SAVE* to substitute under-represented human codons and codon-pairs into the E protein sequences of contemporary strains of DENV1-4, producing either a fully human-cell-deoptimized prM-E (E-Min), or a partially deoptimized prM-E (E-W/Min) to allow for balancing of the vaccine's immunogenicity. Full genomes containing deoptimized E-Min and E-W/Min in the DENV2 backbone were transfected into cells to recover live-attenuated, human-cell-deoptimized vaccine strains. Mice were vaccinated with 10^6 FFU of each DENV vaccine (alone or together), boosted on day 21 and assessed for neutralizing antibodies by PRNT50 and survival after lethal challenge with mouse-adapted wild-type (WT) DENV. Cynomolgus macaques were immunized with a mixture of 10^6 FFU of each DENV vaccine strain. Two doses were administered on study day 1 and 57 and serum neutralizing antibodies were determined on day 57 and 85 by a microneutralization assay.

Results: SAVE deoptimized DENV viruses grew to wild-type (between 10^7 and 10^8 FFU/ml) levels at permissive temperatures (<37C). All vaccine strains generated neutralizing antibody levels comparable to WT. A tetravalent formulation containing all four E-Min strains protected mice from lethal challenge with DENV3. A tetravalent formulation of Codagenix DENV-E-W/Min vaccine elicited a robust and balanced neutralizing antibody response in non-human primates (NHPs) against all four DENV serotypes after a single dose. A second vaccine dose did not boost antibody titers significantly.

Conclusion: The ability to rationally balance the attenuation of multiple vaccine strains, thereby avoiding antibody-dependent enhancement, is a unique advantage of the Codagenix *SAVE* platform. Codagenix DENV vaccine viruses generated balanced, sterilizing immunity in NHPs after one dose.
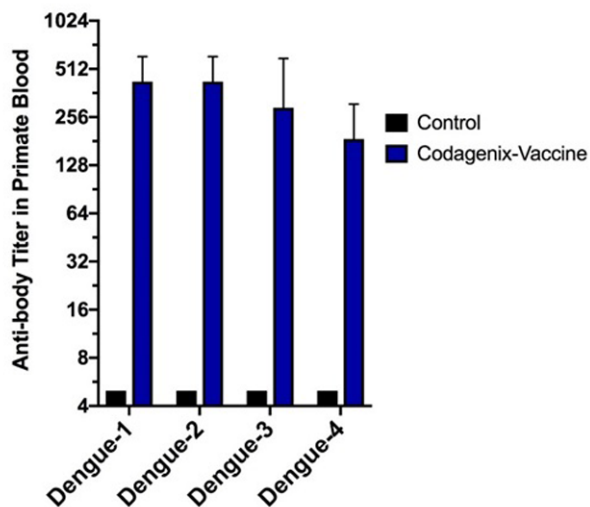

Fig. 1: Codagenix DENV vaccine elicits balanced immunogenicity in NHPs.

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2765. Pediatric Mumps during the 2015–2017 Mumps Resurgence in the United States

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Background: Numerous mumps outbreaks occurred in the United States over the last decade, with outbreaks affecting young adults on college campuses being among the largest and most widely publicized. However, at least half of mumps cases and outbreaks occurred in other age-groups and settings. We describe reported mumps cases among children and adolescents during 2015 through 2017.

Methods: The Centers for Disease Control and Prevention (CDC) analyzed reports of confirmed and probable mumps cases in persons aged ≤18 years (defined here as pediatric mumps) transmitted electronically through the Nationally Notifiable Diseases Surveillance System (NNDSS) by the 52 reporting jurisdictions.

Results: Between January 1, 2015 and December 31, 2017, 49 jurisdictions reported 4,886 pediatric mumps cases (35% of all US reported cases, 13,807); 8 jurisdictions reported >100 cases each, representing 82% of all pediatric cases. Overall, 29 (1%) cases were in infants <1 yr, 406 (8%) were in children aged 1–4 years, 1,408 (29%) in children aged 5–10 years, 1,365 (28%) in adolescents 11–14 years, and 1,678 (34%) in adolescents aged 15–18 years. Most (3,548, 73%) cases did not travel outside the state during their exposure period; only 37 (1%) traveled outside the country. Cases in patients aged 1–4 years were more frequently non-outbreak associated (38%) than those in patients <1 years and 5–18 years (24% and 9%, respectively). Among 3,309 (68%) patients with known number of MMR doses received, 81% of those 5–18 years had ≥2 MMR doses, while 67% of those 1–4 years had ≥1 dose. Median time since last MMR dose for patients with 2 doses was 8 years (IQR: 4, 11 years). Four patients had meningitis and 1 had encephalitis; all were ≥10 years old and previously received 2 MMR doses. Of male mumps patients older than 10 years of age (2,113), 46 (2%) reported having orchitis; of these, 33 (72%) had 2 MMR doses. Sixty-four patients were hospitalized and there were no deaths.

Conclusion: About one-third of cases reported during the recent US mumps resurgence were in children and adolescents. The low rate of mumps complications compared with previous studies suggests mumps complications may not be adequately captured in national surveillance or identified by providers. Providers should remain vigilant that mumps can still occur among fully vaccinated pediatric patients, even those recently vaccinated.

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2766. Identification and Description of Mumps Cases in a Non-Outbreak Setting and Evaluation of the Effectiveness of Mumps Containing Vaccines Over Time

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Background: Despite high coverage for 2 doses of MMR/MMRV vaccine, the United States and other countries have seen increases in outbreaks of mumps, mainly on college campuses and other close communities, which has been attributed to waning immunity to mumps. The objective of this study was to identify mumps cases within Kaiser Permanente Northern California, a large healthcare organization, and to assess waning of vaccine immunity against mumps in a non-outbreak setting.

Methods: Potential cases were identified by international classification of disease (ICD) 9 code 072, ICD 10 code B26 or by laboratory orders for mumps. We conducted medical chart reviews to confirm diagnoses, timing relative to vaccination and clinical characteristics. We selected cases and controls among KPNC born after 1988 who were members for ≥9 months before diagnosis or anchor date and who received their second dose at ages 4 to 6 years, matching cases with controls on geographical area. To assess for risk of mumps in relation to time since a second MMR/MMRV dose, we compared cases and controls using multivariable logistic regression adjusted for age, sex and calendar time of mumps diagnosis.

Results: Among 397 potential cases identified, chart review confirmed 178 (44.8%) as mumps. About half (87/178) were confirmed by both positive laboratory test and clinical diagnosis, with the remainder by clinical diagnosis alone. Median age at diagnosis for the 187 cases was 30 years (range 1 year–91 years). Most cases had parotitis (93%) and there were 7 cases of orchitis. The 34 cases with complete vaccination information were matched to 539,301 controls. The mean time since the second vaccine dose was shorter for cases compared with controls (6.5 years vs. 9.0 years, *P* = 0.008). After adjustment, there was no significantly increased risk of mumps associated with time since second MMR/MMRV dose (adjusted odds ratio = 1.08, 95% CI 0.57–2.05).

Conclusion: In the setting of a large healthcare organization, our results do not provide evidence of waning immunity following 2 doses of MMR/MMRV; however, identifying and confirming mumps cases were challenging and analyses were limited by small number of cases. Large future studies will be needed to confirm whether risk of mumps increases over time in non-outbreak settings.

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2767. Variation in Incidence of Pediatric Herpes Zoster by First- and Second-Dose Varicella Vaccine Formulations

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Background: Varicella (VAR) and measles-mumps-rubella (MMR) vaccines are recommended for children at ages 12–15 months and 4–6 years. These are administered as separate MMR and VAR vaccines (MMR+VAR) or as combined measles-mumps-rubella-varicella (MMRV) vaccine. Herpes zoster (HZ), caused by wild-type or vaccine-strain varicella-zoster virus, can occur in children after varicella vaccination. It is unknown whether HZ incidence after varicella vaccination varies by vaccine formulation or simultaneous receipt of MMR.

Methods: Using data from six integrated health systems, we examined HZ incidence among children who turned 12 months old during 2003–2008 and received varicella and MMR vaccines according to routine recommendations. All HZ cases ≥ 21 days after first varicella vaccination were identified using ICD-9 codes from inpatient, outpatient, emergency room encounters, and claims data, through 2014. HZ incidence was examined by vaccine formulation (MMR+VAR, MMRV, or VAR without same-day MMR) and doses received and compared using incidence rate ratios (IRR).

Results: Among 199,797 children, we identified 601 HZ cases. Crude HZ incidence after first-dose MMR+VAR (18.6 [95% CI 11.1–29.2] cases/100,000 person-years) was similar to the rate after first-dose MMRV (17.9 [95% CI 10.6–28.3] cases/100,000 person-years), but approximately double the rate among those with first-dose VAR without same-day MMR (7.5 [95% CI 3.1–15.0] cases/100,000 person-years); see Table 1. The IRR for HZ after first-dose MMR+VAR or MMRV, compared with VAR, was 2.5 (95% CI 1.4–4.4; *P* = 0.002). When examining any first or second dose formulation, crude HZ incidence was lower after the second varicella vaccine dose (13.9 cases/100,000 person-years), than in the period before the second dose (i.e., between first and second doses or after the first dose in children with only one dose; 21.8 cases/100,000 person-years, *P* < 0.0001). HZ incidence was also lower after two varicella vaccine doses in each of the three first-dose formulation groups.

Conclusion: HZ incidence among children varied by first-dose varicella vaccine formulation and number of varicella vaccine doses. Regardless of the first-dose varicella vaccine formulation, children who received two vaccine doses had lower HZ incidence after the second dose.

Table 1. Herpes zoster crude incidence rates by varicella vaccine formulation and number of doses, 2003-2014

Formulation of first varicella vaccine dose, age 12-18 months (N)	Number of HZ cases following one dose / two doses of varicella vaccine	Overall incidence rate (CI) [1]	Incidence rate after one dose of varicella vaccine (CI) [2]	Incidence rate after two doses of varicella vaccine, by first dose vaccine formulation (CI)	P value [3]
VAR alone [4] (9,386)	8 / 4	7.5 (3.1-15.0)	9.8 (4.7-18.1)	5.0 (1.6-11.7)	0.26
MMR+VAR [5] (126,349)	245 / 176	18.6 (11.1-29.2)	21.5 (13.4-32.6)	15.7 (8.9-25.6)	0.001
MMRV (64,062)	116 / 52	17.9 (10.6-28.3)	24.5 (15.8-36.3)	11.2 (5.6-19.9)	<0.0001
Overall (199,797)	369 / 232	17.9 (10.6-28.3)	21.8 (13.6-33.0)	13.9 (7.6-23.4)	<0.0001

NOTE: HZ = herpes zoster, CI = confidence interval, VAR = single-antigen varicella vaccine, MMR = combination measles, mumps, rubella vaccine, MMRV = combination measles, mumps, rubella, varicella vaccine; incidence rates displayed per 100,000 person-years

[1] Includes all HZ cases following receipt of one or two doses of varicella vaccine

[2] Limited to cases in children following one dose of varicella vaccine, either occurring before the receipt of a second varicella vaccine or in those that received only one dose of varicella vaccine

[3] Comparing HZ incidence after one varicella vaccine dose vs. two varicella vaccine doses, by first dose varicella formulation group; any second dose varicella formulation

[4] Children also received MMR between 12-18 months of age, but at least 30 days before or after VAR

[5] Received both vaccines on the same day

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2768. Does Social Media Contribute to Knowledge About Vaccine Safety?

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Background: Social media is frequently used to share medical information. Current European regulatory guidance for the pharmaceutical industry calls for reporting valid adverse events (AE) derived from social media as well as consideration of non-valid AEs. This guidance is followed when our company utilizes social media related to any company products and interests. Here we evaluate its application to vaccines.

Methods: Posts collected from all screened social media sources (company owned, or company reviewed) were examined (August 1, 2017–February 28, 2019) to identify safety-related information pertaining to any of its 14 licensed vaccines. Posts were classified as valid cases (i.e., containing information about company product, AE, and identifiable reporter), non-valid cases (i.e., company product, AE, but missing an identifiable reporter), or not relevant (no safety-related information; not further analyzed). Valid cases were added to the company's safety database; non-valid cases were reviewed for trends requiring further analysis. Both, valid and non-valid cases, were analyzed as part of routine safety surveillance.

Results: Among 69,682 vaccine-related posts reviewed, 285 (0.4%) were valid; 11,464 (16.5%) were non-valid; 47,966 (83.1%) were not relevant. Most non-valid cases concerned the company's 4-valent (8,934 [78%]) or 9-valent (1,420 [12%]) human papillomavirus vaccines, followed by its measles-mumps-rubella (336 [2.9%]), pneumococcal (282 [2.5%]), and herpes zoster (246 [2.1%]) vaccines. Review of data from selected temporal spikes in posts demonstrated that they were usually attributable to

increased reposts of an original post or to personal views, rather than containing incremental factual new safety data.

Conclusion: Fewer than 1% of posts from relevant social media sources contained sufficient information to be considered valid cases. No new safety signals were identified for any of the vaccines from social media cases (valid or non-valid). Among posts containing safety information, the nature of this information tends to be redundant or sentimental, precluding meaningful safety analyses.

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2769. The Clinical and Economic Impact of MMR Vaccinations to Prevent Measles Importations from US Pediatric Travelers Returning from Abroad

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Background: Although pediatric travelers comprise < 10% of US international travelers, they account for almost half of all measles importations among returning travelers. For travelers 1–18 years with no other evidence of measles immunity, the Advisory Committee on Immunization Practices (ACIP) recommends 2 MMR vaccine doses before departure; 1 dose is recommended for infant travelers (6 to <12 months) and does not count toward their primary immunization series. All US travelers (6 months to < 6 years) are at risk for being undervaccinated for measles because MMR is routinely given at 1 years and 4–6 years.

Methods: We developed a decision tree model to evaluate the clinical impact and cost per case averted of pretravel health encounters (*PHE*) that vaccinate MMR-eligible pediatric international travelers. We compared 2 strategies for infant (6 to < 12 months) and preschool-aged (1 to <6 years) travelers: (1) *no PHE*: travelers departed with baseline MMR vaccination status vs. (2) *PHE*: MMR-eligible travelers were offered vaccination. All simulated travelers experienced a destination-specific risk of measles exposure during travel (mean, 237exposures/10M travelers; range, 19–6,750 exposures/10M travelers); if exposed to measles, travelers were at risk of illness stratified by age and MMR vaccination status (range, 0.03–0.90). Costs include direct medical costs and lost work wages for guardians. Model outcomes included measles cases, costs, and cost per case averted. We varied inputs in sensitivity analyses.

Results: Compared with *no PHE*, *PHE* averted 451 measles cases at $985,000/case averted for infant travelers and 54 measles cases at $1.5 million/case averted for pre-school-aged travelers (table, bottom). *PHE* can be cost-saving for travelers to regions with higher risk of measles exposure and if more MMR-eligible travelers are vaccinated at PHE (Figure 1). At a risk of exposure associated with European travel, PHE had better value when a measles importation led to a higher number of contacts or more US-acquired cases per importation (Figure 2).

Conclusion: *PHE* for pediatric travelers (6 months to <6 years) decreased the number of imported measles cases and saved costs, especially if targeted to travelers with higher-risk destinations, if more MMR-eligible travelers are vaccinated at PHE, or if outbreaks are larger.

Table: Input parameters and base case results in a model of clinical and economic impact of MMR vaccinations to prevent measles importations from US pediatric travelers

	Infant (age 6-<12m)			Preschool-aged (age 1-<6y)			Reference
Model Input Parameters							
Number of past MMR vaccinations	0	1	2	0	1	2	[1]
% of cohort with past MMR vaccination	92%	8%	N/A	8%	52%	40%	[1]
Risk of measles infection, if exposed	90%	16%	N/A	90%	7%	3%	[2,3,4]
US-acquired cases per importation (n)	4	4	N/A	4	4	0	[5,6]
Contacts per importation (n)	1,500	1,500	1,500	1,500	1,500	1,500	[7]
Vaccination of MMR-eligible at PHE		44%			56%		[1]
Cost of vaccination		$90			N/A*		[8]
Cost per PHE				$7			[9]
Cost per measles importation				$13,200			[9]
Cost per US-acquired case				$4,800			[9]
Cost per contact				$550			[7,9]
Model Results							
Measles importations/10M travelers							
No PHE		199			29		
PHE		109			19		
US-acquired cases/importation							
No PHE		797			103		
PHE		436			59		
Cases averted		451			54		
Costs per 10M travelers (USD)							
No PHE		$170.6M			$24.4M		
PHE		$616.5M			$104.4M		
Cost/case averted		$985,000			$1.5M		

*Because MMR-eligible pre-school aged travelers receive a routine dose of MMR early at the PHE, there is no added cost of vaccination.

Abbreviations: MMR: Measles-mumps-rubella; PHE: pretravel health encounter

References: [1] Global TravEpiNet (GTEN) data (2009-18) [2] McLean HQ et al. *MMWR* 2013 [3] Moss WJ *JID* 2011 [4] CDC Yellow Book 2018 [5] Fiebelkorn AP et al. *JPIDS* 2017 [6] Rota et al. *JID* 2011 [7] Ortega-Sanchez IR et al. *Vaccine* 2014 [8] CDC vaccine price list 2019 [9] Hyle EP et al. *Ann Int Med* 2017