Development of a Novel Respiratory Syncytial Virus Controlled Human Infection Model: Phase 1 Study of rRSV A/Maryland/001/11 in Healthy Adult Volunteers

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Learning Objective
Describe a novel challenge model for evaluation of RSV vaccines and therapeutics

Abstract
Respiratory syncytial virus (RSV) is a major cause of morbidity and mortality in infants and young children. It has long been recognized as the most frequent viral cause of bronchiolitis and pneumonia in children under 5 years of age [1] and it also causes substantial disease in the elderly and in immunosuppressed individuals [2]. Despite the high burden of disease, no vaccine is licensed. Apart from the neutralizing antibodies, the correlates of protection for RSV are poorly understood and therefore cannot be used to evaluate the efficacy of vaccines. A controlled human infection model (CHIM) for RSV will help in the evaluation of new prevention and treatment strategies. No RSV challenge strain is currently available in the US. We sought to establish a new CHIM for RSV utilizing a recombinant version of a recently circulating virus, rRSV A/Maryland/001/11, in healthy adult volunteers.

This was an open label, phase 1 study conducted under IND and designed to determine the safety, infectivity, replication and immunogenicity of rRSV A/Maryland/001/11 which is based on a subgroup A RSV isolated from an otherwise healthy adult with significant respiratory illness. Healthy nonpregnant adults age 18-50 with pre-challenge serum RSV neutralizing antibody titers <1:320 by complement-enhanced RSV 60% plaque reduction neutralization assay (PRNT) were recruited and consented to participate in this study. Subjects were screened to exclude ongoing acute or chronic illness and had bedside spirometry to confirm normal lung function. They were admitted to the inpatient unit and were administered 10^5 PFU of rRSV A/Maryland/001/11 intranasally via an atomizer device. They were monitored for adverse events, including decreased pulmonary function, and received symptomatic care as needed. Shedding of the challenge strain in nasal washes was assessed daily by RT-qPCR and by immunoplaque assay. Subjects were eligible for discharge upon two consecutive RT-qPCR titers of <3 log10 genome equivalents/mL on Day 6 or later. Serum antibody responses post-challenge were measured by PRNT and ELISA of IgG for the RSV (A2) fusion (F) glycoprotein.

Twenty volunteers received 10^5 PFU of rRSV A/Maryland/001/11; 15 (75%) experienced respiratory symptoms. The most common complaints were nasal congestion and nasal mucosal erythema (11 volunteers each), rhinorrhea (6), sneezing (5), cough (4), and middle ear effusions (4). The majority of symptoms were mild; none were severe and no volunteer experienced decreased pulmonary function.

Nineteen of 20 volunteers had virus detectable by RT-qPCR on Day 1 after challenge; 9/20 had virus detectable by immunoplaque assay. The mean peak (standard deviation [SD]) RT-qPCR titer was 5.7 (1.8) log10 genomic equivalents/mL; mean peak immunoplaque titer was 2.7 (1.6) log10 PFU/mL. All were culture-negative for RSV by Day 11 after challenge.

The baseline geometric mean (GM) neutralizing antibody titer (SD) was 6.5 log2 (0.9) which increased to 7.4 (1.0) log2 on Day 28 after challenge and 7.5 (0.9) log2 on Day 56. Nine of 20 subjects had a 2-fold or greater increase in PRNTs with

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a geometric fold-change overall of 1.9 log2. Baseline titers measured by IgG ELISA to the RSV F protein were relatively high (GM 11.67, SD 0.9), and only 6/20 had a 2.5-fold or greater increase in ELISA titers.

rRSV A/Maryland/001/11 shows promise as a CHIM challenge virus, with infection demonstrated in 19/20 subjects. Infection with rRSV A/Maryland/001/11 was associated with mild to moderate upper respiratory symptoms without lower respiratory symptoms. We plan to further validate this CHIM and to conduct dose ranging for the optimal dose for use in evaluation of vaccines and therapeutics.

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Development of Single Dose Vaccines Against Emerging Infectious Diseases, Including COVID-19, Using GV-MVA-VLPTM Vector Platform

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Learning Objective
Describe a platform that can deliver safe and effective single dose vaccines for emerging infectious diseases

Abstract
Single-dose protection is a favourable characteristic of a vaccines for emerging infectious disease outbreak response, given the speed of spread of pathogens and the impracticality of multi-dose regimens in the under-resourced settings where outbreaks often occur.

We have utilized our 4th generation MVA vector platform that is improved for high expression and stable transgenes during manufacture, to develop single dose vaccines for WHO Blueprint list of priority diseases such as haemorrhagic fever viruses (Ebola, Sudan, Marburg, and Lassa fever) and Zika. The MVA platform can be combined with the potent immunogenicity of Virus Like Particles (VLPs) or be used to express proteins in their native conformations enabling vaccines that induce full protection after a single dose. Safety and immunogenicity of the platform was shown in animal challenge studies for infectious disease targets and in human studies using MVA-VLP-HIV vaccine candidate. [1]

Vaccine constructs were made using MVA vector technology and fully characterized *in vitro* (e.g., sequencing, WB, Immunostaining, and electron microscopy). For constructions of Ebola, Sudan, Marburg, and Lassa fever vaccine candidates, two genes from each pathogen were used to generate VLPs; GP (major protective antigen) +VP40 (a multifunctional matrix protein recognized as a promising therapeutic target antigen) for Ebola, Sudan and Marburg and GPC+Z genes for Lassa fever vaccine. For Zika vaccine NS1 was used as the protective immunogen since this protein is not associated with induction of Antibody Dependent Enhancement of infection, a potential risk for other envelope based Zika vaccines in development.

Appropriate animal models (e.g., mice, Guinea pigs, and non-human primates) were used to determine immunogenicity and efficacy of vaccine candidates delivered by intramuscular immunizations and challenged by various routes (intracerebral for Lassa and Zika, and intramuscular for Ebola and Marburg). Humoral and cellular immune responses were determined post vaccination and viremia/survival were monitored post-challenge. Analysis of data was performed using GraphPad Prism (GraphPad Software), analysis of variance (ANOVA) ,and Tukey's tests. A p-value <0.05 was considered statistically significant.

All experimental protocols were approved by the Institutional Animal Care and Use and the Institutional Biosafety Committees.

Immunogenicity and efficacy studies for the MVA-VLP-EBOV vaccine candidate performed in Guinea pigs, hamsters, and rhesus macaques at the ABSL4. We demonstrated the ability of our vaccine to provide single-dose protection against a lethal EBOV-Makona challenge in macaques. In Guinea pigs, prime/boost vaccinations with the MVA-VLP-EBOV or MVA-VLP-MARV elicited adequate humoral immune responses as documented by total GP-specific Ab and neutralizing titers, and all the vaccinated animals were protected against the lethal challenge. [2] Because MVA vaccines expressing multiple filovirus GPs have not protected as single dose vaccines against lethal EBOV challenge [3], we hypothesize that the success of our single dose MVA-EBOV vaccine reflects the efficient initiation of B cell responses by VLPs displaying the GP. No viremia was detected post challenge in any vaccinated animals (Guinea pigs or monkeys) demonstrating near

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sterile immunity by the vaccine. Similarly, we showed 100% single-dose protection in a lethal IC challenge mouse model for our MVA-VLP-LASV [4] or MVA-NS1 Zika [5] vaccine with strong T cell responses 10 days post-single vaccination. In rhesus macaques, our Zika vaccine also elicited high levels of NS1-specific Abs, ADCC activity with strong CD8+ T cell producing IL2+IFNg cytokines. The vaccine quickly eliminates the ZIKA-infected cells and eliminated challenge viremia.

In sum we demonstrated for the first-time single dose efficacy with our MVA vaccines in different family of viruses using lethal challenge models, as examples for a broad utility of the platform for other indications. These vaccines will enter human clinical trials in near future.

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Effectiveness of Cell Culture-Based Inactivated Influenza Vaccine Against Medically-Attended, Laboratory-Confirmed Influenza in Northcentral Wisconsin, 2018–2019

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Learning Objective
Describe the effectiveness of cell culture-based inactivated influenza vaccine against medically-attended, laboratory-confirmed influenza

Abstract
Influenza vaccine effectiveness (VE) is suboptimal, especially against A/H3N2. VE against A/H3N2 was 33% in a pooled analysis of ≥29 studies published before early 2015 compared to >50% for A/H1N1 and B. Mutations that occur as a result of replication in eggs during vaccine production can affect antigenic characteristics. Egg-induced mutations in A/H3N2 vaccine strains in 2012–2013 and 2016–2017 are thought to be contributing factors to low VE.

In 2012, the US Food and Drug Administration (FDA) approved Flucelvax® (Seqirus, Inc.). Flucelvax is the first and only influenza vaccine licensed in the US that is manufactured using mammalian cell-culture technology. Beginning in 2017–2018, Flucelvax was produced with a cell-isolated A/H3N2 candidate vaccine virus (CVV). Use of cell-grown CVV instead of egg-isolated CVV may improve VE. We assessed VE of the cell culture-based inactivated influenza vaccine (ccIIV4) and the relative VE of ccIIV4 versus standard inactivated influenza vaccine (IIV4).

Data from two separate test-negative design studies of influenza VE conducted by Marshfield Clinic Research Institute (MCRI) in Wisconsin during 2018–2019 were combined. One study was a single-site study to estimate ccIIV4 effectiveness (ccIIV4 study) among persons age ≥4 years. The other was the Centers for Disease Control and Prevention (CDC)-funded US Influenza Vaccine Effectiveness Network (Flu VE study); only data from patients age ≥4 years enrolled by MCRI were included.

Study procedures were similar across studies. Patients were approached during outpatient primary and urgent care visits for acute respiratory illness (ARI) by research staff between 12/26/2018–4/26/2019. Patients with ARI were eligible if they had a cough with illness duration ≤7 days and had not taken an antiviral. Participants completed a brief questionnaire and provided nasal and oropharyngeal swabs for influenza testing via reverse-transcription polymerase chain reaction. Additional data were extracted from the electronic health record.

Effectiveness of ccIIV4 was estimated by comparing the odds of ccIIV4 vaccination versus no vaccination among influenza positive versus influenza negative participants using multivariable logistic regression. Similarly, relative VE of ccIIV4 versus IIV4 was estimated comparing odds of ccIIV4 versus IIV4 receipt among influenza positive versus negative participants. Analyses were stratified by subtype and age group, when feasible.

There were 2,464 participants age ≥4 years included; 31% from the ccIIV4 study and 68% from the Flu VE study. Mean age of participants was 35 years (SD=23); most were male (60%) and non-Hispanic white (90%). About one-third (31%) tested positive for influenza; 57% A/H1N1pdm09 and 41% A/H3N2. About half (47%) were vaccinated; of which, 67% received ccIIV4 and 18% received IIV4.

Overall, ccIIV4 effectiveness against A/H3N2 was 20% (95% CI: -9%, 41%) and 46% (95% CI: 18%, 65%) among children aged 4–17 years. IIV4 effectiveness against A/H3N2 was -27% (95% CI: -100%, 20%), and 11% (95% CI: -66%, 53%) among

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children aged 4–17 years. Among children aged 4–17 years, relative VE against A/H3N2 of ccIIV4 versus IIV4 was 39% (95% CI: -19%, 69%).

Overall, ccIIV4 effectiveness against A/H1N1pdm09 was 43% (95% CI: 26%, 56%); 54% (95% CI: 27%, 71%) among children aged 4–17 years and 33% (95% CI: 5%, 53%) among adults aged 18–64 years. IIV4 effectiveness against A/H1N1pdm09 was 49% (95% CI: 18%, 68%), 63% (95% CI: 17%, 83%) among children aged 4–17 years and 47% (95% CI: 2%, 72%) among adults aged 18–64 years. Relative VE against A/H1N1pdm09 of ccIIV4 versus IIV4 was -12% (95% CI: -86%, 32%).

During 2018–2019, a season characterized by co-circulation of A/H1N1pdm09 viruses and A/H3N2 viruses that were antigenically distinct from the CVV, there was no difference in VE between ccIIV4 and IIV4 against medically-attended, laboratory-confirmed A/H1N1pdm09. Additionally, ccIIV4 was effective against A/H3N2 among children aged 4-–7 years.

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HBV-24: Immunogenicity and Safety of HEPLISAV-B® in Hemodialysis Patients

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Learning Objective
Describe the immunogenicity and safety profile of a hepatitis B vaccine employing a novel adjuvant in patients on hemodialysis

Abstract
Patients on hemodialysis are at increased risk of exposure to hepatitis B virus (HBV). The Advisory Committee on Immunization Practices (ACIP) recommends that hemodialysis patients receive hepatitis B vaccination. [1] In 2015, an estimated 444,337 patients were on chronic hemodialysis in the US with more than 108,826 patients initiating hemodialysis that year, many of whom likely needed hepatitis B vaccination. [2,3] Unlike healthy individuals, hemodialysis patients require maintenance of anti-HBsAg (antibodies against HBsAg) levels at ≥10 mIU/mL. These patients have impaired anamnestic responses where breakthrough infections have occurred with levels <10 mIU/mL and the duration of protection against HBV depends on the peak post-vaccination antibody level.

HBV vaccine naïve adults with end-stage renal disease undergoing hemodialysis are receiving 4 single-dose injections (0.5 mL per injection) of HEPLISAV-B® [Hepatitis B Vaccine (Recombinant), Adjuvanted] at weeks 0, 4, 8, and 16 in an open-label, single arm clinical trial. Immunogenicity, measured by the seroprotection rate (SPR), is evaluated at week 20, 4 weeks after the last dose. [4] Safety is assessed with post injection reactions within 7 days of each injection and medically attended adverse events within 42 days.

Approximately 50 patients will be included in this interim analysis of the expected 100 patient cohort. Data to be presented include patients who received all study injections, patients who produce a response at week 20, defined as antibodies to hepatitis B surface antigen (anti-HBs) ≥10 mIU/mL, anti-HBs >100 mIU/mL, and anti-HBs >1000 mIU/mL. Safety data on the 4-dose regimen of HEPLISAV-B in hemodialysis patients will also be presented consisting of post-injection reactions and adverse events compared with historical data using 4 double doses of an alum-adjuvanted vaccine in hemodialysis patients. [5]

This interim analysis of the 4 single-dose regimen of HEPLISAV-B will provide important data on an additional potential option for protection against hepatitis B in the majority of hemodialysis patients, a group that has historically been difficult to seroprotect.

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Heat Treatment Exposes a Partially Cleaved 27 Amino Acid Peptide (P27) on the Fusion (F) Protein of Infectious Respiratory Syncytial Virus (RSV)

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Learning Objective
Discuss if physical-chemical treatment, such as heat, can relax and open F protein trimers of ispRSV, exposing a partially cleaved p27, if present

Abstract
Respiratory syncytial virus (RSV) is a global pathogen of children and older adults. [1,2] The monoclonal antibody (mAb) palivizumab is the only licensed product for the prevention of RSV, and its use is limited to a select group of high-risk infants. The RSV fusion protein (F) is a major surface glycoprotein and the primary target for vaccine development. The activated F protein trimer is a metastable quaternary structure (pre-F) that transitions to a stable post-F form. [3] The pre-F has unique antigenic sites associated with potent mAbs. Our group and others have detected antibodies against a 27 amino acid peptide (p27) that is supposed to be cleaved and removed in a fully activated pre-F. [4] We also detected p27 in the F protein of infectious sucrose purified RSV (ispRSV). Our finding challenges the present understanding of the conformation of F protein on infectious viruses often used in vaccines.

Western blot was used to determine if p27 was present on the uncleaved (F0), or cleaved F1 (50 kDa), or F2 (20 kDa) products of ispRSV F protein using a mAb specific to p27 (kindly provided by Novavax, Gaithersburg, MD). Enzyme-linked immunosorbent assay (ELISA) was also used for the detection of p27 in ispRSV. Changes in RSV F quaternary structure were monitored by ELISA with mAbs targeting key antigenic sites corresponding to conformational (Ø) and linear epitopes (I and II). Vials of ispRSV were heated individually at 30, 40, 50, 60, 70, 80, or 90^{o}C for 10 minutes, and subsequently placed at 25^{o}C until analyzed by ELISA. Optical density values from each set of samples were normalized to those from a 25^{o}C unheated ispRSV control. Data were averaged from triplicate data points over three independent experiments and plotted as the standard error of the mean (SEM). Additional F protein controls included prefusogenic F (Novavax) that contained a partially cleaved p27, SC-TM (Pre-F) (Novavax) that does not contain p27, and post-F protein (Sino Biologicals).

A partially cleaved p27 was identified in the F1 subunit of the F protein by Western blot under reducing conditions. p27 was also detected in ispRSV by ELISA. mAb binding of p27 increased with heat treatment of ispRSV, reaching maximum binding at 60^{o}C. Similarly, mAb binding of sites I and II increased with heat treatment reaching maximum binding at 60^{o}C. On the other hand, mAb binding to site Ø, which is a conformational dependent site, decreased with increasing heat treatment reaching its nadir at 60^{o}C. Unlike ispRSV, heat treatment of prefusogenic F, SC-TM, or post-F resulted in decreased mAb binding to sites Ø, I, II and p27. Our data suggest two major findings: 1) a sizeable proportion of F protein in the pre-F conformation of ispRSV contains p27, and 2) p27 remains partially cleaved in the F1 subunit, upstream of the N-terminus of the fusion peptide domain. Also, there are fundamental differences in protein stability between the soluble F protein controls and membrane-bound F in ispRSV after heat treatment. We hypothesize that the partially cleaved p27 caps the fusion peptide of the F protein and remains partially hidden in the hydrophobic pocket of the F protein trimers of ispRSV [6, 7]. Heat treatment relaxes and opens the F trimers into monomers exposing p27 and increasing the availability of the linear antigenic sites to mAb binding.

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Immune-Engineered Antigen Designed to Harness CD4+ T Cell Memory Improves Protection Against Lethal Avian H7N9 Influenza

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Learning Objective
Describe increased vaccine-induced protection against a pandemic influenza strain attained by a novel structure-guided immunogen design approach to harness CD4 T cell memory from seasonal influenza

Abstract
Cross-conserved hemagglutinin (HA)-specific $CD4^+$ T cell epitopes are believed to support protective B cell responses against seasonal influenza. However, in the case of H7N9, considered to have the highest pandemic potential, HA only elicits weak neutralizing antibody responses. In natural infections, patients display delayed development of hemagglutination inhibition (HAI) antibodies and overall lower IgG avidity for H7N9 HA compared to seasonal influenza. H7N9 HA has also been observed to be only weakly immunogenic in the absence of adjuvant in clinical trials. Strategies to optimize H7N9 HA immunogenicity are therefore critical for pandemic preparedness. Because cross-conserved T cell epitopes 'adjuvant' seasonal influenza, we hypothesized that an immune-engineered H7N9 HA incorporating broadly reactive seasonal H3N2 influenza HA-specific memory $CD4^+$ T cell epitopes would boost protective antibody responses and increase protection compared to wildtype H7N9 HA.

We designed two optimized H7N9 HA constructs: Opt1 (three amino acid substitutions replace a reported regulatory T cell (Treg) epitope with a highly conserved and broadly reactive $CD4^+$ T cell epitope from H3-HA) and Opt2 (integratessix H3-HA $CD4^+$ T cell epitopes, one Treg epitope removed). Structure modeling and molecular dynamics simulations of the engineered constructs were performed to evaluate likely stability. Vaccination studies were carried out in HLA-DR3 transgenic mice. Pre-immunity to H3N2 ($1x10^6$ CFU, Hong Kong/2014) was established by intranasal exposure prior to vaccination. Mice were injected with wildtype or engineered H7N9 HA (Opt1 or Opt2) without adjuvant eight weeks post-exposure and boosted twice at four-week intervals. Bulk IgG and HAI titers to H3 and H7 were monitored. Mice were challenged intranasally with H7N9 ($1x10^4$, Anhui/2013) three weeks after the final immunization. Mice were monitored for weight loss and survival; lung viral load was assessed four days post-infection.

Pre-immunity was successfully established through H3N2 infection prior to vaccination. Four weeks after exposure, mice exhibited high HAI titers to H3, but not H7. Vaccination with Opt1 or Opt2 using no adjuvant successfully established anti-H7 IgG titers following a single prime/boost regimen, whereas vaccination with wildtype H7 did not. Mice vaccinated with wildtype H7 required a second boost to display positive titers, albeit to a lesser degree than Opt1/Opt2. This study confirmed the important contribution of H3N2 memory T cell immunity to the engineered HA immune response. Opt1 and Opt2 vaccinated mice challenged with a lethal dose of H7N9 virus demonstrated increased survival two weeks post-infection and were also noted to display delayed and less severe weight loss compared to wildtype HA vaccinated mice ($p<0.001$). Finally, both Opt1 and Opt2 vaccination lowered lung viral load, indicating that the optimized vaccines were able to provoke an efficient response to infection.

These data demonstrate improved protection against H7N9 infection using an unadjuvanted vaccine that is capable of recruiting seasonal influenza T cell memory. Immune-engineering may also be useful for developing more effective seasonal influenza vaccines.

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In Vivo Assembly of Nanoparticles Achieved Through Synergy of Structure-Based Protein Engineering and Synthetic DNA Generates Enhanced Adaptive Immunity

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Learning Objective
Identify potential strategies to employ modern day protein engineering technology in their design of vector-encoded (nucleic acids/viral vectors) vaccines to facilitate direct *in vivo* production of designer vaccines, which are conventionally considered to be challenging and expensive to make, and induce more potent adaptive immunity against infectious diseases

Abstract
Nanotechnologies are considered to be of growing importance to the vaccine field. Through decoration of immunogens on multivalent nanoparticles, designed nano-vaccines can elicit improved humoral immunity. However, significant practical and monetary challenges in large-scale production of nano-vaccines have impeded their widespread clinical translation.

Here, we illustrate an alternative approach integrating computational protein modeling and adaptive electroporation mediated synthetic DNA delivery thus enabling direct *in vivo* production of nano-vaccines. We demonstrated DNA-launched nanoparticles displaying an HIV immunogen spontaneously self-assembled *in vivo* through three complimentary techniques, VRC01-based immuno-gold labelling, pseudo-NATIVE PAGE analysis comparing migration of *in vivo* versus *in vitro* produced nanoparticles, and binding of *in vivo* produced nano-vaccine to murine mannose binding lectin, a protein moiety that specifically binds to repetitive glycan structures on the surfaces of multivalent antigens.

DNA-launched nano-vaccines induced stronger humoral responses than their monomeric counterparts in both mice and guinea pigs, and uniquely elicited CD8+ effector T cell immunity as compared to recombinant protein nano-vaccines. Improvements in vaccine responses were recapitulated when DNA-launched nano-vaccines with alternative scaffolds and decorated antigen were designed and evaluated. Finally, evaluation of functional immune responses induced by DLnano-vaccines demonstrated that, in contrast to control mice, mice immunized with a DNA-launched hemagglutinin nanoparticle vaccine were protected from a lethal H1 influenza challenge at an extremely low dose (1ug of DNA-plasmid). The DNA-launched nano-vaccine conferred significantly improved protection through lowering viral load while protecting mice from weight loss and influenza-induced lung pathology. Additional study of these next-generation *in vivo* produced nano-vaccines may offer advantages for immunization against multiple disease targets, and the dose-sparing feature of the technology may impact global deployment of these designer vaccines.

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Multi-Modal Vaccination Targeting *Clostridioides difficile* Based on a Chromosomally Integrated, Attenuated *Salmonella* Typhimurium Vector Protects Mice from Challenge

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Learning Objectives

- Describe the continued development of a candidate *Clostridioides difficile* vaccine that targets induction of both local (gut) and systemic immunity against *C. difficile* toxins A and B
- Illustrate the use of an attenuated *Salmonella enterica* Typhimurium as a vector for mucosal vaccination, and strategies to ensure stability and safety of the vaccine vector

Abstract

The principle advantage of live *Salmonella*-based vaccines is their ability to deliver antigens to the gut mucosa. Through local invasion, humoral and cellular responses can be elicited locally and systemically. [1] We are using an attenuated *Salmonella* Typhimurium (YS1646) to develop a vaccine for *Clostridioides difficile*. [2] *C. difficile* infection (CDI) is an important nosocomial infection. [3] CDI typically follows antibiotic use that disrupts the gastrointestinal microflora leading to *C. difficile* overgrowth and the production of two major toxins; A and B (TcdA and TcdB). [4] Antibodies directed against these toxins are very likely to be protective. Most current *C. difficile* vaccine candidates are administered intramuscularly (IM), generating a systemic immune response. [5] Using a plasmid-based vaccine candidates, we have demonstrated that multi-modality vaccination schedules based on YS1646 can induce protective responses in mice. [6] Since plasmid-based vaccines are unacceptable for human use, we sought to generate YS1646 strains with chromosomal-integration of the targeted genes.

We are targeting the immunogenic C-terminal receptor binding domains (RBD) of TcdB and TcdA. Using Tn7 chromosomal integration [7], we constructed YS1646 strains that express these RBDs at different phases of *Salmonella* invasion. C57/BL6 mice were vaccinated over 1 week: YS1646 orally by gavage (PO) on days 1, 3 and 5 ($1x10^9$ cfu) with or without recombinant RBDs IM (10ug) on day 1. Antibody titers and survival after *C. difficile* challenge were evaluated. For analysis of antibody titers (serum IgG and intestinal tissue IgA), one-way non-parametric Kruskal-Wallis ANOVA was performed with Dunn's multiple comparison analysis comparing all groups. Statistical significance was considered to have been achieved when $p \leq 0.05$. For analysis of survival, the log rank (Mantel-Cox) test was used to compare all groups to the PBS control group. The Bonferroni method was used to correct for multiple comparisons.

In mice that received both IM and PO dosing, our best candidates elicited high systemic and mucosal antibody titers within 4 weeks of vaccination (e.g., 8,000-15,000 ng/mL of anti-toxin IgG in the serum). In a lethal challenge model 5 weeks after vaccination with the mixed-modality schedule (IM+PO), 6 candidates that targeted either TcdA or TcdB provided 100% protection (vs ~35% survival in unvaccinated mice). Mice vaccinated PO only against TcdB had very low or absent antibody titers in serum but still experienced substantial protection (71-80%). Mice vaccinated PO only against TcdA with one candidate, had high serum IgG titers (5,000-8,000 ug/mL) and 100% protection. This project is focused on the rational design of a *C. difficile* vaccine. We plan to test at least one of the chromosomally integrated candidate strains in additional models (e.g., hamsters, possibly piglets) in preparation for GMP manufacturing, toxicity testing, and a Phase 1 clinical trial.

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Safety and Immunogenicity of Coadministration of Meningococcal Type A Vaccine with Typhoid Conjugate Vaccine in Healthy Children 15–23 Months of Age in Burkina Faso

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Learning Objective
Discuss the safety, reactogenicity, and immunogenicity results of a study of coadministration of meningococcal type A vaccine with typhoid conjugate vaccine in healthy children 15–23 months of age in Burkina Faso

Abstract
The World Health Organization (WHO) recently pre-qualified a single-dose typhoid conjugate vaccine for use in infants as young as 6 months of age. Recent testing of this Vi-based typhoid conjugate vaccine (Vi-TCV) in Nepalese children aged 9 months to 16 years who received one dose demonstrated robust immunogenicity, no safety signal, and 82% efficacy against confirmed typhoid fever. [1] The WHO Strategic Advisory Group of Experts recommends studies of Vi-TCV co-administered with routine childhood vaccines in typhoid-endemic countries. The Burkina Faso immunization schedule includes both capsular group A meningococcal conjugate (MCV-A) and measles-rubella (MR) vaccines at 15 months of age. We tested co-administration Vi-TCV with these routine vaccinations to provide data needed for large-scale uptake of Vi-TCV in sub-Saharan Africa.

The study protocol is published. Briefly, we randomized 15-to-23-month-old children in Ouagadougou, Burkina Faso in a 1:1:1 ratio to receive either Vi-TCV and control vaccine (inactivated polio) with a subsequent MCV-A vaccine 28 days later (Group 1), Vi-TCV and MCV-A (Group 2), or MCV-A and control vaccine (Group 3). To assess vaccine safety, we assessed: 1) reactions within 30 minutes of vaccination, 2) solicited symptoms at 0, 3, and 7 days post-vaccination, 3) other adverse events within 28 days of vaccination, and 4) serious adverse events within 6 months of vaccination. We assessed immunogenicity of Vi-TCV by ELISA at days 0 and 28 in participants randomized to receive Vi-TCV versus control vaccine. We also assessed MCV-A immunogenicity at days 0 and 28 using serum bactericidal antibody (SBA) testing among participants who received MCV-A at enrollment. We summarized the percentage of participants who achieved at least four-fold anti-Vi IgG antibody increase (seroconversion), geometric mean titers (GMTs) with 95% confidence intervals (CI) for SBA, and percentage of participants who achieved a threshold SBA titer of 128 that corresponds with protection. We compared anti-Vi seroconversion (Groups 1&2) and SBA (Groups 2&3) results at pre- and post-vaccination time points.

We enrolled 150 children aged 15–23 months old into three groups: 49 in Group 1, 50 in Group 2, and 51 in Group 3. Solicited symptoms associated with vaccination were similar for TCV and IPV, respectively at day 0 (fever or feverishness 2.0% vs 5.9%, injection site pain 0% vs 1.0%; no irritability, injection site swelling ,or erythema in either group), day 3 (fever or feverishness 2.0% vs 3.9%, irritability 0% vs 2.0%, injection site swelling 0% vs 1.0%; no injection site pain or erythema in either group), and day 7 (fever or feverishness 2.0% vs 0%, irritability 2.0% vs 0%; no injection site pain, injection site swelling, or erythema in either group). Post-vaccination seroconversion for anti-Vi IgG antibody was similar for participants who received TCV with IPV vs TCV with MCV-A (89.6% vs 94.0%, p=0.43). For participants who received MCV-A at enrollment, post-vaccination MCV-A antibody GMT measured by SBA was similar for participants who received MCV-A with TCV vs MCV-A with IPV (13,385 [95%CI 9,784-18,311] vs 9,410 [95%CI 6,009-14,736], p=0.20), and a similar percentage achieved protective post-vaccination SBA titer $\geq$128 (100.0% vs 98.0%). Vi-TCV was well-tolerated and did not show a safety signal when co-administered with routine 15-month vaccination in Burkinabe children. Vi-TCV immunization resulted in a robust immune response without evidence of interference with MCV-A. Vi-TCV can be co-administered with MCV-A as part of routine childhood vaccination.

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Therapeutic Application of a YS1646 *Salmonella* Typhimurium Vectored Vaccine in Mice Chronically-Infected with *Schistosoma mansoni*

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Learning Objectives

- Describe a novel and effective candidate *Schistosoma mansoni* therapeutic vaccine
- Discuss the use of attenuated *Salmonella* Typhimurium as a vaccine delivery platform

Abstract

Schistosomiasis is a fresh-water-borne parasitic disease caused by trematode worms of the genus *Schistosoma*. With >250 million people infected worldwide and ~800 million people at risk, the World Health Organization considers schistosomiasis to be the most important human helminth infection. [1,2] Praziquantel is an oral anthelminthic that paralyzes the adult worms and has an efficacy of 85–90%. [3] However, resistance is a growing concern [4,5] and treatment does not prevent re-infection. Several prophylactic non-living vaccines are in pre-clinical and clinical development, but only one has been assessed for therapeutic effect in an animal model with modest results. [6] Live attenuated *Salmonella* have multiple potential advantages as vaccine vectors. [7,8] We have repurposed an attenuated *Salmonella enterica* Typhimurium strain (YS1646) to produce such a vaccine that targets Cathepsin B (CatB), a digestive enzyme important for parasite survival during several stages of the parasite life cycle. [9]

Based on our prior work testing various plasmid constructs in a murine model of prophylactic vaccination [10], we selected one promising strain (YS1646 bearing nirB_SspH1_CatB) for evaluation as a therapeutic vaccine. Female C57BL/6 mice were infected with 150 *S. mansoni* cercariae. Once infection was well-established, mice were immunized at either two or four months post-infection. A multi-modality immunization schedule was used that included three oral (PO) doses of CatB-bearing YS1646 on days 1, 3, and 5 as well as an intramuscular (IM) dose of recombinant CatB on day one. Serum (IgG) responses to CatB were monitored by ELISA. Mice were sacrificed at intervals post-vaccination to assess adult worm and egg burden (liver and intestinal tissue) that were expressed relative to the saline control group numbers. Data were analyzed by one-way ANOVA with Tukey's multiple comparison correction. P values less than 0.05 were considered significant.

Although all animals were infected with *S. mansoni*, serum anti-CatB IgG levels were significantly increased in immunized animals (e.g., 5,362 ± 931 ng/mL vs 2,348 ± 126 ng/mL at 4 weeks after vaccination: $p<0.001$). Compared to the mock-vaccinated animals, all parasitological outcomes (worm numbers and hepatic/intestinal egg burdens) were 40–50% reduced at 4 weeks post-vaccination with further reductions (approximately 55–70%) at 8 weeks post-vaccination. Both relative and absolute reductions in worm numbers and hepatic/intestinal egg burdens continued to increase over time as mice were sacrificed 12, 16, and 24 weeks post-vaccination, suggesting that the vaccine led to a slow but progressive loss of adult worms and/or female worm fecundity. We are currently generating chromosomally-integrated *Salmonella* strains to produce a more acceptable vaccine for eventual human use (i.e., stability, no antibiotic resistance). More than 250 million individuals are currently afflicted by schistosomiasis for whom only a single worm-targeting drug is currently available (i.e., praziquantel). A vaccine that has both prophylactic and therapeutic activity would be ideal for use in conjunction with mass treatment campaigns with praziquantel.

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Vaccine Effectiveness Against Influenza-Related Hospitalizations and Serious Respiratory Events During the 2017–2018 Influenza Season: Comparison Between Quadrivalent Cell-Based and Egg-Based Influenza Vaccines

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Learning Objective
Assess the relative vaccine effectiveness of quadrivalent cell-based and egg-based influenza vaccines to prevent influenza-related and respiratory-related hospitalizations/emergency room visits and all-cause hospitalizations, among subjects 4–64 years old, and for different age subgroups and a high-risk subgroup

Abstract
Viral adaptation during traditional egg-based influenza vaccine manufacturing has been identified as a potential reason for the limited effectiveness of seasonal influenza vaccines. Cell-based vaccine manufacturing avoids egg-adaptation selection in the antigenic structures and thereby improves the match between vaccine antigens and recommended World Health Organization's (WHO) seed viruses, which potentially increases the vaccine effectiveness. This study aimed to evaluate if the prevention of egg-adaptation changes within the cell-based quadrivalent influenza vaccine (QIVc) improves the vaccine effectiveness of the egg-based quadrivalent influenza vaccine (QIVe) by reducing influenza-related and respiratory-related hospitalizations/emergency room (ER) visits among subjects 4–64 years old during the 2017–2018 influenza season.

A retrospective cohort analysis was conducted among subjects 4–64 years old vaccinated with QIVc or QIVe using administrative claims data in the US (IQVIA's Real-World Data Adjudicated Claims – US Database). Baseline characteristics included age, gender, payer type, Department of Health and Human Services region, Charlson Comorbidity Index, comorbidities, month of flu vaccination, indicators of frail health status, and pre-index hospitalization. The adjusted number of events and rates (per 1,000 vaccinated subject-seasons) of influenza-related hospitalizations/ER visits, respiratory-related hospitalizations/ER visits (e.g., pneumonia, asthma/chronic obstructive pulmonary disease [COPD]/bronchial and other respiratory events), and all-cause hospitalizations were calculated using inverse probability of treatment weighting and Poisson regression (following CMS/FDA statistical methodology [1]). Sub-analyses for different age subgroups (4–17 years, 18–64 years, 50–64 years) and a high-risk subgroup were conducted. The high-risk group was defined following the Influenza Green Book from Public Health England [2] and included subjects between 18–64 years old with one of the following conditions: chronic liver disease, chronic respiratory disease, diabetes, morbid obesity, pregnancy, chronic heart disease, immunosuppression, chronic kidney disease, chronic neurological disease, asplenia or dysfunction of the spleen.

During the 2017–2018 influenza season, 555,538 recipients of QIVc and 2,528,524 of QIVe were identified. Adjusted results show that rVE for QIVc was significantly higher compared to QIVe for influenza-related hospitalizations/ER visits overall (14.40% [95% CI: 8.83%–19.63%]). Similar findings were obtained for the 18–64 and 50–64 years subgroups and for the high-risk subgroup with rVEs of 13.09% (95% CI: 6.79%–18.96%), 9.36% (95% CI: 0.31%–17.58%), and 10.07% (95% CI: 1.14%–18.18%), respectively. Overall, QIVc was 11.77% (95% CI: 10.43%–13.09%), 8.32% (95% CI: 5.94%–10.65%), and 6.86% (95% CI: 4.93%–8.76%) more effective than QIVe for prevention of all-cause hospitalizations, and hospitalization/ER visits related to asthma/COPD/bronchial and other respiratory events, respectively. Similar trends were seen for the 18–64 years, 50–64 years, and high-risk subgroups; for instance, rVEs for QIVc compared to QIVe against all-cause hospitalizations were 12.98% (95% CI: 11.72%–14.23%), 5.09% (95% CI: 2.98%–7.16%), and 7.39% (95%

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CI: 5.56%–9.19%), respectively. Within the pediatric sub-group, rVE for QIVc compared to QIVe was significantly higher for hospitalization/ER visits related to pneumonia (32.98% [95% CI: 13.67%–47.97%]) and asthma/COPD/bronchial events (13.42% [95% CI: 4.42%–21.57%]). In conclusion, in adjusted analysis, QIVc reduced influenza-related and respiratory-related hospitalizations/ER visits and all-cause hospitalizations compared to QIVe overall and across multiple age groups and a high-risk subgroup during 2017–2018 influenza season.

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