BEHAVIORAL SCIENCE AND VACCINE HESITANCY

Development and Evaluation of an Educational Human Papillomavirus (HPV) Vaccine Comic Book for College Students in Northeast Ohio: An Application of the Integrative Behavior Model

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Learning Objective
Develop an educational HPV vaccine comic book for target populations with average to low coverage rates to improve knowledge and beliefs regarding intention to complete HPV vaccination and reduce the rates of HPV-associated diseases and cancer

Abstract
Human papillomaviruses (HPV) cause several types of cancers and genital warts in both males and females. In the US, young adults, especially college students, are mostly affected. Scientific evidence shows that HPV vaccine is safe and effective; however, its coverage remains lower than other vaccines for young adults. This implies missed vaccination opportunities. There is a need to improve HPV vaccination promotion strategies in this population. Comic books are potentially effective for health education of diverse groups, because they are easily accessible, low-cost, engaging and unobtrusive. They may help to improve knowledge and beliefs regarding HPV vaccination, increase its acceptance and uptake, as well as decrease HPV-related diseases.

This is a mixed methods study. In 2017, we recruited a diverse population of 18 to 26-year-old male and female students from a college in northeast Ohio. Using qualitative methods, we identified the salient beliefs regarding HPV vaccination completion within one year. We conducted multiple linear regression analysis and Pearson's correlation to examine predictors of intention to complete HPV vaccination within one year among unvaccinated participants using constructs form the Integrated Behavior Model (IBM). We developed an educational HPV/HPV vaccine comic book informed by evidence from target population-based studies on HPV vaccination, reputable health literacy tools, pilot testing, and the IBM. We hypothesized that this intervention would improve college students' HPV vaccine knowledge, beliefs, attitude, perceived norm, personal agency, and intention to complete HPV vaccination within 1 year. Using a quasi-experimental pre-posttest survey design, we evaluated the effect of the intervention on the participants' HPV vaccine knowledge, beliefs, attitude, perceived norm, personal agency, and intention to complete HPV vaccination within 1 year.

Most of the participants [n=304, males (28%), females (72%)] who completed the pre-posttest surveys reported that the comic book is acceptable, easy to read, understandable, relevant, and has high quality information and graphics. Only 29% reported they completed the recommended three doses of HPV vaccine. Multiple linear regression analysis (n=157) showed age (b=-0.11*); race (b=0.81*); instrumental attitudes (b=0.43*); injunctive norms (b=0.20*); and descriptive norms (b=0.55**) were significant predictors of intention to complete HPV vaccination within 12 months [R2=0.47, F(8)=16.12, p<0.0001] among unvaccinated study participants. Overall, the intervention proved to be effective in creating positive changes. Mean HPV/HPV vaccine knowledge score increased from 50%–90%, McNemar's test showed statistically significant higher levels of understanding in all the knowledge questions. Paired t-test analyses showed increases in mean score for HPV knowledge: 7.15**, CI=6.60-7.69; dimensions of Attitudes (instrumental: 0.81**, SD=1.13; experiential: 0.57**, SD=1.21); Perceived norms (injunctive: 0.48**, SD=1.00; descriptive: 0.12*, SD=0.66); and Personal agency (autonomy: 0.48**, SD=1.26; capacity: 0.60**, SD=1.42) as well as Intention to complete HPV vaccination within 12 months: 1.51, CI=1.28-1.72 among unvaccinated participants. Significant positive changes were also noted in targeted beliefs [*=p<0.05, ** =p<0.0001].

Findings will aid researchers to develop effective interventions for increasing HPV vaccine coverage. Further research will explore use of comic books to increase vaccine uptake for populations of various ages in primary and secondary schools as well as in clinics.

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Increasing Vaccine Compliance Among College Freshmen

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Learning Objectives

- Identify vaccine knowledge deficits among incoming college freshmen and increase awareness of vaccine-preventable diseases on college campuses
- Determine the influence of an educational module on the perceptions and behaviors of incoming freshman regarding vaccinations

Abstract

College students living in close quarters have a heightened risk for contracting meningococcal meningitis and other communicable diseases such as influenza and pertussis. [1] Currently, Brigham Young University (BYU), a private university in Utah, does not have vaccine requirements for students. [2] In July 2018, the State Board of Regents (SBOR) in Utah updated a policy regarding vaccine education of college age students. [3] In this revised policy, the SBOR clarifies that all students living on campus should receive education about vaccines. Colleges and universities across Utah are now in need of effective strategies to comply with this new policy. To implement this policy, the BYU research team aims to determine current vaccine perceptions and behaviors among BYU freshmen, educate incoming freshmen on preventing communicable diseases, and measure the effectiveness of module. It is hypothesized that this educational intervention will decrease campus vaccine hesitancy.

An online educational module on vaccinations and disease prevention on college campuses was created in collaboration with public health experts, including the Utah County Immunization Coalition (UCIC), the Utah Scientific Advisory Committee (USAC), and the Greater Salt Lake Immunization Coalition (GSLIC). This interprofessional collaboration is vital for successful implementation of community health improvement projects. An email was sent to all incoming BYU freshman notifying them of the opportunity to participate in the study. Participants completed a demographic survey and pre-questionnaire prior to completing the vaccine education module. Upon completion of the module, participants completed a post-module questionnaire in order to evaluate any change in opinions regarding immunizations. They were also asked to list new information learned during the module and any vaccine or communicable disease-related questions. Data was entered into SPSS and reviewed by two researchers for accuracy. The data was then analyzed using a dependent t test.

The percentage of students (N=177) who selected a 10 out of 10 likelihood to be up to date on their own vaccinations increased by 9.6% ($p<.0001$) after the educational module. There was also a 14.7% ($p<.0001$) increase in participants expecting other BYU students to be up to date on immunizations. Additionally the survey measured the students' likelihood to ask BYU classmates or family to be vaccinated. Students who marked 0–3 (strongly unlikely) on the survey to ask family members to be vaccinated decreased by 7.9% ($p<.0001$) and those opposed to asking other students decreased by 21.4% ($p<.0001$).

The survey also asked participants to list any concerns about vaccines. Students who were concerned that others would not stay up to date on their vaccines increased by 11.7% post-module. Additionally, 20% of participants listed cost and access as a concern and requested more information regarding vaccinations.

The module was effective in improving students' perception regarding vaccines and willingness to ask others to be vaccine-compliant. Just a brief educational intervention can help increase vaccine compliance and improve perception and behavior.

Having immunization requirements on college campuses is the best way to increase immunization rates. [4] While not all colleges require immunizations, education is essential to promoting campus-wide compliance and protecting students against communicable diseases.

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Trends in the Uptake of Pediatric Measles-Containing Vaccine in the United States: A Disneyland Effect?

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Learning Objective
Describe trends in the pediatric uptake of measles-containing vaccine in the US following the 2014–2015 Disneyland measles outbreak

Abstract
Measles is a highly contagious viral illness that can effectively be prevented by two-doses of measles-containing vaccine (MCV). [1] While a high proportion of the US population is vaccinated for measles, MCV delays or refusals have contributed to measles outbreaks. [2,3] Among recent outbreaks, the Disneyland measles outbreak that began in December 2014 at the Disneyland theme park in California received a high amount of national media attention beginning in January 2015 [4,5], with national surveys suggesting more than 50% of US parents with young children were aware of the outbreak. [4,6,7] Media attention regarding a health issue can influence health-related behaviors, including vaccine uptake. [4,8,9] Thus, we investigated the relationship between the 2014–2015 Disneyland outbreak and the uptake of MCV by 19 months of age among a nationally representative sample of US children.

We examined age at MCV administration and ≥1-dose MCV coverage by 19 months of age using data from the 2012–2017 National Immunization Survey-Child (NIS-Child). Briefly, NIS-Child recruits a sample of US children to estimate vaccination coverage using healthcare provider records. Coverage is estimated for three age groups annually, representing 13 overlapping birth cohorts across 2012–2017 survey years. We only included participants with adequate provider data and sampling weights. To examine the effect of Disneyland outbreak news coverage, we classified birth cohorts with children <19 months of age as of January 2015 as “exposed”, and cohorts with all children ≥19 months as “unexposed”. A difference-in-differences study design with adjustment for categorical birth cohort was employed to estimate the exposure effect on each outcome, where pneumococcal-containing vaccine (PCV) ≥1-dose coverage or first PCV administration age was included as a control to account for time-varying confounding. Binomial regressions with an identity link function were performed to estimate mean differences in ≥1-dose MCV coverage between exposed and unexposed cohorts. Linear regressions were performed to estimate mean differences in MCV administration age in days. Multivariable analyses adjusted for maternal education, income, and race/ethnicity with exposure-variable interaction terms for each variable. All analyses included sampling weights.

Between 2012–2017, NIS-Child included 90,679 participants with adequate provider data and weights, representing 34,471,357 children. In crude analyses, mean MCV ≥1-dose coverage was 87.2% (95% CI: 86.6%, 87.7%) among unexposed cohorts, with 1.1% (0.3%, 2.0%) higher coverage among exposed cohorts; estimates from our base difference-in-differences model were similar. In multivariable models with exposure-variable interactions for maternal education, household income, and race/ethnicity, the exposure was associated with higher ≥1-dose MCV coverage among children of college-educated mothers with a household income of >$75,000 in multiple race/ethnicity categories (non-Hispanic black only: 4.5%, 95% CI: 1.6%, 7.5%; non-Hispanic other or multiple race: 4.9%, 95% CI: 1.9%, 7.8%; non-Hispanic white only: 5.1%, 95% CI: 4.0%, 6.2%). In crude analyses, mean MCV administration age was 406.0 (95% CI: 405.1, 406.9) days among unexposed cohorts, with mean MCV administration 6.5 (95% CI: 5.1, 7.8) days earlier among exposed cohorts; similar estimates were derived from our base difference-in-differences model. Since trends in MCV administration age by exposure status were similar across maternal education, household income, and race/ethnicity categories, we ran multivariable analyses that did not include exposure-variable interaction terms; estimates were again

similar to crude analyses. Collectively, these data suggest Disneyland outbreak media coverage was associated with greater MCV uptake among children of higher socioeconomic status, and an overall decrease in MCV administration age. These data complement national surveys that reported higher MCV support among parents aware of the outbreak [4], and creation of stricter immunization policies by healthcare providers following the outbreak. [10]

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EPIDEMIOLOGY AND BURDEN OF VACCINE-PREVENTABLE DISEASES

Epidemiology of Seasonal Influenza and Benefit of Influenza Vaccination Among Older Adults in Japan: A Systematic Literature Review and Meta-Analysis

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Learning Objective
Review existing Japanese evidence of epidemiology and disease burden of seasonal influenza for age 50+ years to raise awareness of the unsolved disease burden and of suboptimal effectiveness of currently available standard-dose vaccines

Abstract
Older populations are particularly vulnerable to influenza and often require extensive clinical support. In Japan, nationwide passive sentinel surveillance monitors seasonal influenza but does not capture the full disease burden. Japan currently uses standard dose (SD), egg-based quadrivalent influenza vaccines (QIV) which include both influenza B lineages, after switching from trivalent vaccines (TIV) was endorsed by the Japanese government in 2015–2016 season.

While vaccination programs have generally been shown to be cost-effective, vaccine effectiveness (VE) among older populations has been reportedly sub-optimal. Importantly, hospitalization due to influneza occurs most frequently in the elderly despite the use of antivirals for post-exposure prophylaxis and for treatment. We synthesized existing evidence on epidemiology, VE, and costs of seasonal influenza in adults age over 50+ years.

We performed a PubMed, EMBASE, and ICHUSHI search for articles describing seasonal influenza in Japan, published between 1997–2018, in English or Japanese. Grey literature was also assessed. Systematic reviews, prospective or retrospective observational studies, randomized controlled trials, and economic studies conducted in Japan, describing populations age ≥50 years with laboratory-confirmed influenza or symptomatic influenza disease (influenza-like-illness (ILI) or similar), were included in this study. Articles were excluded if a primary focus was not seasonal influenza. Information from included articles was extracted into a predefined data extraction template which included study characteristics, target population details, and study outcomes.

A random-effects meta-analysis was used to characterize VE of SD among studies reporting this information. A meta-regression approach was used to explore whether study characteristics (subject age; study setting, design, or circulating influenza virus types) were explanatory of the overall relative risk (RR). Four case control studies reported odds ratios (OR); RRs for these studies were estimated. RR estimates were presented as a forest plot and used to estimate VE using the formula RR=1-VE using RR estimates for laboratory-confirmed influenza, where available.

Of 1,147 identified articles, 143 met inclusion criteria. Reported incidence rates varied considerably depending on study design, season, study setting, and, most importantly, case definition. In nursing homes, the maximum reported influenza attack rates were 55.2% and older adults suffered significant influenza disease burden, hospitalizations, and mortality.

Most hospitalizations were in people age >60 years. Sixteen articles reported mortality rates associated with seasonal influenza with a range of case fatality rates from 0.009% to 14.3% depending on baseline health status, case definitions, vaccination rate, comorbid conditions, population size, and prescription of anti-viral medications.

In meta-analysis, overall VE was 19.1% (95% CI: 2.3%–33.0%) with high heterogeneity (I2: 89.1%). There was a trend of lower VE in older people (40.1% in the <65 group; 12.9% in those ≥65; p=0.21). Studies conducted in hospital or nursing home settings reported lower VE (8%) than studies conducted in the community (24%; p=0.37) and VE reported during seasons of H1 virus dominance was slightly higher (22%) than seasons of H3 (19%) or mixed/B virus type circulation (15%). Additional healthcare costs were partially mitigated by vaccine administration.

Despite differences between studies that make comparisons challenging, the influenza burden in elderly Japanese is significant. Influenza VE and related socioeconomic outcomes data were limited and lack generalizability. Further research on influenza management for this population is warranted with an emphasis on characterizing the benefits of prevention.

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Respiratory Viral Infection Surveillance in Pediatric Hematopoietic Stem Cell Transplant Recipients

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Learning Objectives

- Describe the frequency of respiratory viral detection in a cohort of hematopoietic stem cell transplant recipients who participated in one year of an ongoing high dose vs. standard dose influenza vaccine study
- Describe illness severity in subjects with breakthrough influenza in a cohort of hematopoietic stem cell transplant recipients who participated in an ongoing high dose vs. standard dose influenza vaccine study

Abstract

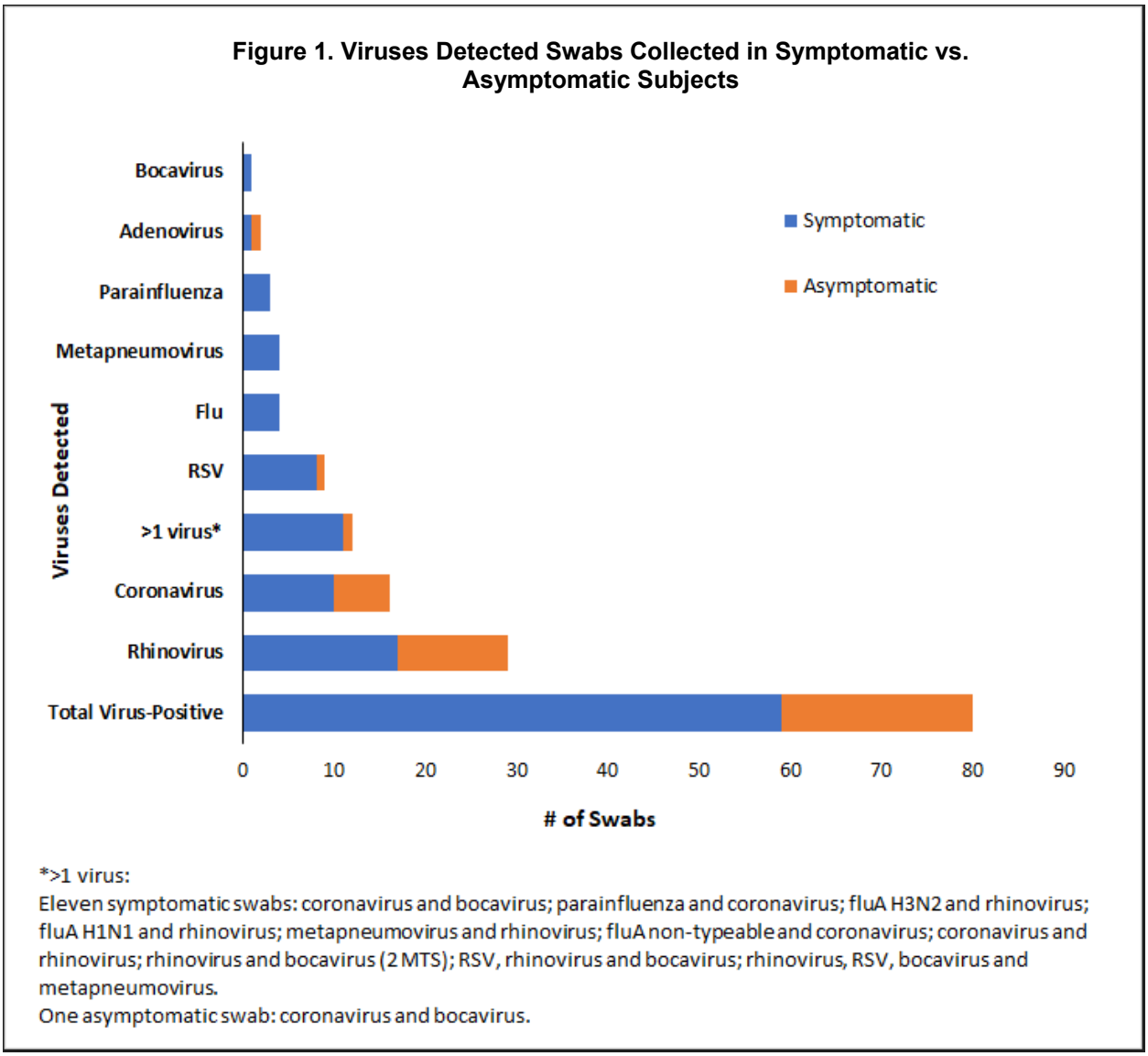
Influenza (flu) is associated with severe morbidity and mortality among hematopoietic stem cell transplant (HSCT) recipients. [1] We performed respiratory viral infection surveillance in pediatric HSCT recipients during an ongoing flu vaccine trial (start date: 9/2016) to determine the frequency of breakthrough flu infections in this high-risk population. The objective of this study is to describe the respiratory viral frequency detection in our cohort who participated in year three of the vaccine study.

Pediatric HSCT recipients were enrolled as part of a phase 2, nine-center, randomized-controlled, double-blinded immunogenicity/safety clinical trial comparing two doses of either high-dose trivalent inactivated flu vaccine or standard dose quadrivalent inactivated flu vaccine. Mid-turbinate nasal swabs (MTS) were collected from subjects who reported symptoms throughout the study period. However, during local flu season, active surveillance was performed through weekly communication, and MTS were also collected at study visits, regardless of symptoms. Specimens were tested using Luminex NxTAG Respiratory Pathogen Panel.

Ninety-one pediatric HSCT recipients were enrolled from 9/2018 to 2/2019; 55% were male, median age was 11.3 years [range: 3.1–18.9 years] and median time from HSCT was 9.3 months [range: 3–35.3 months]. Most subjects (74/91, 81%) had ≥1 MTS collected. Among 155 MTS collected, one or more viruses were detected in 80 MTS (52%). A total of 21/75 (28%) virus-positive specimens were collected from asymptomatic subjects and 59/80 (74%) virus-positive specimens were from symptomatic subjects (Figure 1). Six subjects (7 samples) tested positive for flu A (two H1N1, three H3N2, two non-typable) and all were symptomatic. Three flu-positive subjects had co-infection: two with rhinovirus and one coronavirus. The medically-attended visits associated with flu-positive detection included: hospitalization (n=1), emergency department visit (n=1), and outpatient visit (n=1). The three other subjects did not seek medical attention.

Breakthrough flu was detected in 7% of the pediatric HSCT recipients in our cohort despite flu vaccination; all were symptomatic, but most cases were mild. The study remains blinded as to vaccine formulation. Detection of non-flu viruses in asymptomatic HSCT flu vaccine recipients warrants further investigation to ascertain clinical significance.

Figure 1.



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Systematic Review of Diagnostic Accuracy of Dried Blood Spots for Diagnosis and Seroprevalence of Vaccine-Preventable Diseases

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Learning Objective
Determine the validity and reliability of dried blood spot specimens in measuring the presence and concentration of IgG and IgM antibodies to vaccine-preventable diseases in humans

Abstract
Blood serum and plasma specimens are regarded as the gold standard in assessing population immunity to vaccine-preventable diseases. However, the collection and storage of venous blood samples can be particularly challenging in low-resource settings. [1-4] Dried blood spots can potentially be a feasible alternative to venous blood in low-resource settings, provided these assays can achieve adequate sensitivity and specificity. Studies on the diagnostic accuracy of dried blood spots have been conducted, but the protocols and results have varied widely. [1-4] A systematic review was needed to clarify the use of dried blood spots to measure antibodies to all vaccine-preventable diseases. The aim of this systematic review was to critically review all available data on the diagnostic accuracy of dried blood spots, and to determine the validity and reliability of dried blood spot specimens in measuring IgG and IgM antibodies to vaccine-preventable diseases in humans.

We undertook a comprehensive systematic review and meta-analysis to determine the accuracy and reliability of dried blood spots compared to venous blood in measuring IgG or IgM antibodies to vaccine-preventable diseases. For the overall systematic review, we did a two-stage screening process, first with titles and abstracts and subsequently with full text articles, to identify those that met the pre-defined eligibility criteria. Citations were uploaded into DistillerSR [5] and two reviewers independently screened each article, identified relevant studies, and abstracted the results. Quantitative analyses included data abstraction to generate the four-cell values of diagnostic two-by-two tables for each study. We re-calculated the sensitivity and specificity with 95% confidence intervals for each index-reference test comparison. Information on capillary or venous blood collection and processing methods in the form of dried blood spots was included in the extraction phase. We identified whether studies reported practical aspects in evaluating the use of dried blood spots, including collection, transportation, storage, and processing procedures. For each vaccine-preventable disease, information was summarized and presented in a summary of findings table.

Five thousand two hundred twenty-eight (5,228) potential references were identified in the overall systematic review, and we identified 26 studies that evaluated dried blood spots and 4 that evaluated liquid capillary blood against a recognized reference specimen, usually serum, for a vaccine-preventable disease. The majority of studies utilized capillary blood as the index specimen. We observed wide variation in reporting from studies reporting the measurement of IgM and/or IgG antibodies against different vaccine-preventable diseases. Studies focused on measles, rubella, and dengue typically either reported 2×2 tables or provided the necessary values. Studies focused on other diseases typically measured and reported average antibody concentration, rather than individual-level index and reference test results. As a result, sensitivity and specificity values were unavailable or could not be calculated for a number of studies. The included studies showed good performance of dried blood spots compared with serum in the detection of IgM and IgG antibodies for different vaccine-preventable diseases. Dried blood spot samples, while less vulnerable than serum samples, still require specific storage and temperature conditions to maintain their diagnostic accuracy. Very few authors reported whether appropriate measures were undertaken to ensure sample quality. Dried blood spots are

widely used as index specimens in low-resource settings, certainly more widely used than oral fluid. However, the number of studies concerning dried blood spots identified in our review does not accurately reflect the existing number of studies actually utilizing these specimens in different settings, possibly because the frequent usage of dried blood spots has precluded researchers from conducting additional validation studies.

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VACCINE POLICY, PROGRAMS, AND PRACTICE

Association Between Vaccine Exemption Policy Change in California and Increased Parental Adverse Event Reporting

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Learning Objective
Describe the impact of eliminating non-medical vaccine exemptions on passive surveillance adverse event reporting to alert physicians and public health authorities of concerning trends

Abstract
California Senate Bill 277 (SB277) eliminated non-medical immunization exemptions. Since its introduction on February 19, 2015, the rate of medical exemptions in the state has increased. Filing a report to the Vaccine Adverse Event Reporting System (VAERS) may be perceived as helpful in applying for a medical exemption. Our objective was to describe trends in reporting to VAERS from California coincident with introduction of SB277.

VAERS is a national, passive, vaccine safety surveillance program co-managed by the CDC and FDA. VAERS reports may be submitted by healthcare providers, vaccinees or parents, vaccine manufacturers, and others. The study population included children <18 years (at time of report) living in California for whom a VAERS report was submitted between June 1, 2011 and July 31, 2018. The primary outcome of this study was the proportion of all reports submitted by parents. The secondary outcome was characterization of parent reports. We analyzed reports by study period, vaccinee characteristics, reporting time (time elapsed from vaccine receipt to date of report submission), and type of adverse event. We also performed spatial analysis, mapping reports pre- and post-mandate by county.

We identified 6,703 VAERS reports from California, received June 1, 2011 through July 31, 2018. The proportion of parent reports increased after the implementation of SB277, from 14% to 23%. The median reporting time increased from 9 days in 2013–2014 to 31 days in 2016–2017. After the introduction of SB277, we observed an increase in reports describing behavioral and developmental symptoms among reports submitted 6 months after immunization. These recent changes in reporting patterns coincident with the introduction of SB277, may indicate that more parents are using VAERS to assist in applying for a medical exemption for their child. This highlights the importance of follow-up by physicians, local and county public health authorities, and school district administrative personnel, to ensure that children have a valid reason for a medical exemption. Proposed California Senate Bill SB276 would authorize physicians in the State Department of Health to revoke inappropriate medical exemptions upon review.

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Consideration of Effective Seroprotection Rate and Cost Per Protected Patient as Estimates of Real-World Outcomes in Adult Hepatitis B Virus (HBV) Vaccination

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Learning Objectives

- Discuss the importance of the additional metrics of eSPR and CPP when assessing two-dose vs. three-dose options
- Examine institution's HBV series completion rates in order to best evaluate the clinical-effectiveness and cost-effectiveness of HBV vaccination efforts

Abstract

The Advisory Committee on Immunization Practices (ACIP) recommends vaccination of adults at risk for hepatitis B virus (HBV) infection. For HBV vaccines, compliance with a vaccine's dosing regimen and the rate at which a vaccine generates seroprotection in individuals are key considerations to assess the real-world effectiveness a vaccine's ability to reduce risk of HBV infection. Legacy three-dose adult HBV vaccines are administered on a 0-, 1-, and 6-month schedule. A growing number of studies have shown that real-world completion rates for the three-dose series ranges between 22% and 54%. (Nelson J, et al.; Gunn RA, et al; Trantham L, et al.; Bridges CB, Watson TL, Nelson NP, Bruxvoort K) These real-world completion rates impact the real-world effectiveness of HBV vaccination efforts, and a three-dose vaccine's ability to reduce risk of HBV infection.

The Effective Seroprotection Rate (eSPR) is a measure of efficacy that considers both seroprotection rates from clinical data used to support FDA licensure for all approved adult HBV vaccines, as well as real-world series completion rates for adult HBV vaccines. Considering the per dose vaccine cost and the eSPR, one can calculate a real world effectiveness metric of the true Cost per Protected Patient (CPP). The eSPR and CPP provide policy-makers with a value-oriented approach to consider in their evaluation of adult HBV vaccines.

This analysis calculates the eSPR as a measure of potential “real world” effectiveness of adult HBV vaccines from 1) head-to head seroprotection rates by dose from Phase 3 clinical trial data between a two-dose HBV vaccine administered over one month and a legacy three-dose HBV vaccine administered over six months, and 2) real-world series completion rates by dose from multiple peer-reviewed sources for adult HBV vaccines. The analysis also calculates the CPP for the two-dose vs. three-dose options, applying publicly available sources for each vaccine price.The setting of the analysis is all sites of care where adult vaccination is administered. The relevant population is all adults indicated for administration of adult HBV vaccine.

Based on these data, different levels of eSPR and CPP between the HBV two-dose vs. three-dose vaccine options can be observed providing economic decision makers a value-oriented approach to consider in their assessment of adult HBV vaccines.

When evaluating factors for adult HBV vaccine selection, the eSPR and CPP represent real-world, value-driven approaches, and should be considered among key metrics for comparison. Moreover, it is recommended that any site of care that acquires and administers adult HBV vaccine should examine their own series completion rates in order to best understand eSPR and the CPP metrics in their institution.

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Cost-Effectiveness of Respiratory Syncytial Virus (RSV) Prevention in Mali

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Learning Objective
Evaluate current and novel RSV prevention strategies for potential cost-effectiveness in Malian infants age 0 to 6 months to inform future policy decisions

Abstract
Low and middle-income countries (LMICs) bear the greatest burden of respiratory syncytial virus (RSV)-associated infant morbidity and mortality. [1] However, the only market-approved product for RSV prevention is a humanized monoclonal antibody, palivizumab, which has a price point that is cost-prohibitive for LMICs. Maternal RSV vaccines and longer-lasting monoclonal antibodies, which could be more affordable for these settings, are currently in development. Here, we evaluate the cost-effectiveness of current and novel RSV prevention interventions in Mali, to inform recommendations about product use and country investment in LMICs.

Using epidemiologic and cost data specific to Mali, we estimated the maximum cost-effective price for current and novel RSV preventive interventions (both pediatric and maternal). We constructed monthly cohorts of Malian infants from birth through 6 months of age, modeling age-specific and season-specific exposure to RSV. Epidemiologic parameters were derived from a nested case-control study in Mali that examined community incidence of RSV, and healthcare costs from a clinical trial of influenza vaccines. We simulated health and economic outcomes under the status quo without prevention, seasonal monthly prophylaxis with the current market-approved monoclonal, a single dose of a new long-lasting monoclonal, and maternal vaccination. We measured health impact in disability-adjusted life-years (DALYs), and economic costs in 2017 USD, discounting both by 3 percent annually. We projected DALYs averted spanning 0 to 100 percent intervention coverage. The maximum acceptable cost per dose of each intervention was calculated using a net health benefits framework, WHO standards, and the Mali-specific threshold for “very cost-effective” interventions. We incorporated parameter uncertainty to quantify the real-world range in product threshold costs. Additionally, a one-way (univariate) sensitivity analysis was performed to identify those parameters with greatest influence on the results.

Our analysis indicated that the long-lasting monoclonal antibody would avert the most DALYs. This impact is reflected in the threshold cost for each product: our model predicts interventions would be very cost-effective below costs of $15, $65, and $27 per dose, respectively, for the current monoclonal, new long-lasting monoclonal, and maternal vaccine. A probabilistic analysis incorporating empirical uncertainty in the model parameters indicated 90% confidence that the current monoclonal, long-lasting monoclonal, and maternal vaccine would be very cost-effective at $12, $38, and $22 per dose, respectively. Threshold costs were most improved in scenarios with increased pneumonia and case fatality rates. The Centers for Disease Control and Prevention-negotiated price per dose for pediatric DTaP vaccine is $18, for Hib vaccine the price is $9. [2] In contrast, the lowest Medicaid rebate price for palivizumab is greater than $500 per dose. [3] Based on price comparison with existing vaccines, maternal vaccination is likely to be cost-effective for Mali. However, these price thresholds are substantially lower than the market price for current monoclonal products. Our results highlight the potential benefit and value of novel RSV prevention products in low-income settings.

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El Paso's Health Department Strategies Improve HPV Vaccination Rates Among Adolescents

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Learning Objective
Evaluate three public health strategies aimed at increasing HPV vaccination rates among adolescents 13–19 years receiving services at local health department

Abstract
Human papillomavirus (HPV) is the highest sexually transmitted infection (STI) linked to cervical cancer, nearly 80 million Americans are infected. [1] Adolescents are most likely to acquire a STI such as HPV with 1 in 4 teens affected. [2] Health disparities among ethnic minorities for HPV are also evident. Accordingly, Hispanics have higher rates of HPV cancers than non- Hispanics. [3] This is of concern because the City of El Paso is predominately Hispanic with an 80.96% and persons under age 24 making up 38.81% of the population. [4] Furthermore HPV is vaccine-preventable, however, the yearly vaccination rates in the US are lower than the 80% target goal of the Healthy People 2020 guidelines. [5] To address these disparities, the health department implemented three strategies to increase HPV vaccination rates as part of the Medicaid Waiver.

The "Theory of Planned Behavior" (TPB) was used to guide formation of the three program strategies to increase HPV vaccination rates. [6] These strategies include, (1) community-based immunization events with clinicians providing services outside of the fixed site clinics; (2) clinic referrals to obtain HPV immunization during STI testing; and (3) partnership referrals from schools or organizations using a voucher. The evaluation consisted of a retrospective study design to analyze HPV immunization data from the health department's electronic records. Data collected from participants' electronic records included demographics, number of HPV doses, and dates of administration. Specifically, the criteria for record extraction was ages 13–19 with HPV vaccination during the 2018 calendar year. This criteria yielded 2,284 records which were coded from 1 to 3 based on the strategy used to provide initial vaccine and follow-up doses. These strategies were then compared to a control group who did not participate in any of the strategies and was provided with HPV vaccine through traditional clinical appointment at a fixed site location.

Based on the research study, the completion rate of HPV vaccination series was higher among patients referred by partner organizations using a voucher referral. The subjective norm construct of the TPB guides the voucher referral strategy. The theoretical framework and strategy warrants further assessment as it has a high potential for best practice across health departments. Most importantly, all strategies assisted with increasing HPV vaccination uptake and completion of all recommended series.

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Immunogenicity of Twice-Annual Influenza Vaccination in Older Adults in Hong Kong: A Randomized Controlled Trial

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Learning Objective
Compare the potential advantages and disadvantages of twice-annual influenza vaccination in locations with year-round influenza activity to describe the considerations in designing national influenza vaccination program in countries with different seasonal patterns of influenza activity

Abstract
Older adults are advised to receive inactivated influenza vaccination (IIV) annually in Hong Kong. However, vaccine protection may not span 12 months [1], and twice-annual vaccination could improve protection in locations with year-round activity [2].

We conducted a randomized controlled trial of once-annual versus twice-annual influenza vaccination in adults 70–79 years of age in Hong Kong. All participants received northern hemisphere quadrivalent IIV in autumn/winter 2016–2017 (Round 1). In spring/summer 2017 (Round 2) participants were then randomized to receive placebo or the southern hemisphere trivalent IIV containing a new A(H1N1) antigen but unchanged A(H3N2) and influenza B(Victoria) antigens compared to Round 1. In autumn/winter 2017–2018 (Round 3), all participants received northern hemisphere quadrivalent IIV with identical vaccine antigens to Round 2 plus the same B(Yamagata) antigen used in Round 1. Sera were collected prior to and one month after each vaccination for testing by the hemagglutination inhibition (HAI) assay against vaccine strains. We compared mean-fold rises in HAI titers from pre- to post-vaccination, and geometric mean titers (GMTs) after vaccination.

A total of 404 participants were enrolled. Participants who received IIV in Round 2 had significantly higher GMTs against the vaccine strains of influenza A(H1N1) and A(H3N2) between Rounds 2 and 3. In both groups, mean-fold rises and post-vaccination GMTs against all vaccine strains were statistically significantly lower in Round 3 than Round 1. Receipt of IIV versus placebo in Round 2 did not have a statistically significant effect on post-vaccination GMTs in Round 3. Vaccination in spring/summer 2017 provided improved HAI titers that could bridge protection between annual doses in older adults. The trial will continue to explore patterns in antibody titers in subsequent years when vaccine strains change.

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Impact of the New York State Repeal of Nonmedical Vaccination Exemptions on Schools: Perspectives from a Survey of School Administrators

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Learning Objective
Describe the impact of the New York State repeal of religious vaccination exemptions on a sample of upstate New York public and nonpublic schools

Abstract
In an effort to curb recent measles outbreaks [1], the New York State (NYS) legislature repealed the religious vaccination exemption for public and nonpublic school students. [2] The repeal became effective immediately upon its signing into law on June 13, 2019. [1] Over 26,000 students with religious exemptions, or 0.8% of all NYS students, are anticipated to be affected by the repeal. [3,4] Potential indirect consequences of the law include changes in student enrollment and absenteeism related to compliance, increases in student medical vaccination exemptions, and an increased workload for school administration responsible for assuring compliance. Further, since vaccine beliefs and exemptions tend to geographically cluster and are more common among NYS nonpublic schools [5,6], these issues may disproportionately affect schools. This research aimed to assess the impact of the repeal on upstate NY schools from the perspective of school administrators, who represent the front-line workforce for enforcement and assurance.

We sent an electronic survey to upstate NY (i.e., non-New York City) public and nonpublic school administrators on November 21, 2019 using the REDcap secure survey and data collection tool. We identified upstate NY schools and their administrator contact information using publicly available data from the NYS Department of Education. Our survey aimed to solicit the perspectives of administrators and/or their appointed contacts regarding the impact of the legislation on their school. Briefly, survey questions were related to the school's experiences complying with the new legislation, and changes in student enrollment, absenteeism, and medical vaccination exemptions associated with the new law. The survey also included questions regarding the legislation's effect on school budgets for nonpublic schools charging tuition. Electronic reminders were sent to schools if the survey was not completed within 10 business days. Phone calls were made to identify correct administrator contact information for schools with undeliverable, invalid, or blank email addresses. We used basic descriptive statistics to analyze data from completed surveys, and compared survey responses between nonpublic and public schools using rate ratios and 95% confidence intervals (CIs), since we hypothesized that school experience may differ by school type.

Electronic surveys were sent to 805 nonpublic and 2,825 public schools with administrator contact information, representing 3,630 (93.1%) upstate NY schools. As of December 16, 2019, 284 (7.8%) recruited schools completed the survey, and 56 (1.5%) invitations were undeliverable. Nonpublic schools were 2.8 (95% CI: 2.2, 3.4) times more likely to respond, with 15.5% and 5.6% response rates among nonpublic and public schools, respectively. On average, schools spent 13.3 (95% CI: 8.7, 18.0; median: 5, interquartile range [IQR]: 3, 12) hours on compliance meetings and/or written correspondence, and 11.4 (95% CI: 8.3, 14.4; median 5, IQR: 2, 10) hours addressing questions from parents/guardians; results from nonpublic and public schools were similar. A change in student enrollment was reported by 46.8%, (95% CI: 41.0%, 52.6%) of schools, with nonpublic schools 1.6 (95% CI: 1.3, 2.1) times more likely to experience enrollment changes. The law affected student attendance at 29.4% (95% CI: 24.0%, 34.7%) of schools, with no difference by school type. A change in medical exemptions was reported at 15.5% (95% CI: 11.3%, 19.8%) of schools, with no differences between public or nonpublic schools. Among nonpublic schools charging tuition, 55.9% (95% CI: 46.8%, 65.6%) reported that enrollment changes financially impacted their school, affecting a mean of 12.4% (95% CI: 8.2%, 16.6%; median:

10%, IQR: 2%, 15%) of the school's operating budget. Collectively, these results indicate a significant proportion of schools experienced changes in student enrollment, absenteeism, and medical exemptions; however, these results may not be generalizable to survey nonparticipants.

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Preventing Acute Rises in Hepatitis B Within the Opioid Epidemic: Policy and Primary Care Practice-Based Opportunities to Increase Adult Hepatitis B Vaccination in the United States

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Learning Objectives

- Describe the current adult hepatitis B vaccination rate and risk factors for acquiring hepatitis B in the US
- Develop and implement policy and practice-based strategies to increase adult hepatitis B vaccination in the primary care setting in order to prevent acute rises in hepatitis B within the opioid epidemic

Abstract

The opioid epidemic has caused alarming rises in acute hepatitis B infection, despite hepatitis B being a vaccine-preventable disease. Acute hepatitis B increased 729% in Maine from 2015–2017, 114% in Kentucky, West Virginia, and Tennessee from 2009–2013, and 78% in southeastern Massachusetts in 2017. The rise in hepatitis B has been fueled by a low US adult hepatitis B vaccination rate of only 25%, and 25% of those with unmanaged chronic hepatitis B will develop liver cancer, liver failure, and/or cirrhosis. The purpose of this study was to determine primary care physicians' awareness of current adult hepatitis B vaccination rates and identify opportunities to increase adult hepatitis B testing and vaccination within primary care.

In the first part of this project, we implemented advocacy techniques to closely collaborate with Members of Congress to develop and introduce a Congressional Resolution in the US House of Representatives and US Senate to designate April 30 as National Adult Hepatitis B Vaccination Awareness Day to increase adult hepatitis B vaccination rates in the setting of the opioid epidemic. In the investigative phase of this project in August 2019, primary care internal medicine residents and faculty at a Connecticut Community Health Center were surveyed on their adult hepatitis B testing and vaccination practices. They then attended a session on current hepatitis B testing and vaccination guidelines, and later completed another survey to determine their anticipated practice changes to address adult hepatitis B vaccination and testing.

Of the residents and faculty surveyed, 86% thought that 75% of adults are vaccinated against hepatitis B, rather than the actual vaccination rate of 25%, and 0% realized how low the current adult hepatitis B vaccination rate is. Fourteen percent were unaware that chronic hepatitis B can cause liver cancer without cirrhosis. Eighty-six percent reported caring for 10–19 adults with at least one hepatitis B-associated risk factor in the past month, with 43% caring for over 20 adults with at least one risk factor in the past month. However, 43% reported never considering testing their adult patients for hepatitis B, and 29% reported never considering vaccinating their adult patients for hepatitis B. After the educational session, 71% reported they were much more likely to consider testing, vaccinating, and ordering hepatitis B vaccinations for their adult patients, and 100% reported they were a little or much more likely to order adult hepatitis B testing and vaccination.

Based on this study's findings, there is significant opportunity to increase adult hepatitis B vaccination and testing in the primary care setting, subsequently preventing chronic hepatitis B and hepatitis B-associated liver cancer. In addition, this study further highlights the need for implementing national policies and practices that increase adult hepatitis B testing and vaccination, particularly within the opioid epidemic.

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Relative Effectiveness of aIIV3 versus IIV3, IIV4 and HD-IIV3 in Preventing Influenza-Related Medical Encounters in US Adults ≥65 Years of Age During the 2017-2018 and 2018-2019 Influenza Seasons

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Learning Objective
Describe the relative effectiveness of adjuvanted inactivated influenza vaccine against influenza-related medical encounters

Abstract
Influenza vaccination with standard, egg-derived vaccines (IIV3 and IIV4) in adults ≥65 years is less effective than in other age groups,[1] largely due to immunosenecence. [2, 3] An MF59®-adjuvanted trivalent influenza vaccine (aIIV3), and a high-dose trivalent influenza vaccine (HD-IIV3), have been developed to provide older adults with enhanced levels of protection. Studies have demonstrated that the efficacy of HD-IIV3, [4-12] and the effectiveness of aIIV3 [13-18] are greater than that of standard vaccines. Additional research has demonstrated that aIIV3 induces production of cross-reactive antibodies which provide older adults with a degree of heterologous immunity to non-vaccine antigen viral strains [19-29]. However, few comparative influenza vaccine effectiveness studies have been conducted in older adults. The objective of this study was to determine the relative vaccine effectiveness (rVE) of aIIV3 compared to IIV3, IIV4, and HD-IIV3 in preventing influenza-related medical encounters during the 2017-18 and 2018-19 US influenza seasons.

A retrospective cohort study was conducted among subjects ≥65 years of age vaccinated with one of four influenza vaccinations (IIV3, IIV4, aIIV3, HD-IIV3). The main observation periods were considered from August 1, 2017 to May 19, 2018 [30] and from August 1, 2018 to May 18, 2019 [31]. An integrated dataset was created by linking patient-level electronic medical records (EMRs) with pharmacy and medical claims data. Immunizations were ascertained using vaccine administered CVX, CPT, and NDC codes. The primary outcome was influenza-related medical encounters, defined using ICD-10 codes J09*–J11* (and analogous ICD-9-CM codes) from each patient's EMR and medical claims data [32]. Adjusted odds ratios (ORs) of influenza-related medical encounters were derived from a weighted sample using inverse probability of treatment weighting (IPTW). First, propensity scores were derived from a logit model adjusted for age, sex, race, ethnicity, geographic location, week of vaccination, and health status. The propensity scores were then used to create stabilized inverse probability of treatment weights. Adjusted relative vaccine effectiveness (rVE) was determined using the formula (1-ORadjusted)*100.

In 2017–2018, there were a total of 524,223 subjects in the aIIV3 cohort, 381,881 in the IIV3 cohort, 917,609 in the IIV4 cohort and 3,377,860 subjects in the HD-IIV3 cohort. In 2018–2019, there were a total of 1,031,145 subjects in the aIIV3 cohort, 224,999 in the IIV3 cohort, 915,380 subjects in the IIV4 cohort and 3,809,601 subjects in the HD-IIV3 cohort. Adjusted rVE estimates are shown in Tables 1 and 2.

Table 1. Adjusted relative vaccine effectiveness of aIIV3 versus comparators in the 2017-2018 influenza season

aIIV3 vs.	rVE	Confidence Interval (CI)	
IIV4	18.2	15.8	20.5
HD-IIV3	7.7	2.3	12.8
IIV3	7.5	4.2	10.6

Table 2. Adjusted relative vaccine effectiveness of aIIV3 versus comparators in the 2018-2019 influenza season

aIIV3 vs.	rVE	Confidence Interval (CI)	
IIV4	27.8	25.7	29.9
HD-IIV3	6.9	3.1	10.6
IIV3	25.6	18.2	32.2

In both the 2017–2018 and 2018–2019 influenza seasons in the United States, aIIV3 recipients ≥65 years of age had statistically significantly greater reduction in influenza-related medical encounters, compared with recipients of IIV3, IIV4, and HD-IIV3 recipients.

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VACCINE RESEARCH, DEVELOPMENT, AND PRODUCTION

A Prime-Boost Concept Using a T Cell Epitope-Driven DNA Vaccine Followed by a Whole Virus Vaccine Effectively Protected Pigs in the Pandemic H1N1 Pig Challenge Model

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Learning Objective
Evaluate the impact of an epitope-based vaccine in combination with a conventional vaccine for immunization against swine influenza to improve protection against disease

Abstract
Swine influenza is a highly contagious respiratory viral infection that is responsible for significant financial losses to pig farmers annually. Current measures to protect herds from infection include inactivated whole-virus vaccines, subunit vaccines, and alpha replicon-based vaccines. As is the case for human influenza vaccines, these strategies do not provide broad protection against the diverse strains of influenza A virus (IAV) currently circulating in US swine. Improved approaches to developing swine influenza vaccines are needed. Here, we used immunoinformatics tools to identify class I and II T cell epitopes highly conserved in seven representative strains of IAV in US swine and predicted to bind to prevalent Swine Leukocyte Antigen alleles. The efficacy of an intradermal plasmid DNA vaccine composed of these epitopes against a homosubtypic challenge was compared to an intramuscular commercial inactivated whole virus vaccine and a heterologous prime boost approach using both vaccines.

Thirty-nine IAV-free, 3-week-old pigs were randomly assigned to 1 of 5 groups and received a prime immunization at 4 weeks and boosted at 7 weeks with either the FluSure XP® inactivated vaccine (INACT-INACT), the plasmid DNA T cell epitope-driven vaccine (EPITOPE-EPITOPE), or plasmid DNA vaccine followed by FluSure XP® (EPITOPE-INACT). Control groups included unvaccinated, sham-challenged animals (negative control), and unvaccinated, challenged (positive control). The challenge was done at 9 weeks of age using a 2017 pH1N1 field strain isolated in Iowa in 2017, and pigs were necropsied at day post-challenge 5.

At the time of challenge, all INACT-INACT-IAV pigs, and by day post-challenge 5, all EPITOPE-INACT-IAV pigs were IAV seropositive. IFNγ secreting cells, recognizing vaccine epitope-specific peptides and pH1N1 challenge virus were highest in the EPITOPE-INACT group at challenge. Macroscopic lung lesion scores were reduced in all EPITOPE-INACT pigs while INACT-INACT pigs exhibited a bimodal distribution of low and high scores akin to naïve challenged animals. No IAV antigen in lung tissues was detected at necropsy in the EPITOPE-INACT-IAV group, which was similar to naïve unchallenged pigs and different from all other challenged groups. These results suggest the heterologous prime-boost approach using an epitope-driven DNA vaccine followed by an inactivated vaccine was effective against a homosubtypic challenge, illustrating the utility of immunoinformatic approaches to vaccine design. Further exploration of this vaccine approach as a practical control measure against heterosubtypic IAV infections is warranted.

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Antibody Responses Against Heterologous H5N1 Strains for an MF59-Adjuvanted Cell Culture-Derived H5N1 (aH5N1c) Influenza Vaccine in Adults and the Elderly

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Learning Objective
Describe the potential for MF59-adjuvanted, cell-derived H5N1 vaccine to provide cross protection against other H5N1 strains

Abstract
Rapid production of a vaccine specific to an emerging pandemic influenza strain is critical to the public health response. A supply system solely dependent on an egg-based manufacturing process is at risk of being overwhelmed by highly-pathogenic avian influenza virus that may compromise egg production or viability. To avoid egg supply dependence, Seqirus has applied a cell culture method using mammalian MDCK cells to pandemic vaccine manufacturing.

The ability of cell culture-derived MF59-adjuvanted vaccines to generate cross-reactive immune responses is especially relevant during the early phase of a pandemic, when stockpiled vaccines may need to be used while strain-matched vaccines are being made and in later days of a pandemic when protection against pandemic virus strains that have undergone antigenic drift may be needed. [1-3] In this study, antibody responses were measured against heterologous influenza strain(s) with an MF59-adjuvanted, cell-derived H5N1 vaccine in adult and elderly populations.

In separate but similar studies, a total of 975 subjects 18 to <65 years of age (adults), and 1,388 subjects >65 years of age (elderly), were equally randomized to receive two full or half doses of the MF59-adjuvanted, cell-derived H5N1 vaccine, aH5N1c, three weeks apart. In a pre-defined exploratory analysis, antibody responses against 5 heterologous influenza strains (H5N1 Vietnam, Indonesia, Egypt, Hubei, Anhui) were measured by HI and MN assays on Days 1 and 43 for a subset of the full-dose groups.

For 5 heterologous strains, the GMT on Day 43 in the adult and elderly subjects (full-dose vaccine) significantly increased from baseline. For adults, depending on the heterologous strain, seroconversion (SC) and HI≥1:40 was achieved by 28% to 64% of subjects on Day 43. Notably, the Day 43 SC rate for 3 heterologous strains (H5N1 Egypt, Hubei and Vietnam) had a lower bound of 95% CI at ≥40%, which exceeded the corresponding homologous strain criterion. For the elderly, SC and HI≥1:40 was achieved by 17% to 57% of subjects on Day 43. Again, notable increases in rates for SC and HI≥1:40 were observed for 3 heterologous strains (H5N1 Egypt, Hubei and Vietnam). Immune responses using the MN assay against these heterologous strains were generally higher compared with the HI assay. In adults and the elderly, full-dose aH5N1c vaccine demonstrated increased immunogenicity against heterologous H5N1 of five separate genetic clades. These findings illustrate the potential for MF59 adjuvanted, cell-derived H5N1 vaccine to provide cross protection against other H5N1 strains.

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Modulation of *B. pseudomallei* Immune Responses by Human-like T Cell Epitopes

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Learning Objectives

- Identify immunomodulatory epitopes undermining vaccine efficacy
- Apply guided structural engineering to optimize subunit vaccine formulation

Abstract

Burkholderia pseudomallei (*Bp*) is a bioterror pathogen and the causative agent of melioidosis, a serious and potentially lethal infection. Potential weaponization of *Bp* is of high concern as many strains are inherently resistant to a range of antibiotics and ineffective treatment may result in fatality rates of ~50%. Despite extensive research there are no licensed vaccines, leaving populations vulnerable to deliberate dissemination. Thus far, vaccine trial candidates either have significant safety concerns or have exhibited minimal/short-term resistance. We hypothesize *Bp* regulates immune responses by presenting human-like epitopes to the host immune system, driving the immunosuppressive function of regulatory T cells (Tregs) that may reduce vaccine efficacy. To improve on vaccine candidate selection, we have characterized human-like T cell epitopes within the *Bp* proteome for their ability to reduce immune responses.

Murine models of acute *Bp* infection were established in HLA-DR3 transgenic mice. Mice were inoculated intranasally with *Bp* K96243 at 10x LD_{50}. $CD4^+$ T cell phenotyping was completed on control and infected mice four days post-infection. Splenocytes were assayed by flow cytometry to identify T cell populations and cytokine secretion. Animals were segregated into mild, moderate, and severe infections based on their lung bacterial burden. ANOVA analysis was used to identify significant deviations in immune cell populations as compared to control mice.

Immunoinformatic analysis was applied to 90 immunogenic *Bp* antigens to identify $CD4^+$ T cell epitope content and to characterize cross-conservation with the human proteome. Human-like epitopes were assayed in peripheral blood mononuclear cells (PBMCs) of Thai melioidosis survivors and aged-matched controls provided by collaborators at the Prince of Songkla University. Patient HLA typing was performed to evaluate individual epitope presentation/reactivity. Memory $CD4^+$ T cell-dependent immunosuppressive peptides were identified through a combination of analyses, including significant suppression from baseline response and enhanced suppression compared to unexposed controls (t-test analysis) and immunoinformatics regression analysis comparing increased likelihood of suppressive responses correlating with degree of predicted reactivity.

Previous studies of *Burkholderia* infection and vaccination alluded to a potential role for Tregs in immune evasion but did not demonstrate their activation. We discovered that *Bp*-exposed mice rapidly expand Treg populations early in infection. The severity of lung infection correlates with an increase in IL-10 secreting Tregs and suppression of the Th1 response. To identify potential triggers of Treg activation, we used advanced immunoinformatic tools in the iVAX toolkit to discover human-like *Bp* T cell epitopes with potential to stimulate thymic-educated Tregs. We assessed the regulatory effect of 10 human-like *Bp* epitopes in a standardized “bystander assay”. Inhibition of induced $CD4^+$ T cell proliferation in the presence of these epitopes was assessed using PBMCs donated by melioidosis survivors from Thailand. Flow cytometry analysis identified that 50% of survivor donor-peptide pairs exhibited an immunosuppressive phenotype, compared to 20% of control pairs with reduced proliferation. Donor HLA type was characterized to predict peptide presentation by MHC and logistic regression demonstrated an association between increased human TCR-facing cross-conservation and decreased $CD4^+$ T cell proliferation for several epitopes. Combined with statistical analysis examining

the degree of immunosuppressive effect, we have selected proteins containing 5 of the 10 epitopes to move forward into structural engineering and immune characterization studies, with the goal of improving *Bp* vaccine antigens. Identification of immunosuppressive *Bp* epitopes may enable rational vaccine antigen design for improved protection against melioidosis through minimal, targeted sequence alternations that remove human-like Treg epitopes.

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Efficacy and Safety of a Booster Dose of the MenACWY-TT Vaccine Administered 10 Years After Primary Vaccination with MenACWY-TT or MenACWY-PS

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Learning Objective

Describe the long-term antibody persistence of a MenACWY-TT primary dose administered to adolescents age 11 to 17 years and the safety and immunogenicity of a MenACWY-TT booster given approximately 10 years after primary vaccination to improve meningococcal vaccine strategies for adolescents and young adults

Abstract

The quadrivalent meningococcal ACWY polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT; Nimenrix) is licensed in various countries to prevent disease caused by meningococcal serogroups A, C, W, and Y. In a previous study (NCT00464815), subjects age 11–17 years received a primary dose of MenACWY-TT or a quadrivalent polysaccharide vaccine (MenACWY-PS). Here, we report the long-term antibody persistence of the primary dose and the immunogenicity and safety of a booster dose given 10 years after primary vaccination of subjects (ClinicalTrials.gov# NCT03189745, EudraCT# 2013-001512-29).

Participants were enrolled from the Philippines and received a booster dose of MenACWY-TT at 10 years postvaccination. Antibody persistence 10 years postprimary vaccination and immunogenicity 1 month after the booster dose were evaluated by serum bactericidal activity assays using rabbit complement (rSBA) to assess the percentages of subjects with titers ≥1:8 and ≥1:128 and geometric mean titers (GMTs) for each serogroup. Safety was assessed for the booster dose.

Of 229 subjects enrolled in this extension study, 169 and 58 subjects in the MenACWY-TT and MenACWY-PS groups, respectively, completed the booster phase. The percentages of primary MenACWY-TT recipients with prebooster rSBA titers ≥1:8 and ≥1:128 at year 10 ranged from 71.6%–90.7% and 64.8%–85.2% for all serogroups, respectively, compared with 43.1%–82.4% and 25.5%–76.5% of primary MenACWY-PS recipients; rSBA GMTs for all serogroups were higher in the MenACWY-TT group than in the MenACWY-PS group at year 10. For the MenACWY-TT and MenACWY-PS groups, respectively, the MenACWY-TT booster dose elicited rSBA titers ≥1:8 in 100% and ≥98.0% of subjects; 100% and ≥96.1% of all subjects had rSBA titers ≥1:128. For all serogroups, rSBA GMTs at 1 month after the booster dose were higher than before the booster dose. No new safety signals were observed during the booster phase. Functional antibody responses elicited by MenACWY-TT persisted 10 years after primary vaccination; the booster dose was well tolerated and elicited robust immune responses.

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Immunogenicity, Lot-to-Lot Consistency, and Safety of an MF59-Adjuvanted Cell Culture-Derived H5N1 (aH5N1c) Influenza Vaccine in Healthy Adults

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Learning Objective
Describe an MF59-adjuvanted cell culture-derived H5N1 (aH5N1c) vaccine

Abstract
Influenza vaccine manufacturing has relied on embryonated chicken eggs to produce antigen for over 50 years. During a highly pathogenic avian influenza outbreak both egg quantity and quality may be compromised. Rapid production of vaccine specific against an emerging pandemic influenza strain is critical to controlling spread.

Allocated US Department of Health and Human Services funds have assisted Seqirus Inc. development of an MF59-adjuvanted cell culture-derived monovalent pandemic influenza vaccine. [1] The MF59-adjuvanted cell culture-derived H5N1 (aH5N1c) vaccine is not subject to potential limitations of egg-based production (e.g. requires large quantities of fertilized eggs; potential for egg-adaption of seed virus and antigenic mismatch), and helps address the medical need for a safe and effective pandemic vaccine. [2-3]

This study evaluated immunogenicity and lot-to-lot consistency of 3 consecutively produced lots of aH5N1c pandemic vaccine by H5N1 hemagglutination inhibition (HI) antibody responses in healthy subjects ≥18 years of age, and assessed safety. 3,196 subjects were equally randomized to receive one of 3 consecutively produced aH5N1c vaccine lots or saline placebo, as 2 observer-blinded doses (Day 1 and Day 22). Subjects were equally stratified into 2 age groups, 18 to <65 and ≥65 years of age. Immunogenicity was measured before each vaccination, and on Day 43. Safety was monitored throughout.

HI antibody responses increased after both vaccine doses and at Day 43 both age-appropriate CBER immunogenicity criteria were met.

Table 1.

Percentage of Subjects with HI≥1:40 Day 1 and Day 43				
Age Group	**18 to <65 Years**		**≥65 Years**	
	Active	**Placebo**	**Active**	**Placebo**
Day 1	**N=1,116**	**N=372**	**N=113**	**N=367**
% HI ≥1:40	13.0	15	27.8	24.5
95% CI	(10.7, 15.6)	(11.5, 19.4)	(24.9, 30.9)	(20.1, 29.6)
Day 43	**N=1,076**	**N=349**	**N=1,080**	**N=351**
% HI ≥1:40	95.0	8.5	85.7	20.8
95% CI	(93.4, 96.2)	(5.9, 12.1)	(83.3, 87.9)	(16.6, 25.8)

No changes over time were seen in placebo subjects. Lot-to-lot consistency of aH5N1c vaccine was demonstrated, with the 2-sided 95% CIs for the pairwise comparisons of ratios of GMTs being (0.90, 1.13), (0.86, 1.08), and (0.87,1.09), within the predefined equivalence ranges of 0.667 and 1.5. AEs were more frequently reported in the active treatment

group, but primarily due to solicited local AEs. The majority of solicited local and systemic AEs reported were of mild intensity.

The MF59 adjuvanted, H5N1 influenza vaccine, aH5N1c, manufactured on a cell culture platform, elicited high levels of antibodies and met CBER immunogenicity criteria at Day 43 with a clinically acceptable safety profile. Lot-to-lot manufacturing consistency was demonstrated by equivalence of GMTs.

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Francisella tularensis Live Vaccine Strain (LVS) Effects on Innate Immune Memory

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Learning Objective
Discuss the role of trained monocytes in *Francisella tularensis* Live Vaccine Strain (LVS) vaccinated mice

Abstract
Successful vaccines rely on adaptive immunity, by activating the immune system with an attenuated pathogen or pathogen subunit to elicit a heightened response at subsequent exposures. Traditionally, adaptive immune responses are credited for memory-based immunity. However, recent work with *Mycobacterium tuberculosis* and other pathogens has identified a role for "trained" macrophages in reducing bacterial burdens. Here we studied the potential role of trained monocytes in immune responses to *Francisella tularensis*, an intracellular bacterium that replicates within mammalian macrophages.

We used an *in vitro* culture approach that serves as a functional correlate that predicts vaccine-induced protection. We generated vaccinated mice using *Francisella tularensis* Live Vaccine Strain (LVS). We infected murine bone marrow-derived macrophages from naïve mice, from mice vaccinated intradermally, or from mice vaccinated intravenously with LVS. LVS-infected macrophages were then cultured alone, or co-cultured with naïve splenocytes, splenocytes from mice vaccinated intradermally, or splenocytes from mice vaccinated intravenously.

In co-cultures, immune (but not naïve) splenocytes reduced intramacrophage bacterial replication. However, we observed no differences in control of intramacrophage bacterial replication when comparing co-cultures with naïve macrophages or macrophages from LVS-vaccinated mice. Furthermore, interferon gamma production and nitric oxide levels in supernatants were comparable across conditions. Thus, in the context of this *in vitro* co-culture assay, the data do not support development of trained monocytes in bone marrow from intradermally or intravenously mice vaccinated with LVS. Using other pathogens, other groups have identified trained immunity in myeloid cells derived from the lung. Thus we are currently evaluating monocytes derived from bronchial alveolar lavage.

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Mucosal Correlates of Protection After Influenza Viral Challenge of Vaccinated and Unvaccinated Healthy Volunteers

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Learning Objective
Characterize the nasal mucosal correlates of protection from influenza illness

Abstract
Despite significant global efforts, influenza poses a significant threat to health worldwide. [1-3] The cornerstone of prophylaxis is vaccination, with current influenza vaccines designed to stimulate antibodies targeting the major surface protein, hemagglutinin (HA). [4] Limited vaccine effectiveness has led to interest in developing new improved vaccines. [5] The rational design of novel vaccines will benefit from a deeper understanding of the correlates of protection from influenza illness beyond systemic anti-HA antibodies, which are an imperfect reflection of an individual's immunity to influenza. [6,7] Because the nose is the primary site of influenza exposure and infection, the nasal mucosal correlates of protection are of particular interest. [8] Prior human studies show an inverse correlation between IgA in the nasal mucosa and clinical outcomes including symptoms and duration of viral shedding. [6,9] To better understand the protective role of nasal mucosal immunity, we conducted a human challenge study in persons vaccinated and unvaccinated against influenza.

We enrolled 82 healthy adults age 18–55 years who had not received recent influenza vaccination, regardless of baseline serum hemagglutination inhibition (HAI) titers, at the NIH Clinical Center. Half of the adults received licensed seasonal quadrivalent inactivated influenza vaccination (Flucelvax, Seqirus) prior to viral challenge, while the other half received no vaccination prior to viral challenge. All participants received 10^7 $TCID_{50}$ intranasal dose of the challenge virus, A/Bethesda/MM2/H1N1. Virus administration occurred at least 30 days after vaccination in the vaccinated group. Participants remained isolated in the hospital for a minimum of 9 days with repeated phlebotomy and nasal sampling collections as well as daily evaluation for clinical symptoms and viral shedding. After discharge, participants were followed for 2 months. Laboratory evaluation of participants' serologic and nasal mucosal samples included assays for antibodies targeting HA, neuraminidase (NA), and HA stalk.

Between April and October 2019, 82 healthy adult participants were enrolled, with 41 receiving influenza vaccination and 41 receiving no vaccination. Eight participants withdrew prior to viral challenge (4 from each group), for a total of 74 participants receiving viral challenge. In the vaccinated group, time between vaccination and viral challenge ranged from 35 to 155 days (mean, 63 days). In all participants who received viral challenge, the rate of mild-to-moderate influenza disease (MMID, defined as at least 1 symptom of influenza plus a positive clinical test for influenza) was 68%. MMID was observed in 30 (81%) unvaccinated versus 20 (54%) vaccinated participants (p=0.024). The difference in MMID rates is attributable to a significant reduction in incidence of influenza-related symptoms between the unvaccinated versus vaccinated groups (97% versus 78% respectively, p=0.0281). There was not a significant difference in incidence of shedding (81% versus 62% respectively, p=0.1208). We measured antibodies targeting HA, NA, and HA stalk in participants' serum and nasal mucosa and correlated these to clinical outcomes. Surprisingly, although vaccination afforded a statistically significant reduction in influenza disease, this reduction was limited, with 78% of vaccinated participants experiencing symptoms and 62% shedding virus, making them potentially transmissible.

It is clear that we must further explore the mucosal immunity induced by influenza infection and vaccination if we are to understand the true correlates of protection, which may serve as targets for development of future improved and

broadly protective vaccines. This research was supported by the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) Intramural Research Program.

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Norovirus Neutralization in Human Intestinal Enteroids Reveals Complex Antigenic Relationships Between and Within Genotypes

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Learning Objective
Discuss the antigenic relationships between human norovirus genotypes that could guide in the development of a cross-protective vaccine

Abstract
Human noroviruses are the most common viral agents of acute gastroenteritis. Viruses from genogroup II genotype 4 (GII.4) are responsible for the majority of outbreaks worldwide, primarily due to the emergence of antigenically-distinct variants every 2–8 years. In contrast, non-GII.4 viruses present limited diversification and remain relatively similar at the amino acid level across decades. [1] Thus, most advanced vaccine candidates consider a genogroup 1 component (GI.1) and/or a GII.4 component; however, the sudden emergence and temporal predominance of GII.17 and GII.2 viruses have highlighted the need for a cross-protective norovirus vaccine. The lack of a cell culture system for human noroviruses has impacted our understanding of the role of diversity in immunity. Recently, human intestinal enteroids were shown to be permissive for norovirus infection, which has granted the opportunity to perform neutralization assays to determine the antigenic relationship and level of cross-protection between genotypes.

We produced hyperimmune sera against 10 different virus-like particles (VLPs): two GII.4 variants (Farmington Hills_2002 and Sydney_2012), GII.20, three GII.6 variants (A-C), GII.17, and GI.1. Additionally, chimeric VLPs that presented swapped structural domains, Shell and Protruding, from GI.1 and GII.4 were developed. ELISA and carbohydrate blocking, a surrogate for neutralization [2], were performed and antibody responses were compared to the neutralization titers in human intestinal enteroids infected with either GII.4 or GII.6 noroviruses.

Antibody responses as measured by the immunoassays were specific to the homologous genotype. Likewise, hyperimmune sera raised against VLPs representing different genotypes showed genotype-specific neutralization activity against GII.4 noroviruses in the enteroids system. Sera produced against the GII.4 Farmington Hills_2002 variant were able to neutralize the GII.4 Sydney_2012 virus. Although this suggests that immunity elicited against older strains could provide protection against future variants, further studies are needed to determine the extent of waning immunity and differences between vaccine strategies and natural infections. Sera produced against chimeric VLPs showed that neutralization is primarily achieved by antibodies mapping to the Protruding domain of the norovirus capsid protein. Interestingly, only 2 (variants B and C) out of 3 of the GII.6 hyperimmune sera were able to neutralize the GII.6 virus (a variant B virus). This correlated with the patterns of sera-mediated blocking of GII.6 VLP binding to carbohydrates, suggesting that antigenic differences within certain genotypes may complicate vaccine design. This study provides empirical information on the antigenic differences among genotypes and confirms that the carbohydrate blocking assays may be used as a substitute to determine the antigenic relationships between norovirus genotypes.

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Predicting Vaccine Efficacy Against *Mycobacterium tuberculosis* with a Functional Correlate of Protection, an *In Vitro* Co-Culture Assay Using Alveolar Macrophages

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Learning Objective
Discuss research designed to develop functional assays to predict successful vaccination against *Mycobacterium tuberculosis*

Abstract
Bacille Calmette-Guerin (BCG) is the only licensed vaccine against tuberculosis (TB), but BCG provides poor protection against adult pulmonary TB, and new vaccines are in development. Clinical trials of new TB vaccines are difficult, and additional strategies to measure efficacy of new candidates, such as deriving correlates of protection, are needed. We previously developed an *in vitro* co-culture system to understand vaccine-induced immune mechanisms. In this approach, we used mouse bone marrow-derived macrophages (BM) that were co-cultured with lymphocytes from naïve or BCG-vaccinated mice. [1,2] The level of resulting TB intramacrophage growth control reflected vaccine strength. However, alveolar macrophages (AM) are the first target of TB aerosol infection, and AM are phenotypically different from BM with unique responses to TB infection. In this project, we adapted the *in vitro* co-culture system to use AM. Understanding the mechanisms driving bacterial control in AM by BCG-primed lymphocytes could help establish predictive correlates.

Alveolar macrophages were freshly isolated by bronchoalveolar lavage (BAL) of C57BL/6J mice and cultured in tissue culture plates to create a macrophage monolayer. The macrophage monolayer was infected with *M. tuberculosis* Erdman. Lymphocytes were isolated from spleens of both naïve and BCG-vaccinated mice and added to the TB-infected AM monolayers. TB growth over a week was measured by removing lymphocytes, lysing macrophages, and plating lysates on agar to count colony forming units (CFU). Supernatants and lymphocytes were also collected for future analysis.

We first optimized the multiplicity of infection (MOI; ratio of TB:AM) to achieve measurable *M. tb* uptake by macrophages and maximal intramacrophage bacterial growth. An MOI of 1:10 was selected as optimal for subsequent experiments based on the combination of acceptable initial uptake, readily measurable CFU at all timepoints, and moderate bacterial growth over a week. We then infected AM monolayers with TB and co-cultured them with naïve or BCG-primed lymphocytes. After 7 days, we found substantial TB growth in AM alone and in co-cultures containing naïve lymphocytes, but inhibition of TB growth in co-cultures containing BCG-immune as measured by CFU. Interestingly, co-cultures containing naïve lymphocytes supported greater growth of TB in AM over a week compared to AM alone. Nonetheless, BCG-primed lymphocytes co-cultured with AM controlled TB growth compared to co-cultures with naïve lymphocytes. The basis of these differences and relative strength of bacterial growth control is the subject of future studies. Future work will then focus on determining whether TB growth control in AM by TB-immune lymphocytes predicts protection induced by vaccination *in vivo*.

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VACCINE SAFETY AND MONITORING

Myopericarditis After Vaccination Reported to the Vaccine Adverse Event Reporting System (VAERS), 1990–2018

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Learning Objective
Describe reports to the Vaccine Adverse Event Reporting System **(**VAERS) of myopericarditis after vaccines, to raise awareness among vaccine providers and public health authorities and improve surveillance for this condition

Abstract
Myocarditis (inflammation of the myocardium, or heart muscle) and pericarditis (inflammation of the pericardium, or tissue overlying the heart muscle) often occur together, a condition called myopericarditis. Myopericarditis can range in severity from mild and without symptoms, to severe. [1] Myopericarditis has many causes, most often viral infections, and has been causally linked to smallpox vaccination. [2] Rarely, myopericarditis has been reported after influenza and hepatitis B vaccination. [3,4] Notably, none of these reports described vaccines licensed for use in the US (except smallpox vaccine). The only review of reports to VAERS of myopericarditis covered a limited range of time (2011–2015), and did not include a review of medical records. [5] We sought to more thoroughly describe reports to VAERS of myopericarditis after vaccines licensed for use in the US.

We identified US reports of myopericarditis received by VAERS during 1990–2018 using selected Medical Dictionary for Regulatory Activities Preferred Terms, and included for analysis reports that 1) met a previously published case definition for myopericarditis, [6] or 2) were diagnosed by a physician. We stratified analysis by age group (<19, 19–49, and 50+ years), and analyzed reports by serious or non-serious status, sex, time from vaccination to symptom onset, vaccine(s) administered, and exposure to known causes of myopericarditis, such as infection with coxsackievirus infection. We used Empirical Bayesian data mining to detect vaccine and myopericarditis-related AE pairs reported more frequently than expected. [7, 8]

VAERS received 620,195 reports during 1990–2018: 708 (0.1%) met the case definition or were physician-diagnosed as myopericarditis. Overall, 79% of reports described males, 69% were serious (leading to or prolonging hospitalization, life-threatening illness, permanent disability, congenital malformation, or death), and 72% reported symptom onset within 2 weeks of vaccination. Most commonly reported overall were smallpox (59%) and anthrax (24%) vaccines; most commonly reported administered alone were smallpox (242, 54%) and inactivated influenza (53, 12%) vaccines. When excluding 138 reports describing persons potentially with a known cause of myopericarditis (e.g., coxsackievirus), the most commonly reported vaccines remained unchanged. The highest proportion of serious reports were among persons age <19 years (95%), then 50+ years (85%), then 19–49 years (62%). Proportions of reported sex were comparable among persons age <19 years (56% males) and 50+ years (49% males), but were mostly male among persons age 19–49 years (90% males). The most commonly reported vaccines overall among persons age <19 years were *Haemophilus influenzae* type b (22, 22%) and hepatitis B (18, 18%) vaccines; among persons 19–49 years of age was smallpox vaccine (387, 80%); and among persons age 50+ years were inactivated influenza (31, 38%) and live attenuated zoster (19, 23%) vaccines. Data mining revealed disproportionate reporting of myopericarditis only after smallpox vaccine, a known association. [6] Myopericarditis is rarely reported among vaccines licensed for use in the US: most commonly after smallpox vaccine (typically administered to selected military personnel), [9] and less commonly after other vaccines.

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Primary Ovarian Insufficiency After Vaccination: Reports to the Vaccine Adverse Event Reporting System

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Learning Objective
Describe the characteristics of cases of primary ovarian insufficiency occurring after receipt of a vaccine that were reported to the Vaccine Adverse Event Reporting System

Abstract
Since 2012, 6 cases of primary ovarian insufficiency (POI) temporally associated with receipt of human papillomavirus (HPV) vaccine have been published in medical journals leading to questions about a potential casual association. A Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink study did not find an increased risk for POI after vaccination. We reviewed the Vaccine Adverse Event Reporting System (VAERS) to describe reports of POI after vaccination.

We searched VAERS, a US passive surveillance system, for domestic POI reports received from 01/01/1990 through 12/31/2017 after any vaccination. The search used both Medical Dictionary for Regulatory Activity Preferred Terms and text search for POI and its symptoms. We reviewed all reports and applied the American College of Obstetricians and Gynecologists (ACOG) guidelines for POI diagnosis.

Of 571,178 VAERS reports received, 652 met the search criteria. Clinical review identified 19 reports with a POI diagnosis (Table 1). Most reports (n=16) were received 2013–2017 and median interval between vaccination and reporting was 36 months (range 0–132 months). Symptom onset was available for 2 reports (2 and 10 months). Eleven reports documented irregular menses ≥3 months and 6 had ≥1 laboratory test result used to diagnose POI. Four reports met ACOG diagnostic guidelines. Eighteen of 19 reports described receipt of HPV vaccine with or without other vaccines. Other vaccines reported were meningococcal conjugate vaccine, hepatitis A, varicella, and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis. Three reports described multiple vaccines.

Table 1. Characteristics of POI reports in VAERS

Characteristics	Results n = 19
Median age at vaccination[a] years (range)	14.5 (10–25)
Median age at POI diagnosis years (range)	18 (15–30)
Use of hormonal contraceptives	5 (26.3%)
POI etiology reported[b]	1 (5.3%)
Reporter Manufacturer Parent Healthcare provider	 9 (47.4%) 8 (42.1%) 2 (10.5%)

[a] Age of 1st dose in report. Not reported=5
[b] 47XXX Chromosomal abnormality

POI is rarely reported to VAERS. Most reports contained limited diagnostic information and were submitted after published cases of POI following HPV vaccination. Results of our review do not suggest a safety concern.

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Safety of Excess Doses of Vaccine: Reports from the Vaccine Adverse Event Reporting System (VAERS), 2007–2017

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Learning Objectives

- Describe the most common vaccines administered in excess and reported to the Vaccine Adverse Event Reporting System (VAERS)
- Describe the most common adverse events observed in reports where excess doses of vaccine were administered to a person
- Describe the strengths and limitations of VAERS and how this surveillance system can be used to monitor the safety of vaccines and its applicability to study programmatic errors in immunization programs

Abstract

There are few data available on the safety of an extra dose of vaccine. The administration of an extra dose of a vaccine may occur due to a vaccination error, when there is need to provide one of the antigens of a combination vaccine not readily available as a single antigen, or when there is need to provide immunization in persons with uncertain vaccination histories (e.g., refugees). We assessed adverse events (AEs) most commonly reported following the administration of excess doses of vaccine in the Vaccine Adverse Event Reporting System (VAERS).

We searched VAERS for US reports where an excess dose of vaccine was administered to a person from 1/1/2007 through 7/31/2017 using the following methods: 1) reports containing the specific MedDRA codes: accidental overdose, excess dose administered, incorrect dose administered, multiple drug overdose, overdose, incorrect dosage, and 2) reports containing the text string “extra dose” “excess dose” “overdose” or “additional dose” in the symptom, pre-existing, and medical history sections. We conducted descriptive analyses of reports by age, sex, vaccines administered, vaccines given in excess, type of administration error, or reason for the excess dose, and the most common MedDRA PTs among reports where an AE was described. We reviewed medical records for all serious reports and a random sample of non-serious reports. The most common AEs among reports of excess dose of vaccine administered were compared with the corresponding AEs for all vaccines reported to VAERS during the same period.

Out of 366,815 VAERS reports received, 5,067 (1.4%) reported an excess dose of vaccine was administered; 155 (3.1%) were serious and 3,898 (76.9%) did not describe an AE. The proportions of reports of excess dose increased from 0.8% in 2007 to a peak of 2.4% in 2015. The most common vaccines reported among all reports were trivalent inactivated influenza (15.4%), varicella (13.9%), hepatitis A (11.4%), and measles, mumps, rubella, varicella (11.1%). Among reports where AEs were reported, the most common were pyrexia (12.8%), injection site erythema (9.7%), injection site pain (8.9%), and headache (6.6%). These percentages are comparable with all reports submitted to VAERS during the same study period.

Among reports that included serious AEs, the most common conditions reported were general disorders and administration site conditions (27%), nervous system (11%), and immune system disorders (6%). The most common vaccines given in excess among these serious reports were pneumococcal polysaccharide (20%), influenza (16%), hepatitis B (14%), human papillomavirus (9%), and herpes zoster (8%).

More than three-fourths of reports of an excess dose of vaccine did not describe an AE. Among reports where an AE event was reported, we did not observe any unexpected conditions or clustering of AEs. Querying patients about

vaccination history especially with influenza vaccine, better awareness of specific vaccine recommendations, improved documentation in the medical record, and timely access to vaccination histories may help prevent administration of excess doses of vaccines.

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Surveillance of Vaccine Adverse Events in Pregnant Women Reported to the Vaccine Adverse Events Reporting System (2010-2019)

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Learning Objective

Review adverse events reported to the Vaccine Adverse Events Reporting System for women vaccinated during pregnancy to identify concerning patterns of serious adverse events

Abstract

Vaccination during pregnancy has the potential to protect the mother and infant against vaccine-preventable diseases. The administration of vaccines to pregnant women induces the formation of maternal antibodies that are transferred to the fetus. Currently, the Advisory Committee on Immunization Practices (ACIP) recommends the use of influenza and tetanus diphtheria and pertussis (Tdap) vaccines during pregnancy since 1997 and 2011, respectively. This study assesses the safety of vaccines administered to pregnant women by analyzing reports to the Vaccine Adverse Events Reporting System (VAERS) in the US from 2010–2019.

Vaccine Adverse Events Reporting System (VAERS) reports were searched from January 1, 2010, to October 14, 2019. We conducted a review to identify pregnancy reports for women 12–44 years using text string and searched for “preg” in symptom description and the Medical Dictionary for Regulatory Activities (MedDRA) terms: “pregnancy”, “puerperium”, and “perinatal conditions” and “drug exposure during pregnancy”. All adverse events (AEs) reported to VAERS were coded with MedDRA preferred terms. Serious AEs were categorized as resulting in death, life-threatening, hospitalization, emergency room visit, and disability. Pregnancy-related AEs were further categorized as serious and non-serious. Descriptive statistics including reporting rates to characterize AEs by vaccine type and severity status were conducted. Proportional reporting ratios (PRR) were calculated for reported preferred terms to assess for disproportionately higher reporting of AEs after vaccine administration to pregnant women. AEs of the vaccines with the most frequent reports were compared to overall AEs to assess any unexpected safety concerns. Signal criteria for disproportionality were set at PRR≥2, Yates c2 ≥4 and number of reports ≥3. All analyses used IBM SPSS V25.

VAERS received a total of 3,846 reports for pregnant women in the period of analysis. Of those reports, 1,042 (27%) mentioned a serious AE and 1,012 (26%) mentioned a pregnancy-related serious AE. The maternal mean age for women was 26 years (SD±7.3). The most frequent reports of AEs were for human papillomavirus-4 valent (n=955), tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (n=589), and varivax-varicella virus live (n=467) vaccines. Pregnancy-related serious AEs included 862 spontaneous abortions (<20 weeks), 292 miscarriages, 63 stillbirths (>20 weeks), 51 preterm deliveries (<37 weeks), 11 preterm labors, and 8 birth defects. Outcomes of serious AEs included 5 (0.1%) deaths, 36 (0.9%) life-threatening, 892 (23%) emergency room visits, 223 (5.8%) hospitalization, and 42 (1.1%) disability. PRR screening criteria were met for one of the Tdap vaccines and ectopic pregnancy (PRR 2.0; 95%CI 1.1-4.8). No safety signals were found for all other vaccines. This review identified no new or unexpected vaccine safety concerns among pregnant women who received a vaccine during pregnancy.

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VACCINES AGAINST EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Accuracy and Efficacy of Dengue CYD-TDV Pre-Vaccination Screening with Five Existing IgG Serotests: Retrospective Analysis of Phase 3 Trials

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Learning Objectives

- Provide estimates of the CYD-TDV dengue vaccine efficacy performance under the WHO pre-vaccination screening approach using a number of dengue immunoassays that are currently available in the field and which could therefore be utilized to inform decisions about dengue vaccination
- Provide evidence about the performance characteristics of these assays for the identification of prior dengue infection

Abstract

CYD-TDV dengue vaccine conferred durable protection against dengue hospitalization and severe dengue in individuals previously infected by dengue, while seronegative vaccinees experienced increased risk of these outcomes. [1] WHO has recommended pre-vaccination screening to identify those with prior dengue infection (PDI) who would benefit from vaccination. [2] Applying each of 5 commercially available dengue IgG immunoassays, we assessed the concept of pre-vaccination screening by estimating vaccine efficacy (VE) in test-positive participants in the two randomized placebo-controlled phase 3 studies of the CYD-TDV vaccine (CYD14, NCT01373281; CYD15, NCT01374516). [3-5]

Pre-vaccination sera obtained from subjects in the immunogenicity subsets of CYD14 and CYD15 (n≥3841) were tested by two ELISAs and three rapid diagnostic tests (RDT). Reference serostatus was determined using measured dengue PRNT90, PRNT50 and NS1 IgG ELISA pre-vaccination, enabling evaluation of serotest performance. [6] VE against symptomatic virologically-confirmed dengue (VCD) over 25 months and dengue hospitalization over 6 years from first injection was assessed in test-positive subjects using a Cox regression model, with treatment group (vaccine or placebo) as the only independent variable. Pooled VE [(1-Hazard atio)×100] across all ages (2–16 years) is presented.

Assay specificity was high for all serotests: Euroimmun-IgG-ELISA, 98.8% (95% CI: 97.9–99.3); Panbio-Indirect-IgG-ELISA, 99.2% (98.5–99.6); Biocan-RDT, 99.0% (98.3–9.5); SDBioline-RDT, 96.0% (94.8–97.1); and CTK-RDT, 99.5% (98.9–99.8). Sensitivity of the Euroimmun-ELISA (89.2% [95% CI: 87.9–90.3]) and Panbio-ELISA (92.5% [91.4–93.5]), were substantially higher than that of the SDBioline-RDT (71.1% [69.3–72.8]), Biocan-RDT (52.5% [50.6–54.4]), and CTK-RDT (47.6% [45.7-49.5]). For each serotest, vaccination of test-positive subjects was associated with high VE against VCD (Table 1). Significant protection against hospitalized VCD was evident for test-positive subjects with each serotest except CTK-RDT, for which the estimate was favorable, but the lower 95% CI bound crossed the null.

Table 1. VE against VCD and dengue hospitalization in test-positive subjects

Endpoint	Immunoassay*	Incidence¥ (95%CI) CYD-TDV	Placebo	VE (95%CI)	
VCD (25 months)	ELISA-Euroimmun	0.4(0.2-0.6)	3.0(2.2-4.0)	88.3	(77.4-93.9)
	ELISA-Panbio	0.4(0.2-0.6)	3.0(2.2-3.9)	87.6	(76.7-93.4)
	RDT-Biocan	0.2(0.1-0.6)	2.0(1.2-3.0)	88.8	(66.9-96.2)
	RDT-SDBioline	0.5(0.2-0.8)	2.7(1.9-3.8)	82.8	(66.9-91.1)
	RDT-CTK	0.2(0.0-0.5)	1.7(1.0-2.8)	89.7	(64.6-97.0)
Hospitalized VCD (6 years)	ELISA-Euroimmun	0.1(0.0-0.2)	0.4(0.2-0.6)	72.8	(38.9-87.9)
	ELISA-Panbio	0.1(0.1-0.2)	0.5(0.3-0.7)	77.5	(52.8-89.3)
	RDT-Biocan	<0.1(0.0-0.1)	0.3(0.1-0.5)	92.4	(37.8-99.1)
	RDT-SDBioline	<0.1(0.0-0.1)	0.3(0.2-0.6)	87.2	(54.5-96.4)
	RDT-CTK	<0.1(0.0-0.2)	0.2(0.1-0.5)	73.7	(-5.1-93.4)

*IgG readout only. ¥Cases/100 person-years.

The 5 dengue IgG immunoassays evaluated are suitable temporizing tools to inform vaccination decisions while improved and/or more convenient tests become available. The data indicates consistency in the high vaccine protection against symptomatic dengue and dengue hospitalizations in test-positive individuals, regardless of the test. The more sensitive ELISAs offer the distinct advantage of identifying a larger proportion of individuals who would benefit from vaccination.

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