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Immunological correlates of prevention of the onset of seasonal H3N2 influenza

Presenter: Seiya Yamayoshi - ACOR0010

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Background

The hemagglutination-inhibition (HI) titer has been used for many years as an immunological correlate of protection against influenza since the HI titer correlates with protection against influenza. However, other antibody functions such as inhibition of the conformational change of HA, inhibition of the progeny virion release, inhibition of the sialidase activity of NA, and antibody-dependent cellular cytotoxicity (ADCC) are recently characterized to be important for the suppression of virus growth in vitro or in vivo. Here, we attempted to identify the antibody functions that play a central role in preventing the onset of seasonal influenza.

Method

We utilized the 16 plasma samples obtained from H3N2 influenza patients at 0-2 days after onset. We also utilized 5 plasma samples obtained from serologically confirmed subclinical individuals before infection. We compared the levels of antibodies including neutralization titers, ELISA titers against HA and NA, neuraminidase-inhibition (NI) titers, and antibody-dependent cellular cytotoxicity (ADCC) activities between subclinical individuals and patients who were infected with the seasonal H3N2 virus. We do not perform the HI assay because recent human H3N2 viruses do not have hemagglutination ability.

Result

For antibody titers prior to the H3N2 virus exposure, we found that the neutralization titers and ELISA titers against HA and NA proteins for the subclinical individuals were significantly higher than those for the patients, whereas the NI titers and ADCC activities did not significantly differ between subclinical individuals and patients.

Conclusion

These results suggest that neutralization titers and ELISA titers against HA and NA serve as correlates of symptomatic influenza infection.

Feasibility of assessing influenza vaccine efficacy and correlates of protection against infection and disease among children aged 6-23 months in South Africa

Presenter: Cheryl Cohen - ACOR0012

Cheryl Cohen[2], Jackie Kleynhans[3], Mignon Du Plessis[3], Neil Martinson[4], Jocelyn Moyes[3], Sibongile Walaza[3], Nicole Wolter[3], Mvuyo Makhasi[3], Fahima Moosa[3], Sarah Spenser[1], Myrna Charles[1], Aaron Samuels[1], Stefano Tempia[5], Tumelo Molantoa[4], Bekiwe Ncwana[4], Louisa Phalatse[4], Amelia Buys[3], Alicia Fry[1], Eduardo Azziz Baumgartner[1], Anne Von Gottberg[3]

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Background

It is uncertain whether influenza vaccination prevents infection, attenuates illness, or both. Determining this, and correlates of protection against infection and illness, is important for modelling the effectiveness of influenza vaccine, and for assessing and developing better vaccines. We estimated influenza attack rate, and symptom ascertainment methodologies to inform future vaccine trials.

Method

We conducted a prospective cohort study in children aged 6-23 months. From 2 May-31 October 2022 we ascertained symptoms and temperature measured by nurses at twice weekly visits, and also daily by caregiver using electronic symptom diaries. Mid-turbinate nasal swabs were collected thrice weekly (2 by nurse, 1 by caregiver on the weekend) irrespective of symptoms and tested for influenza using PCR. Serum for serology was collected at the start and end of follow up.

Result

Of 230 healthy screened children, 93 were enrolled of whom 87 (94%) completed 6 months follow up; 44 (47%) were aged 6-11, 34 (37%) 12-17 and 15(16%) 18-23 months; 44 (47%) were female. 95% (4245/4476) of scheduled nurse and 90% (2045/2276) of caregiver swabs, 99% (92/93) of baseline and 97% (90/93) of exit bloods were collected. At scheduled times, 67% (9245/13768) of symptom diaries were completed. PCR-confirmed influenza infection attack rate was 65% (60/93) for ≥1 infection (11(18%) infected individuals had 2 and 1 (2%) had 3 episodes; 30 H1N1pdm09, 12 H3N2, 1 A unsubtyped, 29 B Victoria, 1 mixed). Of 73 infection episodes, 55(75%) had ≥1 symptom, 37 (51%) fever (measured and/or reported), 29 (40%) fever and cough and 5 (7%) sought care (2 pharmacy, 3 clinic). Median infection duration was 7 days (interquartile range 4-9). RNase P human DNA marker was present in 99% (2032/2045) of caregiver-collected swabs, through which 5 additional episodes were identified. Per episode, caregiver's daily report of reported and measured fever were 19% (25/73, 34%) and 11% (15/73, 21%) higher than nurse-reported (11/73, 15%) and -measured fevers (7/73, 10%), respectively.

Conclusion

In this cohort of frequently sampled young children, the influenza attack rate was 65%, with ≥1 symptom reported in 75% of episodes. Caregiver collected swabs were feasible and of good quality; an additional caregiver weekly swab did not substantially increase attack rates. Caregiver diary completion was <70% but added >10% additional symptom data. We successfully retained >94% of enrolled children for 6 months follow up with >90% swab collection compliance. The high incidence of influenza, with >50% febrile, suggests that this platform could be suitable for future trials of vaccine efficacy and correlates of protection against infection and illness in children

3

Assessment of humoral immune responses to repeated influenza vaccination in a multiyear cohort: a five-year follow-up

Presenter: Meng-Hsuan Sung - ACOR0017

Meng-Hsuan Sung[1], Wesley Billings[1], Michael Carlock[2], Hannah Hanley[1], Justin Bahl[1], Andreas Handel[1], Ted Ross[1], Ye Shen[1]

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Background

The long-term effects of host factors on vaccine-elicited immune responses have not been well-studied, and the interactions of host factors with annual influenza vaccinations are yet to be explored.

Method

A total of 386 individuals who received the standard-dose influenza vaccine and enrolled in multiple seasons (≥2) from 2016 to 2020 were included. Host information was prospectively collected, and serum samples were collected before and after vaccination in each season. Linear mixed effect models with restricted maximum likelihood (REML) were applied to repeated measures of hemagglutination inhibition (HAI) composite scores and demographic variables with interaction terms.

Result

The age-related decline in HAI fold changes was more obvious in obese (BMI≥30) participants than in the healthy (BMI<25) and overweight (BMI≥25 & BMI<30) individuals. The interaction between age and BMI (beta=0.003, se=0.001, p-value=0.0497) was positive and statistically significant in the regression analysis with overall subjects. In the subgroup analyses, a mixture pattern of changes in both directions was observed for the main effect of BMI when study participants were stratified by age groups. Additionally, a negative correlation of the interaction between BMI and gender and HAI composite scores (beta=-0.11, se=0.06, p-value=0.047) was detected in adults.

Conclusion

Our analyses indicated disparate vaccine-elicited immune responses between males and females in adults when they were repeatedly vaccinated for at least two seasons. Notably, we found interactive effects between age and BMI on overall immune responses, and between gender and BMI in the adult age group.

4

Evidence from a comprehensive systematic review with meta-analysis suggests probable decline in seasonal influenza vaccine effectiveness with maturation of seasonal influenza vaccination program.

Presenter: George Okoli - ACOR0026

George Okoli[1], Florentin Racovitan[1], Tiba Abdulwahid[1], Syed Hyder[2], Louise Lansbury[2], Christiaan Righolt[1], Salaheddin Mahmud[1], Jonathan Nguyen-Van-Tam[2]

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Background

Repeated seasonal influenza vaccination (SIV) may reduce influenza vaccine effectiveness (VE) among individuals, but the population level effect is not clear. Using SIV program maturation (number of years since program inception) [PM] as proxy for population-level repeated vaccination, we examined the effect on pooled adjusted end-season VE estimates from outpatient test-negative design (TND) studies.

Method

We systematically searched for full-text publications of seasonal influenza VE against laboratory-confirmed influenza after the 2009/10 influenza pandemic up to February 2020 (PROSPERO: CRD42017064595). We obtained SIV program inception year for each country and calculated PM as the difference between the year of deployment and year of program inception. We categorized PM into halves (cut at the median), tertiles, and quartiles, and calculated pooled VE using an inverse variance, random effects model. The primary outcome was pooled adjusted end-season VE against all influenza.

Result

From 11,931 citations, we included 72 full-text articles that met our inclusion criteria. Across the three categorizations of PM, a lower pooled VE against all influenza for all patients was observed with PM. Substantially higher reductions were observed in older adults (≥65 years). Similar observations were made for A(H1N1)pdm09, A(H3N2) and influenza B.

Conclusion

The evidence suggests seasonal influenza VE declines with SIV PM. This study forms the basis for further discussions and examinations of the potential impact of SIV PM on seasonal influenza VE.

5

Identifying correlates and mediators of protection against influenza and COVID-19 with causal mediation analysis

Presenter: Wey Wen Lim - ACOR0028

Wey Wen Lim[3], Eric J Tchetgen Tchetgen[4], JS Malik Peiris[1], Benjamin J Cowling[2]

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Background

Immunobridging is an important tool to accelerate vaccine evaluation and authorization. In the COVID-19 pandemic, neutralising antibodies against the ancestral Wuhan-1 SARS-CoV-2 virus was identified as a correlate of protection (CoP) for COVID-19 vaccines. However, the emergence of SARS-CoV-2 variants capable of immune escape necessitates future vaccine updates with newer circulating strains within a time frame that precludes most efficacy studies. The challenges to evaluating new COVID-19 vaccines in a timely manner are similar to influenza vaccines. Before the COVID-19 pandemic, the identification of new immune correlates of protection (CoPs) for influenza vaccines is an active area of research, as there is growing recognition of the importance of establishing a causal link between existing and new CoPs and protection.

Method

We present here an example of a causal mediation analysis using data from a randomized controlled influenza vaccine trial in children to estimate the proportion of vaccine efficacy mediated by post-vaccination HAI titer, an established CoP for inactivated influenza vaccines. We estimated influenza vaccine effectiveness against laboratory-confirmed influenza A(H1N1), A(H3N2) and B/Victoria with Cox proportional hazards models and then assessed correlations of influenza vaccination with post-vaccination HAI titers and post-vaccination HAI titers and risk of laboratory-confirmed influenza. We estimated the total, direct, and indirect effect of vaccination on the risk of infection using proportional hazards models with inverse odds ratio weighting and calculated the proportion of vaccine efficacy mediated by post-vaccination HAI titers.

Result

Vaccine effectiveness against laboratory-confirmed A(H1N1), A(H3N2) and B/Victoria was estimated to be 58% (95% CI = 26%, 76%), 60% (95% CI = 33%, 76%) and 45% (95% CI = 13%, 66%) respectively. Influenza vaccination is associated with an increase in post-vaccination HAI titers ($p<0.001$) and increasing levels of post-vaccination HAI titers was associated with a reduction in the risk of laboratory-confirmed influenza. The estimated effect mediated by increases in post-vaccination HAI titers against the influenza A(H1N1), A(H3N2), and influenza B/Victoria vaccine strains were 22% (95% CI = 18%, 47%), 20% (95% CI = 16%, 39%), and 37% (95% CI = 26%, 85%).

Conclusion

Post-vaccination HAI titers are mediators of protection for current inactivated influenza vaccines. We believe this method could also be applied to COVID-19 vaccines, where data collected from COVID-19 vaccine efficacy trials can be used to estimate the proportion of vaccine efficacy mediated by post-vaccination rises in neutralising antibodies.

6

Timing of maternal influenza vaccine administration during pregnancy for optimal vaccine effectiveness in infants

Presenter: Anne-Marie Rick - ACOR0034

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Background

Maternal influenza immunization (MII) during pregnancy can protect infants from influenza through decreased exposure to virus and placental transfer of vaccine-induced antibodies. There is limited data on optimal timing of vaccine during pregnancy for optimal infant protection against influenza. We evaluated vaccine effectiveness (VE) of MII, by timing of vaccine administration during pregnancy, against infant influenza during the first six months of life.

Method

We used electronic health records from a retrospective cohort of mother-infant pairs of infants born January 1, 2012 to December 31, 2019 who received longitudinal well-child care within a single health system. We evaluated VE of MII by trimester of vaccination for laboratory-confirmed influenza among infants < 6 months old using multivariable logistic regression (see table footnote for variables). VE estimates were calculated as (1-OR)*100. Women were considered unvaccinated if they had no documented influenza vaccine during pregnancy or received vaccine < 2 weeks prior to delivery.

Result

Of the 44,132 mother-infant pairs included in the analysis, 0.3% (n=141) of infants < 6 months old had laboratory-confirmed influenza. 48.7% of women had no influenza vaccine during pregnancy, 16.4% had vaccine during 1st trimester, 17.1% during 2nd trimester, 15.1% during 3rd trimester, and 2.5% < 2 weeks prior to delivery. Adjusted VE was highest at 88% for 2nd trimester vaccinations (aVE: 88%, 95%CI:66-95%), followed by 1st trimester (aVE: 60%; 95%CI:28-78%). aVE was not significant for infants born to women vaccinated during the third trimester (aVE: 8% (95%CI: -42-40%).

Conclusion

MII during the 1st and 2nd trimester of pregnancy provides moderate to high vaccine protection against influenza for infants during the first 6 months of life. Clinicians should strongly encourage pregnant women to vaccinate early in pregnancy to maximize protection for themselves and their children.

7

MF59-adjuvanted influenza vaccine for preventing cardio-respiratory hospitalizations in adults 65 years and older during the 2019-2020 U.S. influenza season

Presenter: Juliet Dang - ACOR0036

Juliet Dang[1]

[1]CSL Seqirus

Background

Compared with immune responses in younger adults, older adults' immune systems tend to be less responsive to standard-dose egg-grown, inactivated influenza vaccines. Approaches developed to overcome this age-related immunosenescence include adding an adjuvant to the vaccine to boost the recipient's immune response or increasing the dose of influenza virus antigens contained within the vaccine. Two contemporary vaccines were specifically developed to enhance protection: MF59-adjuvanted trivalent influenza vaccine (aTIV) and high-dose trivalent influenza vaccine (HD-TIV). This study investigated the relative vaccine effectiveness (rVE) of aTIV vs. HD-TIV and QIVe in preventing cardio-respiratory related hospitalizations among the elderly.

Method

This retrospective observational cohort study was conducted from September 30, 2019 - March 7, 2020. The data comprised de-identified medical records of adults ≥65 years of age who received a seasonal influenza vaccination (aTIV, HD-TIV, or QIVe) during the 2019-2020 influenza season. Since influenza is associated with adverse cardio-respiratory events, the outcomes evaluated were cardio-respiratory-related hospitalizations and respiratory-related hospitalizations, and specifically influenza-related and pneumonia-related hospitalizations as well as hospitalizations related to myocardial infarction and ischemic stroke. Outcomes were defined as a diagnosis in any position of the claim and separately in the first position (regardless of the diagnoses in the subsequent positions). A doubly robust, inverse probability of treatment weighting methodology was used to obtain odds ratios (ORs) adjusted for age, sex, race, ethnicity, geographic region, vaccination week, health status, frailty, and healthcare resource utilization. rVE was determined using the formula (1-ORadjusted)*100.

Result

During the 2019-20 influenza season, 4,299,594 individuals met the study selection criteria. Of those, 1,083,466 (25.2%) received aTIV, 2,448,403 (56.9%) received HD-TIV and 767,725 (17.9%) received QIVe. aTIV was more effective compared to QIVe and HD-TIV across all cardio-respiratory related hospitalization outcomes (Figure 1). The rVE for the comparison of aTIV vs QIVe was consistently higher than for the comparison of aTIV versus HD-TIV. Consistent trends were observed when limiting to the primary/admitting diagnosis, except for ischemic stroke related hospitalizations for which no difference was observed compared to HD-TIV.

Conclusion

This real-world study demonstrated the benefit of aTIV over QIVe and HD-TIV for the prevention of cardio-respiratory related hospitalization outcomes during the 2019-20 season, including influenza-related hospitalizations.

8

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

Presenter: Faith Ho - ACOR0048

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Background

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

Method

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 2016/17 (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 2017/18 (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.

Result

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.

Conclusion

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.

9

Antibody landscapes to hemagglutinin and neuraminidase proteins of H3N2 influenza viruses in older adults

Presenter: Sook-San Wong - ACOR0051

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Background

Age is an important determinant of the breadth of antibody reactivity to influenza viruses. Older adults have the most complex immune history due to a lifetime of exposures to influenza A viruses (IAVs). Here, we describe the pre and post-infection antibody landscapes of the IAV surface proteins, hemagglutinin (HA) and neuraminidase (NA), for the human H3N2 viruses in a cohort of older adults in Southeastern China.

Method

The study was based on the China Ageing Respiratory infection study (CARES) conducted between 2015 to 2017 in Jiangsu Province, China. The study recruited 1532 individuals 60-89 years-of-age that were monitored for respiratory viral infections. Serum samples were collected every six months for two years. Serum samples from 54 PCR positive individuals for H3N2 IAV infection (H3(+)) and 25 age and gender matched PCR-negative (H3(-)) individuals were used for hemagglutinin-inhibition (HAI) and neuraminidase-inhibition (NAI) assays against 22 H3N2 IAVs in circulation between 1968 and 2019.

Result

HA and NA sequences were available for 39/54 (72%) isolates and most are Clade 3C.2a2 H3N2 IAVs. Prior to infection, the HAI geometric mean titers (GMTs) were <10 against most IAVs except for those circulating before 1977. In contrast, NAI GMTs were >40 to all the strains circulating prior to 2005, suggesting higher assay sensitivity. Notably, the baseline HAI GMT were significantly higher in H3(-) individuals to the reference A/Hong Kong/4801/2014 (H3N2) and other H3 strains in the past 10 years compared to the H3(+) individuals, although the GMT remained lower than 40. No difference in baseline NAI titers were noted between the two groups. After infection, the boosted antibody responses can be grouped into 4 HA and 3 NA antigenic clusters that tracked with time of circulation. Antibody titers was boosted mostly against IAVs within the last 15 years (backboosting), for which the pre-existing titers were also the lowest. The antibody landscapes remained stable at 12 months after infection. In age-stratified analyses, the oldest individuals (80-90 years old) had the highest HA and NA seroconversion rates, particularly to IAVs circulating in the last 15 years compared to those 60-79 years old. Seroconversion to a single antigen (either HA or NA) was more frequently observed in the 60-79 year old age group.

Conclusion

Our findings suggest that older adults were capable of eliciting robust and durable HA and NA antibody responses after infection. Backboosting was most significant for IAVs with low pre-existing titers. NAI-antibodies are readily detectable against past H3N2 strains but HAI-antibodies appeared to be better correlates of protection.

10

Identifying factors that drive post-vaccination Influenza serum HAI antibody titre dynamics

Presenter: David Hodgson - ACOR0062

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Background

Strain-specific serum HAI antibody titre is a well-established estimate for a correlate of protection for Influenza. However, there is huge heterogeneity in post-vaccine antibody titre kinetics between individuals, leaving some more vulnerable to infection and disease than others. Understanding the driving factors behind post-vaccine antibody dynamics is therefore useful for predicting individual-level protection prior to an influenza season. In this study we synthesise a range of studies and determine how different demographic and serological factors combine to influence post-vaccine individual-level antibody kinetics.

Method

By building an individual-level Bayesian regression model which estimates post-vaccination titre trajectories, we explore the effect of age, sex, site, recent vaccination history, and pre-vaccination titre to vaccinating strain, on the magnitude of boosting and waning on these trajectories. This model was fitted to several large-scale multi-year influenza serological cohorts so that the consistency of these effects could be assessed across various seasons and settings.

Result

We find that pre-vaccination titre to vaccinating strains and recent vaccination history are the main drivers of an individual's post-vaccination serum HAI antibody titre. Those with a lower pre-vaccination serum HAI antibody titre have significantly higher fold-rise in antibody levels compared to those with higher serum HAI antibody titres. Further, those who had received at least one influenza vaccine in the previous few years had a lower post-vaccination fold-rise compared to those without previous recent vaccination. The magnitude of the post-peak rate of waning was highly correlated with the magnitude of boosting. Age and sex did not have a significant or consistent influence on antibody dynamics across the datasets considered.

Conclusion

Highly vaccinated individuals with high pre-vaccination serum HAI antibody titres to the vaccinating strain are likely to sustain high titre values post-vaccination, suggesting protection from oncoming infection. By identifying the key factors that drive post-vaccination antibody titre dynamics, we gain a better understanding of the mechanisms which drive the heterogeneous protection afforded by vaccination on both the individual and population-level.

11

Improving the prediction of influenza vaccine effectiveness by refined genetic distance measure

Presenter: Lirong Cao - ACOR0077

***Lirong Cao*[1], *Maggie Wang*[1]**

[1]The Chinese University of Hong Kong

Background

Our previous research demonstrated that genetic distance (GD) on effective mutation (EM) sites can be used to evaluate vaccine effectiveness (VE) in silico in real time.

Method

This study further investigates the relationship between VE and GD on antigenic sites (AS) and identifies key amino acid sites related to vaccine protection against influenza A/H1N1pdm09 (pH1N1) and A/H3N2 between 2009 and 2019 flu seasons.

Result

We found that not any AS on hemagglutinin (HA) and neuraminidase (NA) may cause a decrease in VE, rather, GD on the intersection set of EM and AS is highly predictive of influenza VE. The integrated GD of HA and NA can explain up to 87.8% of VE variations for H3N2. Significant improvement is also found for VE prediction for pH1N1.

Conclusion

Accurate prediction of influenza VE before vaccine deployment may facilitate reverse vaccinology to optimize vaccine antigen design and facilitate government preparedness of epidemics.

12

Impact of seasonal influenza vaccine dose on homologous and heterologous immunity

Presenter: Yang Ge - ACOR0082

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Background

The high-dose (HD) Fluzone influenza vaccine is provided to the elderly population because the standard-dose (SD) version had low immunogenicity and protective effect. Although the increased dose seems to improve homologous protection (against the vaccine strain), the heterologous protection (against other strains) is not well studied. We set out to perform a detailed investigation of the differences between SD and HD vaccines for several recent vaccine years both with respect to homologous and heterologous antibody immune responses.

Method

We used data from human volunteers vaccinated with either the SD or HD Fluzone vaccine during influenza seasons spanning the years 2014-2018. We used a Bayesian hierarchical modeling framework to explore the impact of dose on immune protection as quantified by hemagglutination inhibition titer (HAI). We estimated the additional benefits of HD compared to SD vaccine by strain-specific and vaccine-specific analyses, for both homologous and heterologous immunity.

Result

We found that the HD vaccine led to overall improvement for both homologous and heterologous immunity. In the vaccine-strain specific analyses, across all strains the HD vaccine was associated with a (0.19 (89%CI, -0.1 - 0.44), CI: equal-tailed credible interval) log2 HAI units, stronger increase in HAI titer following vaccination, with the strongest impact noted for the H1N1 vaccine component. We also observed that the HD vaccine overall induced stronger heterologous responses, though there was noticeable variation across vaccine and test strains. In the per-vaccine analyses, HD vaccines showed stronger increases in HAI titer following vaccination against both homologous and heterologous strains, with the homologous response stronger and less variable (overall increase across 5 seasons of 0.21 (89%CI, -0.12 - 0.53) log2 HAI units and the heterologous response showing a reduced and more variable impact (overall increase -0.01 (89%CI, -0.35 - 0.33) log2 HAI units). These findings were robust across different ways of quantifying the vaccine response (seroconversion, post-vaccination titers, and seroprotection).

Conclusion

Overall, the HD influenza vaccine was able to induce better homologous and heterologous antibody immunity. Some exceptions were noted for heterologous immunity, where the increased dose led to reduced immunogenicity. Based on these findings, considering extension of the HD vaccine to other age-groups, and further dose optimization studies seem warranted.

13

Deciphering correlates of protection against airborne transmission of human seasonal H3N2 influenza virus transmission in the ferret model

Presenter: Seema Lakdawala - ACOR0095

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Background

Seasonal and pandemic influenza viruses circulate in the human population, which has prior immunity from previous infection or vaccination. To better capture this immune history, we developed a ferret transmission model where recipient animals have prior immunity from experimental infections given >3 months prior to exposure of a secondary infection. Using this model system, we have previously demonstrated that airborne transmission of a seasonal H3N2 virus was blocked in animals with prior immunity to the 2009 H1N1 pandemic influenza virus (H1N1pdm09). This protection is independent of neutralizing antibody titers and could be related to mucosal immunity or other cellular immune responses.

Method

Due to the lack of ferret immunological reagent, we utilized differential administration routes of either live virus or monovalent inactivated H1N1pdm09 Sanofi vaccine to examine the correlate of protection.

Result

We observed that immunity derived from live virus administered intramuscularly did not protect against H3N2 virus transmission. In addition, no protection from H3N2 transmission was elicited after either intranasal or intramuscular vaccination with a monovalent inactivated H1N1pdm09 vaccine.

Conclusion

These data suggest that protection from airborne transmission of H3N2 viruses is not due to HA-specific cellular or mucosal immune responses. Our findings indicate that mucosal immunity initiated through active viral infection likely provides protection from airborne transmission of heterosubtypic viruses. The impact of prior immunity from vaccination on transmission of influenza viruses is not often examined when developing novel universal vaccine candidates. However, blocking influenza virus transmission through vaccination would have a profound impact during a respiratory pandemic.

14

Economic Impact of Influenza Vaccines on Hospitalization Costs for the US Elderly: A Real-World Economic Assessment of Adjuvanted Trivalent Influenza Vaccine Compared to Quadrivalent Standard-Dose Influenza Vaccine for the 2018-19 and 2019-20 Influenza Seasons

Presenter: Joaquin Mould - ACOR0015

Myron Levin[3], Maarten Postma[5], Stephen Pelton[1], Victoria Divino[4], Mitchell DeKoven[4], Simona Zhou[4], Joaquin Mould-Quevedo[2]

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Background

During the 2018-19 and 2019-20 influenza seasons in the United States (US), adjuvanted trivalent influenza vaccine (aIIV3) was an enhanced influenza vaccine that was available and approved specifically for the 65+yrs population. aIIV3 is expected to reduce the influenza-related burden among older adults compared to quadrivalent influenza vaccines standard-dose (IIV4e) due to greater effectiveness. This study estimated the net cost savings due to the prevention of respiratory and cardio-respiratory hospitalizations among subjects 65+yrs vaccinated with aIIV3 or IIV4e during the 2018-19 and 2019-20 influenza seasons.

Method

A retrospective cohort analysis was conducted using professional fee, prescription claims and hospital charge master data from IQVIA's New Data Warehouse. Baseline characteristics included age, gender, payer type, geographic region, Charlson Comorbidity Index, comorbidities, indicators of frail health status, health seeking behavior, and pre-index hospitalization rates. Inverse Probability of Treatment Weighting (IPTW) was used to adjust for imbalances in measured confounders between groups. Multivariate Poisson regression models were used for further adjustment of clinical outcomes. Economic outcomes included respiratory and cardio-respiratory hospitalization costs. Difference in respiratory and cardio-respiratory hospitalization costs between cohorts vaccinated with aIIV3 or IIV4e was calculated and expressed as a relative vaccine effectiveness (rVE). The study period in season 2018-19 was from August 1, 2018 to July 31, 2019 and in season 2019-20, was from August 4, 2019 to March 7, 2020.

Result

The IPTW sample comprised 716,279 and 845,069 recipients of aIIV3 and 320,197 and 304,050 recipients of IIV4e for seasons 2018-19 and 2019-20, respectively. Following Poisson regression, the adjusted rVEs for cardio-respiratory and respiratory hospitalization for aIIV3 vs IIV4e were 6.2% (CI 95%: 4.8-7.7%) and 8.9% (CI 95%:6.5-11.2%) for season 2018-19; and 6.0% (CI 95%: 4.0-7.9%) and 10.1% (CI 95%: 7.0-13.0%) for season 2019-20. The net cost savings associated with aIIV3 was $548.2 (435.4-660.5) and $202.1 (152.2-251.7) per recipient in terms of prevented cardio-respiratory and respiratory hospitalizations relative to IIV4e in the 2018-19 season. Likewise, the net cost savings associated with aIIV3 in the 2019-20 season were $261.4 (180.5-341.6) and $114.5 (77.0-151.4) per recipient in terms of prevented cardio-respiratory and respiratory hospitalizations relative to IIV4e, respectively.

Conclusion

In the 2018-19 and 2019-20 influenza seasons, aIIV3 was associated with significant cost savings from avoided cardio-respiratory and respiratory hospitalizations costs compared to IIV4e.

15

The Impact of the Influenza Immunization Rate Reduction on U.S. Hospital System Resources. An Influenza and COVID-19 Co-circulation Approach

Presenter: Joaquin Mould - ACOR0014

Van Nguyen[2], Joaquin Mould-Quevedo[1]

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Background

Influenza (flu) disease activity had shown to be higher during 2022/23 season than the same time during the most recent 4 pre-pandemic flu seasons. During the 20/21 flu season, U.S. healthcare providers achieved an overall flu immunization rate of approximately 52%, equating to an estimated 172 million people being vaccinated against flu, an all-time high. In season 21/22, the overall flu immunization rate dropped to 44%; and this season 22/23, a further decline is expected to occur due vaccination apathy and hesitancy to get a flu vaccine at same time as a COVID-19 vaccination. This study evaluated the impact of the reduced flu immunization rate in the U.S. on hospital system resources under a flu and COVID-19 co-circulation scenario.

Method

The impact of the reduced flu immunization rate on hospital resources was estimated using a dynamic age-stratified transmission model. Two U.S. flu seasons (2011-2012 for low incidence and 2017-2018 for high incidence) were used in the analysis to simulate the variation of flu epidemic. Outcome measures include the number of acute hospital beds and Intensive Care Unit (ICU) hospital beds. The COVID-19 variants (Alpha, Delta and Omicron) were used to create an average scenario of the impact on acute beds and ICU beds utilization from COVID-19. The flu vaccine effectiveness (VE) rate was taken from CDC reports to estimate an average VE for all ages for the last 10 seasons (42%). Vaccination rates by age group were estimated using CDC reports and this model assumed immunization with standard-dose, egg-based, quadrivalent flu vaccines for all ages. Total number of acute hospital and ICU hospital beds was assumed in the U.S. at 1,000,000 and 100,000, respectively; with a regular occupancy rate of 70% related to other diseases.

Result

Reducing the U.S. flu immunization rate further in season 22/23 (39%), over a high flu incidence season, the number of acute hospital beds and ICU hospital beds used for influenza are estimated at 210,512 and 31,894, respectively; and for a low flu incidence season those will be estimated at 64,453 and 9,896, respectively. These results, within a COVID-19 pandemic setting, will generate significant pressure on the US hospital system (especially within the high flu incidence season) and would saturate the number of ICU hospital beds in high or low incidence seasons. Only increasing the flu immunization rate up to 70% or higher may prevent any saturation of acute hospital or ICU hospital beds.

Conclusion

Influenza vaccination remains a critical public health tool to improve health outcomes and avoid saturation of hospital system resources, especially those associated to ICU hospital beds within a co-circulation scenario.

16

Pre-season antibody titers and protection against influenza infection in a South African community cohort (PHIRST), 2016-2017

Presenter: Nicole Wolter - ACOR0054

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Background

In a community cohort study, we aimed to determine whether higher pre-season influenza antibody titers were protective against subsequent infection.

Method

Members from approximately 50 randomly selected households were enrolled in each of Klerksdorp (urban setting) and Agincourt (rural setting) in 2016 and 2017. Participants were followed for 6 (2016) and 10 (2017) months, spanning the influenza season. Nasopharyngeal swabs were collected twice weekly irrespective of symptoms and tested for influenza by real-time reverse transcription polymerase chain reaction (PCR). Serum specimens were collected at the beginning and end of the follow-up period; a four-fold or higher increase in antibody titer by the hemagglutination inhibition (HAI) assay on pre- and post-season sera was considered indicative of infection. A multivariable mixed effects hierarchical logistic regression model, controlling for clustering by site and household, was used to assess the association between pre-season antibody titers (reference group: titre of <20) and subsequent PCR-confirmed influenza infection, adjusting for HIV infection and age group.

Result

Of 1100 individuals enrolled, 850 (77%) had pre-and post-season serology results. The serology attack rate was 34% (143/420) in 2016 and 37% (161/430) in 2017, while the PCR attack rate was 30% (125/420) in 2016 and 37% (157/430) in 2017. One individual received the influenza vaccine. Of 937 (85%) individuals with pre-season serology results, 5% (47/937), 13% (124/937), 6% (59/937) and 4% (38/937) had PCR-confirmed A(H1N1)pdm09, A(H3N2), B/Victoria or B/Yamagata subsequent infection respectively. Individuals with pre-season A(H1N1)pdm09 titers of 40-59 (adjusted odds ratio (aOR) 0.13, 95% confidence interval (CI) 0.03-0.67) and ≥60 (aOR 0.16, 95%CI 0.06-0.44) were less likely to be infected with A(H1N1)pdm09. Individuals with pre-season A(H3N2) titers of 40-59 (aOR 0.32, 95%CI 0.13-0.77) were less likely to be infected with A(H3N2) but not significantly for ≥60 (aOR 0.54, 95%CI 0.29-1.01). Higher titers against B/Victoria or B/Yamagata did not protect against B/Victoria infection (titre 40-59: aOR 0.45, 95%CI 0.16-1.21, titre ≥60: aOR 0.38, 95%CI 0.13-1.10) or B/Yamagata infection (titre 40-59: aOR 1.48, 95%CI 0.55-3.94, titre ≥60: aOR 0.46, 95%CI 0.15-1.40), respectively.

Conclusion

Serology showed higher infection attack rates than PCR. High pre-season titers protected against infection with the matching influenza subtype for A(H1N1)pdm09 and A(H3N2), but not for B/Victoria or B/Yamagata possibly due to HAI serologic cross-reaction between B/Victoria and B/Yamagata or small numbers. This highlights the potential of prior immunity to reduce the risk of infection.

17

Trends of influenza B/Yamagata antibodies from 2012/2013 to 2021/2022 in Italy in the context of potential lineage extinction

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Background

B/Yamagata viruses exhibited weak antigenic selection in recent years, reducing their prevalence over time and requiring no update of the vaccine component since 2015. Sequences of the B/Yamagata haemagglutinin (HA) genome segment uploaded in influenza surveillance databases experienced a major decrease since 2019 and, to date, no B/Yamagata viruses have been isolated or sequenced since March 2020.

This study investigates the prevalence of antibodies against the B/Yamagata vaccine strain B/Phuket/3073/2013 in the general population from 2012/2013 season onward.

Method

Human serum samples collected in Italy from 2012/2013 to 2021/2022 season were tested by haemagglutination inhibition (HI) assay against B/Phuket/3073/2013 strain. 100 samples were tested for each season.

Antisera from previous B/Yamagata strains reaching back to the 2001/2002 season (B/Guangdong/120/2000, B/Jiangsu/10/2003, B/Florida/4/2006, B/Wisconsin/01/2010, B/Massachusetts/02/2012) were also tested by HI against B/Phuket/3073/2013 strain.

Result

About 61.9% of the samples showed HI antibodies to B/Phuket/3073/2013. Notably, 21.7% had protective antibody levels (HI titer ≥40). The prevalence of antibodies at protective levels in the seasons from the isolation of the strain and its inclusion in the vaccine was between 11% and 25%, with no significant changes observed in subsequent years (Figure 1). The only exception is the 2020/2021 season, during which a significant increase to 48% of samples showing protective antibody levels was observed, in line with the increase in influenza vaccine coverage during the pandemic.

B/Yamagata antisera showed increasing HI titers with the chronological succession of seasons, from B/Guangdong/120/2000 (HI titer of 80) to B/Massachusetts/02/2012 (HI titer of 640), denoting a certain grade of cross-reaction/cross-protection among B/Yamagata strains.

Conclusion

Results from this study show a consistent prevalence of antibodies against B/Yamagata virus circulating in almost a decade. The prolonged use of a well-matched influenza vaccine together with a low antigenic diversity of B/Yamagata viruses in recent years may have facilitated a strong reduction in B/Yamagata circulation. This, combined with COVID-19 pandemic restrictive conditions from year 2020, may have potentially let to the extinction of this lineage.

18

Hybrid approach to estimate influenza antibody titers associated with decreased risk of influenza#

Presenter: Brendan Flannery - ACOR0065

Brendan Flannery[1], Kelsey Sumner[1], Lauren Grant[1], Min Levine[1]

[1]CDC

Background

Estimating immunologic correlates of protection for influenza vaccines has required large studies with multiple blood draws, active surveillance to confirm influenza virus infection, and occurrence of sufficient virus-specific infections to achieve minimal sample size. We describe a hybrid approach leveraging an ongoing test-negative design (TND) vaccine effectiveness (VE) study and simultaneous immunogenicity studies to estimate the association of antibody titers against circulating virus with protection against laboratory-confirmed illness during the influenza season.

Method

The hybrid approach will use two components of CDC's Flu VE Network platform. In randomized vaccine immunogenicity studies, sera will be collected pre- and four weeks post-vaccination and post-season. For individuals in the cohort who experience acute respiratory illness (ARI) during follow-up, respiratory specimens for influenza testing and additional sera will be collected during acute and convalescent phases of illness. Concurrently, in the TND study, respiratory swabs, sera, and vaccination status will be collected from patients with ARI presenting for care at participating clinics; convalescent sera will be collected 4 weeks later for influenza cases. Serum antibodies against cell-grown wild-type influenza viruses will be analyzed against multiple immunological markers. Rates of intra-season antibody waning from the entire immunogenicity cohort will be used to estimate pre-season or post-vaccination antibody titers associated with protection. Using both studies, statistical analyses will estimate antibody titers at different time points associated with influenza illness during a season.

Result

Sample size estimation: Assuming a 5% influenza attack rate, an immunogenicity study including 1000 participants would identify 50 influenza cases for estimation of attack rate by post-vaccination antibody titer. Assuming 30% influenza virus infection among 500 patients enrolled in the TND study, 150 influenza cases and 350 test-negative controls (acute sera only) would provide estimates of percent influenza virus infection by antibody titer at time of illness.

Conclusion

Assessing associations between antibody titers at time of illness, infection risk, and vaccine effectiveness can be achieved with relatively small sample sizes, providing a novel hybrid approach to explore immune correlates against influenza.

19

Evaluating the potential cost effectiveness of maternal influenza vaccination by administration trimester in Nepal: A modeling study

Presenter: Collrane Frivold - ACOR0076

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Background

Pregnant people are at increased risk of influenza morbidity/mortality, making vaccination a high priority in this population to protect themselves, their fetuses, and their infants. The COVID-19 pandemic has also increased global demand for seasonal influenza vaccines and highlighted the importance of equitable access to maternal immunization. WHO currently recommends seasonal influenza vaccination during pregnancy; however, the optimal timing of vaccination is unknown. The objective of this study was to evaluate the potential cost effectiveness of maternal influenza vaccination by administration trimester in Nepal.

Method

We performed a cost-effectiveness analysis (CEA) from the Ministry of Health and Population (MoHP) and societal perspectives comparing influenza vaccine administered in the second or third trimester to no vaccination over a lifetime time horizon. We estimated quality-adjusted life years (QALYs) and total costs using a decision tree model representing a cohort of pregnant people 15-49 years and newborns <6 months in Nepal. We obtained model inputs from the literature, including country-level data when available. Model data included influenza disease burden, average life expectancy, direct medical costs, direct non-medical costs, and indirect costs. All costs were presented in 2021 USD, and a 3% discount rate was applied to all future life years. We performed a one-way sensitivity analysis to identify drivers of uncertainty.

Result

From the MoHP perspective, total costs were $105,625, $1,340,158, and $1,724,155 for no, second trimester, and third trimester vaccination; total QALYs lost were 14,358, 13,305, and 12,763. From the MoHP perspective, the incremental cost per QALY gained was $1,172 for second trimester versus no vaccination and $708 for third versus second trimester vaccination. From the societal perspective, third trimester vaccination dominated no vaccination and extended dominated second trimester vaccination. These findings were most sensitive to uncertainty in the vaccine price, delivery costs, influenza mortality rates, and vaccine effectiveness.

Conclusion

This study represents the first maternal influenza vaccine CEA focused on Nepal or an LMIC within South-East Asia. Comparing third to second trimester vaccination, the intervention has the potential to be cost effective if a decision maker is willing to pay up to $708 for each QALY gained (MoHP perspective) or cost saving (societal perspective). These cost-effectiveness data are critical to informing decision-making in combination with studies of other tradeoffs between second and third trimester vaccination to guide implementation and reduce disparities in global influenza vaccine access within low-resource settings such as Nepal.

20

Receipt of seasonal influenza vaccines in homeless shelters in King County, WA (USA) during the 2019-2020, 2020-2021 influenza seasons

Presenter: Julia Rogers - ACOR0086

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Background

People experiencing homelessness face unique challenges in accessing influenza vaccines compared to the general population. We described seasonal influenza vaccine uptake in a

shelter population, comparing predictors of uptake between two influenza seasons, both pre- and peri-COVID-19 pandemic onset.

Method

We conducted repeated cross-sectional surveys at 23 shelters in King County, WA in the 2019-2020 (10/2/19-5/31/21) and 2020-2021 (10/1/19-5/31/21) influenza seasons as part of an ongoing respiratory virus surveillance study. Shelter residents ≥3 months of age were originally eligible to participate; this expanded to include shelter staff from 4/1/2020 onwards. Final survey responses for each season were included from participants with multiple responses over the study period. P-values indicating significant predictors of uptake were calculated using chi-squared tests. Multivariate logistic regression models were used to assess: (1) if uptake differed between the seasons as the COVID-19 pandemic emerged; and (2) whether COVID-19 vaccine intent/uptake was associated with 2020-2021 seasonal influenza vaccine uptake.

Result

In total, 1,544 (85% residents) and 1,539 (78% residents) participants completed surveys in the 2019-2020 and 2020-2021 seasons, respectively. Seasonal influenza vaccine uptake was substantially highest among those 5-11 years (65%), female (46%), White-identifying (48%) and those that received the previous year's vaccine (46%) in 2019-2020 ($p<0.05$); it was highest among those ≥65 years old (61%), White-identifying (56%), shelter staff (48%), and with ≥1 chronic condition (52%) in 2020-2021 ($p<0.05$). Overall uptake was 40% in 2019-2020 and 44% in 2020-2021. A participant's odds of receiving an influenza vaccine in the 2020-2021 season were 63% higher compared to the previous season (aOR 1.63, 95% CI 1.29 - 2.06). The most commonly reported reason for not receiving an influenza vaccine was "Reason not listed" in 2019-2020 (30%) and "No time" in 2020-2021 (36%). Receipt of the previous season's vaccine was a predictor of current season's uptake in 2019-2020 ($p<0.001$), but not of 2020-2021 seasonal uptake ($p=0.097$). In 2020-2021, participants who responded that they intended to receive the COVID-19 vaccine when available to them, or had received ≥1 dose, were more likely to have received their seasonal influenza vaccine at time of survey response (aOR 2.42, 95% 1.80 - 3.27).

Conclusion

These multi-season survey responses indicate that the COVID-19 pandemic may have altered shelter populations' influenza illness risk perceptions and health seeking behaviors, impacting seasonal influenza vaccine uptake and predictors.

21

Knowledge, attitude and practices of poultry handlers towards avian influenza in communities surrounding L. Victoria, Uganda

Presenter: Derrick Bary Abila - ACOR0088

Derrick Bary Abila[1]

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Background

Avian influenza (AI) disease causes huge losses to the poultry industry as well as human life. One of the key drivers to AI disease outbreak is the inadequate knowledge among communities that are at risk. Therefore, awareness creation is critical in the control of the

disease. This study aimed to assess the knowledge, attitudes and practices (KAP) of poultry handlers towards AI disease in at risk communities surrounding Lake Victoria.

Method

A cross sectional study was conducted among poultry handlers using structured questionnaires. Frequency tables and bar graphs were constructed to show distribution of respondent's characteristics and a Chi square test was used to compare poultry handlers KAP against socio-demographic characteristics with a level of significance set at α ≤0.05. A bivariate and multivariate analysis was carried out to examine the relationship between the primary outcome variable (KAP) and the related predictors.

Result

Of the 426 participants, (199/426, 47 %) were female. Catholics formed the highest number of participants (150/426, 35 %). The biggest number of participants came from Katabi Sub County (331/427, 77%).Overall, (126/426, 30%) had good knowledge about AI disease prevention and control. Regarding attitudes, (402/426, 94%) of participants had a positive attitude towards AI prevention and control and considered AI a serious disease. Most participants 70% agreed to practice safer activities towards the prevention and control of AI. In the multivariate analysis, being a protestant and having attained tertiary education were found to be statistically significant factors influencing knowledge of poultry handlers at 0.037 and 0.045 respectively (p≤0.05).

Conclusion

This study recommends providing at risk communities with more knowledge on the prevention and control of AI disease.

23

Determinants of COVID-19 mRNA booster vaccine effectiveness and waning against the Omicron variant: a systematic review and meta-regression analysis

Presenter: Joshua Nealon - ACOR0092

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Background

Waning of COVID-19 vaccine efficacy/effectiveness (VE) has been observed across multiple settings and epidemiological contexts. Many populations have now received third or fourth "booster" doses. Omicron subvariants are circulating widely, and immunological and other factors which may affect VE are widespread. We conducted a systematic review of COVID-19 VE studies and performed a meta-regression analysis to improve understanding of determinants of waning.

Method

Systematic review of PubMed, medRxiv and other sources for peer-reviewed and preprint studies on 31 October 2022. Studies were confined to those describing VE from hybrid immunity or third/fourth mRNA COVID-19 vaccine doses [due to limited data with other vaccines] against Omicron. Covariates included: age; prior infection (hybrid immunity); study design; disease severity; homologous/heterologous vaccination; subvariant; and statistical methods used. We used meta-regression models, adjusting for confounders, with weeks since last vaccine dose modelled as a restricted cubic spline, to estimate VE as a function of time since vaccination.

Result

We identified 54 eligible studies reporting 266 distinct VE estimates. Most estimates (167; 63%) described 3-dose vaccination, with 37 and 38 estimates (14% each) describing 4-dose vaccination and 2-dose hybrid immunity, and 29 estimates (9%) reporting VE of 3-dose hybrid immunity. Approximately 70% of estimates were derived from comparisons with unvaccinated populations. Waning was generally observed irrespective of strain, number of doses, or comparator population (Figure 1). Estimated VE was higher for severe than mild disease endpoints. 3-dose mRNA vaccination against severe disease was 91% (95% CI: 87 - 93%) 4 weeks after vaccination, declining to 68% (60 - 75%) after 20 weeks (Table 1). Estimated 4-dose VE was lower at 77% (67 - 84%) after 4 and 54% (21 - 73%) after 20 weeks.

Conclusion

Time-since vaccination appears to be an important determinant of booster dose VE, a finding which may support seasonal COVID-19 booster doses. Integration of VE and immunological parameters - and longer-term data including from other vaccine types - are needed to better-understand determinants of clinical protection.

24

Assessing the feasibility of a participatory daily antigen rapid testing surveillance (DARTS) system for SARS-CoV-2 infection in Hong Kong

Presenter: Nicole Ngai Yung Tsang - ACOR0103

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Background

The fifth and sixth waves of COVID-19 Omicron epidemic have caused unprecedented breakdown of PCR testing capacity for official case verification in Hong Kong. Aimed to provide a stable and reliable alternative data for surveillance of pandemic activity, a community-based participatory surveillance system was established using daily rapid antigen tests (RAT). However, the feasibility of building and maintaining a large cohort committing for regular RAT self-testing over an extended period of time for surveillance purpose remains poorly understood.

Method

We implemented an ad-hoc surveillance platform by enrolling 10000+ individuals over the territory. Participants were scheduled to regularly perform a RAT with a self-sampled throat-and-nasal swab, irrespective of symptom or exposure history, on an assigned day of the week. Daily point prevalence of COVID-19 infection was disseminated real-time on an online dashboard (https://covid19.sph.hku.hk/dashboard). A small incentives of approximately USD$50 were given to participants who had full compliance and submitted 100% of the scheduled RAT testing. We evaluated the feasibility of the surveillance system using the CDC guideline.

Result

A representative cohort of 10,800 individuals was recruited and successfully followed up over 9 months (1 March 2022-16 January 2023), with a high retention rate of 99%. A cumulative number of 403,095 RAT results were captured, enabling the system to track the changing trajectory of the Omicron pandemic, with a rapidly subsiding phase from an initial high value of 12.7% (8.4-18.7) in March to a baseline activity (0.1-0.3%) over May, and stepwise increase phase from 0.4% in June to 5.7%(3.4-9.2) in December during the period of BA.5 predominance, followed by a stepwise reduction to 1.7%(0.7-3.7) in January 2023. Most participants considered the system simple (98%) and stable (97%). An overall high average compliance (96%) was maintained over the surveillance period.

Conclusion

The successful establishment and maintenance of DARTS demonstrated that it is logistically and technically feasible for building an ad-hoc participatory large-scale surveillance system using RAT for situational awareness of the disease activity during an evolving community epidemic.

25

A heterologous prime and boost vaccination strategy for induction of cross-protective immunity using stockpiled H5 influenza virus vaccines

Presenter: Christine Oshansky - ACOR0005

Christine Oshansky[1]

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Background

Previous studies suggest that heterologous antigen prime and boost vaccination regimens may be superior to homologous prime and boost in generating cross-reactive immune responses to antigenically divergent influenza viruses. Because an emerging influenza virus will likely not exactly match a strain for which a vaccine exists, this study examined the potential feasibility of priming a naïve human population with an H5 vaccine and boosting with a heterologous H5 vaccine for rapid response.

Method

A randomized, double-blind, Phase 2 clinical study was conducted to assess the safety and immunogenicity of a homologous or heterologous vaccination series with adjuvanted, inactivated monovalent influenza H5 vaccines stored in the U.S. National Pre-pandemic

Influenza Vaccine Stockpile (NPIVS). A panel of H5 vaccines from different clades was carefully chosen based on the relative antigenic distance between the HAs of pre-pandemic vaccine strains and relative to the currently circulating H5 influenza viruses. Using various HA antigens from the NPIVS, we administered either two doses of adjuvanted vaccine separated by 21 days or two doses of adjuvanted vaccine separated by 21 days followed by a third dose 120 days after the second dose.

Result

Here, we show 1) the antigenic characteristics of two antigens used for prime and boost and 2) how the sequence in which the priming and boosting antigens are administered may be important for optimal elicitation of immune responses against antigenically divergent viruses. Preliminary results suggest that heterologous prime and boost vaccination results in increased cross-reactive antibody titers and seroprotection rates to antigenically divergent viruses as compared to the homologous regimen.

Conclusion

In past pandemic influenza emergencies, a vaccine exactly matching the antigenic properties of the pandemic influenza virus was not available until many months following identification of virus. This study indicates the potential feasibility of priming a naïve human population with a homosubtypic H5 vaccine for boosting with a matched vaccine within a relatively short antigenic distance, and the induction of cross-protective immune responses that may provide a level of protection in the event of an influenza pandemic emergency.

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the U.S. Department of Health and Human Services or its components.

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Dissection of the human pre-existing HA-reactive antibody response to next generation COBRA influenza vaccines.

Presenter: Giuseppe Sautto - ACOR0008

Giuseppe Sautto[1]

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Background

Vaccination with Computationally Optimized Broadly Reactive Antigens (COBRA) of influenza hemagglutinins (HA) confers a broad protective antibody (Ab) response against multiple influenza strains belonging to different subtypes in influenza naïve as well as in preimmune pre-clinical animal models, such as mice, ferrets and non-human primates.

Dissection of the Ab response at the monoclonal Ab level and following COBRA HA vaccination revealed the elicitation of peculiar Ab populations capable of neutralizing multiple influenza strains within a subtype.

Upcoming clinical trials will confirm if COBRA vaccination can elicit or recall the same breadth of Ab response in human subjects. As another pre-clinical assessment, the evaluation of the Ab response to historical influenza vaccine strains as well as to COBRA HA in subjects vaccinated with the standard of care (SOC) inactivated influenza vaccine (IIV), will be fundamental to assess the characteristics of the pre-existing Ab repertoire in different age groups.

Method

In this work, we longitudinally evaluated the Ab breadth of binding and functional activity of sera, plasmablasts (PBs) and memory B cells (Bmem) obtained from SOC IIV vaccinated participants belonging to 3 different age groups (young adults, middle age and elderly subjects) against H1N1, H3N2 and influenza B historical vaccine strains as well as against multiple H2N2 and H5N1 strains. We also evaluated the capability of sera and memory B cells (Bmem) to recognize COBRA HA as a correlate of their Ab breadth and recall potentials. Additionally, to functionally profile the donor Ab response at a higher resolution, monoclonal antibodies (mAbs) generated from the donor PBs and Bmem were characterized for their breadth of binding, functional activity, extent of somatic hypermutation and heavy and light chain subfamily genes.

Result

Interestingly, mAbs that were able to recognize COBRA HA were also endowed with a broad recognition and functional activity against multiple historical influenza strains, and showing a similar mechanism of binding to mAbs generated in COBRA pre-clinical animal models as revealed by their structural characterization.

Conclusion

These results suggest that COBRA HA-based vaccines may be capable of eliciting and recalling Abs endowed with a cross-reactive and cross-neutralizing activity that will contribute in conferring a broad immune response to circulating influenza virus variants, including pre-pandemic strains.

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Increase in IFNgamma secretion by PBMCs as correlate of cellular protection against influenza infection

Presenter: Olga Pleguezuelos - ACOR0009

Olga Pleguezuelos[1]

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Background

A randomized, double-blind, placebo-controlled, single-centre phase 2b clinical trial (ClinicalTrials.gov: NCT02962908; EudraCT: 2015-001932-38) was conducted in the Netherlands to evaluate the immunogenicity of FLU-v in healthy adults. FLU-v is a subunit broad-spectrum influenza vaccine that induces T-cell responses and non-neutralising antibodies against short regions in the M1, M2 and NP proteins that are conserved in influenza A and B strains. FLU-v was administered as 500 µg/0.5ml dose adjuvanted in Montanide ISA-51 (Seppic)(1 dose, n=51) or nonadjuvanted (2 doses 21 days apart, n=58) and compared to adjuvanted (n=26) or nonadjuvanted placebo (n=32). The study was funded by the European Commission Directorate-General for Research and Innovation, European Member States (FP7-Health No. 602012).

Method

PBMCs were isolated from blood samples collected prior vaccination and post-vaccination (days 42 and 180) and were cultured in vitro with the vaccine antigens. After 24h, multiparametric flow cytometry was carried out to measure CD4+ and CD8+ T-cells positive

for IFNgamma, TNFalpha, IL-2, and CD107a markers. IFNgamma was also measured in the PBMC supernatants by ELISA. Further exploratory IFNgamma/Granzyme B ELISpot were performed to evaluate reactivity against FLU-v antigens but also to evaluate cross-reactivity against inactivated influenza strains (A/H3N2, A/H1N1, A/H5N1, A/H7N9, B/Yamagata). Subjects were monitored post-vaccination during the flu season (1st Dec to 31st March) and were swabbed if they developed a sudden influenza systemic symptom together with a respiratory symptom. Correlations between the different immune parameters measured and protection from infection were explored aiming to identify a potential correlate of protection for FLU-v.

Result

From all immune markers measured, subjects that experienced at least a 3-fold increase in IFNgamma secretion to FLU-v antigen in vitro did not test positive for influenza infection. A clear threshold could not be established for the other immune markers tested. In terms of cross-reactive responses, correlations were established between the IFNgamma/Granzyme B responses to the vaccine antigens and the responses to the different inactivated influenza strains, indicating that FLU-v induces cross-reactive responses against a broad range of influenza strains.

Conclusion

Quantification of the IFNgamma secretion by ELISA is a simple assay with the potential to become a correlate of protection for FLU-v. It is likely that different broad-spectrum influenza vaccines will require different correlates of protection and thresholds specific for their target and mode of action.

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Cytomegalovirus vaccine vector-induced, effector memory T cells protect cynomolgus macaques from lethal aerosolized heterologous influenza challenge

Presenter: Jonah Sacha - ACOR0011

Meenakshi Tiwary[1], Daniel Malouli[1], Roxanne Gilbride[1], Leanne Whitmore[4], Michael Gale[4], Nicholas Maness[2], Scott Hansen[1], Douglas Reed[3], Simon Barratt-Boyes[3]

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Background

A novel vaccine approach to influenza that overcomes the problem of viral sequence diversity and provides long-lived heterosubtypic protection is urgently needed to protect against both seasonal and pandemic influenza viruses. To circumvent the problem of HA and NA sequence variability, we hypothesized that lung-resident effector memory T cells induced by cytomegalovirus (CMV)-vectored vaccines expressing conserved internal influenza antigens would protect against lethal heterologous influenza challenge.

Method

We constructed two sets of cynomolgus macaque CMV (CyCMV) vaccines expressing 1918 influenza M, NP, and PB1 antigens (CyCMV/influenza) using bacterial artificial chromosome technology. One set utilized full length (FL)-CyCMV, while the other utilized double deleted (dd)-CyCMV devoid of all identified inhibitors of unconventional T cell priming, to create vaccine sets that prime either conventional MHC-Ia- (FL-CyCMV) or MHC-E- and MHC-II- (dd-CyCMV) restricted CD8+ T cells targeting influenza internal proteins. Two separate groups of six Mauritian cynomolgus macaques (MCM) each received two subcutaneous doses of each vector set three months apart. A third group of six MCM received no vaccine and served as the control group. Beginning sixteen weeks after final vaccination, macaques were challenged in blinded groups with 5.5 log10 PFU of aerosolized H5N1 (A/Vietnam/1203/2004), then monitored via telemetry, plethysmography, and bronchoalveolar lavage (BAL).

Result

Both FL- and dd-CyCMV/influenza vaccines induced lung-resident effector memory influenza-specific T cells. FL-CyCMV/influenza induced CD8+ T cells that were MHC-I-restricted, while dd-CyCMV/influenza induced CD8+ T cells that were either MHC-E or MHC-II restricted. Following challenge with aerosolized H5N1 influenza, all six unvaccinated MCM died by seven days post infection due to acute respiratory distress syndrome. While FL-CyCMV/influenza protected 2/5 MCM from death, this did not reach statistical significance as one MCM was lost during the vaccine phase. In contrast, dd-CyCMV/influenza protected 4/6 MCM from death following aerosolized H5N1 challenge (p=0.04). This protection did not correlate with CD8+ T cells, regardless of MHC restriction, but rather with the magnitude of influenza-specific CD4+ T cells present in blood and BAL prior to challenge.

Conclusion

These data demonstrate that CMV-induced effector memory T cells targeting conserved internal influenza proteins can provide protection against highly pathogenic heterologous influenza challenge and establish proof-of-concept for effector memory T cell-based vaccines in the development of universal influenza vaccines.

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Quantification of influenza antibody vaccine responses accounting for both vaccine strength and breadth

Presenter: Andreas Handel - ACOR0023

Andreas Handel[1]

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Background

Influenza vaccine-elicited immune responses ineffectively protect against strains that are antigenically different from the vaccine strains. One goal of a future universal influenza vaccine is to provide broad protection against a range of heterologous strains. It is currently unclear how to quantify breadth of protection to allow comparison across different future vaccine candidates.

Method

We propose and explore approaches to quantify both the strength and breadth of antibody HAI response following vaccination. We evaluate the use of different distance measures between vaccine strain and other strains. Specifically, we explore time, sequence, and antigenic cartographic distance measures.

Result

We show that area under the HAI-titer curve measures for these distance measures can provide a possible way to quantify vaccine strain strength that includes heterologous responses. We find that time-based distance is an unreliable approach, while sequence- and antigenic cartographic-based measures lead to more robust findings. We illustrate the potential use of our proposed methods by comparing overall antibody responses between standard-dose and high-dose Fluzone vaccines.

Conclusion

We explored different approaches towards quantification of overall influenza vaccine responses. We showed that such approaches might be useful for future vaccine candidate selection.

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Bicistronic self-amplifying mRNA (sa-mRNA) vaccines targeting seasonal influenza A viruses are protective and immunogenic in a ferret model

Presenter: Nedzad Music - ACOR0029

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Background

Antigenic drift within HA is the primary reason for the limited effectiveness of the seasonal influenza vaccine. Conversely, NA, the second most abundant glycoprotein on the surface is more conserved among different influenza strains and NA-mediated immune responses have been demonstrated to have immunologically beneficial features.

Method

We designed multiple sa-mRNA constructs expressing HA and/or NA from two human seasonal influenza strains, H1N1 and H3N2 respectively. Those constructs were tested in ferret model.

Result

Conclusion

These results suggest next-generation bicistronic sa-mRNA vaccines expressing HA and NA induce potent antibody responses to both antigenic targets, and, when formulated as an influenza vaccine, provide an opportunity to increase the breadth of protection through cross-neutralizing anti-HA antibodies.

Attachment:

Bicistronic self-amplifying mRNA (sa-mRNA) vaccines targeting seasonal influenza A viruses are protective and immunogenic in a ferret model.

Current influenza vaccines are designed to elicit strain-specific neutralizing antibodies primarily against the highly variable viral surface glycoprotein, hemagglutinin (HA). Antigenic drift within HA is

the primary reason for the limited effectiveness of the seasonal influenza vaccine. Conversely, neuraminidase (NA), the second most abundant glycoprotein on the surface is more conserved among different influenza strains and NA-mediated immune responses have been demonstrated to have immunologically beneficial features in pre-clinical and clinical studies. Additionally, large scale egg-based vaccine production systems have indicated several issues resulting in egg adaptation mutations which may significantly alter the immunogenicity. In the current study, vaccines delivered via sa-mRNA formulations harboring both HA and NA were tested in a ferret model to assess the immunogenicity and protective capacity. Animals challenged with matched H1N1 or H3N2 seasonal influenza viruses had lower viral loads in the upper respiratory tract and lung tissue specimens compared to mock immunized animals or immunized with monocistronic sa-mRNA vaccines expressing either HA or NA alone. On top of the immunogenicity derived from HA, adding an NA component resulted in the induction of broadly reactive NA-mediated humoral responses against antigenically drifted influenza strains in immunized ferrets. Increased NA-mediated neutralization titers also coincided with reduced viral loads, further suggesting the added benefit of including the NA component in seasonal influenza vaccines. Given that the generation of mRNA vaccines are independent of *in ovo* systems, adaptive alterations of epitopes are avoided.

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Neutralization profiling of anti-HA stem influenza antibodies with panel of representative influenza viruses

Presenter: Adrian Creanga - ACOR0035

Adrian Creanga[1], Rebecca Gillespie[1], Geoffrey Simberg[1], Sarah Andrews[1], Masaru Kanekiyo[1]

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Background

Development of next-generation influenza vaccines able to confer durable protection against ever-evolving influenza variants or emerging viruses from the animal reservoir will have a major impact on global public health. Discovery of broadly neutralizing antibodies (bnAbs) targeting conserved epitopes on influenza hemagglutinin (HA) head and stem domains set the blueprint for next-generation influenza vaccines that can elicit broader protective immunity. Deep characterization of the neutralization breadth and potency of bnAbs allows further refinement of vaccine candidates with desired properties.

Method

In an effort to develop and standardize a high-throughput influenza neutralization assay for biosafety level 2 laboratory, we built a panel of representative replication-restricted reporter (R3) influenza viruses carrying a reporter gene to replace an essential viral gene (i.e., PB1). For this study, we compared the neutralization profiles of bnAbs targeting the membrane-proximal epitope (N = 8) or the central epitope (N = 8) on group 1 H1 HA stem using 22 R3 influenza viruses. These bnAbs were isolated at the Vaccine Research Center from samples collected during a clinical trial conducted with the investigational H1 HA stabilized stem nanoparticle vaccine in 2019-2020.

Result

Neutralization profile of these bnAbs revealed that the potency of membrane proximal epitope-specific bnAbs decreases significantly against H1N1 viruses circulating before 1977, whereas central stem epitope-specific bnAbs neutralize H1N1 viruses circulating in humans between 1933 and 2018 with comparable potencies. Moreover, most of the central stem

bnAbs neutralize non-H1N1 group1 influenza A viruses (i.e., H5N1, H2N2, H6N1), while only one membrane proximal bnAb can neutralize H5N1 and H2N2 viruses. Although the epitope residues of membrane-proximal and central epitopes are conserved among H1N1 viruses, we found a single residue associated with increased resistance to bnAbs targeting the membrane-proximal epitope.

Conclusion

Neutralization profiling of anti-HA stem bnAbs with a panel of R3 influenza viruses reveals limited breadth of neutralization by the bnAbs targeting the membrane-proximal epitope in comparison to bnAbs targeting the central epitope. This analysis offers deeper understanding of the antibody-virus interactions and facilitates in-depth characterization of neutralizing antibody response elicited by influenza vaccination or infection, which will provide critical insights towards developing a universal influenza vaccine strategy.

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Influenza vaccine and immune correlates of secondary protection against adverse acute cardiovascular events: a review and suggestions for future research on next generation influenza vaccine

Presenter: Mohammad Abdul Aleem - ACOR0041

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Background

Immune protection-correlates of influenza vaccine for influenza virus are widely studied. Research on mechanisms of influenza vaccine generally focused on role of humeral and cellular components of immune system to provide required protection against incidence of influenza infection. However, epidemiological evidence indicate influenza may also precipitate adverse cardiovascular events like acute myocardial infarction (AMI). Influenza virus can potentially de-stabilize the chronic state of atherosclerotic plaque and subsequent plaque-rupture by influencing atherogenic immune inflammatory cytokine mediators a crucial underlying pathophysiology of AMI. It's well established atherosclerosis a chronic inflammatory disease engaging attributes of inflammatory mediators for progression, sudden rupture, superimposed thrombosis leading to AMI. Evidence from RCTs showed protective effect of influenza vaccine against AMI. Influenza vaccine can stabilize atherosclerotic plaque thereby slowing its progression and rupture consequently preventing AMI.

Method

We conducted literature review on immunology of influenza, influenza vaccine and vaccines against atherosclerosis to develop hypothesis and suggestions for future research on next generation influenza vaccine.

Result

We hypothesize the very "immunological mechanisms of protection of influenza vaccine primarily targeted against influenza virus" itself may provide "secondary or bystander type cross-protection" against atherosclerosis progression and AMI. We further hypothesize this

"athero-protection" of influenza vaccine may originate through modulation of "systemic pro- vs. anti-inflammatory cytokine balance" favoring anti-inflammatory wing of immune system in body exerted by influenza vaccine. We believe deeper background of this protection may be related to influenza vaccine-associated epigenetic reprogramming of immunological cardiovascular risk-genes that would otherwise behave provocatively. Several atherosclerosis research groups around the world are studying various antigens (such as LDL or selected apoB-100 peptides) to develop immunomodulatory vaccines against atherosclerosis and AMI.

Conclusion

We suggest future preclinical research on developing next generation influenza vaccine can consider focusing to better understand, as part of overall vaccine strategy, the immunomodulatory effect of influenza vaccine antigen to favorably balance the pro- vs. anti-inflammatory homeostasis of body to prevent adverse acute cardiovascular events and also can study how to further modify or alter "influenza vaccine antigen epitopes" to epigenetically reprogram the provocative expressions of immune pro- vs. anti-inflammatory cardiovascular risk-genes.

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Immune Response Profile Induced by Live M2SR (M2-Deficient Single Replication) Influenza Vaccine and Protection Against Human Challenge with a Substantially Drifted H3N2 Strain

Presenter: Pamuk Bilsel - ACOR0043

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Background

Protection by M2SR (M2 deficient Single Replication) H3N2 vaccine was assessed in a phase 2a study in which the challenge virus was drifted from the vaccine. M2SR is an intranasal (IN) live vaccine containing hemagglutinin (HA) and neuraminidase (NA) selected from targeted influenza A strains. M2SR undergoes a single round of infection in the nasal mucosa but evokes an immune response profile similar to wild-type influenza viruses.

Method

A blinded, randomized, placebo-controlled human challenge study (EudraCT #: 2017-004971-30) was conducted at SGS in Belgium. M2SR contained HA and NA from A/Brisbane/10/2007 (H3N2). Adults, 18-55 year old, seronegative for the challenge strain (A/Belgium/4217/2015) received a single IN dose of saline or 108 TCID50 of vaccine. Four weeks later, 99 participants were challenged IN with 106 TCID50 H3N2 challenge virus and assessed for safety, infection and symptoms. . Immune responses pre- and post-vaccination were analyzed by multiple immune assays and evaluated for association with protection from influenza challenge.

Result

Adverse events and reactogenicity were similar between placebo and M2SR recipients following immunization. M2SR induced broad-spectrum immune responses including serum and mucosal antibodies and T cell responses as shown in Table below.

After challenge, 71% of placebo subjects were infected in contrast to 54% in M2SR. Moreover, only 36% of M2SR subjects with vaccine induced serum microneutralization titers against the

challenge virus were infected (P=0.0273), a protection rate of 49% relative to placebo. Further evaluation of M2SR subjects' immune responses by multivariate logistic regression analysis suggested that serum humoral responses were most associated with protection against influenza illness while mucosal secretory IgA responses were important for protection from infection.

Conclusion

M2SR protected healthy adults against influenza infection and illness with a highly drifted challenge strain. The immune profile associated with human protection includes cross-reactive serum antibody responses induced by the IN M2SR vaccine. M2SR shows potential for improved protection compared to current influenza vaccines.

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Bivalent H1 and H3 COBRA Recombinant Hemagglutinin Vaccines Elicit Seroprotective Antibodies against H1N1 and H3N2 Influenza Viruses from 2009 to 2019

Presenter: Ted Ross - ACOR0045

***Ted Ross*[1], *James Allen*[1]**

[1]Cleveland Clinic Florida

Background

Commercial influenza virus vaccines often elicit strain-specific immune responses and have difficulties preventing illness caused by antigenically drifted viral variants. In the last 20 years, the H3N2 component of the annual vaccine has been updated nearly twice as often as the H1N1 component, and mismatches between the wild-type (WT) H3N2 vaccine strain and circulating H3N2 influenza strains lead to greatly reduced vaccine efficacy.

Method

Modern methods of developing computationally optimized broadly reactive antigens (COBRAs) for H3N2 influenza viruses utilize current viral surveillance information to design more broadly reactive vaccine antigens. Here, next generation recombinant hemagglutinin (rHA) H3 COBRA hemagglutinin (HA) antigens were evaluated in mice and ferrets.

Result

In the pre-immune models, monovalent formulations of J4 and NG2 elicited broadly reactive antibodies against recently circulating H3N2 influenza viruses from 2019. Bivalent mixtures of COBRA H1 and H3 rHA, Y2 + J4, as well as N1 and N2 COBRA NA protein outperformed multiple WT H1+H3 and WT NA vaccine mixtures by eliciting, not only seroprotective antibodies against H1N1 and H3N2 isolates from 2009 to 2022, but also B and T cells against additional broadly reactive epitopes on multiple "future drifted " H1N1 and H3N2 strains.

Conclusion

Overall, the newly generated COBRA HA antigens, namely, Y2, J4, and NG2, had the ability to induce broadly reactive antibodies and cellular responses in influenza-naive and pre-immune animals. Therefore, COBRA HA/NA antigens elicit additional protective immune responses beyond correlates of seroprotective HAI antibodies against panels of antigenically drifted historical H1N1 and H3N2 vaccine strains from 2009 to 2022.

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Antibody effector functions are increased by seasonal vaccination for pandemic influenza viruses but baseline differences determine infection

Presenter: Sophie Valkenburg - ACOR0053

Sophie Valkenburg[1]

[1]The University of Melbourne

Background

Influenza viruses are extremely diverse and vaccine mediated protection by current whole virion inactivated vaccines elicit strain specific neutralising antibodies as the main protective function. Seasonal influenza vaccination in children in 2009 resulted in 47% vaccine effectiveness against H1N1pdm influenza virus. Some classes of antibodies can cross-react between seasonal, pandemic and avian influenza viruses and may have a protective role against limiting acquisition or severity of influenza virus infection. Antibodies can mediate effector functions such as antibody dependent cellular cytotoxicity (ADCC), directing immune cells to kill infected cells, or engulf them by phagocytosis (ADCP), which are respectively mediated by FcgR3A and FcgR2A engagement on B cells, Natural Killed (NK) cells and Macrophages.

Method

In this study, we utilised a large biobank of immune serum from a randomised control trial of seasonal influenza vaccination in children at the onset of the 2009 H1N1 pandemic, and tracked over the subsequent 5 years. To quantify influenza-specific antibodies before and after vaccination, and pandemic infection, we used a systems serology approach using bead multiplex approach which coupled FcR dimer proteins, a diverse HA proteins including HA-stem constructs, and antibody subclasses (IgG1/2/3) and isotypes (IgG/A1/M).

Result

We found that vaccination increased HA-specific antibodies, in terms of magnitude and FcR effector functions, even to the pandemic virus H1/2009 HA and NA proteins, which declined within one year post vaccination and then remained stable as per other viral proteins. Total H1/2009 HA IgG, and IgG2, was higher in children who were not vaccinated and uninfected compared to unvaccinated infected children, suggesting a protective role of cross-reactive HA antibodies. However, whilst vaccination increased IgG1 response against vaccine and related proteins, it did not impact infection status, possibly masking baseline protective effects seen in unvaccinated uninfected children. Whereas opposing trends for IgG1 versus IgG3 were found in unvaccinated children and infection.

Conclusion

The antibody effector response is boosted by vaccination however vaccine breakthrough infection occurs despite these increases. Baseline differences in the pandemic cross reactive antibody effector function may protect from infection.

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Consensus-Sequence Structural Immunogen Design (CoSSID).

Presenter: Eva-Maria Strauch - ACOR0072

Eva-Maria Strauch[1]

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Background

Substantial structural and sequence information for Influenza's surface proteins is available. These robust data can be used to guide atomic-level, structural re-design of the influenza HA protein to improve vaccine design. Computational protein design has advanced remarkably in the last 15 years.

Method

We established a computational, structural prototype protocol named Consensus-Sequence Structural Immunogen Design (CoSSID). It uses consensus sequence design in combination with structural modeling. Thus, it enables us to exhaustively sample the possible sequence space while evaluating the trimeric HA molecule in a realistic structural composition. This allows us to efficiently select candidates and biochemically analyze them before testing their immunological properties.

Result

We have executed this protocol for H1 strains and have identified several interesting candidates. More than 50% of our designs expressed well as a monodisperse trimeric protein and and most designs had higher melting temperatures than vaccine strains, indicating higher stability. Several designed HAs had HAI titers against multiple strains, even an H3 strain. Several induced antibody responses that enabled viral clearance in the lungs of mice after a challenge with Bris/18. Competition assays with broadly neutralizing antibodies illustrated that at least two had highly diverse antibodies targeting the head region, stem, and anchor epitopes and efficiently off competed the broadly neutralizing antibodies for several H1 strains and H3 strains.

Conclusion

We believe our methods provides a powerful approach for consensus design for fast evolving viruses.

Immune correlates of a broadly protective H1N1 Influenza Vaccine

Presenter: Jonathan Heeney - ACOR0074

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Background

A Digitally designed, Immune Optimised, Synthetic vaccine (DIOSynVax) platform was developed to induce broad H1N1 immunity against seasonal, zoonotic and pandemic influenza threats. As the most recent influenza pandemic originated from swine, we utilised the swine challenge model to correlate vaccine efficacy with immune responses including HAI, neutralising antibodies to hemagglutinin as well as neuraminidase against divergent swine, human and pandemic H1N1 strains.

Method

Two doses of the pan-H1N1 vaccine and controls were administered twice at 4w intervals to 4 grps of swine (5/grp). Controls received whole inactivated virus (WIV) representing swine and human H1N1 influenza vaccine strains. Pigs were challenged with A/swine/England/1353/2009(H1N1) (sw/EN/09) (matched to the control WIV swine vaccine), 10w post-prime. Efficacy was measured as reduced viral RNA nasal shedding. Serum neutralising titers were monitored using pseudotype neutralisation (pMN), enzyme-linked lectin assay (ELLA) and hemagglutination inhibition (HAI). T-cell ELISpots and Nucleoprotein competition ELISA were also utilised to determine additional correlates of protection.

Result

Monitored at specific time points, the immune responses induced pre and post challenge were both humoral and cellular. Post-vaccination anti-HA titers were elicited against sw/EN/09 (A,E) and A/Victoria/2454/2019(H1N1) (VC/2454/19) (B,F). Neutralising titers obtained via pMN (A,B) and HAI (E,F) showed similar patterns with the highest titers at 42 days post-immunisation in vaccinated groups (minimum IC50 values of 1000 (A,B) and HAI titres of 80 (E,F)). Similarly NA titers were induced (C,D). Antigen specific IFNγ SFCs derived from swine PBMCs were similar among all vaccination groups pre-challenge, but noticeably higher for the DIOS DNA group post challenge (G). For all groups, titers were higher for homologous antigen-virus combinations compared to mismatched antigen-virus. Post-challenge, a marked reduction of viral shedding was detected in the DIOS (n=5) and WIV1353 (n=5) groups. Notably, despite high anti-HA and anti-NA titers, the group vaccinated with the human WIV was unable to prevent viral shedding.

Conclusion

Protective immunity correlated with HAI, anti-HA and anti-NA neutralising titers in groups vaccinated with the DIOS pan-H1N1 and WIV1353 vaccines but not for WIVVIC. This study demonstrates that immune correlates of protection extending beyond HAI protect against virus shedding; with novel vaccine antigens shown to recruit broader range of immunological effector mechanisms important for pan- or Universal Influenza vaccine strategies.

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A Composite Influenza Peptide Vaccine Comprised of Highly Conserved Hemagglutinin, Neuraminidase and Matrix Protein Epitopes Induced Broad Serum Antibodies to Seasonal and Pandemic Influenza Strains

Presenter: Clara J. Sei - ACOR0087

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Background

Improved vaccine strategies for seasonal and pandemic influenza control are a public health priority. A composite, multi-epitope peptide vaccine that contains highly conserved epitopes to Hemagglutinin (HA), Neuraminidase (NA) and Matrix Ectodomain (M2e) antigens may provide a new approach for producing a cost-effective universal influenza vaccine. The composite peptide vaccine formulated with ALFQ adjuvant and given intramuscularly (IM), induced robust immune responses to seasonal Group 1 and 2 influenza viruses and to the HA, NA and M2e peptides (Sei, et al, Vaccines, 2021). In addition, the peptide vaccine induced an extended and durable immunity to influenza (manuscript in preparation). Here we report robust immune response in mice to seasonal influenza B and to potential pandemic strains H5N1 and H5N6.

Method

ICR mice were immunized on days 0, 21 and 35 with 20 µg of a composite influenza peptide vaccine comprised of unconjugated HA+NA (Flu Pep11) and M2e+Tcell (Flu Pep5906) epitopes (peptides) formulated with AddaVax™ adjuvant and injected either IM or subcutaneously (SQ). Serum antibody responses to composite vaccine antigens, component peptides, different subtypes of influenza A (H1N1, H3N2, H5N1, H5N6), and influenza B (Yamagata) viruses were analyzed by ELISA. Serum antibody functional activity was determined using microneutralization assay.

Result

Mice immunized IM with the composite influenza peptide vaccine demonstrated robust serum antibody responses to HA+NA (Flu Pep11) and M2e+Tcell (Flu Pep5906) on day-21 after a single dose and maintained high antibody titers throughout the 56-day study period. In contrast, mice immunized SQ developed good antibody titers by day-21 that continued to rise over the 56-day period with subsequent vaccine booster immunizations. The immunization groups demonstrated similar antisera binding activity to individual HA, NA, M2e peptides and to different subtypes of influenza A and influenza B viruses. In addition, strong cross-neutralizing antibodies against influenza viruses (including Group 1 and Group 2) were induced.

Conclusion

The multi-epitope composite peptide vaccine was highly immunogenic in mice and produced strong humoral responses with broadly reactive serum antibodies against peptides and influenza A (H1N1, H3N2, H5N1, H5N6) and influenza B viruses. Serum antibody recognition of influenza epitopes on peptides and influenza viruses with evidence of robust and durable cross-neutralizing antibodies may provide a strong indicator of protective immunity and offer a viable pathway towards a universal influenza vaccine. A Phase I clinical trial is projected for 2023 using these composite influenza peptides formulated with ALFQ adjuvant.

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Analysis the immunogenic effects of site-specific glycosylation on the Gansu H7N9 HA protein

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Background

Avian Influenza virus H7N9 is one influenza subtype virus that has caused 6th epidemic waves of human infections in China since 2013. In the present, it was reported that the current H7N9 antiserum standards showed the weak inhibition of the emerging Avian Influenza H7N9 Gansu strain (A/Gansu/23277/2019), suggesting the difference on the antigenicity with previous H7N9 vaccine strains. Gene sequencing alignment revealed that the Gansu H7N9 HA (GSH7) contains two glycosylation sites (N141 and N167, H7 numbering with signal peptide) near the receptor binding domain, which were not found in the HAs of A/Anhui/1/2013 and A/Guangdong/17SF003/2016 H7N9 vaccine viruses. Less information was known about their effect on HA immunogenicity for neutralization antibody induction.

Method

In the study, we generated recombinant type of GSH7 protein (rGSH7) with different N-glycosylation patterns to study the effect of site-specific glycan on HA properties. Two single mutants (rGSH7-A and rGSH7-B), one double mutant (rGSH7-C) and the original rGSH7 were constructed and expressed by the insect cell system. SRD assay was performed to characterize the affinity of the rGSH7 variants with home-built rabbit anti-GSH7 antiserum. The mouse immunization experiment was performed to compare their immunogenicity for inducing protective antibody against H7N9 vaccine viruses.

Result

In the beginning, mass spectrometry was used to confirm the status of site-specific glycan on each recombinant protein candidates. By mutating the N-glycan from either N141 (rGSH7-A), or N-167(rGSH7-B), or both N-glycosylation sites (rGSH7-C), these rGSH7 variants had their hemagglutination activity reduced 50-75%, suggesting these two glycosylation sites were involved in the HA-SA receptor interaction. In the SRD assay with the home-built rabbit antiserum, we found that precipitation ring diameter of rGSH7-A was nearly the same with that of rGSH7, while the ring sizes of the rGSH7-B or rGSH7-C were reduced 50%. After three intramuscular injections with rGSH7 or variants (20μg/dose with adjuvant), mice produced similar neutralize antibodies response to against the Gansu vaccine virus. Additionally, we found that mouse antisera raised by rGSH7 variants presented the cross activity to neutralize the Anhui and Guangdong vaccine viruses.

Conclusion

Our results demonstrated that the glycosylation at N141 and N167 residues might act a role to affect the hemagglutination of rGSH7 protein, and the elimination of these site-specific glycans might be capable of inducing the broad-spectrum neutralization antibody response in mouse. The study could provide in-depth information that site glycan modification could benefit the development of protein-based avian influenza vaccine with broad spectrum potency.