

**CORRELATES OF PROTECTION FOR
NEXT GENERATION INFLUENZA VACCINES:
LESSONS LEARNED FROM THE
COVID PANDEMIC**

SEATTLE 1-3 MARCH 2023



PROGRAMME

WELCOME



Bill & Melinda Gates Foundation, Conference Center, 500 5th Avenue N, Seattle, WA 98109

THE ORGANIZING COMMITTEE:

REBECCA COX

University of Bergen, Norway

ALI ELLEBEDY

University of Washington at St.Louis, USA

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MHRA, UK

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WHO Collaborating Centre / University of Melbourne, Australia

S. MARK TOMPKINS

University of Georgia, USA

JERRY P. WEIR

Food and Drug Administration (FDA), USA



DEAR COLLEAGUES,

It is a great pleasure to welcome you to the isirv meeting on **Correlates of Protection for Next Generation Influenza Vaccines: Lessons Learned from the COVID-19 Pandemic** which is kindly being hosted and supported by the Bill and Melinda Gates Foundation with additional support from the Task Force for Global Health's Global Funders Consortium for Universal Influenza Vaccine Development and the National Institute for Allergy and Infectious Diseases. This is the third in a series of isirv meetings on Correlates of Protection against Influenza, with the last being held in Siena, Italy in April, 2019. At that time, we could not have imagined that less than one year later, a newly emerged coronavirus would cause a pandemic resulting in devastating losses of human life and compromising the global economy and the conduct of daily life. The COVID-19 pandemic challenged vaccinologists to use transformational technologies to produce effective vaccines against the SARS-CoV-2 virus in record time.

This meeting seeks to review lessons learned from the COVID-19 pandemic and the use of transformational vaccine platforms and developmental processes to inform the way forward to identify and validate new immune correlates of protection against influenza for accelerated development of improved seasonal influenza vaccines, as well as vaccines that provide broader, more durable protection that may mitigate future influenza pandemics. In addition, the meeting seeks to review newly gained knowledge on immune correlates of protection for next-generation influenza virus vaccines, identify the most relevant immunological assays needed for evaluation of respiratory virus vaccines, discuss assay standardization and harmonization and the use of immune correlates of protection in the vaccine regulatory process.

This meeting brings together investigators from public health, academia, industry, regulatory agencies and funding organizations to discuss a way forward for the accelerated development of next generation influenza vaccines. We hope that all participants have a productive meeting and encourage you all to take an active part in discussions and interactions over the 3-day meeting.

ON BEHALF OF THE ORGANIZING COMMITTEE:

REBECCA JANE COX

University of Bergen
Norway

JACQUELINE KATZ

The Task Force for Global Health,
U.S.A

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PROGRAMME



DAY 1 WEDNESDAY 1 March

08:00 Registration / Poster Mounting

09:00 WELCOME AND OPENING REMARKS

KEITH KLUGMAN Bill & Melinda Gates Foundation, USA

SESSION A

LESSONS LEARNED FROM THE COVID-19 PANDEMIC AND NEW COVID-19 VACCINE PLATFORMS

Chairs: JACQUELINE KATZ The Taskforce for Global Health, USA
ROS HOLLINGSWORTH Bill & Melinda Gates Foundation, USA

09:05 Lessons Learned from New COVID Vaccines

SARAH GILBERT University of Oxford, UK

09:35 Lessons Learned from the COVID Pandemic

CHERYL COHEN University of Witwatersrand, South Africa

09:55 What Can We Learn from the Human Challenge of SARS-CoV-2 and Influenza?

CHRIS CHIU Imperial College London, UK

10:20 SARS-CoV-2 Correlates of Protection

MILES DAVENPORT Kirby Institute, UNSW Sydney, Australia

10:40 BREAK

SESSION B

NEXT GENERATION/UNIVERSAL INFLUENZA VACCINE

Chairs: OTHMAR ENGELHARDT Medicines and Healthcare Products Regulatory Agency (MHRA), UK
KANTA SUBBARAO WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Australia

11:10 Universal Influenza Vaccine

FLORIAN KRAMMER Icahn School of Medicine at Mount Sinai, USA

11:40 Next Generation Influenza Vaccines

AARON SCHMIDT Harvard Medical School; Ragon Institute of MGH, MIT and Harvard, USA

12:00 Correlates of Protection from Cohort Studies to Guide Next Generation Influenza Vaccine

AUBREE GORDON University of Michigan, USA

12:20 Correlates of Protection for Next Generation/Universal Influenza Vaccine

ARNOLD MONTO University of Michigan, USA

12:40 LUNCH

SESSION C

MUCOSAL CORRELATES OF IMMUNITY AND PROTECTION

Chairs: ALI ELLEBEDY Washington University School of Medicine, USA
REBECCA JANE COX University of Bergen, Norway

- 14:00** **Mucosal Correlates of Immunity and Protection**
PETER OPENSHAW Imperial College London, UK
- 14:30** **Mucosal Data from LAIV**
KANTA SUBBARAO WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Australia
- 15:00** **The Role of Mucosal Immunity to Influenza**
STACEY SCHULTZ-CHERRY St Jude Children's Research Hospital, USA
- 15:20** **Local Immunity After Influenza Vaccination**
REBECCA JANE COX University of Bergen, Norway
- 15:40** **The Role of Local Antibodies in SARS CoV-2 Protection**
JENNIFER GOMMERMAN University of Toronto, Canada

16:00 **BREAK**

SESSION D

IMMUNOLOGY: B AND T CELL RESPONSES

Chairs: FLORIAN KRAMMER Icahn School of Medicine at Mount Sinai, USA
DIANE POST National Institute of Allergy and Infectious Diseases (NIAID), USA

- 16:30** **Role of Non HI Antibodies in Protection from Influenza**
GALIT ALTER Harvard Medical School, USA
- 17:00** **Role of B Cells in Protection after Influenza Vaccination**
ALI ELLEBEDY Washington University School of Medicine, USA
- 17:30** **CD8 T Cells in Protection from Influenza**
PAUL THOMAS St. Jude Children's Research Hospital, USA
- 18:00** **Role of T Cells in Vaccine Responses**
SHANE CROTTY La Jolla Institute for Immunology, USA

18:30 **WELCOME RECEPTION - POSTER SESSION I**

DAY 2 THURSDAY 2 March

SESSION E

IMMUNOLOGICAL ASSAYS: LESSONS FROM INTERNATIONAL CONSORTIA

Chairs: REBECCA JANE COX University of Bergen, Norway
PAUL THOMAS St Jude Children's Research Hospital, USA

- 09:00** **Lessons Learned from SARS CoV-2 Assays**
DAVID MONTEFIORI Duke University School of Medicine, USA (**Remote**)
- 09:30** **Lessons Learned from FLUCOP: HA Antibody Assays**
OTHMAR ENGELHARDT Medicines and Healthcare Products Regulatory Agency (MHRA), UK
- 10:05** **Lessons Learned from FLUCOP: NA Antibody Assays**
EMANUELE MONTOMOLI University of Siena, Italy
- 10:20** **Lessons Learned from FLUCOP: T Cell Assays**
GWENN WAERLOP Ghent University, Belgium

10:40 **BREAK**

SESSION F

REGULATORY SESSION

Chairs: JERRY WEIR U.S Food and Drug Administration (FDA), USA
CHRIS ROBERTS National Institutes of Health (NIH), USA

- 11:10** **Introduction to Regulatory Hurdles for Next Generation Influenza Vaccines**
DAVID VAUGHN Bill & Melinda Gates Foundation, USA
- Regulators' Perspective**
JERRY WEIR Food and Drug Administration (FDA), USA
MARCO CAVALERI European Medicines Agency (EMA), Netherlands (**remote**)
- 11:30** **PANEL DISCUSSION: How Can Correlates of Protection Help the Regulatory Process for Licensure of New Vaccines?**
- SARAH GILBERT University of Oxford, UK
CHRIS CHIU Imperial College London, UK
CHRIS ROBERTS National Institutes of Health (NIH), USA
DAVID VAUGHN Bill & Melinda Gates Foundation, USA
JERRY WEIR Food and Drug Administration (FDA), USA
MARCO CAVALERI European Medicines Agency (EMA), Netherlands (**Remote**)

12:30 **LUNCH**

SESSION G OPTIMAL STUDY DESIGN FOR ESTABLISHING CORRELATES OF PROTECTION

Chairs: **JOE BRESEE** The Taskforce for Global Health, USA
SHEENA SULLIVAN WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Australia

13:45

Influenza Vaccine Effectiveness

SHEENA SULLIVAN WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Australia

14:15

Novel Study Design to Support Correlates of Protection Studies

PETER B. GILBERT University of Washington, USA

14:45

Mathematical Modelling of Correlates of Protection

MILES DAVENPORT Kirby Institute, UNSW Sydney, Australia

15:05

PANEL DISCUSSION – Study Design for Correlates of Protection

AUBREE GORDON University of Michigan, USA

MILES DAVENPORT Kirby Institute, UNSW Sydney, Australia

SHEENA SULLIVAN WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Australia

PETER B. GILBERT University of Washington, USA

16:00

BREAK

SESSION H ORAL ABSTRACTS

Chairs: **S. MARK TOMPKINS** University of Georgia, USA
EMANUELE MONTOMOLI University of Siena, Italy

16:30 -
18:00

Antibody titers and shedding dynamics of seasonal influenza infections in a South African community cohort (PHIRST), 2016-2017

MOLLY SAUTER Princeton University, USA [ACOR0070]

Impact of COVID-19 vaccination on duration of viral shedding in asymptomatic and symptomatic infection

NICOLE NGAI YUNG TSANG WHO Collaborating Centre for Infectious Disease Epidemiology and Control, Hong Kong [ACOR0091]

Characterization of Viral Shedding and Particle Release from Humans Experimentally Infected with Seasonal H3N2 virus

SEEMA LAKDAWALA Emory University, USA [ACOR0096]

Trends in the age immunity profile of respiratory viruses throughout the COVID19 pandemic in Seattle, 2020-2022

CECILE VIBOUD Fogarty International Center, USA [ACOR0102]

Protective cross-reactive human monoclonal antibodies against influenza virus neuraminidases targeting the conserved catalytic site

JULIA LEDERHOFER Vaccine Research Center/NIAID/NIH, USA [ACOR0033]

Mapping the differential adaptive immune dynamics to distinct influenza vaccine modalities using human tonsil organoids

LISA WAGAR University of California Irvine, USA [ACOR0097]

Baseline innate and T cell populations are correlates of protection against symptomatic influenza virus infection independent of serology

ROBERT METTELMAN St. Jude Children's Research Hospital, USA [ACOR0069]

18:00

EVENING RECEPTION - POSTER SESSION II

DAY 3 FRIDAY 3 March

SESSION I ORAL ABSTRACTS

Chairs: CHRIS CHIU Imperial College London, UK
STACEY SCHULTZ-CHERRY St. Jude Children's Research Hospital, USA

09:00 -
10:30

Distinct functional humoral immune responses are induced after live attenuated and inactivated seasonal influenza vaccination

XIN TONG MIT and Harvard, USA [ACOR0001]

Assessment of multiple immune correlates of protection against influenza using acute and convalescent sera from influenza natural infection

MIN LEVINE Centers for Disease Control and Prevention, USA [ACOR0040]

Immune-history based correlates of protection for influenza and SARS-CoV-2

TOMER HERTZ Ben Gurion University of the Negev, Israel [ACOR0061]

Post-vaccine cytokine levels that correlate with breakthrough influenza infections

EWAN P. PLANT Food and Drug Administration, USA [ACOR0002]

Influenza vaccine responses to A(H1N1)pdm09 antigens in 2020 and 2021 among repeatedly vaccinated healthcare workers

STEPHANY SANCHEZ-OVANDO University of Melbourne, Australia [ACOR0027]

Age-dependent induction of stalk-reactive antibodies with ADCC reporter activity by administration of a live-attenuated influenza virus vaccine to children

JUAN MANUEL CARRENO QUIROZ Icahn School of Medicine at Mount Sinai, USA [ACOR0064]

Pre-existing SARS-CoV-2 antibodies and risk of breakthrough infection in a prospective cohort, Seattle, March-November 2022

ALPANA WAGHMARE University of Washington, USA [ACOR0101]

10:30 **BREAK**

SESSION J ORAL ABSTRACTS

Chairs: FLORIAN KRAMMER Icahn School of Medicine at Mount Sinai, USA
DIANE POST National Institute of Allergy and Infectious Diseases (NIAID), USA

11:00 -
12:30

Matrix M adjuvanted H5N1 vaccine elicits broadly neutralizing antibodies and neuraminidase inhibiting antibodies in humans that correlate with in vivo protection

FAN ZHOU University of Bergen, Norway [ACOR0019]

Human influenza virus challenge identifies cellular correlates of protection for oral vaccination

DAVID MCILWAIN Stanford University, USA [ACOR0079]

An influenza hemagglutinin stem-only Immunogen elicits a broadly cross-reactive memory B cell response in humans

SARAH ANDREWS National Institutes of Health, USA [ACOR0039]

SARS-CoV-2 correlates of protection conferred by natural immunity: comparative analysis of pre-exposure neutralizing antibody titers against Delta and Omicron variant infection

KAIYUAN SUN National Institutes of Health, USA [ACOR0021]

Detailed estimates of correlates of protection for SARS-CoV-2, stratified by key VOC and key covariates

TIM RUSSELL London School of Hygiene and Tropical Medicine, UK [ACOR0098]

Antibody effector function and T cell responses to homologous and heterologous inactivated or mRNA vaccines against SARS-CoV-2

CAROLYN COHEN University of Hong Kong, Hong Kong [ACOR0013]

12:30 **LUNCH**

SESSION K
RECAP OF SESSIONS A-D

13:30 -
14:30

GROUP DISCUSSION

Lessons Learned from COVID for Identifying Correlates of Protection and Developing Consensus on Immune Responses to Target

FLORIAN KRAMMER Icahn School of Medicine at Mount Sinai, USA

SARAH GILBERT University of Oxford, UK

REBECCA JANE COX University of Bergen, Norway

KANTA SUBBARAO WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Australia

CHERYL COHEN University of Witwatersrand, South Africa

14:30 **BREAK**

SESSION L
RECAP OF SESSIONS E-G

15:00 -
16:00

GROUP DISCUSSION

The Way Forward in Correlates of Protection and their Detection for Next Generation Vaccines

JERRY WEIR FDA, USA

JACQUELINE KATZ The Taskforce for Global Health, USA

OTHMAR ENGELHARDT Medicines and Healthcare Products Regulatory Agency (MHRA), UK

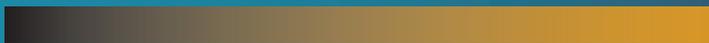
SHEENA SULLIVAN WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Australia

S. MARK TOMPKINS University of Georgia, USA

16:00 **END OF MEETING - CLOSING REMARKS**

ROS HOLLINGSWORTH Bill & Melinda Gates Foundation, USA

O R A L A B S T R A C T S



B Y S E S S I O N

ANTIBODY TITERS AND SHEDDING DYNAMICS OF SEASONAL INFLUENZA INFECTIONS IN A SOUTH AFRICAN COMMUNITY COHORT (PHIRST), 2016-2017

Presenter: Molly Sauter - ACOR0070

Molly Sauter⁵, Nicole Wolter², Stefano Tempia¹¹, Jackie Kleynhans¹, Jocelyn Moyes³, Meredith L McMorrow⁶, Lorens Maake¹, Amelia Buys¹, Florette K Treurnicht², Orienka Hellferscee², Azwifarwi Mathunjwa¹, Neil A Martinson¹⁰, Kathleen Kahn⁷, Limakatso Lebina⁹, Katlego Mothlaoleng⁹, Floidy Wafawanaka⁷, Francisc Xavier Gómez-Olivé⁷, Thulisa Mkhencele¹, Kaiyuan Sun⁴, Cecile Viboud⁴, Bryan Grenfell⁵, Anne Von Gottberg², Cheryl Cohen³, For the PHIRST Group⁸

¹Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa, ²Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa; School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, ³Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa; School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, ⁴Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America, ⁵Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America; Department of Ecology and Evolutionary Biology, Princeton University, Princeton, New Jersey, United States of America, ⁶Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; Influenza Program, Centers for Disease Control and Prevention, Pretoria, South Africa, ⁷MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, ⁸N/A, ⁹Perinatal HIV Research Unit, MRC Soweto Matlosana Collaborating Centre for HIV/AIDS and TB, University of the Witwatersrand, South Africa, ¹⁰Perinatal HIV Research Unit, MRC Soweto Matlosana Collaborating Centre for HIV/AIDS and TB, University of the Witwatersrand, South Africa; DST/NRF Centre of Excellence for Biomedical Tuberculosis Research, University of the Witwatersrand, Johannesburg, South Africa; Johns Hopkins University Center for TB Research, Baltimore, Maryland, United States of America, ¹¹School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; Influenza Program, Centers for Disease Control and Prevention, Pretoria, South Africa; MassGenics, Duluth, Georgia, USA

BACKGROUND

We studied the impact of pre-season influenza antibody titers on the kinetics of viral shedding, using serology and polymerase chain reaction (PCR) data from a household cohort study in South Africa.

METHOD

Prior to the winters of 2016 and 2017 about 280 individuals from both a rural and an urban setting in South Africa were enrolled, and serum samples were collected. Influenza antibody titers were measured with a hemagglutination inhibition assay (HAI) against the A(H1N1)pdm09, A(H3N2), B/Yamagata, and B/Victoria subtypes circulating each season. Throughout the season, nasopharyngeal swabs were collected twice per week for real-time reverse transcription PCR testing. PCR cycle thresholds were used to model individual-level shedding kinetics and estimate shedding duration and peak viral load for each individual's first influenza episode. A mixed effects linear regression was used to analyze the relationship between shedding dynamics and log transformed pre-season titers, adjusting for age, HIV infection, study site, and year.

RESULT

Over the two study years, there were 244 infections for which the shedding dynamics could be estimated and pre-season HAI titers determined (30 A(H1N1)pdm09, 117 A(H3N2), 59 B/Victoria, and 38 B/Yamagata). No individuals included in this analysis received an influenza vaccine during the study. For infections with A(H3N2), each 4-fold pre-season titer increase correlated with about a 0.70 day decrease in duration of infection (95% confidence interval (CI) -1.29 to -0.12). There was no significant association between duration of A(H1N1)pdm09 (95% CI -0.38 to 0.27), B/Victoria (95% CI -1.19 to 1.60), or B/Yamagata (95% CI -1.25 to 1.15) episodes and pre-season titers. There was also no correlation between pre-season titers and estimated peak viral loads for all circulating subtypes including A(H3N2). For both duration and peak viral load, age demonstrated a stronger correlation than the pre-season titer, with younger age associated with greater shedding, and stronger signals for type A over type B.

CONCLUSION

Higher pre-season HAI titers were significantly associated with a decrease in duration of shedding for A(H3N2), but not for the other three circulating subtypes or for peak viral load which could be an issue of power due to smaller samples sizes. As shedding patterns underlie risk of transmission, this highlights the potential of prior immunity to reduce transmission in instances of influenza infections, at least for A(H3N2). The strong residual relationship between age and infection kinetics suggests that HAI titers might not be an encompassing measure of susceptibility to shedding and we speculate that cell mediated immunity might play a more important role.

SESSION H

IMPACT OF COVID-19 VACCINATION ON DURATION OF VIRAL SHEDDING IN ASYMPTOMATIC AND SYMPTOMATIC INFECTION

Presenter: Nicole Ngai Yung Tsang - ACOR0091

Nicole Ngai Yung Tsang¹, Hau Chi So¹, Benjamin J Cowling¹, Gabriel M Leung¹, Dennis Kai Ming Ip¹

¹WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

BACKGROUND

Transmission risk of asymptomatic infection, as reflected by the duration of viral shedding, is inherently difficult to study, for the enrolment of asymptomatic cases without presentation at clinical settings. Although the vaccine effectiveness in preventing severe and symptomatic SARS-CoV-2 infection is better elucidated, its impact on viral shedding and transmissibility remained largely unknown, which carried important public health implications for seedling downstream infections in the community. A regular testing approach irrespective of symptoms enables the capture of asymptomatic infections for estimating their viral shedding, which would help to inform targeted clinical management and public health measures.

METHOD

A random and representative cohort of 14,800 individuals aged 5 or above were recruited to a large-scale prospective community surveillance in Hong Kong (HK). Regular self-testing of rapid antigen tests (RAT) has been conducted for 9 months (between March 1 and December 21, 2022)

with a pooled nasal and throat swab irrespective of symptom and exposure status to monitor the longitudinal viral shedding pattern as a proxy to ascertain SARS-CoV-2 transmissibility during the 5th wave in HK with omicron (BA.2& BA.5) predominance. Symptomatology and vaccination history were ascertained continuously. Kaplan-Meier curves of RAT conversion and multivariate Cox proportional-hazards regression model were used to estimate the hazard ratio (HR) of RAT conversion by variant, symptomatology, and vaccination status. A higher HR indicates shorter duration of viral shedding.

RESULT

A total of 2548 (17.2%) participants were confirmed by a SARS-CoV-2 rapid antigen test (RAT), whom were being followed up for a total of 17721 person-days. The median duration of RAT positivity was 7 days (mean 7.0, SD 2.7). Older adults were associated with a longer duration of shedding (HR 0.8, 95% CI 0.7-0.9). Comparing symptomatic (1617, 63%) and asymptomatic cases (931, 37%) revealed no significant difference in their shedding duration (HR 1.1; 0.96-1.2). Two doses or more of CoronaVac (HR 1.5, 1.3-1.8) or BNT162b2 (HR 1.2, 1.1-1.4) shortened the duration of shedding.

CONCLUSION

Our study used regular rapid antigen testing, irrespective of symptoms and exposure risk, to examine viral shedding of asymptomatic and symptomatic infection. Comparing to symptomatic cases, the similar duration of viral shedding amongst the one-third of COVID-19 cases whom were asymptomatic highlighted their potential for transmitting the diseases in the community. Completion of vaccination, with either CoronaVac or BNT162b2, is useful to shorten the shedding duration of asymptomatic and symptomatic COVID-19 cases.

SESSION H

CHARACTERIZATION OF VIRAL SHEDDING AND PARTICLE RELEASE FROM HUMANS EXPERIMENTALLY INFECTED WITH SEASONAL H3N2 VIRUS

Presenter: Seema Lakdawala - ACOR0096

Seema Lakdawala¹, Nishit Shetty⁴, Meredith Shephard², Nicole Rockett³, Jessica Traenkner², Hollie Macenczak², Valerie Le Sage³, Shamika Danzy², Nahara Vargas Maldonado², Lucas Ferreri², Colleen Kraft², Anice Lowen², Linsey Marr⁴, Nadine Roupheal²

¹ C1Emory University, ² Emory University, Atlanta, GA, ³ University of Pittsburgh, Pittsburgh, PA, ⁴ Virginia Tech, Blacksburg, VA

BACKGROUND

Airborne transmission of respiratory viruses requires the expulsion of viruses into the air from the respiratory tract. Correlation between the concentration of respiratory aerosols containing virus and viral shedding in nasal or oral cavities is a gap in the field of transmission of airborne viruses. Using the expertise at Emory University in infectious diseases human challenge models, we set out to sample these sites simultaneously during an influenza challenge study. Understanding the release of viruses into the environment provides a mechanism to study transmission potential. Incorporation of these methodologies into future human challenge studies and development of human transmission models are necessary to assess the potential for novel vaccination regimens to disrupt airborne transmission of influenza viruses.

METHOD

In July - Sep 2022, eight participants were admitted to Emory University Hospital inpatient research unit and infected intranasally with influenza A/Perth/16/2009 (H3N2) virus (obtained from hVivo, UK). Nasal swabs and saliva were collected every day for 7 days post infection for assessment of infectious viral titer and genome copy numbers. Air samples were collected in a condensation sampler coupled to a particle counter daily from each participant during 10 min of speaking without a mask, 10 min of tidal breathing, and 10 min speaking with a mask.

RESULT

The size distribution of particle release was patient specific, and some participants shed higher particle numbers than others. We observed 6 out of 8 participants shed infectious virus in nasal swabs, nasal lavage or saliva. In these 6 participants, the aerosol size distribution did not change during viral shedding. Analysis of viral genomes in air samples is ongoing.

CONCLUSION

Individuals infected with influenza A virus shed virus from nasal and oral cavity. The total amount and size distribution of expelled aerosols during speaking or breathing did not change during the course of viral infection.

SESSION H

TRENDS IN THE AGE IMMUNITY PROFILE OF RESPIRATORY VIRUSES THROUGHOUT THE COVID19 PANDEMIC IN SEATTLE, 2020-2022

Presenter: Cecile Viboud - ACOR0102

Samantha Bents⁴, Emily Martin⁷, Amanda Adler⁶, Elizabeth Krantz⁸, Amanda Perofsky³, Rachel Blasevic⁸, Terry Stevens-Ayers⁸, Claire Andrews⁸, Louise Kimball⁸, Robin Prentice¹, Lea Starita², Peter Han¹, Janet Englund⁶, Michael Boeckh⁸, Cecile Viboud⁵

¹ Brotman Baty Institute, University of Washington, ² Brotman Baty Institute, University of Washington; Department of Genome Sciences, University of Washington, ³ Brotman Baty Institute, University of Washington; Fogarty International Center, National Institutes of Health, ⁴ Fogarty International Center and National Institute of Allergy and Infectious Diseases, National Institutes of Health, ⁵ Fogarty International Center, National Institutes of Health, ⁶ Seattle Children's Research Institute, ⁷ University of Michigan, ⁸ Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center

BACKGROUND

The circulation of endemic respiratory viruses was greatly perturbed during the pandemic period, with out-of-season activity reported in 2021-2022. Here we assessed changes in pre-existing antibodies to respiratory viruses throughout the COVID-19 period by age group and pathogen.

METHOD

We collected 1200 serum samples from immuno-competent children aged 0-12 years who visited Seattle Children Hospital and 900 adults who donated blood to Bloodworks Northwest clinics. Samples were collected at 3 representative time points of the COVID19 pandemic (Aug-Nov 2020; Aug-Nov 2021; May-Aug 2022). We assessed antibody titers to 12 respiratory viruses, including

influenza, respiratory syncytial virus (RSV), and seasonal and pandemic coronaviruses via multiplex electrochemiluminescence neutralization panels. We evaluated changes in log of antibody titers by age group, time point and pathogen.

RESULT

At the end of a nearly typical winter season (2020 time point), there was a marked gradient of antibody titers with age for RSV and influenza A, a weaker gradient for seasonal coronaviruses and influenza B/Yamagata, and no gradient for influenza B/Victoria or SARS-CoV-2.

Changes in antibody titers throughout the pandemic period were most pronounced in young children. Titers to influenza A/H3 decreased significantly between 2020 and 2022 in all age groups under 5 years (Kruskall-Wallis p-value < 0.01) but remained stable in older children and adults. Changes were typically less pronounced for other influenza subtypes. Human coronaviruses and RSV antibody titer levels dropped between 2020 and 2021 and rebounded in 2022. The largest changes in titers were observed for HCoV 229E in children under 5 years, and for HCoV NL63 and RSV in children under 9 years (all p-values ≤ 0.02). Children 1-2-yo experienced the most consistent drop in antibody titers across a larger subset of pathogens including RSV, influenza A and B, and seasonal coronaviruses HKU1/229E/NL63. In contrast, the pandemic had little effect on titers among children over 10 years and adults.

CONCLUSION

Young children experienced an immunity gap to endemic viruses during the COVID19 pandemic, and this was most pronounced for influenza A/H3, RSV, and seasonal coronaviruses 229E and NL63. The immunity gap evidenced for influenza A/H3 could have driven the unusual resurgence of this virus in fall 2022 and the pressure on pediatric wards. Further modeling work should explore how frequency of exposure, waning immunity, and viral evolution contribute to the immune age profile of different pathogens.

SESSION H

PROTECTIVE CROSS-REACTIVE HUMAN MONOCLONAL ANTIBODIES AGAINST INFLUENZA VIRUS NEURAMINIDASES TARGETING THE CONSERVED CATALYTIC SITE

Presenter: Julia Lederhofer - ACOR0033

Julia Lederhofer⁴, Andrew J. Borst¹, Sarah F. Andrews³, Julie Raab³, Christina Yap³, Daniel Ellis¹, Adrian Creanga³, Adam K. Wheatley², Adrian B. McDermott³, Barney S. Graham³, Neil P. King¹, Masaru Kanekiyo³

¹ Institute for Protein Design, University of Washington, Seattle, United States; Department of Biochemistry, University of Washington, Seattle, United States, ² Peter Doherty Institute, University of Melbourne, Melbourne, Australia, ³ Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, United States, ⁴ Vaccine Research Center/NIAID/NIH

BACKGROUND

Each year, influenza has a significant morbidity and mortality and poses global public health and economic challenges, necessitating the continued development of effective vaccines to this ever-changing virus. The two viral surface glycoproteins on influenza virions, the hemagglutinin (HA)

and neuraminidase (NA), facilitate viral entry and egress from host cells, respectively. Although NA is a key target of licensed antivirals, it has been underappreciated as a viable target of broadly protective antibodies until recently. Identification of such broadly protective antibodies targeting the viral NA provides not only additional potential countermeasures but also a blueprint to design vaccines targeting the sites of vulnerability.

METHOD

We used recombinant NA tetramer probes to isolate memory B cells from a convalescent individual of H3N2 influenza infection by flow cytometry. NA-specific memory B cells were single-cell sorted and sequenced their immunoglobulin genes. Immunoglobulins were recombinantly produced and assessed their binding to recombinant NAs derived from various influenza A and B viruses. We also performed functional assays including neuraminidase activity inhibition and virus inhibition assays. One cross-reactive NA antibody termed NCS.1 was also structurally characterized by using cryo-EM.

RESULT

We show that the antibodies derived from isolated B cells not only bound tightly to N1 subtype NAs, but also to influenza B NA along with avian influenza NAs. One such antibody, termed NCS.1, was protective in vivo against influenza B virus challenge and inhibited neuraminidase activity of viruses carrying multiple NA subtypes. Cryo-EM structure of the NCS.1 Fab-N5 NA complex revealed that this antibody used an extended CDR H3 loop to interact with the catalytic pocket of NA analogous to the recently discovered broadly cross-reactive antibody 1G01.

CONCLUSION

These findings illustrate the ability of humans to generate broadly cross-reactive NA-directed antibodies through infections and/or vaccinations by targeting the conserved catalytic site. Further, our NCS.1 along with another recently discovered antibody DA03E17 reaffirms that the elicitation of these 1G01-like broadly cross-reactive antibodies in humans may be possible, and together they pave the way for the design of NA-based vaccines.

SESSION H

MAPPING THE DIFFERENTIAL ADAPTIVE IMMUNE DYNAMICS TO DISTINCT INFLUENZA VACCINE MODALITIES USING HUMAN TONSIL ORGANIDS

Presenter: Lisa Wagar - ACOR0097

Jenna Kastenschmidt¹, Suhas Sureshchandra¹, Aarti Jain¹, Jenny Hernandez-Davies¹, Rafael De Assis¹, Zachary Wagoner¹, Andrew Sorn¹, Mahina Mitul¹, Aviv Benchorin¹, Elizabeth Levendosky³, Gurpreet Ahuja², Qiu Zhong², Douglas Trask¹, Jacob Boeckmann¹, Algimantas Jasinskas¹, Naresha Saligrama³, Huw Davies¹, Lisa Wagar¹

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BACKGROUND

Highly effective vaccines elicit specific, robust, and durable adaptive immune responses and ideally stimulate local immune responses at the natural site of infection to mediate optimal protection. However, it has been challenging to understand and design vaccine candidates with these properties beyond empirical testing in animal models and validation in clinical trials.

To make advances in informed vaccine design, it is critical that we understand the cellular dynamics underlying human adaptive immune responses to different antigen formats. There is also a renewed interest in utilizing intranasal vaccines as a strategy to stimulate protective immunity against respiratory viruses in the upper respiratory tract. However, predictors and correlates of protection from mucosa-targeting vaccines have been difficult to quantify. Tonsils are considered both lymphoid and mucosal tissues; they are also accessible from otherwise-healthy patients. In this study, we sought to understand how antigen-specific B and T cells are activated and participate in adaptive immune responses within the mucosal site.

METHOD

We used a human tonsil organoid platform to elucidate the dynamics of Ag-specific cells in primary human tonsils as they responded to inactivated and live-attenuated influenza vaccines and wild-type viruses. Tonsil organoids are a useful model of human adaptive immunity that can recapitulate numerous aspects of the developing B and T cell response. A major advantage of organoid platforms is the ability to test multiple conditions, including different composition, dose, time points, within the same donor. We used the tonsil organoid platform to investigate how host and Ag features alter the magnitude and quality of the B and T cell response on a per-individual basis.

RESULT

Each antigen format elicited distinct B and T cell responses, including differences in their magnitude, diversity, phenotype, function, and breadth. These differences culminated in striking changes in the corresponding antibody response. A major source of antigen format-related variability is the ability to recruit naive vs. memory B cells to the response, which was validated by depletion and reconstitution experiments.

CONCLUSION

These findings have important implications for vaccine design and the generation of protective immune responses in the upper respiratory tract. The tonsil organoid platform allowed us to address the effect of Ag modality in human cells while controlling for the inter-individual variability. We have established the cellular and antibody dynamics associated with distinct influenza vaccine modalities, which can be used in the future to profile in vivo immune responses during clinical trials.

SESSION H

BASELINE INNATE AND T CELL POPULATIONS ARE CORRELATES OF PROTECTION AGAINST SYMPTOMATIC INFLUENZA VIRUS INFECTION INDEPENDENT OF SEROLOGY

Presenter: Robert Mettelman - ACOR0069

Robert Mettelman³, Aisha Souquette³, Lee-Ann Van de Velde³, Kasi Vegesana³, E. Kaitlynn Allen³, Taylor Wilson³, Christina Kackos³, Jennifer DeBeauchamp³, Sanja Trifkovic³, Timothy Wood¹, Lauren Jelley¹, Richard Webby⁴, Q. Sue Huang², Paul Thomas³

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BACKGROUND

Evidence suggests cell-mediated immunity (CMI), comprising antigen-specific CD4 & CD8 T cells, and innate immunity mediate resistance to influenza and confer protection after vaccination. While antibody (ab) responses to influenza HA and NA are known mediators of protection, fewer studies have resolved the contribution of cellular responses independently from existing ab titers. Thus, individual cell populations correlated with protection from influenza independently from or synergistically with ab responses remain to be identified in humans as well as the relative contributions of cellular and humoral immunity to a protective anti-influenza response.

METHOD

Baseline PBMCs from adults enrolled in SHIVERS-II, a study of influenza vaccination and infection in New Zealand, collected pre-season or 14 days-post vaccination. Flow cytometry resolved CMI and innate cell populations from 206 adults across influenza vaccination and infection conditions. Anti-influenza serum ab titers were determined by HAI and NAI assays. Univariate logistic regression (LR) identified individual and co-regulated cellular correlates of protection and susceptibility to symptomatic influenza in vaccinated and unvaccinated adults. Random forest (RF) and multivariate LR models were used to analyze cellular covariates together with anti-influenza ab titers, vaccine status, and demographics to define baseline cell populations predicting risk of symptomatic influenza.

RESULT

We found baseline cell profile is a stronger risk predictor of symptomatic influenza than vaccination, demographics, or serology by univariate, multivariate, and RF modeling. Protection correlated with diverse & polyfunctional influenza-responsive CD4 & CD8 T cells, humoral-associated cTfh & mDCs, Th17 cells, and CD16+ cytotoxic & cytokine-producing NKs. Susceptibility correlated with inflammatory CD16- NK, $\gamma\delta$ T, and TNF α mono-producer CD8 cells. A trained RF model categorizing symptomatic influenza showed improved model accuracy with cellular (86%) over demographic and serologic covariates (61%). VIP analysis showed cellular variables comprise 28/30 top covariates, with ICOS+ cTfh the most important. A multivariate LR model showed reduced risk of symptomatic influenza associated with naive, CD107a, and Th17 CD4s, while increased risk was associated with anti-IBV(Yam) HAI titers, CD8 TNF α +, and $\gamma\delta$ T cells.

CONCLUSION

Our study argues that composition of baseline cellular immunity is a stronger predictor of symptomatic influenza susceptibility than vaccination, demographics, or serology. Our results underscore the complexity of baseline cellular immunity and provide support for vaccine design strategies targeting optimized cell subsets and improved methods to compare vaccine effectiveness.

DISTINCT FUNCTIONAL HUMORAL IMMUNE RESPONSES ARE INDUCED AFTER LIVE ATTENUATED AND INACTIVATED SEASONAL INFLUENZA VACCINATION

Presenter: Xin Tong - ACOR0001

*Xin Tong*¹

¹ Ragon Institute of MGH, MIT and Harvard

BACKGROUND

Several influenza vaccines are currently approved and globally deployed including the intramuscular inactivated influenza virus (IIV/FluZone) and the mucosal replication-competent live attenuated influenza vaccine (LAIV/FluMist). Previous studies have demonstrated that, compared to IIV/FluZone/FluZone, LAIV/FluMist induced comparable neutralizing antibody responses but demonstrated significantly higher T-cell responses in young children. Conversely, LAIV/FluMist induced only moderate increases in serum antibody responses in adults. Differences in adult responsiveness have been attributed to the potential role of pre-existing immunity that may attenuate the ability of the vaccine virus to replicate within the respiratory tract. However, despite these differences in HAI, little is known about the ability of these two vaccine platforms to promote antibody effector functions and how they are modulated by pre-existing immunity.

METHOD

Thus, given our emerging appreciation for the role of Fc-associated functions in protection against virus-driven diseases, we aimed to profile the functional humoral immune responses induced by both IIV/FluZone and LAIV/FluMist vaccines. We hypothesized that these vaccines drive distinct antibody functional profiles due to the different routes of administration and susceptibility to pre-existing immunity. Using the previously established systems serology platform, we profiled the Fc-profiles induced by IIV/FluZone and LAIV/FluMist against a panel of influenza hemagglutinin (HA) and neuraminidase (NA) antigens, including both contemporaneous antigens, as well as historical, future, and computationally derived influenza antigens.

RESULT

Distinct profiles of influenza-specific antibody profiles and functions were observed between the two vaccine platforms, with IIV/FluZone inducing significantly higher antibody titers and Fc-receptor-binding capabilities. Conversely, LAIV/FluMist promoted higher levels of antibody-dependent cell functions across various influenza strains, particularly against the NA component. Multivariate antibody analysis further highlighted the significantly different overall functional humoral immune profiles induced by the two vaccines, marked by differences in IgG titers, FcR binding, and both NK cell-recruiting and opsonophagocytic antibody functions. These results highlight the striking differences in antibody Fc-effector profiles induced systemically by two distinct influenza vaccine platforms.

CONCLUSION

Our study presents the first comprehensive functional and humoral comparison between the two types of influenza vaccines and provides insights underlying the comparable protection observed by these two influenza vaccines despite their striking differences in serological immunogenicity.

ASSESSMENT OF MULTIPLE IMMUNE CORRELATES OF PROTECTION AGAINST INFLUENZA USING ACUTE AND CONVALESCENT SERA FROM INFLUENZA NATURAL INFECTION

Presenter: Min Levine - ACOR0040

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BACKGROUND

Existing studies on correlates of protection against influenza are mostly based on hemagglutination inhibition (HI) antibodies against egg-propagated vaccine antigens rather than wild type circulating viruses that cause infection. Furthermore, other antibody responses mediating virus neutralization, neuraminidase inhibition (NAI) and hemagglutinin (HA) stalk binding may also contribute to protection but the association between antibody levels and protection is not well understood.

METHOD

Adults (≥ 18 years) with acute respiratory illness were enrolled in US Flu VE network site clinics in 2018-19 and tested for influenza by reverse transcription-polymerase chain reaction (RT-PCR). For influenza positive patients, acute sera were collected within 7 days from symptom onset, followed by convalescent sera collection 28 days later. For influenza-negative adults, only acute sera were collected. Sera were tested against wild type cell-grown viruses that caused infection by HI [for A(H1N1)pdm09] or microneutralization (MN) [for A(H3N2)] assays, and by NAI, HA stalk antibody assays. Associations between acute-phase HI, MN, NAI, and HA stalk antibody titers with RT-PCR-confirmed influenza were analyzed by cox proportional hazard models.

RESULT

Acute sera from 112 RT-PCR confirmed A(H1N1)pdm09 infected patients, 63 RT-PCR confirmed A(H3N2) infected patients, and 134 influenza negative adults were analyzed. Patients infected with A(H1N1)pdm09 had significantly lower ($p < 0.05$) HI and N1 NAI antibodies than influenza negative adults, regardless of influenza vaccination status and vaccine type. Similarly, MN antibodies to A(H3N2) wild type viruses and N2 NAI antibodies were also significantly lower ($p < 0.05$) in A(H3N2) infected patients than uninfected controls. In the cox regression analysis, for A(H1N1)pdm09, HI and N1 NAI titers were correlated with infection status ($p < 0.05$). HI titer of 19 against wild type cell-grown A(H1N1)pdm09 virus and N1 NAI titer of 21 were associated with a 50% reduction in the risk of A(H1N1)pdm09 infection. However, HA stalk antibody titers were lower ($p < 0.05$) in infection cases than uninfected controls only for A(H1N1)pdm09 infection but not for A(H3N2) infection. Lastly, infection induced HI, MN, NAI and HA stalk antibody rises in convalescent sera.

CONCLUSION

Antibodies in the acute sera reflect the host immune status at the time of the infection. HI, MN and NAI antibodies correlated with protection against both A(H1N1)pdm09 and A(H3N2) infection, whereas HA stalk antibodies were only associated with A(H1N1)pdm09 protection. Measuring antibody titers against cell-grown wild type viruses causing infection may improve estimation of correlates of protection.

IMMUNE-HISTORY BASED CORRELATES OF PROTECTION FOR INFLUENZA AND SARS-CoV-2

Presenter: Tomer Hertz - ACOR0061

Tomer Hertz², Shlomia Levy¹, Hanna Oppenheimer¹, Daniel Ostrovsky¹, Shosh Zismanov¹, Ayelet Shagal¹, Lilach Friedman¹, Yonat Shemer-Avni¹, Ran Taube¹, Lior Neshet¹, Youyi Fong³, Peter Gilbert³

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BACKGROUND

Seasonal influenza and variants of concern of SARS-CoV-2 pose a serious global problem. While vaccination is the most effective strategy for reducing influenza and SARS-CoV-2 related morbidity and mortality, there is extensive heterogeneity in vaccine induced immune responses, driven by multiple factors, such as age, sex and immune history. We hypothesized that immune-history antibody profiles can be used to predict risk of infection from respiratory viruses.

METHOD

To study the predictive power of baseline immune-history (BIH), we utilized samples from influenza and SARS-CoV-2 clinical trials, in which symptomatic infections were identified using PCR. We used antigen microarrays to generate baseline antibody profiles to a panel of influenza HA and NA proteins, and to a panel of SARS-CoV-2 variants of concern spike proteins.

RESULT

We identified IgG and IgA baseline markers that were correlates of protection (COPs) using logistic regression models adjusted for baseline covariates. Since IgA and IgG profiles were weakly correlated, we considered combinations of IgG and IgA markers as COPs, and found that they yielded improved COPs. The strongest association with infection risk for SARS-CoV-2 infection was reduced IgG levels to RBD mutants and IgA levels to VOCs, which was a COP in the three-dose group (HR=6.34, p=0.008) and in the four-dose group (HR=8.14, p=0.018). In our influenza study, the strongest CoP was based on IgA BIH to H3N2 strains.

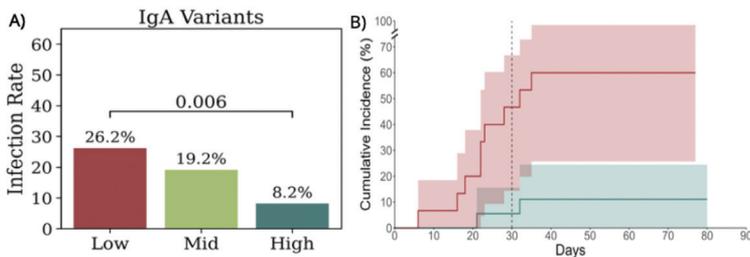


Figure 1: SARS-CoV-2 Immune-history to variants of concern is a COP of SARS-CoV-2 infection. (A) We ranked 609 participants in a Pfizer booster study by baseline IgA responses to SARSCoV-2 variants and used quartiles to define BIH groups. D30 Infection rates were significantly higher in the low-BIH group. (B) Cumulative incidence plots of the low (red) and high (green) response groups at d90 using a combination of IgG to RBD mutants and IgA to VOCs (HR = 8.17, p = 0.01)

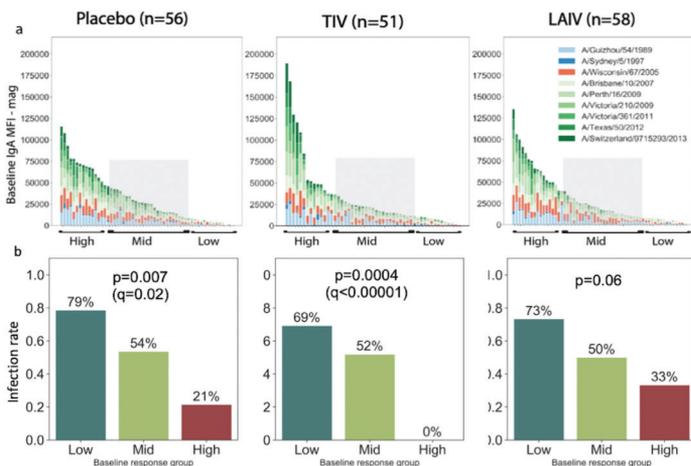


Figure 2: Baseline influenza immune history antibody profiles are highly heterogeneous across individuals and are a COP for influenza disease. (a) Baseline H3N2 IgA immune-history profiles of 162 individuals from the FLUVACS trial that compared placebo, TIV and LAIV vaccines. Subjects were ranked by quartiles (b) Infection rates for the low-, mid- and high-BIH groups.

CONCLUSION

Our analyses demonstrates that individuals with low baseline immune-history are at increased risk of respiratory infections even following vaccination. Thus, we identify a highly susceptible population that remains susceptible despite apparent responsiveness to vaccines. Our data demonstrate that baseline binding antibody markers are significantly associated with infection risk and may be utilized to identify individuals most at risk from future exposures.

SESSION I

POST-VACCINE CYTOKINE LEVELS THAT CORRELATE WITH BREAKTHROUGH INFLUENZA INFECTIONS

Presenter: Ewan P. Plant - ACOR0002

Ewan P. Plant³, Weichun Tang³, Hang Xie³, Zhiping Ye³, Angelia Eick-Cost¹, Jay Bream², Courtney Gustin⁴, Mark⁴

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BACKGROUND

Influenza vaccines prime the immune system to prevent severe disease if a person is subsequently exposed to the virus. Priming the immune system may include activating B-cells (to produce antibodies) and/or T-cells. Cytokines are signals that engage or suppress different components of

the immune system to optimize the response. There are gaps between the basic science mapping the immune response to vaccination and the clinical trials demonstrating vaccine efficacy. Small studies have identified changes in cytokines levels after vaccination, but these analyses have been hampered by high variances, and it is not known if observed changes impact vaccine efficacy. Post-vaccination antibody titers for inactivated influenza virus (IIV) vaccines correlate with protection but breakthrough infections do sometimes occur. We investigate the changes in cytokine levels after vaccination in subjects that subsequently suffered breakthrough infections.

METHOD

The Department of Defense stores routine serum samples from personnel, and these are associated with medical records. Samples from 256 vaccinated subjects who subsequently suffered breakthrough influenza infections were identified. Sera collected 1-21 days post-vaccination were compared with pre-vaccination samples and with post-vaccination samples from matched healthy controls. Cytokines were measured using 96-well multiplex plates from R&D Systems in a Luminex FlexMap 3D multiplex plate reader. The mean and standard deviation of each group were calculated, and Student t-tests performed to evaluate differences.

RESULT

Differences in cytokine levels were observed after either IIV or live attenuated influenza vaccines (LAIV) vaccination compared with pre-vaccination levels. Sufficient sample availability ameliorated the challenges of high variance observed in smaller studies. There is overlap for some cytokine responses among IIV and LAIV recipients, but other responses are unique to the type of vaccine. This verifies that different vaccine modalities engage different components of the immune system. Higher levels of the soluble CD25 cytokine after IIV vaccination were associated with breakthrough infections, and higher levels of interleukins that stimulate inflammation were associated with breakthrough infections after LAIV vaccination. Differences were not observed with antibody titers indicating the role of other components of the immune response.

CONCLUSION

We identified differences in the response of subjects who suffered breakthrough infections compared to those who did not. Discovery of links between post-vaccination cytokine response and breakthrough infections expands our understanding of how influenza vaccines work and may help future vaccine development.

INFLUENZA VACCINE RESPONSES TO A(H1N1)pdm09 ANTIGENS IN 2020 AND 2021 AMONG REPEATEDLY VACCINATED HEALTHCARE WORKERS

Presenter: Stephany Sanchez-Ovando - ACOR0027

Stephany Sanchez-Ovando⁸, Annette Fox⁶, Arseniy Khvorov⁶, Yeu-Yang Tseng⁶, Louise Carolan⁶, Jessica Hadiprodjo⁶, Chris Blyth⁹, Allen Cheng⁴, Julia Clark², Kristine Macartney⁵, Helen Marshall¹, Peter Wark⁷, Kanta Subbarao⁶, Adam Kucharski³, Sheena G. Sullivan⁶

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BACKGROUND

Repeated administration of influenza vaccines appears to incrementally attenuate immunogenicity and effectiveness, especially when successive vaccines are antigenically similar. Although these effects appear to be worse for A(H3N2), they are also observed for A(H1N1)pdm09, which has shown increasing antigenic diversity in recent years

METHOD

A cohort of Australian health care workers (HCWs) was followed for post-vaccination antibody responses across two years during which influenza did not circulate (2020-2021). Vaccine administered in 2020 contained an A/Brisbane/02/2018-like H1N1 antigen, while in 2021 an antigenically distinct A/Victoria/2570/2019-like antigen was included. Pre-vaccination, 14 days and 7 months post-vaccination sera were assessed in haemagglutination inhibition (HI) assay against influenza A(H1N1)pdm09 vaccine viruses from the corresponding years to assess pre/post vaccination antibody titres. Differences in titre were compared by prior vaccination history.

RESULT

A total of 1384 HCWs contributed sera in the two years. Among them, 96 were previously unvaccinated (vaccinated in 0/5 prior years) and 778 were frequently vaccinated ($\geq 5/5$ prior years). While frequent vaccination attenuated titres and titre rises in both years, the effect was substantially diminished in 2021. Notably, only 16% of frequently vaccinated versus 80% of previously unvaccinated HCWs seroconverted in 2020 versus 80% and 86%, respectively in 2021.

The 2021 vaccine strain differed from all prior H1N1pdm09 vaccines at HA positions N129D, K130N and N156K, which are within prominent antigenic sites. Additionally, only the 2021 vaccine strain had 185I, which was present in seasonal H1N1s. We are currently investigating whether these substitutions facilitated a stronger or more specific immune response through mechanisms such as escape from memory dominance or recall of memory against prior seasonal strains. Sera are being titrated against viruses from the alternate year, and against reverse genetics viruses bearing single substitutions. PBMCs are being assessed to compare the frequency and phenotype of H1 HA reactive B cells induced.

CONCLUSION

The H1N1 vaccine antigen used in 2021 induced substantially greater antibody responses than the 2020 antigen, particularly among frequently vaccinated HCW. Investigations are underway to understand how antigenic changes in the 2021 antigen may have enhanced immunogenicity.

AGE-DEPENDENT INDUCTION OF STALK-REACTIVE ANTIBODIES WITH ADCC REPORTER ACTIVITY BY ADMINISTRATION OF A LIVE-ATTENUATED INFLUENZA VIRUS VACCINE TO CHILDREN

Presenter: Juan Manuel Carreno Quiroz - ACOR0064

Juan Manuel Carreno Quiroz³, Philip Meade³, Kaori Sano¹, Johnstone Tcheou³, Ariel Raskin³, Gagandeep Singh³, Madhumathi Loganathan³, Benjamin Francis³, Dominika Bielak³, Ya Jankey Jagne⁴, Hadijatou J Salah⁴, Florian Krammer², Thushan I De Silva⁵

¹ Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, ² Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Center for Vaccine Research and Pandemic Preparedness (C-VARPP), Icahn School of Medicine at Mount Sinai, New York, NY, USA; Department of Pathology, Molecular and Cell Based Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA, ³ Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Center for Vaccine Research and Pandemic Preparedness (C-VARPP), Icahn School of Medicine at Mount Sinai, New York, NY, USA., ⁴ Vaccines and Immunity Theme, Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, Banjul, The Gambia, ⁵ Vaccines and Immunity Theme, Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, Banjul, The Gambia; The Florey Institute for Host-Pathogen Interactions and Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK.

BACKGROUND

Initial exposures to influenza viruses may imprint a group-specific signature on immunity that impacts future responses to infection or vaccination. Here, we assessed if these responses could be modulated by administration of a live attenuated influenza virus (LAIV) vaccine at early stages of life.

METHOD

Children between ages 24 to 59 months, with different exposure histories (naïve, H1+, H3+ or H1+H3+), received one of two LAIV formulations (2016-17 and 2017-18) containing distinct H1N1 components. Serum and oral fluid samples were analyzed for antibodies against the hemagglutinin stalk and the neuraminidase (NA) of group 1 and group 2 influenza viruses.

RESULT

The 2018 LAIV formulation containing an updated H1N1 component, induced higher stalk reactive antibodies in serum with strong effector functions, while no significant changes were detected in NA-reactive antibodies in serum or in stalk- or NA- secretory IgA (sIgA) in oral fluid. This phenotype and the overall response to vaccination was stronger in younger children. Moreover, higher induction of stalk-reactive antibodies against group 1 or 2 correlated with lower pre-vaccination antibody titers.

CONCLUSION

Our findings suggest that the number of prior exposures - influenced by age -, the antibody levels prior to vaccination, and the LAIV formulation impact on the response to LAIV administration. Our data also show that LAIV may be a tool for 'equivalent imprinting' at early stages of life.

PRE-EXISTING SARS-CoV-2 ANTIBODIES AND RISK OF BREAKTHROUGH INFECTION IN A PROSPECTIVE COHORT, SEATTLE, MARCH-NOVEMBER 2022

Presenter: Alpana Waghmare - ACOR0101

Elizabeth Krantz⁴, Emily Martin², Cecile Viboud³, Louise Kimball⁴, Rachel Blazevic⁴, Terry Stevens-Ayers⁴, Claire Andrews⁴, Samantha Bents³, Peter Han¹, Robin Prentice¹, Lea Starita¹, Michael Boeckh⁴, Alpana Waghmare⁵

¹ Brotman Baty Institute, University of Washington, ² Department of Epidemiology, University of Michigan School of Public Health, ³ Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, ⁴ Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Center, ⁵ Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Center; Department of Pediatrics, University of Washington

BACKGROUND

We assessed the impact of pre-existing SARS-CoV-2 humoral immunity on the risk of breakthrough infections in a cohort of adults followed during the Omicron period.

METHOD

In this prospective cohort study, individuals were enrolled from March-May 2022 and followed for 6 months in the Seattle area. Participants were asked to report respiratory symptoms weekly. Upon symptoms, a testing kit was delivered to participants' home for self-collection of a nasal swab; samples were tested by PCR for the presence of SARS-CoV-2 and 24 other respiratory pathogens. Blood was collected at enrollment, 3 and 6 months. A multiplex electrochemiluminescence neutralization assay was used to test for antibodies to 15 antigens from SARS-CoV-2 and other viruses (MSD, Inc). We evaluated the risk of SARS-CoV-2 breakthrough infection as a function of antibody levels at enrollment. Baseline was defined as the date of the initial blood draw. Cumulative incidence curves were compared using Gray's test.

RESULT

The median age of the 199 participants was 48 years (range 21 - 91) and 77% were female. At baseline, 198 (99.5%) of participants were vaccinated, 184 (92%) had received ≥ 3 vaccine doses and 48 (24%) reported prior SARS-CoV-2 infection. The median days since last known SARS-CoV-2 vaccination or infection was 136 (range 0 - 226). Over the 6 month follow up, 104 of 199 participants (52%) had at least one symptomatic respiratory infection, with 179 total respiratory infections detected by PCR. The 6-month cumulative incidence of SARS-CoV-2 was 37.5% (95% confidence interval 29.7 - 45.2), followed by rhinovirus (21.5%; 15.8 - 27.7) and seasonal coronaviruses (ranging from 5.0% (2.6-8.7) for NL63 to 0.5% (0.0-2.6) for HKU1). The cumulative incidences of influenza and RSV were 1% each.

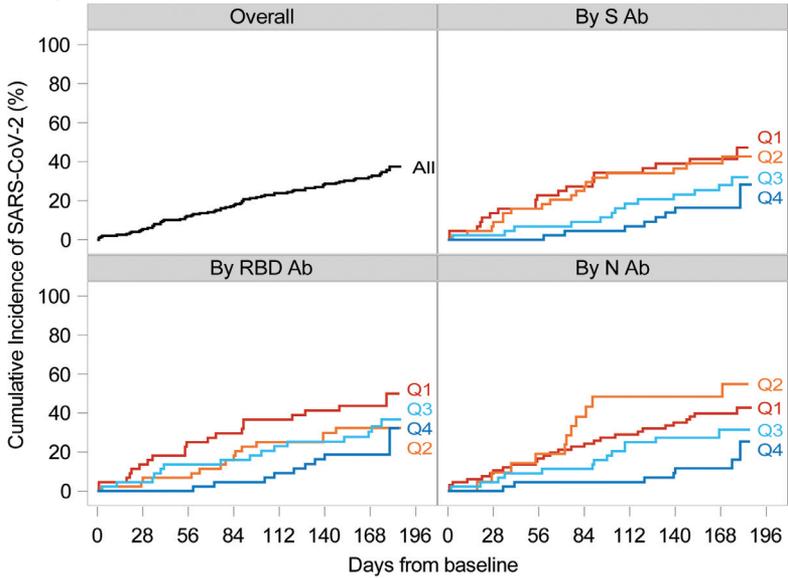
Based on preliminary antibody data available for 88% of the cohort, we found a gradient of decreasing risk of SARS-CoV-2 infection with higher quartile of pre-existing SARS-CoV-2 antibody titers to the spike (S) ($p=0.02$), nucleocapsid (N) ($p=0.006$) and receptor binding domain (RBD) antigens ($P=0.05$) (Fig). Differences in the risk of SARS-CoV-2 infection were most pronounced for anti-N antibodies.

CONCLUSION

In a highly vaccinated cohort followed during the circulation of several distinct Omicron lineages, we found that higher levels of pre-existing antibodies titers were associated with lower risk of SARS-CoV-2 breakthrough infection.

(Figure overleaf)

Figure: Cumulative incidence of SARS-CoV-2 infection by quartiles of antibodies. Day 0 is the first day of follow-up.



SESSION J

MATRIX M ADJUVANTED H5N1 VACCINE ELICITS BROADLY NEUTRALIZING ANTIBODIES AND NEURAMINIDASE INHIBITING ANTIBODIES IN HUMANS THAT CORRELATE WITH IN VIVO PROTECTION

Presenter: Fan Zhou - ACOR0019

Fan Zhou⁴, Lena Hansen⁴, Gabriel Pedersen¹, Gunnveig Grødeland², Rebecca J. Cox³

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BACKGROUND

The highly pathogenic avian influenza (HPAI) H5N1 viruses constantly evolves causing epizootic outbreaks with increased geographical spread and sporadic zoonotic infections can occur. Vaccination is the most cost-effective measure to combat influenza virus. Therefore, vaccines capable of eliciting broadly protective antibody responses are desired and under development and evaluation in preclinical models and clinical trials.

METHOD

We conducted a dose escalating phase 1 clinical trial of 30µg HA non-adjuvanted, 1.5, 7.5, and 30µg HA with Matrix M adjuvant in healthy volunteers (15 adults each group). Blood samples were collected pre and at multiple time points post vaccination. We investigated the kinetics

of multi-faceted humoral immunity induced by the vaccine using a panel of assays including hemagglutination inhibition assay, microneutralization assay, pseudotype-based neutralization assay, enzyme-linked lectin assay, ELISA, and luciferase reporting antibody-dependent cell-mediated cytotoxicity assay. Mice receiving post vaccine human serum transfer were challenged with RG14 virus to assess if vaccine elicited antibody responses confer protection against HPAI H5N1 virus.

RESULT

An evaluation of sera from vaccinees against pseudotyped viruses covering all (sub)clades isolated from human influenza H5N1 infections demonstrated that the adjuvanted vaccines (7.5µg and 30µg) elicited rapid and robust increases of broadly cross-neutralizing antibodies against all clades. In addition, the adjuvanted vaccines also induced multifaceted antibody responses including hemagglutinin stalk domain specific, neuraminidase inhibiting, and antibody-dependent cellular cytotoxicity inducing antibodies. The lower adjuvanted dose (1.5µg) showed delayed kinetics, whilst the non-adjuvanted vaccine induced overall lower levels of antibody responses. Importantly, we demonstrate that human sera post vaccination with the adjuvanted (30µg) vaccine provided full protection against a lethal virus challenge in mice. Of note, when combining our data from mice and humans we identified the neutralizing and neuraminidase inhibiting antibody titers as correlates of in vivo protection.

CONCLUSION

Our study shows Matrix M adjuvanted virosomal H5N1 vaccine elicits rapid, robust and broadly protective multi-faceted humoral immune response in humans, in which neutralizing and neuraminidase inhibiting antibody titers work as correlates of in vivo protection.

SESSION J

HUMAN INFLUENZA VIRUS CHALLENGE IDENTIFIES CELLULAR CORRELATES OF PROTECTION FOR ORAL VACCINATION

Presenter: David McIlwain - ACOR0079

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BACKGROUND

Developing new influenza vaccines with improved performance hinges on defining new correlates of protection (CoP). Influenza vaccines today have been optimized to enhance the serum HAI response, yet developing improved protection may require identifying and enhancing additional immune mechanisms. One method of inducing enhanced protection may occur by eliciting a mucosal immune response, such as with a tablet vaccine based on recombinant adenovirus expressing the HA protein (VXA-A1.1).

METHOD

Subjects were randomized to receive either VXA-A1.1, inactivated influenza quadrivalent vaccine (Fluzone), or placebo at a 2:2:1 ratio. 90-120 days later, 143 eligible volunteers were challenged with H1-pandemic influenza virus (A/CA/like(H1N1)pdm09) at a dose of 9e5 TCID50. Protection

against infection was assessed by counting the number of subjects with symptoms and shedding of influenza virus. Shedding was determined by nasopharyngeal swabs and qRT-PCR starting after the first 36 hours to exclude pass-through infection. Immune responses were measured in serum by HAI and MN titers, and in PBMCs by antibody-secreting cells and IFN- γ ELISPOT. Cellular responses were further characterized by flow cytometry and mass cytometry.

RESULT

Both Fluzone and VXA-A1.1 protected against influenza infection, with Fluzone having 38% efficacy and VXA-A1.1 having 48% efficacy. Mass cytometry characterization of vaccine-elicited cellular immune responses identified shared and vaccine-type-specific responses across B and T cells. For example, both vaccines elicited CD4⁺ aTfH cells, but elevated levels of CD4⁺ aTfH and CD8⁺ EM T-cell subsets positive for the mucosal homing integrin alpha4/beta7 were restricted to only VXA-A1.1 recipients. For VXA-A1.1, plasmablasts positive for integrin alpha4/beta7, phosphorylated STAT5, or lacking expression of CD62L at day 8 post-vaccination were significantly correlated with protection from developing viral shedding following virus challenge. Random forest models were used to construct an effective classifier of VXA-A1.1 conferred protection based on cellular immune responses, and to examine important CoP for each vaccine. HAI was the strongest CoP for the injected vaccine, whereas cellular immune responses including HA-specific antibody-secreting cells were the strongest CoP for the oral vaccine.

CONCLUSION

These findings reveal the characteristics of vaccine-elicited cellular CoP for an oral influenza vaccine, which appear to be different than those of an injected vaccine. The trial is registered under NCT02918006.

SESSION J

AN INFLUENZA HEMAGGLUTININ STEM-ONLY IMMUNOGEN ELICITS A BROADLY CROSS-REACTIVE MEMORY B CELL RESPONSE IN HUMANS

Presenter: Sarah Andrews - ACOR0039

Sarah Andrews¹, Lauren Cominsky¹, Rebecca Gillespie¹, Geoffrey Shimberg¹, Julie Raab¹, Jason Gorman¹, Adrian Creanga¹, Katherine Houser¹, Peter Kwong¹, Alicia Widge¹, Masaru Kanekiyo¹, Adrian McDermott¹

¹ National Institutes of Health

BACKGROUND

Current yearly seasonal influenza vaccines primarily induce an antibody response directed against the immunodominant but continually diversifying hemagglutinin (HA) head region. These antibody responses provide protection against the vaccinating strain but little cross-protection against other strains or subtypes. In contrast, the antibody response to the conserved HA stem region is more broadly protective, but subdominant to HA head-directed responses. To focus the immune response on the HA stem region, we developed a stabilized H1 stem immunogen that lacks the immunodominant head.

METHOD

We analyzed the human B cell response to this H1 HA stem-only immunogen displayed on a nanoparticle (H1ssF) in healthy adults in a Phase I clinical trial (NCT03814720). Using flow cytometry and single-cell sorting and sequencing we evaluated the magnitude, cross-reactivity and repertoire of the plasmablasts and memory B cells elicited by this experimental vaccine.

RESULT

We observed a strong plasmablast response and sustained elicitation of cross-reactive HA stem-specific memory B cells after vaccination with H1ssF, higher than what is typically seen after seasonal influenza vaccination. Further, we found that two epitopes on the H1 stem were targeted by the B cell response with a highly restricted immunoglobulin repertoire unique to each epitope. On average, two thirds of the H1 stem-specific B cell and serological antibody response recognized a central epitope on the H1 stem and exhibited broad neutralization across group 1 influenza virus subtypes. The remaining third recognized an epitope near the viral membrane anchor and was largely limited to H1 strains.

CONCLUSION

All together, we demonstrate that an HA immunogen lacking the immunodominant HA head elicits a robust and broadly neutralizing HA stem-directed B cell response in humans.

SESSION J

SARS-CoV-2 CORRELATES OF PROTECTION CONFERRED BY NATURAL IMMUNITY: COMPARATIVE ANALYSIS OF PRE-EXPOSURE NEUTRALIZING ANTIBODY TITERS AGAINST DELTA ANDOMICRON VARIANT INFECTION

Presenter: Kaiyuan Sun - ACOR0021

Kaiyuan Sun⁸, Jinal N. Bhiman¹, Stefano Tempia⁶, Jackie Kleynhans⁵, Vimbai Sharon Madzorera¹, Qiniso Mkhize¹, Haajira Kaldine¹, Meredith L McMorrow⁹, Nicole Wolter³, Jocelyn Moyes⁵, Maimuna Carrim³, Neil A Martinson¹³, Kathleen Kahn¹⁰, Limakatso Lebina¹², Jacques D. du Toit¹¹, Thulisa Mkhencele², Cécile Viboud⁷, Cheryl Cohen⁵, Anne Von Gottberg⁴, Penny L. Moore¹

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Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America, ⁸ Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States of America., ⁹ Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; COVID-19 Response, Centers for Disease Control and Prevention, Atlanta, Georgia, United States., ¹⁰ MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, ¹¹ MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa., ¹² Perinatal HIV Research Unit, University of the Witwatersrand, South Africa, ¹³ Perinatal HIV Research Unit, University of the Witwatersrand, South Africa; Johns Hopkins University Center for TB Research, Baltimore, Maryland, United States of America

BACKGROUND

Few studies have evaluated infection-induced neutralizing antibody (nAb) titers as correlates of protection (CoP) against specific SARS-CoV-2 variants of concern.

METHOD

We used data from the PHIRST-C study, which comprised 1200 individuals in 222 rural and urban households in South Africa. Sera were collected before and after the Delta and Omicron BA.1/2 waves. Infections were inferred using anti-nucleocapsid antibody kinetics in paired sera. For sera collected prior to the Omicron BA.1/2 wave, we measured nAb titers (reflected as 50% inhibitory dilution (ID50)) against D614G (anti-D614G titers) and Omicron BA.1 (anti-BA.1 titers). For sera collected prior to the Delta wave, we only measured anti-D614G titers. We categorized titers as: nonresponsive (ID50 <20, the assay detection limit), low (ID50 20-100), medium (ID50 101-1000), and high (ID50 >1000). We restricted the analysis to HIV-uninfected individuals who had not received a COVID-19 vaccine (827 individuals for the Delta wave, 639 individuals for the Omicron wave) and modeled the relationship between pre-exposure nAb titers and protection against Delta infections (305 episodes) and BA.1/2 infections (421 episodes). This was achieved by fitting participants' infection status to a household chain binomial transmission model, adjusting for demographics, variants' intrinsic transmissibility, and "force-of-infections" within the household and from the community, among other potential confounding factors.

RESULT

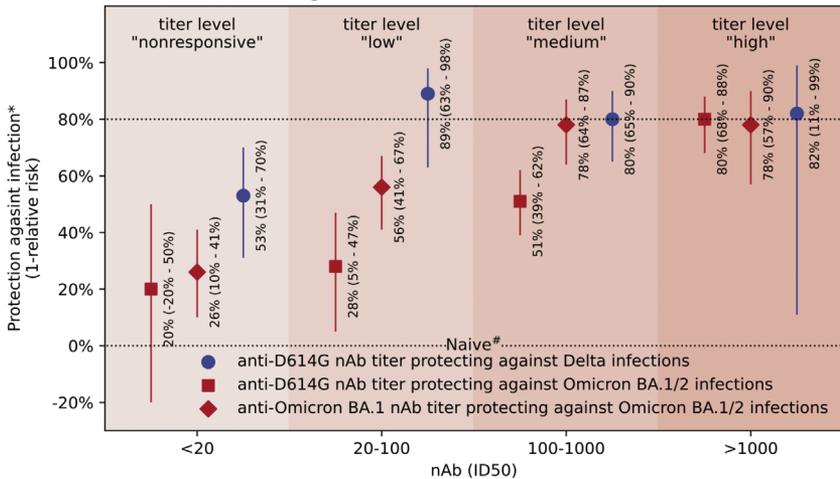
The risk of infection was associated with the level of pre-exposure neutralizing titers and infecting variant, with overall better protection from infection against Delta compared to BA.1/2 (Figure). Previously infected individuals with nonresponsive anti-D614G titers experienced 53% protection against Delta infection compared to naïve individuals. Protection against Delta infection was +80% for low anti-D614G titers and above. For anti-D614G titers against Omicron BA.1/2 infection, the low and medium categories of anti-D614G nAb conferred significantly lower protection against Omicron BA.1/2 than Delta and the nonresponsive category conferred no significant protection. As compared to anti-D614G nAb, anti-BA.1 nAb achieved better or non-inferior protection against Omicron BA.1/2 across all titer levels.

CONCLUSION

Infection-induced, pre-exposure serum nAb titers correlate with protection against reinfections in observational data. However, the relationship between nAb titers and protection depends on the degree of immune escape in the circulating variant compared to the variants responsible for prior infection. In addition, there could be protection even in the absence of detectable nAb titers, suggesting other immune responses in protection.

(Figure opposite)

Infection-induced, pre-exposure nAb titer levels as correlates of protection against Delta and Omicron infections



* Dots and vertical lines are maximum likelihood estimates and 95% confidence intervals

Baseline category is population naive to SARS-CoV-2

SESSION J

DETAILED ESTIMATES OF CORRELATES OF PROTECTION FOR SARS-CoV-2, STRATIFIED BY KEY VOC AND KEY COVARIATES

Presenter: Tim Russell - ACOR0098

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BACKGROUND

Correlates of protection (COP) for SARS-CoV-2 provide the post-exposure risk of infection on an individual-level. They are critical for evaluating the population-level of immunity against circulating variants of concern (VOC). However, due to novel VOCs and varied individual-level exposure histories, arriving at accurate COP estimates requires detailed datasets.

METHOD

Cross-sectional studies are unable to control for complex exposure histories, nor other key covariates likely associated with antibody dynamics. Using data from an ongoing, prospective, observational cohort - the UCLH-Crick LEGACY study - whereby adults healthcare workers are occupationally screened by PCR test for SARS-CoV-2 between 2020-2023, we built a hierarchical Bayesian antibody dynamics model. We fit it to each individual's longitudinal neutralising antibody data, while controlling for key covariates, e.g., age, sex, test site, etc. We compare each individual's unobserved titre value at the time of a subsequent exposure, against the contemporaneous titre values in the population.

RESULT

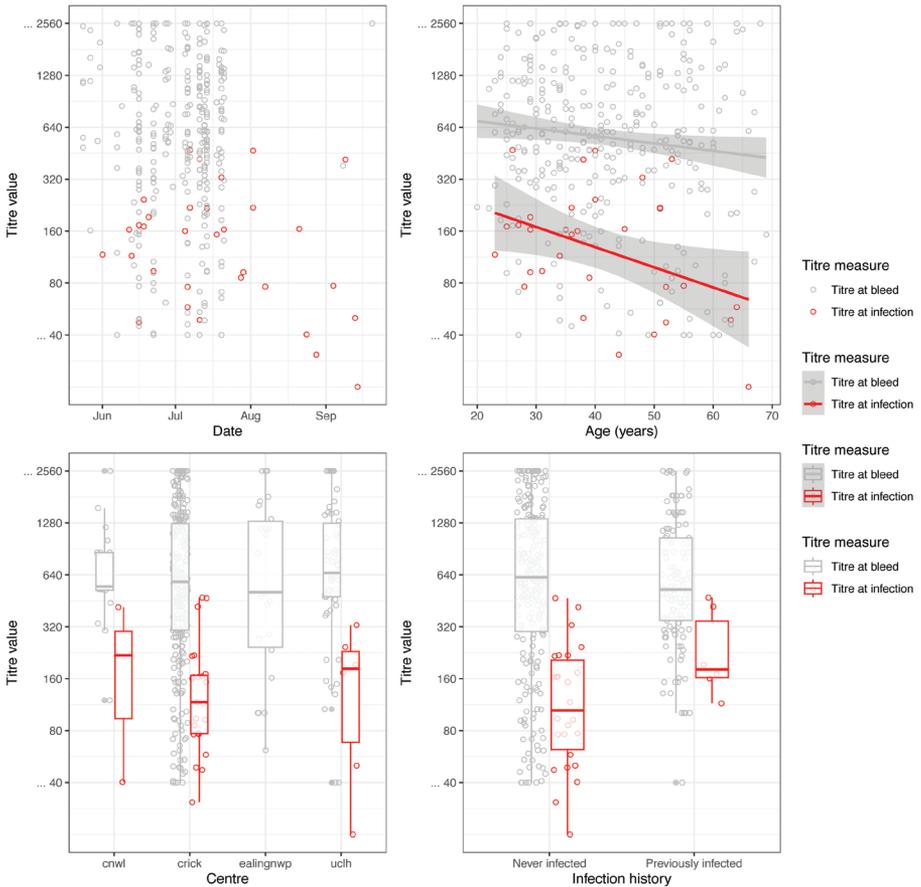
We categorised individuals as either infection naive (no natural infection) or exposed (to one or more of BA.1, BA.2 or BA.4/5) between December 2021-January 2023, i.e. whether their third antigenic encounter was caused by a vaccine or infection with an Omicron substrain. We present COP results for risk of infection against BA.1, BA.2 and BA.4/5, stratified by their exposure type and a number of key covariates.

CONCLUSION

Given the complex immunity landscape, produced by unique exposure histories, an ever-evolving pathogen and stark differences in intervention strategies between countries, consensus on variant-specific correlates of protection is still pending. However, combining high-quality datasets with novel Bayesian inference models provides a key step to reaching them. Lastly, our covariate adjustment is adaptable and The LEGACY study will continue for the foreseeable future. Therefore, as novel variants emerge, we will update our estimates, providing near to real-time estimation of variant-specific COP.

(Figure opposite)

BA5_infection



SESSION J

ANTIBODY EFFECTOR FUNCTION AND T CELL RESPONSES TO HOMOLOGOUS AND HETEROLOGOUS INACTIVATED OR MRNA VACCINES AGAINST SARS-CoV-2

Presenter: Carolyn Cohen - ACOR0013

Carolyn A. Cohen¹, Nancy H. L. Leung⁵, Prathanporn Kaewpreedee¹, Kelly W. K. Lee¹, Janice Zhirong Jia¹, Alan W. L. Cheung¹, Samuel M. S. Cheng⁴, Leo L. M. Poon³, J. S. Malik Peiris³, Benjamin J. Cowling⁵, Sophie A. Valkenburg²

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BACKGROUND

Inactivated vaccine CoronaVac and mRNA BNT162b2 are two of the most widely used vaccines against SARS-CoV-2 and have variable efficacy. Booster doses are necessary to combat waning immunity and protect against variants. Spike neutralising antibodies are the major defined immune correlate of protection, however RBD mutations may make these antibodies less effective at blocking virus entry to cells. Here we aim to assess alternative correlates of protection including S and non-S antibodies with Fc effector function, antibody avidity, CD4+ and CD8+ T cell responses, which play a critical role in recognition of variants, protection against severity, aiding recovery and viral clearance. Different boosting of these responses following third dose vaccination with both CoronaVac and BNT162b2 may have different implications in protecting against severe disease long term.

METHOD

We conducted an open-label randomised trial in Hong Kong to explore potential correlates of protection from a third dose of homologous and heterologous vaccination with CoronaVac (CC-C, BB-C) and BNT162b2 (CC-B, BB-B). In the humoral compartment, we used ELISA based assays to evaluate S and N specific IgG, FcγRIIIa- and FcγRIIIa-binding antibodies, and IgG avidity in 20 participants from each group at pre and post booster time points. In the T cell compartment, PBMCs were stimulated with an overlapping peptide pool representing S alone or Nucleocapsid, Envelope and Membrane proteins of ancestral SARS-CoV-2. Intracellular cytokine staining was used to measure IFNγ+ CD4+ and CD8+ T cell responses by vaccination.

RESULT

We show that at day 28, Ancestral and Omicron S antibody responses were significantly higher in BNT162b2 booster recipients than CoronaVac, regardless of first dose. N antibody responses were raised in homologous boosted CoronaVac donors (CC-C) only. In the T cell compartment S CD4+ T cells were boosted in CoronaVac primed donors only, and NEM responses did not increase with any booster dose. Vaccines used for priming tended to define the S vs NEM preference of response, where CC primed responses have higher NEM than S IFNγ, and BB primed have higher S than NEM, regardless of booster. At day 182 post booster, both T cell and antibody S and non-S responses were not significantly different in any vaccine groups, with an exception for S FcγRIIIa-binding remaining significantly higher in CC-B than CC-C.

CONCLUSION

At one month post booster, vaccine induced S and NEM specific T cell responses are equivalent in all vaccine groups. S IgG effector function and avidity are higher in BNT162b2 boosted donors. Pre-existing S and NEM, and vaccine boosted S CD4+ and CD8+ T cell responses may therefore contribute to similar infection rates and severity in all vaccine combinations in Hong Kong.

POSTER LISTING



CORRELATES OF PROTECTION OF CURRENT INFLUENZA VACCINES

- 1 Immunological correlates of prevention of the onset of seasonal H3N2 influenza**
Presenter: **Seiya Yamayoshi** ACOR0010

- 2 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

- 3 Assessment of humoral immune responses to repeated influenza vaccination in a multiyear cohort: a five-year follow-up**
Presenter: **Meng-Hsuan Sung** ACOR0017

- 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

- 5 Identifying correlates and mediators of protection against influenza and COVID-19 with causal mediation analysis**
Presenter: **Wey Wen Lim** ACOR0028

- 6 Timing of maternal influenza vaccine administration during pregnancy for optimal vaccine effectiveness in infants**
Presenter: **Anne-Marie Rick** ACOR0034

- 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

- 8 Immunogenicity of Twice-annual Influenza Vaccination in Older Adults in Hong Kong: A Randomized Controlled Trial**
Presenter: **Faith Ho** ACOR0048

- 9 Antibody landscapes to hemagglutinin and neuraminidase proteins of H3N2 influenza viruses in older adults**
Presenter: **Sook-San Wong** ACOR0051

- 10 Identifying factors that drive post-vaccination Influenza serum HAI antibody titre dynamics**
Presenter: **David Hodgson** ACOR0062

- 11 Improving the prediction of influenza vaccine effectiveness by refined genetic distance measure**
Presenter: **Lirong Cao** ACOR0077

- 12 Impact of seasonal influenza vaccine dose on homologous and heterologous immunity**
Presenter: **Yang Ge** ACOR0082

- 13 Deciphering correlates of protection against airborne transmission of human seasonal H3N2 influenza virus transmission in the ferret model**
Presenter: **Seema Lakdawala** ACOR0095

-
- 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-Quevedo** ACOR0015

EPIDEMIOLOGY

-
- 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-Quevedo** ACOR0014
-
- 16 Pre-season antibody titers and protection against influenza infection in a South African community cohort (PHIRST), 2016-2017**
Presenter: **Nicole Wolter** ACOR0054
-
- 17 Trends of influenza B/Yamagata antibodies from 2012/2013 to 2021/2022 in Italy in the context of potential lineage extinction**
Presenter: **Serena Marchi** ACOR0057
-
- 18 Hybrid approach to estimate influenza antibody titers associated with decreased risk of influenza**
Presenter: **Brendan Flannery** ACOR0065
-
- 19 Evaluating the potential cost effectiveness of maternal influenza vaccination by administration trimester in Nepal: A modeling study**
Presenter: **Collrane Frivold** ACOR0076
-
- 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
-
- 21 Knowledge, attitude and practices of poultry handlers towards avian influenza in communities surrounding L. Victoria, Uganda**
Presenter: **Derrick Bary Abila** ACOR0088
-
- 22 Emergency preparedness and integrated surveillance potential of a rapid COVID-19 diagnostic for airport quarantine in Bangladesh**
Presenter: **Farzana Zaman** ACOR0089
-
- 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
-
- 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

CORRELATES OF PROTECTION FOR NEXT GENERATION / UNIVERSAL INFLUENZA VACCINES

-
- 25 A heterologous prime and boost vaccination strategy for induction of cross-protective immunity using stockpiled H5 influenza virus vaccines**
Presenter: **Christine Oshansky** ACOR0005
-
- 26 Dissection of the human pre-existing HA-reactive antibody response to next generation COBRA influenza vaccines**
Presenter: **Giuseppe Sautto** ACOR0008
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- 27** Increase in IFN γ secretion by PBMCs as correlate of cellular protection against influenza infection
Presenter: **Olga Pleguezuelos** ACOR0009
-
- 28** Cytomegalovirus vaccine vector-induced, effector memory T cells protect cynomolgus macaques from lethal aerosolized heterologous influenza challenge
Presenter: **Jonah Sacha** ACOR0011
-
- 29** Quantification of influenza antibody vaccine responses accounting for both vaccine strength and breadth
Presenter: **Andreas Handel** ACOR0023
-
- 30** Bicistronic self-amplifying mRNA (sa-mRNA) vaccines targeting seasonal influenza A viruses are protective and immunogenic in a ferret model
Presenter: **Nedžad Music** ACOR0029
-
- 31** Neutralization profiling of anti-HA stem influenza antibodies with panel of representative influenza viruses
Presenter: **Adrian Creanga** ACOR0035
-
- 32** 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
-
- 33** 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
-
- 34** 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
-
- 35** Antibody effector functions are increased by seasonal vaccination for pandemic influenza viruses but baseline differences determine infection
Presenter: **Sophie Valkenburg** ACOR0053
-
- 36** Consensus-Sequence Structural Immunogen Design (CoSSID)
Presenter: **Eva-Maria Strauch** ACOR0072
-
- 37** Immune correlates of a broadly protective H1N1 Influenza Vaccine
Presenter: **Jonathan Heeney** ACOR0074
-
- 38** 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
-
- 39** Analysis the immunogenic effects of site-specific glycosylation on the Gansu H7N9 HA protein
Presenter: **Tsai-Chuan Weng** ACOR0094
-

Abstracts for poster presentations can be found on the website, www.isirv.org

IMMUNE RESPONSES AND IMMUNOLOGICAL ASSAYS FOR INFLUENZA

- 1 A rapid and flexible microneutralization assay for serological assessment of influenza viruses**
Presenter: **Kalee Rumfelt** ACOR0006

- 2 ImmunoSpot assays enable in-depth assessment of B cell reactivity against SARS-CoV-2 and seasonal influenza**
Presenter: **Greg Kirchenbaum** ACOR0018

- 3 Integrated Drivers of Basal Immunity and Acute Responses to Influenza Infection in Diverse Human Populations**
Presenter: **Aisha Souquette** ACOR0020

- 4 Evaluation of neutralizing antibodies in nasal mucosa among humans received intranasal vaccination against influenza viruses**
Presenter: **Akira Ainai** ACOR0030

- 5 Antigenic analysis of influenza hemagglutinin using a streamlined neutralization assay IRINA**
Presenter: **Larisa Gubareva** ACOR0032

- 6 A rapid distinction of the potential zoonotic risk of avian influenza virus by a modified hemagglutination test**
Presenter: **Jie-Long He** ACOR0038

- 7 Antibody landscapes of H7N9 patients from wave 1 to wave 5 in China and its association with autoimmune markers**
Presenter: **Xia Lin** ACOR0046

- 8 Quantifying the breadth of cross-reactive antibody responses to influenza A(H3N2)**
Presenter: **Bingyi Yang** ACOR0055

- 9 An integrated serological platform for immunogenicity readouts and the elucidation of potential correlates of protection for influenza haemagglutinin- and neuraminidase-based vaccines**
Presenter: **Nigel Temperton** ACOR0060

- 10 Towards an Improved Wild-type Sequence Based Hemagglutination Inhibition Assay for the Evaluation of Influenza Vaccines: Challenges and New Developments**
Presenter: **Vivek Shinde** ACOR0066

- 11 Assessment of Neuraminidase Antibody Responses to an Octavalent Influenza mRNA vaccine using a Multiplex Neuraminidase SeroAssay**
Presenter: **Irina V Ustyugova** ACOR0083

- 12 Transcriptomic profiling of vaccination versus Post-Influenza infection**
Presenter: **Stephany Sanchez-Ovando** ACOR0090

- 13 Dissecting the longevity and cross-reactive antibody responses after quadrivalent inactivated influenza vaccine immunization in children**
Presenter: **Sarah Lartey Lartey Jalloh** ACOR0093

REGULATORY CHALLENGES FOR NEXT GENERATION OF INFLUENZA VACCINES

- 14 Study of oligonucleotide polymorphisms of the influenza virus using high-resolution melting (HRM) analyzing of PCR products**
Presenter: **Galina Landgraf** ACOR0075

CORRELATES OF PROTECTION FOR SARS-CoV-2 AND BROADLY PROTECTIVE CORONAVIRUS VACCINE

- 15 B Cell Memory Responses to Four Different COVID-19 Vaccine Platforms**
Presenter: **Camila Coelho** ACOR0004
-
- 16 Rapid detection of SARS-CoV-2 neutralizing immunity**
Presenter: **Kei Miyakawa** ACOR0007
-
- 17 Overview of Humoral Immune Response to SARS-CoV-2 Variants in Patients and Vaccinees Following Homologous and Heterologous Vaccinations**
Presenter: **Claudia Maria Trombetta** ACOR0016
-
- 18 Intranasal vaccine with ODN2006 as an adjuvant induces cross-protective secretory IgA antibodies against SARS-CoV-2 variants, reducing the potential risk of lung eosinophilic immunopathology**
Presenter: **Takuya Hemmi** ACOR0022
-
- 19 Protection Against COVID-19 Outpatient Illness by Level of SARS-CoV-2 Receptor Binding Domain Binding Antibody at the Time of Illness, U.S. Flu VE Network**
Presenter: **Kelsey Sumner** ACOR0037
-
- 20 Immune responses to COVID-19 vaccines among healthcare workers in Hong Kong**
Presenter: **Benjamin Cowling** ACOR0042
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- 21 SARS-CoV-2 antibody responses are better for mRNA versus adenoviral vector (AdV) vaccines: results from a cohort of Australian healthcare workers**
Presenter: **Sheena Sullivan** ACOR0047
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- 22 Antibody and B cell cross-reactivity and kinetics following asymptomatic versus symptomatic SARS-CoV-2 infection**
Presenter: **Sheena Sullivan** ACOR0049
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- 23 Estimating the health-related quality of life benefit of prophylactic treatment for COVID-19 in immunocompromised people**
Presenter: **Michael Watt** ACOR0056
-
- 24 Protective effectiveness of prior SARS-CoV-2 infection and hybrid immunity against Omicron infection and severe disease: a systematic review and meta-regression**
Presenter: **Harriet Ware** ACOR0063
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- 25 Serologic correlates of protection against infection of COVID-19 vaccines: preliminary findings from a randomised trial of homologous and heterologous inactivated and mRNA third-dose vaccination (the Cobovax study)**
Presenter: **Nancy Hiu Lan Leung** ACOR0068
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- 26 Immune-focused SARS-CoV-2 nanoparticles interrogate antibody specificity and protection**
Presenter: **Kylie Konrath** ACOR0073
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- 27 Antibody correlates of protection against symptomatic SARS-CoV-2 infection for Alpha, Delta, Gamma and Zeta variants: analysis from two randomized controlled trials in the UK and Brazil**
Presenter: **Elaine Shuo Feng** ACOR0078
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- 28 Assessment of the correlation between SARS-CoV-2 serum neutralization titers and post-vaccination infections among healthcare workers from the Prospective Assessment of Seroconversion (PASS) Study**
Presenter: **Carol Weiss** ACOR0080
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- 29 Cellular and Humoral Immune Responses and Breakthrough Infections After Two Doses of BNT162b Vaccine in Healthcare Workers (HW) 180 Days After the Second Vaccine Dose**
Presenter: **Paolo Cantaloni** ACOR0081
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- 30 Lack of correlation between pre-Omicron wave antibody titers and Omicron infection measured by pseudovirus neutralization activity against the original vaccine strain**
Presenter: **Emily Martin** ACOR0100
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Abstracts for poster presentations can be found on the website, www.isirv.org

UPCOMING MEETING

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7th ISIRV-AVG CONFERENCE

in person

THERAPEUTICS:
LESSONS LEARNED FROM COVID-19

WEDNESDAY 3 - FRIDAY 5 MAY 2023

Marriott Seattle Waterfront Hotel USA

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