Poster Reception II

Paola Cristina Resende - AOXI0611

Five distinct zoonotic transmissions of Influenza A variants, swine to humans, during the 2020-2021 COVID-19 pandemic in Brazil

Paola Cristina Resende[2], Maria Ogrzewalska[2], Fernando Couto Motta[2], Jonathan Lopes[2], Luciana Appolinario[2], Braulia Caetano[2], Ighor Arantes[2], Elisa Cavalcante Pereira[2], Larissa Macedo Pinto[2], Thauane Silva[2], Irina Riediger[3], Maria do Carmo Debur[3], Acácia Maria Lourenço Francisco Nasr[4], Rosana Aparecida Piler[4], Andrea Simao[5], Rejane Schaefer[1], David Brown[2], Marilda Siqueira[2]

[1]EMBRAPA, [2]FIOCRUZ, [3]LACEN-PR, [4]SES-PR, [5]UEL

Background

Influenza A has been detected in the Brazilian swine population and occasionally it causes zoonotic transmission events, such as the H1N2v reported in 2015. Here we describe a series of zoonotic cases of Influenza A detected in the southern Brazilian region (Paraná State, PR) over an 18-month period. PR has the largest swine production industry in the country.

Method

Nasopharyngeal samples were collected by the National Surveillance Program, viruses detected by real time RT-PCR and genome sequencing was conducted for characterization and phylogenetic reconstruction. Enhanced local epidemiological surveillance was also performed in the attempt to monitor possible Influenza variant clusters in the human population.

Result

Up to 5 Influenza zoonotic events (swine-human) were reported in four different cities in PR. The first one occurred in a slaughterhouse worker 22-year-old (y.o) initially notified as a COVID-19 suspected case in April 2020. It was caused by an H1N2v, and the genomic constellation revealed a H1 associated to viruses from 2006-07 (A/Brisbane/59/2007-like), a N2 related strains from 1998 (A/Panama/2007/1999-like) and internal genes from strains circulating in 2009-12 (A/California/7/2009-like). The second event occurred in Rebouças in November 2020 in a 4 y.o farm resident child and another H1N2v strain was responsible for the case with a different origin of genes; the H1 was related to H1N1p from 2009-12 (A/California/7/2009-like). The third case reported was a 32 y.o man, a resident of Toledo in February 2021 infected with an H1N1pdm09v, all genes related to 2009-12 H1N1p (A/California/7/2009-like). The two last cases were related to each other and occurred in July 2021 in a mother 27 y.o and her 10 y.o son, resident in rural area of Santa Helena. Both were infected with an H3N2v (H3 and N2 from seasonal influenza H3N2 and internal genes internal genes from 2009-12 H1N1p (A/California/7/2009-like). Despite systematic analysis of genomes from all Influenza A samples collected in the same period and region as these variants, no additional variants were detected.

Conclusion

The diversity of variants found in PR State, reinforces the need to strengthen surveillance for Influenza animal-human transmission events. PR is an example of the human sentinel units in areas near to swine production and the maintenance of surveillance even during the COVID-19 pandemic, it helped the detection of these cases. The fact that such variants continue to emerge even during the low levels of influenza circulation worldwide, demonstrates the necessity of continuous surveillance of these viruses, with monitoring and timely assessment of risks associated with the emergence of zoonotic influenza strains with pandemic potential.

Poster Reception II

Marilda Siqueira - AOXI0522

Surveillance of influenza A and SARS-CoV-2 in wild and domestic animals in Brazil

MARIA OGRZEWALSKA[9], Marina Galvão Bueno[8], Leonardo Corrêa da Silva Junior[6], Anny Hellen Abreu Santos[2], Francisco Borges Costa[2], Fernando Couto Motta[6], Mia Ferreira de Araújo[6], Ana Beatriz Machado Lima[6], Deborah Fernandes Wailante[6], Roberto Leonan M. Novaes[3], Socrates F. Costa-Neto[3], Iuri Veríssimo[3], Stephany Nardi[3], Beatriz Maria[3], Marina Carvalho Furtado[3], Patricia Emilia Bento Moura[1], Guilherme Amaral Calvet[5], Sandro Antonio Pereira[5], Artur Augusto Velho Mendes Junior[7], Rodrigo Caldas Menezes[7], Isabella Dib Ferreira Gremião[7], Lucas Keidel[7], Maria Corrêa Lopes[7], Renato Orsini Ornellas[7], Ricardo Moratelli[4], Marcione Oliveira[11], Nadia Cavalcante[10], Marilda Mendonca Siqueira[6]

[1]Comparative and environmental virology laboratory (LVCA), Oswaldo Cruz Institute, Fiocruz, [2]Department of Parasitology, Maranhão State University, [3]Environmental Health Area, Fiocruz Atlantic Forest, Oswaldo Cruz Foundation, Fiocruz, [4]Environmental Health Area, Fiocruz Atlantic Forest, Oswaldo Cruz Foundation, Fiocruz, Rio de Janeiro, Brazil, [5]Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil,, [6]Laboratory for Respiratory Viruses and Measles of the Oswaldo Cruz Institute (IOC/Fiocruz), [7]Laboratory of Clinical Research on Dermatozoonoses in Domestic Animals, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, [8]Laboratory of Comparative and Environmental Virology (LVCA)-IOC/Fiocruz, [9]Laboratory of Respiratory Viruses and Measles, Oswaldo Cruz Foundation, FIOCRUZ, [10]National History Museum of Ceará, Brazil, [11]Vertebrate Department, National Museum of Rio de Janeiro, Brazil

Background

Animals are reservoir hosts for a wide diversity of viruses that threaten human health, including influenza A viruses (Orthomyxoviridae) and diverse coronaviruses (Coronaviridae). Since the initial outbreak of SARS-CoV-2, which causes the COVID-19 pandemic, there have been numerous reports of animals becoming infected with the virus, however, their role as new potential hosts for SARS-CoV-2 is still not clear. On the other hand, influenza A viruses already are known to spread and cause respiratory disease in humans and in a wide range of animals, including domestic and wild birds, pigs, horses, and dogs, with sporadic outbreaks in seals, whales, ferrets and cats. Moreover, recently influenza A viruses were found in bats in Central and South America emphasizing the need of constant surveillance of the virus. Thus, this study focused on the monitoring of possible infection in wild and domestic animals by influenza A and SARS-CoV-2 in Brazil.

Method

Oral, rectal and/or nasal swabs were collected from wild and domestic animals in three different regions in Brazil: North (Maranhão State), Northeastern (Ceará State) and Southeastern (Rio de Janeiro State). Genetic material was extracted from the biological samples collected, , and the samples were analyzed by real-time RT-PCR for influenza A virus and SARS-CoV-2.

Result

Since January 2021 till May 2022, samples of swine (N = 200), dogs (67), cats (33), primates (Callithrix sp. 60), marsupials (Didelphis aurita, 15), wild and synanthropic rodents (Mus musculus [1], Oligoryzomys sp. [2], Rattus norvegicus [3], Rattus rattus [5]), and 615 bats (Emballonuridae [2], Molossidae [5], Noctilionidae [4], Phyllostomidae [588], Vespertilionidae [16]) were collected and tested and none was found positive for influenza A or SARS-CoV-2.

Conclusion

Although there is still a lot to learn about how SARS-CoV-2 affects different animal species, our results show that tested animals are not easily infected with SARS-CoV-2 under natural conditions, and there is no evidence that infected animals spread the virus to other animals or to people. The expansion of wild animal sampling is necessary to understand their role in the epidemiology of SARS-CoV-2 and other potentially zoonotic pathogens, in natural environments shared with humans. Systematic surveillance of influenza viruses in pigs and a variety of viruses in bats is a key measure for pre-warning the emergence of the next pandemic.

Poster Reception II

Isabel Bergeri - AOXI0322

Crafting the Mosaic: Resilient systems for surveillance of respiratory viruses of pandemic potential

Isabel Bergeri[2], Joshua A MOTT[2], Richard Pebody[1], Pushpa Wijesinghe[4], Hala Abou-Elnaja[6], Sangjun Moon[7], Lidia Redondo-Bravo[5], Belinda Herring[3], Maya Allan[2], Boris I Pavlin[2], Maria Van Kerkhove[2], Wenqing Zhang[2], Sylvie Briand[2]

[1]World Health Organization Regional Office for Europe, Copenhagen, Denmark, [2]World Health Organization, Geneva, Switzerland, [3]World Health Organization, Regional Office for Africa, Brazzaville, Congo, [4]World Health Organization, Regional Office for South-East Asia, New Delhi, India, [5]World Health Organization, Regional Office for the Americas (Pan American Health Organization), Washington DC, United States of America, [6]World Health Organization, Regional Office for the Eastern Mediterranean, Cairo, Egypt, [7]World Health Organization, Regional Office for the Western Pacific, Manila, Philippines

Background

The COVID-19 acute pandemic response phase has begun moving toward plans for sustained control and medium to longer-term public health management. There is a pressing global need for a strategic framework for surveillance of respiratory viruses of pandemic potential to enable countries to assess their surveillance objectives and prioritize technical and financial investments in these surveillance systems. This will help assure that those respiratory viruses can be resiliently detected and monitored on an ongoing basis, in a coordinated fashion at national and supranational levels.

Method

We developed the evidence-base for a "mosaic" of complementary surveillance systems, each efficiently targeted to best meet inter-pandemic early warning, monitoring and evaluation objectives. Country inputs on priority public health objectives, surveillance systems used to meet those objectives, needed enhancements, and lessons learned from the COVID-19 pandemic were gathered using regional surveys, online country-level surveys, focused country discussions, regional country consultations. Consolidated results then served as the foundation for a WHO global consultation in May 2022, with attendees from countries, WHO, and external partner and donor organizations

Result

A constellation of systems necessary to address early warning needs includes sensitive outbreak detection with One Health coordination, strong interconnected clinical-epidemiological networks, and event-based outbreak detection systems. Once circulating in human populations on a seasonal basis, sentinel integrated surveillance approaches focused on "quality over quantity" are essential for monitoring viruses, as are strong non-sentinel laboratory networks, both linked with genomic testing, where feasible. New approaches adopted during the COVID-19 pandemic hold promise as important complements to existing surveillance systems; including participatory surveillance, formalized clinical networks, and the continuation of systems to monitor health care capacities. There is also a continued need for special studies and standardized outbreak investigations to meet key inter-pandemic objectives, that are also ready for rapid use during emergencies or future pandemics.

Conclusion

This strategic framework will leverage existing global and regional surveillance guidance. Countries may use the framework to (i) identify priority unmet surveillance objectives, and the systems to be used to meet those objectives; (ii) prioritize needed surveillance enhancements during and after this pandemic; (iii) develop enhanced implementation plans; (iv) strengthen coordination between surveillance systems to enhance response; and (v) prioritise local and international partner technical assistance and investments.

Poster Reception II

Gifty Mawuli Sarpong - AOXI0203

Combined virological surveillance of SARS-CoV-2 and Influenza in Ghana in 2021

Ivy Asantewaa Asante[1], Gifty Mawuli Sarpong[1], Yaw Awuku-Larbi[1], Stephen Nyarko[1], Richard Asomadu Obeng[1], Esinam Aku Apefa Amenuvor[1], Mildred Adusei-Poku[2], Linda Boatemaa[1], Vanessa Magnusen[3], Jennifer Wutsika[1], Samuel Ago[1], Lorreta Kwasah[1], Juliet Wordui[1], Roberta Tackie[1], Daniel Mingle[4], William Asiedu[4], Edward Nyarko[4], Dennis Laryea[5], Franklin Asiedu-Bekoe[5], Shirley Nimo-Paintsil[6], Naiki Attram[6], Terrel Sanders[6], William Kwabena Ampofo[1]

[1]National Influenza Centre, Noguchi Memorial Institute for Medical Research, University of Ghana, [2]National Influenza Centre, Noguchi Memorial Institute for Medical Research, University of Ghana; Department of Medical Microbiology, University of Ghana Medical School, [3]National Influenza Centre, Noguchi Memorial Institute for Medical Research, University of Ghana; West African Centre for Cell Biology of Infectious Pathogens, University of Ghana, [4]Public Health Division 37 Military Hospital, Ghana Armed Forces, [5]Public Health Division, Ghana Health Service, [6]US Naval Medical Research Unit Ghana Detachment

Background

The Global Influenza Surveillance and Response System (GISRS) recommends the integration of SARS-CoV-2 into influenza sentinel surveillance systems globally. In line with this, the Ghana National Influenza Center (Ghana-NIC), intiated combined detection of SARS-CoV-2 infections. We report on the co-circulation of influenza viruses and SARS-CoV-2 in Ghana in 2021

Method

Outpatients and inpatients meeting the WHO case definitions for respiratory illness from 29 influenza sentinel sites in public health facilities between January 4, 2021 and December 23, 2021 formed the study population and provided respiratory samples. These respiratory samples were processed at the Ghana-NIC for the detection of influenza/SARS-CoV-2 viruses using polymerase chain reaction multiplex primers/probes and assays provided by the United States Centres for Disease Control and Prevention (US-CDC). The results enabled the determination of rates of influenza and SARS-CoV-2 infection among patients with respiratory illness.

Result

Over the reporting period, a total of 4,022 samples were processed; 3,547 outpatient and 475 inpatients. Influenza and SARS-CoV-2 were detected in 11% (438/4022) and 22% (858/4022) of all samples processed, respectively. Of the influenza positives, 80% were A(H1N1)pdm09. Coinfections of Influenza and SARS-CoV-2 were detected in 0.40% (14/3547) of outpatients and 0.42% (2/475) of inpatients. Influenza and SARS-CoV-2 were more commonly detected in males than in females, as well as in individuals aged 25 to 44 years.

Conclusion

The presence of dual infections of influenza and SARS-CoV-2 indicate the value of simultaneous investigation of multiple pathogens. These findings show the effectiveness of integrating surveillance for respiratory illness for enhanced and targeted public health interventions such as case detection, management and immunization.

Poster Reception II

Martin Zickler - AOXI0002

Replication of SARS-CoV-2 in adipose tissue determines organ and systemic lipid metabolism in hamsters and humans

***Martin Zickler*[1], *Stephanie Stanelle-Bertram*[1]**

[1]Leibniz Institute for experimental Virology (HPI)

Background

Obesity belongs to one of the independent risk factors of severe COVID-19 outcome. In this study, we aimed to elucidate the role of adipose tissue in SARS-CoV-2 infection.

Method

We analyzed autopsy-derived adipose tissue samples from deceased COVID-19 patients. Infection experiments with SARS-CoV-2 were performed in human stem cell-derived adipocytes. Metabolomic studies were performed in plasma of SARS-CoV-2 infected Syrian golden hamsters as well as in COVID-19 patients.

Result

SARS-CoV-2 RNA was detected in 10 out of 19 male individuals in at least one adipose tissue sample analyzed. Viral RNA in adipose tissue was only found in overweight or obese males (BMI ≥ 25). This correlation was not seen in samples of female individuals (n=12). Infection experiments in human stem cell-derived adipocytes revealed replication of SARS-CoV-2 depending on the adipogenic differentiation state and corresponding angiotensin converting enzyme 2 (ACE2) expression. Treatment with the lipase inhibitor tetrahydrolipstatin reduced viral titers by 100-fold in mature adipocytes indicating a dependency on lipid droplet metabolism. Further reduction in viral titers was achieved by combination treatment with atorvastatin, most probably caused by decreased ACE2 expression.

Syrian golden hamsters infected with SARS-CoV-2 showed infectious viral titers in adipose tissue 1 and 3 days post infection (dpi). Virus was cleared 6 dpi suggesting a sufficient innate immune response supported by pronounced upregulation of isg15 on day 3 post infection. In metabolomic analysis of plasma samples obtained from infected hamsters, we detected an abundance of triglycerides (TG) enriched in polyunsaturated fatty acids (PUFA) and a reduction of TGs enriched in monounsaturated (MUFA) and saturated fatty acids (SFA), typical for de novo lipogenesis (DNL). Plasma samples of COVID-19 patients showed a similar trend towards lower concentration of MUFA, SFA-containing TGs.

Conclusion

In conclusion, we show that replication of SARS-CoV-2 in adipose tissue alters the lipid metabolism of hamsters and humans.

Poster Reception II

Valérie Lecouturier - AOXI0103

SARS-CoV2 preS dTM-AS03 vaccine boosters induce broad and persistent cross-neutralizing responses against SARS-CoV-2 variants of concern in primed non-human primates

Valérie Lecouturier[4], Vincent Pavot[4], Catherine Berry[4], Michael Kishko[3], Natalie G. Anosova[3], Dean Huang[3], Tim Tibbitts[3], Alice Raillard[4], Sylviane Gautheron[4], Cindy Gutzeit[1], Marguerite Koutsoukos[2], Roman M. Chicz[3]

[1]GlaxoSmithKline, Rixensart, Belgium, [2]GlaxoSmithKline, Wavre, Belgium, [3]Sanofi, Cambridge, MA, USA, [4]Sanofi, Marcy-l'Etoile, France

Background

Since late 2021, the continuous emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants that evade neutralizing antibodies, combined with the waning immunity, has triggered surges of COVID-19 in most parts of the world, despite high vaccine coverage. Our SARS-CoV-2 spike recombinant protein vaccine formulated with the AS03 adjuvant (CoV2 preS dTM-AS03) has demonstrated high immunogenicity and efficacy in a Phase 3 clinical trial against variants such as Delta in naïve subjects.

Method

Given the increasing seroprevalence due to both vaccination and high infection rates, we evaluated the vaccine performance when used as booster vaccine in primed macaques and explored breadth against the more divergent variant Omicron and SARS-CoV-1.

Result

We showed that, after a prime with the mRNA or recombinant spike protein subunit vaccine candidates, one booster dose of CoV2 preS dTM-AS03, (monovalent D614 (WT) or B.1.351 (Beta), or bivalent D614 + B.1.351 formulations), significantly and durably boosted neutralizing antibodies against the parental strain and induced cross-neutralizing antibodies against close and divergent SARS-CoV-2 variants of concern (Alpha, Beta, Gamma, Delta and Omicron) as well as SARS-CoV-1. Moreover, the booster consolidated memory B cell responses to high and more homogeneous levels.

Conclusion

The potent and prolonged booster effect up to 6 months against variants of concern shown in macaques could provide a unique benefit for future booster vaccination campaigns.

Poster Reception II

Valérie Lecouturier - AOXI0104

A bivalent subunit SARS-CoV2 preS dTM (D614 and B.1.351) with AS03-adjuvant vaccine induces broad and long-term neutralizing responses against SARS-CoV-2 variants in naïve non-human primates

Valérie Lecouturier[4], Catherine Berry[6], Vincent Pavot[6], Michael Kishko[5], Natalie G. Anosova[5], Dean Huang[5], Tim Tibbitts[5], Alice Raillard[6], Sylviane Gautheron[6], Cindy Gutzeit[1], Marguerite Koutsoukos[2], Galit Alter[3], Roman M. Chicz[5]

[1]GlaxoSmithKline, Rixensart, Belgium, [2]GlaxoSmithKline, Wavre, Belgium, [3]Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA, USA, [4]Sanofi, [5]Sanofi, Cambridge, MA, USA, [6]Sanofi, Marcy-l'Etoile, France

Background

Our SARS-CoV-2 spike recombinant protein vaccine based on the parental strain (D614) and formulated with the AS03 adjuvant (GSK) has demonstrated high immunogenicity and efficacy against SARS-CoV-2 variants such as Delta in clinical trials in naïve subjects.

Method

In early 2021, the Beta spike (B.1.351) antigen was selected to update the vaccine formulation, as it displayed the greatest breakthrough infections against the parental (D614) vaccines, before the Delta and Omicron surges.

Result

In naïve macaques, the combination of the B.1.351 Spike antigen with the D614 parental Spike, in a bivalent (D614+B.1.351) vaccine formulation with AS03 adjuvant, extended the breadth of neutralization to Beta, Gamma, Mu and, surprisingly, Omicron variants, in addition to the neutralizing responses against D614 and Delta conferred by the parental CoV2 preS dTM-AS03 (D614) vaccine, while no negative interferences between the two components were observed. Both monovalent and bivalent vaccine formulations induced high and consistent Spike-specific memory B cell responses three months post-immunization. Importantly, the neutralizing antibody titers reached stable levels three to four months after primary immunization and are sustained up to six months.

Conclusion

The antibody persistence provided by the CoV2 preS dTM-AS03 vaccine, combined with the increased breadth of neutralization conferred by the bivalent formulation in naïve NHPs, supports the bivalent (D614+B.1.351) CoV2 preS dTM-AS03 vaccine for primary immunization in naïve individuals, pending efficacy is demonstrated in the ongoing clinical trial.

Poster Reception II

Zhunan Li - AOXI0040

Distinctive Antibody Landscapes Resulting from Influenza Infection and Vaccination

Zhunan Li[1], Feng Liu[1], Stacie Jefferson[1], Lauren Horner[1], Paul Carney[1], Brendan Flannery[1], James Stevens[1], Terrence Tumpey[1], Min Levine[1]

[1]Centers for Disease Control and Prevention

Background

Influenza vaccinations and natural infections induce complex antibody responses, hemagglutinin (HA)/neuraminidase (NA) subtype specific and cross-subtype antibodies, which are dependent upon an individual's exposure history to infections and/or vaccinations. We developed a high throughput 32 multiplex influenza antibody detection assay (MIADA) (MAGPIX®) to better understand the antibody landscape and to differentiate antibody responses following influenza virus infection or vaccination.

Method

The MIADA platform incorporates 27 HA globular head, ectodomain, and/or stalk from A(H1N1), A(H1N1)pdm09, A(H2N2), A(H3N2), A(H5N1), A(H7N9), A(H9N2), A(H13N9), influenza B viruses, NAs (N1, N2, and N9), and influenza A nucleoprotein (NP). Pre- (S1) and post- (S2) vaccination sera collected from adults (19-49 yrs), who received quadrivalent inactivated influenza vaccines (IIV4) in 3 influenza seasons: 2016-17 (n=15), 2018-19 (n=21), and 2019-20 (n=20) were analyzed. Acute (S1) and convalescent (S2) sera were collected from RT-PCR confirmed influenza B (n=44) and A(H1N1)pdm09 (n=85) virus infected persons and single S1 sera (n=248) were collected from persons that were negative for influenza in 2019-20 season. Twenty-nine paired sera from RT-PCR confirmed influenza A(H3N2) infections in 2018-19 season were also analyzed by MIADA.

Result

Distinctive antibody profiles between infection and vaccination were detected by MIADA. The most significant increases in median fluorescent intensities (MFIs) following influenza vaccines or infections were detected against HAs from the vaccine antigens (vaccination) or infecting virus (infected persons). Influenza B virus infected persons only had antibody rises against HAs from influenza B viruses. Influenza A(H1N1)pdm09 infection elicited antibody against H1 HA and N1 NA, while A(H3N2) infection elicited antibodies to H3 HA and N2 NA; both elicited antibodies against influenza A NP. HA Antibodies in S1 sera from influenza negative persons were significantly higher than those in S1 sera from either influenza B or A(H1N1) infected persons ($p<0.05$), suggesting the HA antibody levels are likely associated with protection from infection in influenza negative persons. Vaccination induced the antibody responses to multiple antigens including HAs, NAs, and/or NP from both influenza A and B that were related to vaccine components, allowing differentiation of vaccination from infection by the MIADA assay. The IIV4 induced antibodies only against H1 HA stalk, but not to H3 HA stalk and lower NA antibody responses compared to infection.

Conclusion

Antibody landscapes can provide in-depth analysis of the antibody responses to influenza virus infection and vaccination.

Poster Reception II

Jessie Chung - AOXI0016

Vaccine effectiveness against A(H3N2) viruses in the United States during 2021-22, US Flu VE Network

Jessie Chung[8], Brendan Flannery[8], Manjusha Gaglani[2], Kayan Dunnigan[1], Krissy Moehling Geffel[7], Mary Patricia Nowalk[7], Sara Tartof[3], Ana Florea[3], Edward Belongia[5], Huong McLean[5], H. Keipp Talbot[9], Carlos Grijalva[9], Karen Wernli[4], C. Hallie Phillips[4], Emily Martin[6], Arnold Monto[6], Juliana DaSilva[8], John Barnes[8], Manish Patel[8]

[1]Baylor Scott & White Health, [2]Baylor Scott & White Health; Texas A&M University College of Medicine, [3]Kaiser Permanente Southern California, [4]Kaiser Permanente Washington Health Research Institute, [5]Marshfield Clinic Research Institute, [6]University of Michigan School of Public Health, [7]University of Pittsburgh Schools of the Health Sciences; University of Pittsburgh Medical Center, [8]US Centers for Disease Control and Prevention, [9]Vanderbilt University Medical Center

Background

Influenza vaccine effectiveness (VE) estimates were not available for the 2020-21 influenza season due to historically low circulation of influenza globally. Circulation of influenza in the U.S. in late fall through early winter of the 2021-22 influenza season provided data for interim season estimates of VE against outpatient medically attended laboratory-confirmed influenza.

Method

In the US Influenza VE Network, patients aged ≥6 months seeking care for acute respiratory illness including fever/feverishness or cough within 7 days of illness onset were enrolled across seven study sites at ambulatory clinics including emergency departments. Influenza vaccination status was obtained from electronic records or self-report. Respiratory specimens were tested for influenza and SARS-CoV-2 by RT-PCR. A subset of influenza-positive specimens was sequenced using whole genome sequencing. Influenza A(H3N2) VE was estimated using a test-negative design as 100% x (1 - OR), where OR is the odds ratio from multivariable logistic regression models adjusted for site, age, month of illness onset, and days between illness onset and specimen collection.

Result

Of 3,636 patients enrolled from November 2021-February 2022, 177 (5%) tested positive for influenza A(H3N2), 16 for influenza A with no subtype result available, one for A(H1N1)pdm09, and none for influenza type B; 11 (6%) of 194 influenza-positive patients were co-infected with SARS-CoV-2. Of 3,442 influenza-negative patients, 1,514 (44%) tested positive for SARS-CoV-2. All 65 sequenced A(H3N2) viruses belonged to genetic clade 3C.2a1b subclade 2a.2. Overall, 39% of A(H3N2)-positive patients and 49% of influenza-negative patients were vaccinated. Adjusted VE against medically attended influenza A(H3N2) virus infection was 16% (95% confidence interval [CI]: -16, 39). After excluding influenza-negative, SARS-CoV-2-positive patients aged ≥5 years eligible to receive COVID-19 vaccination in the United States, adjusted VE against A(H3N2) was 31% (95% CI: 3, 51).

Conclusion

The first VE estimates available since the 2019-20 season suggest that influenza vaccination in 2021-22 provided low-to-no protection against mild/moderate outpatient medically attended laboratory-confirmed influenza A(H3N2) infection. Estimates will be updated when the influenza season has concluded.

Poster Reception II

Lenee Blanton - AOXI0023

Influenza vaccine effectiveness among adults 65 years of age and older: A systematic review of high dose inactivated, adjuvanted inactivated, and recombinant influenza vaccines

Lenee Blanton[2], Jessie Chung[1], Jill Ferdinands[1], Rachel Holstein[1], LIsa Grohskopf[1]

[1]CDC, [2]Centers for Disease Control and Prevention

Background

Annual influenza vaccination is recommended for adults >=65 years in the U.S. Studies have noted greater benefit of high-dose inactivated (HD-IIV), MF59-adjuvanted inactivated (aIIV), and recombinant (RIV) influenza vaccines (collectively enhanced influenza vaccines or EIVs) vs standard-dose unadjuvanted inactivated vaccines (SD-IIVs) in this age group. We systematically reviewed evidence for vaccine efficacy/effectiveness (VE) of EIVs compared with SD-IIVs and one another.

Method

Manuscripts were retrieved via systematic search of MEDLINE, EMBASE, CINAHL, Scopus, The Cochrane Library, and ClinicalTrials.gov from 1/1990-8/2021 for randomized (RCT) and observational studies reporting relative VE (rVE) of EIVs with SD-IIVs and one another. Two investigators independently screened and reviewed reports, abstracted data, and assessed risk of bias of eligible papers. Outcomes included influenza-associated illness, outpatient/emergency department visits, hospitalizations, and deaths.

Result

Of 10,169 manuscripts screened, only 3 RCTs were retrieved comparing EIVs vs SD-IIVs against lab-confirmed influenza (LCI): a 2-season study noting rVE of 24% (95%CI 10, 37) of HD-IIV relative to SD-IIV, and 2 1-season studies with a pooled rVE of 18% (95%CI -17, 43) of RIV vs SD-IIV. 22 observational studies were included and covered more seasons; but risk of potential bias was higher in these studies. Retrospective cohort studies (RCS) examining influenza-associated hospitalization defined by diagnostic codes, for which the most data were found for HD-IIV vs SD-IIV and the least (1 study in 1 season) for RIV vs SD-IIV. rVE varied substantially by season for both HD-IIV and aIIV vs SD-IIV; benefit was observed in some but not all seasons for either vaccine. In observational studies, rVE varied for comparisons of HD-IIV to aIIV. One single-season RCS noted greater benefit of RIV over HD-IIV and aIIV against code-defined influenza-associated hospitalization.

Conclusion

There is evidence of benefit favoring each EIV over SD-IIV in adults >=65 years of age; however, there is no strong evidence that favors one EIV over others among studies providing direct comparisons. In comparisons of EIVs with SD-IIVs and with one another, RCTs (the highest quality evidence) are extremely limited in number and range of influenza seasons covered. Observational data are available for more seasons and suggest greater benefit of each EIV over SD-IIV in at least some studies in some seasons, but most of these studies are limited by potential for bias and use of non-LCI outcomes. Despite this, considerations of observational study results may be important given variability of VE across influenza seasons.

Poster Reception II

Maria Sundaram - AOXI0030

Influenza B vaccine effectiveness: exploring the impact of lineage-specific prior vaccination history

Maria Sundaram[2], David McClure[2], Edward Belongia[2], Jennifer King[2], Emily Martin[5], Arnold Monto[5], Richard Zimmerman[6], Krissy Moehling Geffel[6], Manjusha Gaglani[3], Kempapura Murthy[4], Michael Jackson[1], Jessie Chung[7], Brendan Flannery[7], Huong McLean[2]

[1]AllStripes, [2]Center for Clinical Epidemiology and Population Health, Marshfield Clinic Research Institute, [3]Center for Research in Vaccines and Infections, Baylor Scott and White Medical Center, [4]College of Medicine, Baylor Scott and White Health, [5]Department of Epidemiology, University of Michigan School of Public Health, [6]Department of Family Medicine, University of Pittsburgh, [7]US Centers for Disease Control and Prevention

Background

Influenza B viruses cause disease with comparable severity to influenza A viruses. Immunologic cross-reactivity between B lineages might be influenced by vaccination history. We examined these relationships in the US Influenza Vaccine Effectiveness (Flu VE) Network.

Method

Patients with outpatient acute respiratory illness were enrolled from 2011-12 through 2019-20 seasons and tested for influenza by RT-PCR. Individuals testing negative, or with B/Victoria (B/Vic) or B/Yamagata (B/Yam) illness, were included in the analysis. Individuals were excluded if enrolled outside periods of influenza B circulation, vaccinated ≤14 days before illness onset, or received an unknown or enhanced vaccine type. Multivariable models assessed odds of lineage-specific B virus infection vs. no influenza for different vaccine exposure histories, adjusting for site, seasonal peak, sex, smoking status, race, health status, and high-risk conditions. Lineage-specific vaccine effectiveness (VE) was calculated as 100*(1-aOR).

Result

The analysis included 24,792 individuals for VE against B/Vic (1,777 B/Vic cases) and 27,219 for VE against B/Yam (2,560 B/Yam cases). Vaccination with B/Vic both in the prior season and in the current season conferred limited protection against B/Vic (VE: 36.5; 95% CI: -25.9, 67.9). However, vaccination with B/Yam in the prior season and B/Vic in the current season was highly effective against B/Vic (VE: 79.0; 95% CI: 63.1, 88.0). Conversely, vaccination with a B/Yam strain both in the prior season and current season was highly protective against B/Yam (VE: 73.4; 95% CI: 64.3, 80.2). VE was lower for vaccination with a B/Vic strain in the prior season and a B/Yam strain in the current season (VE: 57.5; 95% CI: 42.8, 68.4). VE against B/Vic for individuals who received quadrivalent inactivated vaccine (QIV) in the current season and no vaccine in the prior season was 39.5 (95% CI: 27.1, 49.8), compared with a VE of 23.1 (95% CI: 11.2, 33.4) for those who received QIV in both seasons. VE estimates for these groups were not substantially different for VE against B/Yam (VE: 51.7; 95% CI: 42.6, 59.3 for no prior vaccine and QIV current season; VE: 50.8; 95% CI: 42.6, 57.9 for QIV both seasons).

Conclusion

We observed diverse influenza B VE point estimates according to lineage match between prior and current season vaccines, with wide confidence intervals. These differences were not symmetric between B/Yam-to-B/Vic vs. B/Vic-to-B/Yam vaccination histories. Complex interactions might contribute to these effects, including within-lineage antigenic distance between vaccine and circulating B viruses, antigenic distance between sequential B lineage strains, and birth cohort effects (imprinting).

Poster Reception II

Christine Wadey - AOXI0049

Use of heterologous antisera to determine influenza potency using the single radial diffusion assay

Christine Wadey[1], Steve Rockman[2]

[1]Seqirus, [2]The University of MelbourneDepartment of Immunology and Microbiology, Parkville, Australia, Seqirus Australia

Background

The potency of inactivated seasonal influenza vaccine is harmonised by establishing the haemagglutinin (HA) content by the compendial single radial diffusion (SRID) method. SRID reagents (antigen and antisera) are prepared and calibrated by regulatory agencies which distribute these reagents as standards for testing seasonal influenza vaccines. Most often, these reagents are developed following the biannual announcement of the subtypes to be included in the vaccine by the WHO in February and September for the Northern and Southern hemisphere respectively. There is a significant time lag after this announcement for the generation, dispensing, freeze drying, calibration and distribution of these reagents The generation of homologous reagents constrains the time to release seasonal vaccine.

Method

This presentation tests the application of heterologous antisera to determine the potency of influenza vaccine using Single Radial Immunodiffusion (SRD) compared to standard homologous antisera.

Result

Heterologous sheep antiserum showed cross-reactivity in the SRD assay to viruses in closely related clades and subclades, and in some cases across multiple more distantly related clades.

Conclusion

The results demonstrate that with sufficiently related strains, use of existing heterologous sheep antisera provide a suitable replacement to generation of stocks of homologous antiserum for SRD potency determination. The application of heterologous sera will enable the earlier release of seasonal vaccine in instances where homologous antisera are not available to match the strain selected by WHO for seasonal influenza vacine manufacture due to late strain selection, poor response of sheep to the nominated strain, or an urgent need for vaccine release due to virus prevalence or impact.

Poster Reception II

Emiko Mukai - AOXI0070

Inactivated influenza vaccination did not reduce influenza viral load at diagnosis among young Japanese children during the 2013/2014 through 2017/2018 influenza seasons

Emiko Mukai[3], Wakaba Fukushima[6], Saeko Morikawa[7], Keiko Nakata[7], Satoshi Hiroi[7], Masashi Fujioka[8], Tohru Matsushita[12], Megumi Kubota[10], Yoshina Yagi[16], Tetsuhisa Takechi[15], Yoshio Takasaki[14], Shizuo Shindo[13], Yuji Yamashita[17], Takato Yokoyama[18], Yumi Kiyomatsu[9], Kazuhiro Matsumoto[2], Akiko Maeda[4], Kyoko Kondo[11], Kazuya Ito[5], Tetsuo Kase[6], Satoko Ohfuji[6], Yoshio Hirota[1]

[1]Clinical Epidemiology Research Center SOUSEIKAI Medical Group (Medical Co. LTA), Fukuoka 813-0017, Japan, [2]Department of Public Health, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan, [3]Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Osaka, Japan, [4]Department of Public Health, Osaka Metropolitan University Graduate School of Medicine, Osaka 545-8585, Japan, [5]Department of Public Health, Osaka Metropolitan University Graduate School of Medicine, Osaka 545-8585, Japan; Healthcare Management, College of Healthcare Management, Miyama 835-0018, Japan; Clinical Epidemiology Research Center SOUSEIKAI Medical Group (Medical Co. LTA), Fukuoka 813-0017, Japan, [6]Department of Public Health, Osaka Metropolitan University Graduate School of Medicine, Osaka 545-8585, Japan; Research Center for Infectious Disease Sciences, Osaka Metropolitan University Graduate School of Medicine, Osaka 545-8585, Japan, [7]Department of Virology, Osaka Institute of Public Health, Osaka 537-0025, Japan., [8]Fujioka Pediatric Clinic, Tondabayashi 584-0074, Japan, [9]Kiyomatsu Pediatric Clinic, Fukuoka 814-0021, Japan, [10]Kubota Children's Clinic, Osaka 544-0033, Japan, [11]Management Bureau, Osaka Metropolitan University Hospital, Osaka 545-8586, Japan, [12]Matsushita Kids' Clinic, Kadoma 571-0030, Japan, [13]Shindo Children's Clinic, Fukuoka 814-0121, Japan, [14]Takasaki Pediatric Clinic, Fukuoka 819-0052, Japan, [15]Takechi Clinic for Pediatrics & Internal Medicine, Osaka, Japan, [16]Yagi Pediatric Clinic, Yao 581-0871, Japan, [17]Yamashita Pediatric Clinic, Itoshima 819-1112, Japan, [18]Yokoyama Children's Clinic, Kasuga 816-0801, Japan

Background

Uncertainty remains about the association between inactivated influenza vaccination and nasopharyngeal viral load at influenza diagnosis in young children, though only inactivated influenza vaccines have been distributed in Japan.

Method

From the influenza seasons of 2013/14 to 2017/18, at pediatric clinics, eligible participants under 6 years old with pre-defined influenza-like illness and influenza-positive status with real-time RT-PCR were involved in this observational study. Influenza viral load was measured for epidemic subtypes/lineages of each season: A(H1N1)pdm09 for 2013/2014 and 2015/2016, A(H3N2) for 2014/2015 and 2016/2017, and B(Yamagata) for 2017/2018. The influenza vaccination status of the current season was obtained from maternal and child health handbooks or medical records. Using median dichotomized viral load as an outcome, a mixed-effect multilevel logistic regression model was applied to estimate the multivariable-adjusted odds ratio (AOR) and 95% confidence interval (CI) for higher viral load.

Result

A total of 1,185 influenza-positive children were analyzed. The median log10 copy number of viral load (copies/mL) was 5.5 (interquartile range, 4.6 to 6.1). The viral load did not differ by vaccination status: 5.5 for dose 0, 5.7 for dose 1, and 5.5 for dose 2 (p=0.67). AOR of those vaccinated (dose 1 or dose 2) compared with those unvaccinated (dose 0) was 1.19 (95%CI: 0.86-1.64). Other factors showing significant association with higher viral load were positive results of A(H1N1)pdm09 and A(H3N2) in comparison to that of B(Yamagata). The respective AOR was 3.25 (95%CI: 2.28-4.64) and 1.81 (95%CI: 1.32-2.49). Significantly elevated AOR against higher viral load was also observed for higher body temperature at influenza diagnosis and shorter duration from symptom onset to specimen obtainment.

Conclusion

No association was detected between inactivated influenza vaccination and viral load at influenza-positive diagnosis. Subtypes, body temperature, and time elapsed from symptom onset were significantly associated with the level of viral load.

Poster Reception II

Allyn Bandell - AOXI0096

Real-World Effectiveness of Live Attenuated and Inactivated Influenza Vaccines in Children During Multiple Seasons: 2016-2021

Allyn Bandell[2], Ulrike Baum[1], George Kassianos[3]

[1]Finnish Institute for Health and Welfare, [2]Medical Affairs, AstraZeneca, [3]President British Global & Travel Health Association; General Practitioner, Wokingham, England, UK

Background

Influenza is associated with a substantial burden in children, and annual influenza vaccination with live attenuated influenza vaccine (LAIV) or inactivated influenza vaccines (IIVs) is recommended for the pediatric population in many countries. The real-world effectiveness of influenza vaccines can vary substantially between seasons and influenza subtypes. This study evaluated LAIV and IIV effectiveness in children during the 2016/17 through 2020/21 influenza seasons.

Method

Quadrivalent LAIV (LAIV4) and IIV effectiveness studies conducted in the pediatric population from 2016/17 through 2020/21 were identified from published literature, congress presentations, public health websites, and personal communication with national investigators.

Result

For the influenza seasons between 2016/17 and 2019/20, estimates for vaccine effectiveness (VE) against infection (all influenza strains) ranged from 20% to 74% for LAIV4 and from -20% to 68% for IIV in children (Figure). For the most recent measurable season in 2019/20, all-strain VE (95% confidence interval) with LAIV4 was 45.4% (12.6, 65.9%) for children aged 2-17 years (yrs) in the UK, and 66.0% (58.3, 72.4%) for children aged 2-6 yrs in Finland. VE estimates for LAIV were unavailable from the US for 2019/20 due to limited use of LAIV that season. Equivalent overall VE of quadrivalent IIV (IIV4) was 51.8% (36.5, 63.5%) for children aged 2-6 yrs in Finland, and 34% (19, 46%) and 40% (22, 53%) for children aged 6 months-8 yrs and 9-17 yrs, respectively, in the US. No VE estimates for IIV were available from the UK between 2017/18 and 2019/20, as LAIV is the recommended influenza vaccine for children in the UK, except when contraindicated. In 2019/20, LAIV4 VE against influenza subtype A(H3N2) was 30.5% (-18.5, 59.2%) for children aged 2-17 yrs in the UK and 61.9% (52.7, 69.3%) against all influenza A subtypes for children aged 2-6 yrs in Finland. VE of IIV4 against all influenza A subtypes was 48.6% (30.7, 61.8%) for children aged 2-6 yrs in Finland and 23% (-3, 42%) and 29% (-7, 52%) against A(H1N1)pdm09 for children aged 6 months-8 yrs and 9-17 yrs, respectively, in the US. LAIV4 VE against influenza B was 80.3% (63.7, 89.3%) for children aged 2-6 yrs in Finland. VE of IIV4 against influenza B was 61.5% (21.7, 81.0%) for children aged 2-6 yrs in Finland and 39% (20, 54%) and 43% (23, 58%) against B/Victoria for children aged 6 months-8 yrs and 9-17 yrs, respectively, in the US. During the 2020/21 season there was insufficient influenza circulation to ascertain VE estimates.

Conclusion

VE estimates for LAIV and IIV have varied during recent seasons. Overall, VE for LAIV and IIV in children was moderate and generally comparable between vaccine types.

Poster Reception II

Victor Huber - AOXI0097

Evaluation of US expert opinion on the association between influenza vaccine effectiveness (VE) and egg-based manufacturing technology

Victor Huber[11], Lauren Angelo[6], David Canaday[1], Shirley Delair[10], Ngozi Ezike[4], Ravi Jhaveri[9], Chris Nyquist[2], Meera Varman[3], Renuga Vivekanandan[3], Radek Wojcek[5], Karita Ambrose[8], Abigail Sporer[8], Archana Chatterjee[7]

[1]Case Western, Cleveland, OH 44106, United States, [2]Children's Hospital, Colorado, Aurora, CO 80045, United States, [3]Creighton University, Omaha, USA, [4]Department of Public Health, Chicago Ave, Chicago, IL 60651, United States, [5]Medialis Ltd., UK, [6]Rosalind Franklin, North Chicago Illinois, USA, [7]Rosalind Franklin, North Chicago, Illinois, USA, [8]Seqirus, US, [9]University Feinberg School of Medicine, Northwestern, University Feinberg School of Medicine, Northwestern, [10]University of Nebraska Medical Center 982162 Nebraska Medical Center Omaha, Nebraska 68198-2162, [11]University of South Dakota Vermillion, SD 57069, United States

Background

BACKGROUND: Influenza is associated with a significant disease burden in the US. Vaccination has been recognized as the most successful strategy for reducing influenza-related disease burden, but mean influenza vaccine effectiveness (VE) over the last ten years has only been 35% for H3N2. This low effectiveness has been attributed to several factors, including egg adaptations. These mutations occur only when the virus is propagated in eggs, which may lead to genetic and antigenic dissimilarities impacting influenza VE. Despite newer technologies being available, egg-based influenza vaccines remain the most frequently used. The evidence of a relationship between egg-based manufacturing and influenza VE remains largely disassociated, except for two recent consensus studies with European experts. There is a need to expand the consensus by increasing the number of experts and their geographical diversification to strengthen the body of evidence on the topic.

Method

METHODS: Of 11 US influenza experts recruited, 10 participated, doubling the number from the previous EU consensus. The methodology followed the 2020 European consensus, where the research question was broken down into antigenic drift, egg adaptations, and manufacturing component principles. The evidence for these principles was assessed by experts in a novel two-stage online study design to observe proportional group awareness and consensus. Evidence comprised references from updated 2020 systematic reviews along with references suggested by experts during the first stage, awareness round of this study. In the second stage, summaries of each reference were presented to experts, who rated the extent to which they agreed that it constituted support of its component principle on a 5-point Likert scale. In a final question, experts were asked whether they agreed that overall, the evidence supported a mechanistic basis for reduced influenza VE due to egg-based manufacturing.

Result

RESULTS: US experts agreed that all component principles had a majority of strong or very strong supporting evidence (52-86%), similar to European results (70-90%). As with European experts, US experts agreed that global surveillance, WHO candidate vaccine virus selection, and manufacturing stages involving eggs were the most likely to impact influenza VE. They agreed unanimously that there is a mechanistic basis for reduced influenza VE due to egg-based manufacturing.

Conclusion

CONCLUSION: There is now US and European expert agreement for the increased risk of reduced influenza VE resulting from egg-based manufacturing techniques. Increasing the use of non-egg-based manufacturing that avoids egg-adaptations is a currently available strategy that may improve influenza VE.

Poster Reception II

David Burbidge - AOXI0100

NA antigenic drift between H3N2 clades may have contributed to decreased vaccine effectiveness for the A/New Caledonia/71/2014 LAIV during the 2017-18 season.

David Burbidge[1], Jonathan Crowe[1], Oliver Dibben[1]

[1]AstraZeneca UK

Background

Influenza vaccine strain selection is predicated on haemagglutinin (HA) protein antigenicity. Relatively little is understood about the importance of neuraminidase (NA). The FluMist/Fluenz live attenuated influenza vaccine (LAIV) contained the same H3N2 component (A/New Caledonia/71/2014 - A/NC14) in both the 2016-17 and 2017-18 influenza seasons. A/NC14 demonstrated moderate vaccine effectiveness (VE) in the UK in 2016-17 but showed no significant VE in the UK in 2017/18. Here, we aimed to determine whether antigenic changes in the NA protein of circulating influenza viruses may have contributed to the reduction in VE in 2017-18.

Method

Changes in NA antigenicity between the 3c.2a and 3c.2a1 clades of H3N2 viruses were assessed. The 3c.2a clade (which includes A/NC14) was the predominantly circulating clade during the 2016-17 season, whilst the 3c.2a1 viruses were predominant in 2017-18. An enzyme-linked lectin assay (ELLA) was optimised for LAIV viruses using anti-NC14 ferret antisera, in order to determine differences in NA antigenicity between the two clades. Additionally, a cell-based NA neutralisation assay was developed to confirm that changes in inhibition of NA activity translated to differences in inhibition of virus replication in the presence of NC14-specific antibodies.

Result

By ELLA, it was found that anti-A/NC14 ferret antisera gave significantly greater inhibition of NA proteins of viruses from the 3c.2a clade (2016-17) than from the 3c.2a1 clade (2017-18). All 3c.2a1 viruses tested showed at least a 3-fold reduction in inhibition, with most showing a >4-fold decrease. Furthermore, NA neutralisation assay data showed that 3c.2a virus replication in cell culture was significantly more inhibited than 3c.2a1 by anti-A/NC14 NA antibodies.

Conclusion

Taken together these data showed that NA antigenic drift between 2016-17 and 2017-18 circulating viruses significantly impacted NA-mediated virus neutralisation by anti-A/NC14 antisera. This may have contributed to the reduced A/NC14 VE in 2017-18. These novel findings could potentially be applied to the development of more antigenically matched and effective vaccine strains in future seasons.

Poster Reception II

Joshua Petrie - AOXI0091

Contributions of vaccination and infection to SARS-CoV-2 seroprevalence in a rural Wisconsin cohort from November 2020 to September 2021.

Joshua G. Petrie[4], David Pattinson[3], Jennifer P. King[1], Gariele Neumann[3], Lizheng Guan[3], Peter Jester[3], Fatimah S. Dawood[2], Carrie Reed[2], Melissa A. Rolfes[2], Edward A. Belongia[1], Yoshihiro Kawaoka[3], Huong Q. McLean[1]

[1]Center for Clinical Epidemiology & Population Health, Marshfield Clinic Research Institute, [2]Centers for Disease Control and Prevention, Influenza Division, [3]Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, [4]Marshfield Clinic Research Institute

Background

Quantifying population levels of SARS-CoV-2 antibodies is important for informing ongoing pandemic response and forecasting population risk of infection. We described the development of SARS-CoV-2 serum antibodies following infection and vaccination from November 2020 to September 2021 in the ongoing Prospective Assessment of COVID-19 in a Community (PACC) cohort in central Wisconsin.

Method

PACC participants of any age were randomly sampled from the larger community. Active illness surveillance was performed with SARS-CoV-2 identification by RT-PCR. Vaccination was determined from local and state registries. Blood was collected at enrollment (November 2020 - April 2021), and at 12 (January - June 2021) and 24 weeks (April - September 2021) after enrollment. All serum specimens were tested by ELISA against Spike (S) and S receptor binding domain (RBD) antigens. Prior to March 2021, only specimens from individuals with evidence of infection or S/RBD seropositivity were tested against nucleocapsid (N); from March 2021 onward, all collected specimens were tested against N. Seropositivity endpoints were determined for combined S/RBD, N alone, and combined S/RBD/N.

The monthly proportion of seropositive individuals was calculated by age group, vaccination (≥ 1 dose), and infection status. The overall monthly proportion of seropositive individuals was estimated using least-square mean predictions from age-adjusted generalized estimating equation logit models accounting for repeated measures.

Result

This analysis included 4,409 serum specimens from 1,520 individuals. At baseline through November 2020, 5% (95% CI: 3%, 8%) of the cohort was S/RBD/N seropositive with little variation by age. After vaccines became available in December 2020, S/RBD/N seropositivity steadily increased reaching 64% (95% CI: 58%, 69%) in June 2021 and plateauing thereafter. Monthly S/RBD-specific seropositivity tracked with vaccine uptake and increases by age tracked with age-specific vaccine availability. N-specific seropositivity was stable (range: 11%, 16%) from March to August 2021 when few infections were identified in the cohort. Among those S/RBD/N seropositive in August and September 2021 (69%), 14% were unvaccinated with prior infection, 8% were unvaccinated without documented prior infection, 13% were vaccinated with prior infection, and 65% were vaccinated without prior infection.

Conclusion

Approximately two-thirds of the cohort was seropositive by the fall of 2021, and vaccination was the primary driver of this high level of seropositivity. Additional blood specimens have been collected beginning February 2022 for assessment of the effects of SARS-CoV-2 Delta and Omicron infections, and booster vaccine doses on population immunity.

Poster Reception II

Michael Carlock - AOXI0062

A Computationally Optimized Broadly Reactive Hemagglutinin Elicits Neutralizing Antibodies Against Strains of Influenza B Viruses from Both Lineages

Michael Carlock[1], Ted Ross[2]

[1]University of Georgia, [2]University of Georgia; Case Western Reserve University; Cleveland Clinic

Background

Antigenic drift of influenza virus continues to plague the efficaciousness of seasonal influenza vaccines. Wild-type (WT) strains in vaccines produce antibodies specific for the circulating virus that was dominant at time of selection. Manufacturing and distribution of vaccines take months, and influenza continues to circulate and mutate during this time. Frequently, enough mutations accumulate that render these vaccine-induced antibodies non-neutralizing. This especially occurs with influenza A viruses, the leading cause of influenza infections, but also with influenza B viruses (IBV) which cause similar severe disease. The two IBV lineages, Victoria and Yamagata, have cocirculated since their divide in the late 1980s. The introduction of a quadrivalent influenza vaccine formulated with both lineages increased vaccine effectiveness against IBV infections, but it has continued to be extremely variable, ranging from 34-76% per the CDC. To combat these inconsistencies, we developed a computationally optimized broadly reactive antigen (COBRA) hemagglutinin (HA) for influenza B which elicits the production of antibodies with a broader specificity than wild-type strains.

Method

B-COBRA or WT HA antigens expressed on the surface of virus-like particles (VLPs) were used to vaccinate ferrets pre-immunized with influenza B virus. Three months post-infection with either a Victoria or Yamagata virus, ferrets were bled and then vaccinated a single time with VLPs. Four weeks post-vaccination, ferrets were bled again. Collected sera was tested in a hemagglutination-inhibition (HAI) assays to quantify antibody levels. Additionally, virus-neutralizing serum antibodies were detected using the focal-reduction assay (FRA).

Result

Pre-immune ferrets had high serum HAI titers (HAI >1:40) and neutralized strains from the same lineage, but there was low-to-no seroprotection or neutralization against viruses in the opposite lineage. Ferrets vaccinated with B-COBRA HA antigens generated higher overall antibody titers against a broad panel of IBV strains, including future strains, and were more effective in neutralizing virus. Moreover, B-COBRA HA vaccinated ferrets were able to overcome possible "antigenic sin" and produce cross-lineage, seroprotective antibodies.

Conclusion

Wild-type strains have a limited specificity, but B-COBRA HA antigens elicit more broadly reactive antibodies compared to seasonal influenza vaccines. Not only do B-COBRA HA antigens elicit protection against a wider array of co-circulating and future drifted strains, their cross-lineage nature could allow manufacturers the option of using this single HA protein instead of producing antigens for both lineages.

Poster Reception II

Delphine Guyon-Gellin - AOXI0108

HOW TO DRASTICALLY IMPROVE INFLUENZA PREVENTION? THE ADDITION OF A T-CELL COMPONENT TO INCREASE CURRENT VACCINE EFFICACY: PRECLINICAL AND EARLY CLINICAL RESULTS

Judith Del Campo[1], Jessika Tourneur[1], Paul Willems[1], Delphine Guyon-Gellin[1], Alexandre Le Vert[1], Florence Nicolas[1]

[1]Osivax

Background

While vaccines eliciting neutralizing antibodies against the Hemagglutinin (HA) are effective in preventing influenza in the absence of antigenic variations, cellular immunity to the well-conserved influenza Nucleoprotein (NP) is associated with broad-spectrum protection against influenza disease.

Combining these two types of responses (antibody and cellular) against two different antigens (HA and NP) would better mimic the immune responses generated by a natural infection and therefore is anticipated to confer higher and broader protection against flu.

OVX836 is an unadjuvanted recombinant vaccine composed of the NP sequence of Influenza A virus fused to Oligodom®, OSIVAX's proprietary self-assembling nanoparticle technology. We have previously shown that OVX836 alone is safe, immunogenic and protective in both mice, ferrets and humans. Here, we evaluate the co-administration of OVX836 with conventional quadrivalent seasonal influenza vaccine (QIV).

Method

Concomitant injections of OVX836 and QIV intramuscularly.

Preclinical development: mice immunogenicity and challenge studies

Clinical trial (ongoing): randomized, double-blind, controlled Phase 2a trial evaluating immunogenicity and safety of the co-administration of OVX836 & QIV compared to QIV.

Result

Mice immunogenicity: NP-specific T-cell response levels similar after immunization with OVX836 or OVX836+QIV, while being significantly superior to either placebo or QIV. HAI response levels similar after immunization with QIV or OVX836+QIV while being significantly superior to either placebo or OVX836.

Mice efficacy: Vaccination with OVX836 concomitantly with QIV induced better protection than QIV alone against lethal challenges with influenza A strains, as evidenced by significantly lower lung viral loads 4 days post-infection. This observation was repeated with three different matched and mismatched challenge A-strains when comparing OVX836+QIV vs. QIV: A/Victoria/1975 H3N2, $p = 0.0001$, A/WSN/1933 H1N1, $p = 0.0001$ A/California/2009 H1N1, $p = 0.0001$.

Human clinical trial: Recruitment is ongoing for a Phase 2a trial evaluating the concomitant administration of OVX836 with QIV. Safety outcomes will be available by the time of the congress.

Conclusion

In preclinical models, co-administration of OVX836 and QIV was found safe with no immune-interference observed between the two vaccines and induces better protection than QIV alone against lethal challenges with three different A-strains. OVX836 and QIV are being tested in co-administration in a phase 2a clinical trial for which safety results will be available by the time of the congress.

Poster Reception II

Marten Heeringa - AOXI0025

Comparability of antibody titers against seasonal influenza vaccine strains using cell- and egg derived target viruses in hemagglutination inhibition assays

Marten Heeringa[1], Deborah Molrine[1], Matthew Hohenboken[1], Vince Matassa[1]

[1]Seqirus

Background

Influenza vaccines manufactured with cell-based technology provide a close match to the hemagglutinin of WHO-selected strains, whereas egg-based production may result in antigenic changes to the hemagglutinin of vaccine viruses due to egg-adaptation. For clinical trials assessing the immunogenicity of influenza vaccines, the target virus selected for hemagglutination inhibition (HI) assays may affect antibody titer results. We conducted post-hoc analyses on post-vaccination immunogenicity data from a recently completed pediatric study to compare cell- and egg derived target virus HI titers in a pairwise manner across 4 vaccine strains within two vaccine groups.

Method

Performance characteristics of assays using cell- and egg-derived target viruses for each of the 4 vaccine strains were evaluated with Deming regression, Lin's agreement statistics and Bland-Altman plots. For Deming regression, slope and intercept estimates and their two-sided 95% confidence intervals and scatter plots of derived log-transformed titers were determined. Lin's agreement statistics were computed to generate the concordance correlation coefficient, precision and accuracy parameter estimates. Bland-Altman plots were generated to describe the comparability between titers obtained with cell- and egg-derived target virus assays for each vaccine by constructing the limits of agreement.

Result

Deming regression analysis showed that the point estimates for slopes of the regression line comparing titers measured in cell- and egg-derived target virus assays were generally close to 1 for each vaccine strain, consistent with a strong positive linear relationship. Bland-Altman plots indicated a very small percentage of results outside the 95% limits of agreement. The direction and magnitude of the mean differences between cell- and egg-derived target virus data were generally similar across strains. Lin's concordance correlation coefficient ranged from 0.63 to 0.89. The precision component (Pearson's correlation coefficient) was 0.67 to 0.91. The accuracy coefficient was 0.93 to 1.00 across strains, which indicates the best-fit line locates relatively close to the 45° line through the origin.

Conclusion

Statistical comparative analyses of vaccine antibody titers measured in hemagglutination inhibition assays demonstrate an overall strong positive correlation between cell-derived and egg-derived target virus data but not concordance.

Poster Reception II

Min Levine - AOXI0041

Multiple Factors impact Antibody Responses to A(H3N2) viruses Following Influenza Vaccination

Min Levine[1], Feng Liu[2], F Liaini Gross[2], Stacie Jefferson[2], Crystal Holiday[2], Yaohui Bai[2], Terrence Tumpey[2]

[1]Influenza Division, Centers for Disease Control and Prevention, [2]Influenza Division, Centers for Disease Control and Prevention. Atlanta, Georgia, USA.

Background

Influenza vaccine effectiveness (VE) can vary by season, subtypes, and age groups. A(H3N2) has the most variable and often the lowest VE compared to other subtypes. To improve VE and identify more effective vaccination strategies especially for high risk populations, it is imperative to gain better understanding of the underling immune mechanisms that can affect influenza vaccine immunogenicity and VE.

Method

We conducted a comprehensive analysis of vaccination sera collected from recent influenza seasons (2016-2022) in the United States, across all vaccine eligible age groups (children 6 mon-17 yrs, adults 18-65 yrs and elderly > 65 yrs), from persons who received egg-based, cell-based and recombinant vaccines. We analyzed neutralizing antibody responses to vaccine and circulating viruses pre- and post- vaccination.

Result

Decreased VE can occur when predominantly circulating viruses were antigenically drifted from the vaccine viruses. Due to the widespread circulation of 3C.2a viruses, several 3C.2a virus strains have been chosen as A(H3N2) vaccine components in recent seasons. Compared to wild type viruses, egg-based 3C. 2a vaccine viruses have an egg-adapted change at T160K in the hemagglutinin (HA), causing a loss of glycosylation in antigenic site B. In seasons with 3C.2a strains as the A(H3N2) vaccine component, antibody responses to cell- compared to egg-propagated vaccine viruses were significantly reduced due to egg-adapted changes following vaccination with egg-based vaccines, whereas the reduction was less pronounced following vaccination with cell-based and recombinant vaccines. Furthermore, vaccine egg-adaptation had differential impact on antibody responses across different age groups, in part, due to diverse host immune priming histories. In pediatrics, immunologically naïve children vaccinated with egg-adapted vaccines mostly mounted antibodies targeting egg-adapted epitopes, whereas those previously primed with natural infection mounted broader antibody responses to circulating viruses even when vaccinated with egg-based vaccines. In elderly, repeated boost of vaccine egg-adapted epitopes significantly reduced antibody responses to the wild type viruses. Lastly, despite the antigenic differences, current season vaccination can back boost antibody responses to previous season vaccine viruses, providing increased breath of antibody responses that can be beneficial in seasons when viruses from both new and old antigenic clusters co-circulate.

Conclusion

Multiple factors, and compounding effect of several factors can impact the immunogenicity of influenza vaccines against circulating A(H3N2) viruses.

Poster Reception II

Yingxia Wen - AOXI0047

Influenza self-amplifying vaccines encoding influenza internal proteins raise robust both cellular immune responses

Yingxia Wen[1], Evan Rossignol[1], Cheng Chang[1], Giuseppe Palladino[1]

[1]Seqirus

Background

Seasonal vaccination with influenza viral surface glycoproteins hemagglutinin (HA) or combinations of HA and neuraminidase (NA) is an effective means of reducing the incidence and severity of influenza infection. However, protection is incomplete in part due to mismatches between vaccine and circulating strains. One strategy for more complete protection is the addition of highly conserved influenza internal proteins as influenza vaccine antigens. Here we present our platform that is based on the next-generation of mRNA vaccine, self-amplifying mRNA, which is capable of durable antigen expression at low doses. Specifically, we characterize the immunogenicity of sa-mRNA that encode internal flu proteins NP and M1, alone or in combination with bicistronic HA-NA vaccines.

Method

We immunized BALB/c mice with two doses three weeks apart with various sa-mRNA constructs encoding M1, NP, or M1-NP together from influenza A or B. Additionally, we compare immunogenicity of tricistronic HA-NA-M1 or HA-NA-NP vaccines to the immunization strategy of bivalent vaccines composed of bicistronic HA-NA and M1-NP together. Serological responses against both HA and NA were assessed by ELISA, hemagglutination inhibition, NA inhibition, and virus microneutralization. Cell-mediated immune responses were measured by intracellular cytokine staining in response to HA, NA, NP, or M1 antigens.

Result

We show that immunization with sa-mRNA encoding influenza internal proteins NP and M1 generates robust both CD4+ and CD8+ cellular immune responses to these internal proteins when administered alone or co-administered with a HA-NA vaccine. Importantly, when internal protein vaccines were administered with HA-NA vaccines, we do not observe diminished serological responses to HA and NA.

Conclusion

Next generation sa-mRNA vaccines present an opportunity for the addition of internal protein antigens NP or M1 to HA-NA vaccine strategies to increase the antigenic breadth of seasonal influenza vaccines.

Poster Reception II

Mark Thompson - AOXI0060

Comparison of the Immunogenicity of Egg-Grown Inactivated Influenza Vaccine and Recombinant-Hemagglutinin Influenza Vaccine among Infrequently and Frequently Vaccinated Healthcare Personnel: A Randomized Open-Label Trial in Israel

Mark Thompson[2], David Greenberg[6], Alon Peretz[5], Ashley Fowlkes[3], Avital Hirsch[4], Mark Katz[4], Laura Edwards[1], Arnold Monto[7], Gabriella Newes-Adeyi[1], Min Levine[3], Eduardo Azziz-Baumgartner[3], Emily Martin[7], Ran Balicer[4]

[1]Abt Associates Inc, Atlanta, GA, USA, [2]Centers for Disease Control and Prevention, [3]Centers for Disease Control and Prevention (CDC), Atlanta, USA, [4]Clalit Research Institute, Tel Aviv, Israel, [5]Clalit Research Institute, Tel Aviv, Israel; Rabin Medical Center, Petah Tikva, Israel, [6]Soroka University Medical Center, Ben Gurion University of the Negev, Beer-Sheva, Israel, [7]University of Michigan, Detroit, MI, USA

Background

Influenza vaccine effectiveness (VE) in preventing influenza illness was low in a prospective cohort of healthcare personnel (HCP) in Israel. VE was particularly low against A(H3N2), which might be due to egg adaptations in A(H3N2) vaccine strains or poorer immunogenicity in repeated vaccinees. We conducted a randomized trial among HCP in Israel to compare humoral immune responses of two northern hemisphere 2019-2020 influenza vaccines: a quadrivalent egg-grown inactivated influenza vaccine (IIV4; Vaxigrip) to a recombinant hemagglutinin-protein quadrivalent influenza vaccine (RIV4; FluBlok).

Method

Participants were randomly allocated (October 2019 to January 2020) to receive either IIV4 or RIV4 during weeks when both vaccines were available; during weeks when RIV4 was not available, participants received IIV4. Sera collected 1-month after vaccination were tested by hemagglutination inhibition (HI) for egg-propagated A(H1N1), egg-propagated A(H3N2), and cell-propagated A(H3N2) from the vaccine strains.

Result

The 366 participants who received IIV4 did not differ from the 207 RIV4 recipients in socio-demographic or health characteristics. At 1-month post-vaccination, RIV4 elicited higher geometric mean titer (GMT) and mean-fold rise in GMT (MFR) in HI than IIV4 against A(H1N1) and both egg- and cell-propagated A(H3N2). The post-vaccination GMTs of RIV4 recipients were significantly higher than IIV4 recipients by 2.1-fold for A(H1N1), 1.4-fold for egg-propagated A(H3N2), and 2.2-fold for cell-propagated A(H3N2) (p-values < 0.0001). A significantly higher percentage of RIV4 recipients (66%) achieved very high titers (≥160) against cell-propagated A(H3N2) compared with IIV4 recipients (33%; p < 0.0001). These trends were noted among both infrequently vaccinated HCP (23% vaccinated in 0-2 of the previous 5 years) and frequently vaccinated HCP (67% vaccinated 3-5 of the previous 5 seasons).

Conclusion

RIV4 had improved immunogenicity against A(H1N1) and A(H3N2) vaccine strains and among both infrequent and frequent vaccinees. RIV4 elicited a particularly high antibody response to the cell-propagated A(H3N2) strain which was most like the circulating strain during that season. Findings are placed in the broader context of efforts to optimize the benefits from seasonal influenza vaccines to healthcare personnel.

Poster Reception II

Hannah Stacey - AOXI0067

Investigating the influence of influenza vaccine formulation on original antigenic sin responses in a longitudinal cohort of children

Hannah Stacey[2], Ali Zhang[2], Jann Ang[2], Pardeep Singh[1], Mark Loeb[1], Matthew Miller[2]

[1]Michael G. DeGroote Institute for Infectious Disease Research; Health Research Methodology, Evidence, and Impact; Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada, [2]Michael G. DeGroote Institute for Infectious Disease Research; McMaster Immunology Research Centre; Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON, Canada

Background

Influenza virus infection results in 3-5 million serious illnesses each year, with children representing a significant proportion of those affected. Several seasonal influenza vaccines are available, including inactivated influenza vaccines (IIVs), live-attenuated influenza vaccines (LAIVs), and adjuvanted inactivated influenza vaccines (AIIVs). These vaccines primarily elicit antibodies against the variable hemagglutinin (HA) head domain. However, "universal" vaccines that stimulate broadly-neutralizing antibodies (bnAbs) are in development. Seasonal vaccine effectiveness (VE) varies greatly from year-to-year, and this variability has, in-part, been proposed to be a consequence of 'Original Antigenic Sin' (OAS). OAS describes a phenomenon wherein the first exposure to influenza virus shapes subsequent immune responses to vaccinations or infections. Antibody titers against the first strain an individual is exposed to are boosted through repeated exposure to antigenically related strains. In the context of seasonal vaccination, OAS boosts antibodies against conserved, but non-neutralizing epitopes. Thus, OAS may be detrimental during seasonal vaccination but may prove to be beneficial when targeting conserved epitopes such as the HA stalk. While the serological consequences of OAS have been well-established, no studies have directly examined the impact of OAS antibodies on VE or the impact of vaccine formulation on OAS. This question is especially important in the context of childhood vaccinations, since children are a high-risk group for serious influenza virus infections and are often naïve to influenza virus prior to vaccination.

Method

Two cluster-randomized control trials longitudinally followed Hutterite children in three consecutive influenza seasons. The first compared LAIV and IIV between 2012-2015, the second AIIV and IIV between 2016-2019. A subset of pre- and post- vaccination serum samples were tested by hemagglutination inhibition and antibody dependent cellular cytotoxicity assays to measure vaccine strain specific and bnAbs, respectively.

Result

OAS-like responses were observed following successive vaccination in both trials, with IIV causing the most profound OAS. AIIV overcame OAS, particularly in response to H3 vaccine components, and induced the strongest bnAb response in children. Interestingly, bnAbs were induced following the first vaccine exposure, regardless of formulation, in children with no prior immune history to influenza.

Conclusion

These findings will help inform the selection of the most appropriate seasonal influenza vaccines for children, and the formulatons that may be most appropriate for "universal" influenza vaccines.

Poster Reception II

JUHO SONG - AOXI0074

Live Recombinant NDV vectored vaccine expressing the HA of H9N2 Avian influenza virus suppresses viral replications in chickens

JUHO SONG[1]

[1]KONKUK UNIVERSITY

Background

Due to extensive circulation in domestic poultry species in Eurasia, Eurasian H9N2 low pathogenic avian influenza virus(LPAIV) has further evolved into three distinct lineages: G1, Y280, and Korean. Korean lineage H9N2 LPAIVs, originally divided from Y439-like viruses, were localized, specifically in Korea (Youk et al., 2021). Recently, G57 genotype of Y280 lineage H9N2 viruses have been detected in Korea in 2020 (Youk et al., 2021). The introduction and country-wide spread of Y280-lineage H9N2 viruses calls for new vaccine effort with updated vaccines strain that matches the antigenicity of currently circulating viruses. Avian influenza virus (AIV) causes severe to mild disease in various poultry species. H9N2 LPAIV infections in poultry causes decrease in egg production, morbidity, and mortality when combined with secondary bacterial infections.

Method

1. Prepare Cells and viruses
2. Construction of K148 clone containing Hemagglutinin gene of H9N2 Y280 lineage
3. Virus rescue and propagation
4. Viral purification and Western blotting
5. Viral growth properties
6. Experimental design
7. Serological analysis
9. Statistical Analysis

Result

Generation of rK148/Y280-HA virus : The plasmid encodes the full genome of K148 and HA gene of N20-132 was successfully constructed as described in figure 1A. The rescue of rK148/Y280-HA was verified by hemagglutination assay. After three consecutive passages in 9-11 days old SPF embryonated chicken eggs, viral genome was extracted for HA sequence analysis. No mutations were observed in the HA sequence of rK148/Y280-HA.

Conclusion

Recent introduction of Y280-lineage H9N2 avian influenza virus into Korean poultry industry have rendered the current vaccine regimen ineffective(Kye et al., 2021). The vaccine currently used in Korea does not antigenically match the Y280-lineage H9N2 avian influenza viruses responsible for recent outbreaks. Although Korean-lineage H9N2 viruses have been successfully controlled using inactivated oil-adjuvanted vaccine, newly introduced Y280-lineage H9N2 viruses have rapidly spread throughout the country, causing outbreaks in all corners of the poultry industry in Korea(Youk et al., 2021). Transitioning of vaccine regimen to using only Y280-lineage H9N2 antigen would be premature as there is limited evidence to prove complete eradication of Korean-lineage H9N2 in Korea. In this study we generated recombinant NDV K148 vaccine candidate expressing Y280 lineage H9 hemagglutinin (HA) for the protection against both NDV and H9N2 AIV while accounting for the need to continue vaccinating for Korean-lineage H9N2. Implementation of rK148/Y280-HA will allow for vaccination and protection for antigenically Y280-lineage H9N2 avian influenza virus outbreaks in chickens.

Poster Reception II

Hitoshi Takahashi - AOXI0095

Production of cell-cultured seasonal influenza vaccine viruses with genetic stability and maintained antigenicity

Hitoshi Takahashi[1], Seiichiro Fujisaki[1], Hideka Miura[1], Itsuki Hamamoto[1], Mina Nakauchi[1], Eri Nobusawa[1], Hideki Hasegawa[1]

[1]National Institute of Infectious Diseases

Background

Seasonal influenza vaccines are commonly produced with embryonated chicken eggs around the world. Recently, the antigenicity of egg-cultured vaccine viruses has deviated from that of circulating influenza viruses due to egg-adapted mutations in the vaccine viruses. To avoid this deleterious effect on vaccine antigenicity, the possibility of using a cell-based vaccine as a seasonal influenza vaccine has recently been considered. We are also conducting the feasibility study for introduction of cell-based vaccine in Japan. However, it has been confirmed that some vaccine viruses have acquired mutations that may affect their antigenicity in the process of producing cell-cultured vaccine viruses. In this study, we investigated the production of cell-cultured vaccine viruses with genetic stability and maintained antigenicity by regulating the virus infection to cellular receptors.

Method

The HAs of influenza viruses bind to glycans that end with sialic acid (Sia) linked to galactose by α-2,3 or α-2,6-linkages. Previous studies have shown that enhancing human influenza virus infection to α-2,6-sialoglycans on cultured cells is important for viral genetic stability. We attempted to enhance virus infection to α-2,6-sialoglycans by blocking α-2,3-sialoglycans using lectins or antibodies specific for α-2,3 Sia. Qualified MDCK cells (NIID-MDCK) developed by NIID were used, and the expression of α-2,3 or α-2,6-sialoglycans on the cell surface was examined. Lectins specific for α-2,3 Sia were added to NIID-MDCK cells to evaluate binding activity and cytotoxicity. NIID-MDCK cells with lectins specific for α-2,3 Sia were infected with A/H3N2 viruses, viral titers in the supernatant were measured and changes in HA and NA amino acid sequences were confirmed.

Result

Both α-2,3 and α-2,6-sialoglycans were expressed on the NIID-MDCK cell surface. The binding activity of lectins specific for α-2,3 Sia to NIID-MDCK cells increased in a dose-dependent manner, while a slight cytotoxicity was observed with high-dose lectin. Infectious titer of A/H3N2 viruses passaged in NIID-MDCK cells supplemented withα-2,3 Sia specific lectin was confirmed, and several HA amino acid mutations in these viruses were suppressed.

Conclusion

This study suggests that it is possible to produce cell-cultured vaccine viruses with genetic stability by enhancing virus infection to α-2,6-sialoglycans using α-2,3 Sia specific lectin. We plan to further investigate using α-2,3 Sia specific antibodies for cell-cultured vaccine viruses production, and to examine the genetic stability and maintained antigenicity of produced these vaccine viruses.

Poster Reception II

Vivek Shinde - AOXI0102

Long term durability of antigen-specific polyfunctional CD4 T-cell responses against vaccine-homologous and antigenically drifted viruses: Results of a Phase 3 Trial of a Recombinant Quadrivalent Hemagglutinin Saponin-adjuvanted Nanoparticle Influenza Vaccine in Older Adults

Vivek Shinde[1], Haixia Zhou[1], Wayne Woo[1], Joyce Plested[1], Tim Vincent[1], Bin Zhou[1], Mingzhu Zhu[1], Chuan-Feng Shih[1], Shane Cloney-Clark[1], Rongman Cai[1], Gary Albert[1], Michael Massare[1], Lou Fries[1], Gale Smith[1], Iksung Cho[1], Greg Glenn[1]

[1]Novavax, Inc.

Background

There is an urgent public health need for more effective seasonal influenza vaccines. We developed a recombinant quadrivalent hemagglutinin saponin-adjuvanted (Matrix-M) nanoparticle influenza vaccine (qNIV; NanoFlu), and recently reported results of a phase 3 trial, wherein qNIV demonstrated immunologic non-inferiority to an egg-derived quadrivalent inactivated influenza vaccine (IIV4; Fluzone Quadrivalent) and showed improved cross-reactive HAI and neutralizing against antigenically drifted A(H3N2) and B viruses. qNIV also induced potent post-vaccination (Day 7) polyfunctional antigen-specific effector CD4+ T-cell responses, which were 126-189% higher compared to IIV4. We now report on long term durability of post-vaccination antigenic-specific polyfunctional CD4+ T-cell responses.

Method

In this phase 3 trial, we randomized 2652 participants aged ≥65 years 1:1 to receive a single intramuscular dose of qNIV or IIV4, and assessed, in a subset of 32 participants, pre- and post-vaccination (Days 0, 7, 28, 364) antigen-specific polyfunctional effector memory and total CD4+ T-cell responses against vaccine-homologous A/H3N2 (A/Kansas) and B-Victoria (B/Maryland) strains; and against antigenically drifted A/H3N2 (A/Cambodia) and A/H1N1 (A/Wisconsin) strains. Cytokine/activation markers γ-interferon, TNF-α, IL-2, and CD40L were assessed by intracellular cytokine staining.

Result

qNIV induced substantial post-vaccination triple-cytokine/activation marker staining total CD4+ T cell responses which peaked at Day 7, remained elevated at Day 28, and persisted above baseline one year after vaccination, whereas by contrast, corresponding responses elicited by IIV4 increased minimally at Day 7, and generally returned to baseline by Day 28 and persisted at baseline through Day 364.

Post-vaccination Day 7, 28, and 364 triple-cytokine/activation marker staining total CD4+ T cell responses induced by qNIV were higher than IIV4 for A/Kansas (qNIV to IIV4 ratio of geometric mean counts [GMCR] at successive timepoints: 3.38, 2.60, and 1.66 fold higher); for B/Maryland (GMCR: 5.06, 3.07, 2.08 fold higher); for A/Cambodia (GMCR: 4.84, 3.14, 1.85 fold higher); for A/Wisconsin (GMCR: 4.90, 3.18, 1.96 higher). Corresponding double- and quadruple-cytokine/activation marker responses followed a similar pattern for each strain, as did double-, triple-, and quadruple- cytokine/marker for effector memory responses.

Conclusion

qNIV produced qualitatively and quantitatively enhanced long term polyfunctional CD4+ T-cell responses, which may help to improve the performance of seasonal influenza vaccines, especially in the older adult population.

Poster Reception II

Jennifer King - AOXI0026

Booster Dose of mRNA Vaccine Increased Protection Against SARS-CoV-2 Infection During Period of Omicron Circulation in A Rural Wisconsin Cohort

Jennifer King[2], Joshua Petrie[1], David McClure[1], Melissa Rolfes[4], Jennifer Meece[5], David Pattinson[3], Gabriele Neumann[3], Carrie Reed[4], Fatimah Dawood[4], Yoshihiro Kawaoka[3], Edward Belongia[1], Huong McLean[1]

[1]Center for Clinical Epidemiology & Population Health, Marshfield Clinic Research Institute, [2]Center for Clinical Epidemiology and Population Health, Marshfield Clinic Research Foundation, [3]Department of Pathobiological Sciences, School of Veterinary Medicine, University of Madison-Wisconsin, [4]Influenza Division, Centers for Disease Control and Prevention, [5]Integrated Research & Development Laboratory, Marshfield Clinic Research Institute

Background

Evidence of waning of vaccine effectiveness (VE) of COVID-19 messenger RNA (mRNA) vaccines emerged in summer 2021 after initially high VE. A booster dose was recommended for certain high-risk groups and gradually expanded to include all people aged ≥12 years in the US by January 2022. During a period of Omicron circulation, we estimated relative VE after receipt of mRNA booster dose versus a primary two-dose series in an ongoing community cohort study.

Method

This analysis used data collected from an ongoing prospective community cohort study assessing SARS-CoV-2 infection in rural central Wisconsin, US. Participants of all ages were randomly sampled from a defined cohort in which nearly all residents receive care from Marshfield Clinic Health System. Participants reported symptoms weekly and self-collected an anterior nasal swab when reporting one or more of the following: fever, cough, loss of smell or taste, sore throat, muscle/body aches, shortness of breath, or diarrhea. SARS-CoV-2 infection was defined as a positive RT-PCR result from a clinically collected nasopharyngeal or self-collected swab. This analysis included vaccinated persons aged ≥12 years who were booster dose eligible (≥5 months after completion of the primary series) during a period of high Omicron circulation in Wisconsin (12/20/2021-02/24/2022). We estimated relative VE of booster versus primary series using Cox proportional hazards models with time-varying vaccination status and age at vaccination. Primary series vaccinated person-time began 12/20/21 or ≥5 months after completion of the second dose, whichever was later, and ended at receipt of the third dose or end of study period. Booster dose vaccinated person-time began 12/20/2021 or ≥14 days after receipt of the third dose, whichever was later. Vaccination status was determined from local and state immunization registries and vaccination cards.

Result

Twenty-six percent (230/884) participants completed the primary series without boosting (median 223 days from 2nd dose to 12/20/2021), and 654 (74%) received a booster dose by the end of follow-up (median 275 days from 2nd dose and 33 days from booster to 12/20/2021). There were 82 (9.3%) SARS-CoV-2 infections, 46 after the primary series and 36 after a booster dose. SARS-CoV-2 incidence was 9.6/10,000 person-days after the booster dose and 34.6/10,000 person-days after the primary series (relative VE: 66%, 95% CI: 46-79%). Results were similar when excluding immune compromised participants and those with prior infection.

Conclusion

A booster dose added significant protection against SARS-CoV-2 infection compared to waning protection ≥5 months from primary series during a period of widespread Omicron circulation.

Poster Reception II

Haruaki Nobori - AOXI0134

Pharmacokinetic parameters and pharmacodynamics of ensitrelvir (S-217622) in animal models of SARS-CoV-2 infection

Haruaki Nobori[1], Keita Fukao[1], Takayuki Kuroda[1], Kaoru Baba[2], Kazumi Matumoto[2], Masaaki Nakashima[1], Sayuri Noda[1], Shinpei Yoshida[1], Yukari Tanaka[1], Ryosuke Watari[1], Ryoko Oka[1], Yasuyuki Kasai[1], Takao Shishido[1], Teruhisa Kato[1]

[1]SHIONOGI & Co., Ltd., [2]Shionogi TechnoAdvance Research & Co., Ltd.

Background

Novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become the global public health concern. Ensitrelvir (S-217622), a small molecule 3CL protease inhibitor discovered by Hokkaido university and Shionogi, exhibited in vitro and in vivo efficacy against SARS-CoV-2 and is proceeding with global clinical trials. Here, we show pharmacokinetic (PK) parameters and in vivo antiviral activity of ensitrelvir against SARS-CoV-2 using mouse and hamster infection models.

Method

BALB/c mice or Syrian hamsters were infected with SARS-CoV-2 variants including gamma, delta, omicron, and mouse-adapted strains. From one day after infection, the mice or hamsters were orally treated with ensitrelvir. Viral titers in the lung of the animals at various time points were measured by TCID50 method using VeroE6/TMPRSS2 cells. The plasma concentrations of ensitrelvir were determined by High performance liquid chromatography with tandem mass spectrometry (LC-MS/MS). The relationship between PK parameters (Cmax, AUC0-48hr, C48hr, TimeHigh [total time above the target]) and anti-viral effect of ensitrelvir was evaluated 3 days after infection in mice.

Result

Oral administration of ensitrelvir from one day after infection reduced lung virus titer in mice and hamsters infected with SARS-CoV-2. In the PK/PD (pharmacodynamics) analysis of mice, the coefficients of determination of TimeHigh (10 × protein-adjusted EC50 [PA-EC50]), AUC0-48hr/PA-EC50, C48hr/PA-EC50, TimeHigh (5 × PA-EC50), and Cmax/PA-EC50 against virus titer reduction were 0.775, 0.735, 0.734, 0.647, and 0.311, respectively. In hamsters, the plasma concentration of ensitrelvir during treatment correlated with reduction of the lung virus titer.

Conclusion

The PK parameters associated with the sustained plasma concentration of ensitrelvir, TimeHigh and C48hr correlated well with reduction of lung virus titers in mice. It was suggested that maintaining plasma concentration of ensitrelvir was necessary for exerting antiviral activity throughout the administration period. Since ensitrelvir showed a low clearance and long elimination half-lives in clinical trial, it is expected that once-daily dosing of ensitrelvir shows antiviral activity in COVID-19 patients.

Poster Reception II

Masaaki Nakashima - AOXI0136

The antiviral activity of ensitrelvir (S-217622) against various SARS-CoV-2 strains

Masaaki Nakashima[1], Haruaki Nobori[1], Sho Kawashima[1], Kae Inoue[2], Takashi Hashimoto[2], Yoko Kajiwara[1], Shiori Takebayashi[1], Ryuichi Yano[1], Alice Yoshikawa[1], Yuki Maruyama[1], Miki Tanimura[1], Qianhui Zhang[1], Michiyo Kanazu[2], Hideko Kaneda[2], Shota Uehara[1], Yuki Matsui[1], Takumi Adachi[1], Yuji Morikawa[1], Masatomo Rokushima[1], Teruhisa Kato[1]

[1]Shionogi & Co., Ltd., [2]Shionogi TechnoAdvance Research & Co., Ltd.

Background

Novel coronavirus disease (COVID-19) has become a global public health concern. Since the first emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019, a number of mutant strains have been isolated all over the world. These SARS-CoV-2 mutants mainly contain amino acid substitutions in the spike protein, the target of SARS-CoV-2 vaccines, and some mutations have also been reported in nsp5, which encodes 3C-like protease (3CLpro), the target of ensitrelvir (S-217622). Here we show the inhibitory activity of ensitrelvir against these mutants in enzyme assay and antiviral assay using various cell lines.

Method

Prevalence of 3CLpro mutations were analyzed using the data of Global Initiative on Sharing All Influenza Data (GISAID, https://www.gisaid.org/). The inhibitory activities of ensitrelvir against mutant 3CLpros (G15S, T21I, L89F, K90R, P108S, and P132H) in enzyme assay were evaluated by monitoring the amounts of the substrate of 3CLpro and the cleavage product using mass spectrometry. In vitro antiviral activity of ensitrelvir against SARS-CoV-2 mutant strains (alpha, beta, gamma, delta, and omicron) was evaluated using VeroE6 cells expressed human transmembrane protease, serine 2 (VeroE6/TMPRSS2), or HEK293T cells expressing both human angiotensin-converting enzyme 2 (ACE2) and TMPRSS2 (HEK293T/ACE2-TMPRSS2), and human airway epithelial cells (hAEC).

Result

Ensitrelvir exhibited 3CLpro inhibitory activity against G15S, T21I, L89F, K90R, P108S, and P132H mutant at IC50 = 8.0 to 15.0 nmol/L (wild-type IC50 = 13.2 nmol/L). Ensitrelvir exhibited in vitro antiviral activity against SARS-CoV-2 Alpha, Beta, Gamma, Delta, and Omicron strains at EC50 = 0.29 to 0.50 μmol/L in VeroE6/TMPRSS2 cells and at EC50 = 0.026 to 0.064 μmol/L in HEK293T/ACE2-TMPRSS2 cells and against SARS-CoV-2 delta and omicron strains at EC90 = 0.0514 to 0.160 μmol/L in hAEC.

Conclusion

Ensitrelvir showed the comparable enzyme inhibitory activity against major 3CLpro mutants reported in GISAID and a comparable antiviral activity against mutant strains using various cell lines. As these data support the antiviral effect of ensitrelvir against previous major epidemic strains, we are expecting the ongoing Phase 3 clinical studies to likewise provide positive results on current epidemic strains.

Poster Reception II

Keita Fukao - AOXI0168

Ensitrelvir (S-217622), a small molecule inhibitor of 3C-like protease of SARS-CoV-2, reduced mortality, improved virus-induced lung inflammation and respiratory dysfunction in animal models.

Keita Fukao[1], Haruaki Nobori[1], Takayuki Kuroda[1], Naomi Anan[1], Kaoru Baba[2], Kazumi Matsumoto[2], Ryoichi Tashima[1], Minako Tajiri[1], Teruhisa Kato[1], Takao Shishido[1]

[1]SHIONOGI and CO., LTD., [2]Shionogi TechnoAdvance Research

Background

COVID-19 pandemic is major public health concerns worldwide, and currently, the treatment options are limited. Ensitrelvir (S-217622) is a novel orally available small molecule inhibitor of 3C-like (3CL) protease of SARS-CoV-2, an essential enzyme for viral replication. Ensitrelvir exhibits in vitro efficacy against various SARS-CoV-2 variants, including alpha, beta, gamma, delta, and omicron strains. In a randomized phase 2 study in Japan, ensitrelvir reduced both viral titer and RNA levels. In this study, we evaluated the effect of ensitrelvir on mortality, lung inflammation and the loss of respiratory function caused by SARS-CoV-2 infection in animal models.

Method

BALB/c mice or Syrian hamsters were inoculated with SARS-CoV-2 variants including delta, omicron and mouse-adapted strains. From day 1 after infection, the mice or hamsters were orally treated with various doses of ensitrelvir twice daily for 5 days. Survival and body weight of the animals were examined once daily. Lung histopathology, lung weight, cytokine/chemokine levels and respiratory function (SpO2) were evaluated as indicators of disease progression after infection. When the mice lost more than 20% of their body weight compared to their weight pre-infection of virus, they were euthanized and regarded as dead according to humane endpoints.

Result

Ensitrelvir significantly eliminated mortality and ameliorated body weight loss compared to vehicle in a dose-dependent manner. In addition, ensitrelvir also significantly reduced inflammatory cytokine/chemokine levels in the lungs, with an ameliorated lung weight increase due to infection. Furthermore, the severity of the infection-related pulmonary lesions was reduced in lung histopathological evaluation, leading to an improved respiratory function in ensitrelvir treated groups.

Conclusion

Oral dosing of ensitrelvir exhibited significant therapeutic efficacy against mortality, lung inflammation and respiratory dysfunction caused by SARS-CoV-2 infection in mice and hamsters. These results support potential benefit of ensitrelvir treatment for COVID-19 patients.

Poster Reception II

Ellesandra Noye - AOXI0140

Previous obesity increases the severity of influenza virus infection via the induction of innate immune training

Ellesandra Noye[6], Katina Hulme[6], Kevin Gillinder[1], Melanie Wu[6], Georgina McCallum[6], Samuel Brown[6], Marcus Tong[6], Conor Bloxham[5], Helle Bielefeldt-Ohmann[7], Nathalie Verzele[6], Jane Sinclair[6], Trinh Dang[1], Keng Yi Chew[6], Alexander Khromykh[7], Kate Schroder[2], David Burgner[4], Larisa Labzin[2], Siroon Bekkering[3], Kirsty Short[7]

[1]Diamantina Institute, The University of Queensland, Brisbane, Australia, [2]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia, [3]Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia;Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands., [4]Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia;Department of Paediatrics, University of Melbourne, Melbourne, Australia;Department of Paediatrics, Monash University, Melbourne, Australia, [5]School of Biomedical Sciences, The University of Queensland, Brisbane, Australia, [6]School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Australia, [7]School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Australia;Australian Infectious Diseases Research Centre, The University of Queensland, Brisbane, Australia

Background

Obesity increases the severity of influenza. It is unknown whether this susceptibility is reversed by weight loss and whether obesity has persistent deleterious effects on the immune response to influenza virus. This is particularly pertinent as recent data suggests obesity can epigenetically 'train' the innate immune system in an NLRP3-dependent manner, making it hyper-responsive to future immune stimuli. This may result in an exacerbated pro-inflammatory response and increased influenza severity, despite a history of weight loss.

Method

An in vivo model of previous obesity was established in C57BL/6 mice. Mice were given ad libitum access to either a high-fat or low-fat diet for 20-weeks, or they received 10 weeks of a high-fat diet followed by 10 weeks of a low-fat diet. After 10 weeks on low-fat diet, previously obese mice had an equivalent body weight and percentage body fat to 'lean' mice that received the low-fat diet only.

Result

Following intranasal inoculation with pH1N1, obese and previously obese mice had increased disease severity compared to lean mice, which was associated with an increased pro-inflammatory response. In NLRP3-deficient mice, obesity had no long-term effects on severity of influenza virus infection. To confirm enhanced severity in previously obese mice is associated with a 'trained' innate immune response, CD45+ (i.e. hematopoietic) lung and bone marrow cells were isolated from uninfected mice and stimulated ex vivo with viral mimetic R848, LPS and Pam3Cys. Following stimulation, bone marrow cells from previously obese mice exhibited enhanced proinflammatory cytokine responses relative to lean mice. This was accompanied by alterations in global chromatin expression of bone marrow cells, and changes in percentages of bone marrow myeloid progenitors. This innate immune 'training' may be related to disruption of tight-junction integrity (i.e. leaky gut) as a consequence of a high-fat diet, as 10 weeks of high-fat diet results in enhanced circulating LPS in these mice.

Conclusion

Obesity can have long-lasting effects on the innate immune response to IAV infection. This study provides evidence that a high-fat diet induces gut permeability and increased circulating LPS which. This may epigenetically reprogram innate immune cells towards a hyperinflammatory state (innate immune training). This may contribute to increased severity of IAV infection outcomes in previously obese mice. Understanding the immunological consequences of the obesity epidemic in humans is extremely important to improving outcomes to influenza and other pandemic viruses.

Poster Reception II

Aaron Frutos - AOXI0201

Timing of Influenza Virus Exposure in Early Childhood among Nicaraguan Children

Aaron M Frutos[2], Guillermina Kuan[5], Philip Meade[3], Lora Campredon[2], Sergio Ojeda[4], Roger Lopez[6], Nery Sanchez[5], Angel Balmaseda[1], Florian Krammer[3], Aubree Gordon[2]

[1]Centro de Salud Sócrates Flores Vivas, Ministry of Health, Managua, Nicaragua; Laboratorio Nacional de Virología, Centro Nacional de Diagnóstico y Referencia, Ministry of Health, Managua, Nicaragua, [2]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA, [3]Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, New York, USA, [4]Laboratorio Nacional de Virología, Centro Nacional de Diagnóstico y Referencia, Ministry of Health, Managua, Nicaragua, [5]Sustainable Sciences Institute, Managua, Nicaragua; Centro de Salud Sócrates Flores Vivas, Ministry of Health, Managua, Nicaragua, [6]Sustainable Sciences Institute, Managua, Nicaragua; Laboratorio Nacional de Virología, Centro Nacional de Diagnóstico y Referencia, Ministry of Health, Managua, Nicaragua

Background

Timing of first influenza virus exposures in young children remains poorly characterized despite the importance of early life exposures on immunity against the virus. We present influenza virus exposure timing based on symptomatic viral surveillance and serologically detected antibody response to influenza virus in young children from 2011-2019.

Method

Children enrolled before age three in the Nicaraguan Pediatric Influenza Cohort Study, a community-based, prospective study in Managua, Nicaragua, from 2011-2019 were included in this analysis. Respiratory samples were collected when participants presented with symptoms of respiratory illness. These samples were tested for influenza A and B virus using reverse transcriptase-polymerase chain reaction (PCR). Blood samples were collected annually from participants. The IgG antibody response to the hemagglutinin of 13 different virus strains, subtypes, and lineages (one pre-pandemic H1N1, four pandemic H1N1s, four H3N2s, two influenza B/Yamagata/16/88-like lineages, and two influenza B/Victoria/2/87-like lineages) were measured using an influenza virus protein microarray. To evaluate young children's immune response to influenza virus over time, we limited this analysis to samples collected after six months and before six years of age.

Result

904 participants provided 851 respiratory samples that were PCR+ for influenza A or B virus and 3,182 blood samples before age six. 795 participants had blood samples collected at age one. Before age two, 489 (62%) of these participants had a previous influenza A virus infection with 260 (33%) and 369 (46%) with H1N1pdm and H3N2 infections, respectively. 186 (23%) participants had a previous influenza B virus infection with 114 (14%) infections from the B/Victoria/2/87-like lineage, and 76 (10%) from the B/Yamagata/16/88-like lineage. 140 (18%) were previously infected with both influenza A and B virus. 249 (31%) showed no previous influenza virus infections.

Among 303 participants with samples collected at age 5, 295 (97%) had a previous influenza A virus infection, 233 (77%) from H1N1pdm, and 287 (95%) from H3N2. 122 (77%) participants had a previous influenza B virus infection with 108 (36%) from the B/Victoria/2/87-like lineage, and 165 (54%) from the B/Yamagata/16/88-like lineage. 229 (76%) previously had both influenza A and B virus infections. 4 (1%) participants with samples collected at age 5 had no detectable influenza virus infection before age six.

Conclusion

First influenza virus infections occurred for most children before age two. Prior influenza B virus infection was less common than influenza A virus infection, with a significant proportion of participants aged 0-6 years not having detectable influenza B virus antibodies.

Poster Reception II

Jill Ferdinands - AOXI0115

Efficacy and effectiveness of high-dose influenza vaccine compared with standard-dose influenza vaccine among older adults: A systematic review and meta-analysis

Jill Ferdinands[1], Lenee Blanton[1], Elif Alyanak[1], Jessie Chung[1], Rachel Holstein[1], Alicia Fry[1], Lisa Grohskopf[1]

[1]US Centers for Disease Control

Background

Seasonal influenza causes substantial morbidity and mortality in older adults. High-dose inactivated influenza vaccine (HD-IIV), with increased antigen compared to standard-dose influenza vaccines (SD-IIV), is licensed in the United States for use in people aged ≥65 years.

Method

We reviewed evidence of relative efficacy/effectiveness of HD-IIV vs. SD-IIV among adults aged ≥65 years for prevention of influenza-associated hospitalizations. We included randomized (RCT) and observational studies reporting comparative effectiveness of HD-IIV, indexed between January 1, 1990, to September 7, 2021, in MEDLINE, Embase, CINAHL, Scopus, The Cochrane Library, and ClinicalTrials.gov. Inverse variance meta-analysis was used to derive random-effects pooled effectiveness estimates. Results from randomized trials were reported as rate ratios; results from observational studies were reported as rate ratios, relative risks (RRs), or odds ratios (ORs) depending upon study design.

Result

Thirteen studies were identified through full-text review of 3,545 studies. All comparisons included trivalent HD-IIV (HD-IIV3) versus SD-IIV (trivalent and quadrivalent formulations). No RCTs were identified that used laboratory-confirmed influenza hospitalizations as a protocol-specified primary outcome. Among three estimates from three RCTs - one a secondary analysis of serious events (including hospitalizations) occurring in a large clinical trial that included influenza cases confirmed by unspecified testing done outside of study procedures, one a post-hoc analysis in which hospitalizations were reviewed by clinicians for likelihood of being secondary to influenza, and one a cluster-randomized trial examining pneumonia- and influenza-coded hospitalizations among nursing home patients - the pooled rate ratio was 0.81 (95% CI: 0.67, 0.97) favoring HD-IIV3. Eight retrospective cohort studies using diagnostic code defined outcomes contributed 39 estimates, with a pooled RR for influenza hospitalization of 0.91 (95% CI: 0.89, 0.93) favoring HD-IIV3. Two additional observational studies contributed three estimates, with a pooled OR for influenza hospitalization of 0.71 (95% CI: 0.57, 0.88) favoring HD-IIV3.

Conclusion

Evidence from three RCTs suggests benefit of HD-IIV3 versus SD-IIV for prevention of influenza hospitalizations among older adults, but outcome definitions varied substantially, and estimates were not derived from protocol-driven testing. Observational studies suggest that HD-IIV3 might be more effective than SD-IIV at reducing influenza hospitalizations, with HD-IIV3 associated with a 9% to 29% reduction in risk of hospitalization compared to SD-IIV.

Poster Reception II

Carlos Grijalva - AOXI0153

Effectiveness of influenza vaccines in preventing infections in households: a case-ascertained study

***Carlos Grijalva*[3], *Huong McLean*[2], *Yuwei Zhu*[4], *Ahra Kim*[4], *Natasha Halasa*[4], *Alexandra Mellis*[1], *Carrie Reed*[1], *Edward Belongia*[2], *Keipp Talbot*[4], *Melissa Rolfes*[1]**

[1]Centers for Disease Control and Prevention, [2]Marshfield Clinic Research Institute, [3]Vanderbilt University Medical Center, [4]VUMC

Background

While studies regularly assess the effectiveness of influenza vaccines for preventing illness warranting medical attention, few studies have evaluated their effectiveness in preventing influenza infections in households.

Method

A case-ascertained study was conducted in Tennessee and Wisconsin during 3 consecutive influenza seasons (2017-2018-2019-2020). Index patients with laboratory-confirmed influenza infection and their household members were recruited and enrolled within 7 days of the index patient's symptom onset. After enrollment, index patients and other household members completed symptom diaries and self-collected nasal swabs daily for 5 or 7 days. Vaccination status was determined based on the date of disease onset of the index patient; an individual was considered vaccinated if seasonal vaccination was received at least 14 days prior to the index patient's disease onset. The study was restricted to those eligible for influenza vaccination and excluded those who received vaccination less than 14 days prior to the index patient's disease onset. Influenza infections were confirmed through reverse transcription-polymerase chain reaction. The odds of laboratory-confirmed influenza infection were compared between vaccinated and unvaccinated household contacts. Vaccine effectiveness for prevention of infections among enrolled household members was estimated as 1-adjusted odds ratio of infection, using a multivariable logistic regression model for clustered household data that adjusted for age, sex, season, site and number of household members. Exploratory subgroup analyses by age group, season, and vaccination status of the index patient were conducted.

Result

A total of 1587 household members of 694 index patients were included. The median age for household contacts was 31 years (interquartile range: 10-41 years), 53% were female and 88% were white. Among these household members, 51% were vaccinated, and 24% had a laboratory-confirmed influenza infection during follow-up. The estimated vaccine effectiveness against laboratory-confirmed influenza infection among household contacts was 35% (95% CI: 15 - 50%). Subgroup analyses were generally consistent with the main vaccine effectiveness estimates, but some estimates had limited precision (Figure).

Conclusion

Influenza vaccination was associated with a reduced risk of laboratory-confirmed influenza infection among household members after infection was introduced into their households.

Poster Reception II

Carlos Grijalva - AOXI0156

Intensity and trajectory of symptoms among people with SARS-CoV-2 infections

Carlos Grijalva[9], Keipp Talbot[10], Jonathan Schmitz[10], Christopher Lindsell[10], Edwin Asturias[7], Rasika Behl[5], Edward Belongia[4], Natalie Bowman[8], Samuel Dominguez[7], Kate Ellingson[6], Hector Izurieta[3], Jessica Lin[8], Karen Lutrick[6], Yvonne Maldonado[5], Son McLaren[2], Huong McLean[4], Daniel Olson[7], Suchitra Rao[7], Lisa Saiman[2], Ellen Sano[2], Clea Sarnquist[5], Melissa Stockwell[2], Rosita Thiessen[5], Constance Ogokeh[1], Carrie Reed[1], Alexandra Mellis[1], Melissa Rolfes[1]

[1]Centers for Disease Control and Prevention, [2]Columbia University, [3]Food and Drug Administration, [4]Marshfield Clinic Research Institute, [5]Stanford University, [6]University of Arizona, [7]University of Colorado, [8]University of North Carolina, [9]Vanderbilt University Medical Center, [10]VUMC

Background

Few studies have longitudinally characterized the intensity and trajectories of symptoms of SARS-CoV-2 infections, and the potential role of vaccination in modulating those symptoms.

Method

The Respiratory Viral Transmission Network (RVTN)-Sentinel is an ongoing case-ascertained study conducted at 7 sites in the United States. After informed consent was obtained, index cases and their household members were enrolled. Participants completed symptom diaries and self-collected nasal swabs daily for 10 days. Vaccination received at least 2 weeks prior to the index case's symptom onset date defined vaccination status (fully vaccinated [2 or more doses] and unvaccinated; participants with only 1 dose were excluded). SARS-CoV-2 infection was detected using transcription-mediated amplification. Symptom intensity was standardized as the proportion of cumulative symptoms present on each day according to four domains: systemic (4 symptoms), upper respiratory (4), lower respiratory (4) and gastrointestinal (3). Daily median standardized proportions of symptoms were calculated starting on the date of symptoms onset by domain, overall and according to variant circulation period (pre-Omicron and Omicron, including all ages), vaccine eligible groups (children [5-17 years old] and adults) and vaccination status.

Result

Among 319 participants (from 102 households) with available test results, 207 had laboratory-confirmed SARS-CoV-2 infection and met our study selection criteria. The proportion of unvaccinated adult cases who remained asymptomatic was 0% (0/4) during the pre-Omicron and 15% (3/20) the Omicron period. In children, the proportions were 18% (3/17) and 18% (4/22), respectively. Symptom patterns for pre-Omicron (n=18) and Omicron (n=35) periods among unvaccinated symptomatic cases are displayed in Figure 1. Among children ages 5-17 years with at least one symptom reported (n=56), the median standardized proportions on their symptom onset date were 25%, 25%, 12.5% and 0% for systemic, upper respiratory, lower respiratory and gastrointestinal symptoms, respectively. The corresponding proportions for symptomatic adults (n=120) were 25%, 25%, 0%, 0%. Symptom trajectories by age groups and vaccination status are shown in Figure 2.

Conclusion

Preliminary findings from this ongoing study suggest important symptom variability among children and adults infected with SARS-CoV-2. Results on associations between vaccination status and symptoms intensity and trajectory will be updated as sample size increases.

Poster Reception II

Josephine Boxmeer - AOXI0121

A Prospective Cohort Study on Pregnancy Outcomes in Women Immunized with Seasonal Quadrivalent Influenza Vaccine (QIV) During Pregnancy

Chris Robinson[1], Janine Oberye[5], Josephine Boxmeer[5], Jessica Albano[8], Hugh Tilson[9], Anthony Scialli[3], John A. Vanchiere[2], Ellis Ides[4], Daphne Sawlwin[4], Matthew Hohenboken[6], Jonathan Edelman[7]

[1]Charleston Maternal Fetal Medicine, Summerville, SC; University of South Carolina, [2]LSU Health Science Center, Shreveport, LA, US, [3]Scialli Consulting LLC, Washington DC, US, [4]Seqirus Australia Pty Ltd, Parkville, VC, AU, [5]Seqirus Netherlands B.V., Amsterdam, NE, [6]Seqirus USA Inc., Cambridge, MA, US, [7]Seqirus USA Inc., Summit, NJ, US, [8]Syneos Health, US, [9]UNC Gillings School of Global Public Health, Chapel Hill, NC, US

Background

Influenza immunization rates in pregnancy remain below public health goals. This US based cohort study collected data on pregnancy outcomes and events of interest among women immunized with AFLURIA QUADRIVALENT® (QIV) during pregnancy, to compare to national data.

Method

The QIV pregnancy registry was a prospective observational cohort study conducted over four consecutive influenza seasons. Pregnant women were enrolled any time after routine vaccination with QIV, but prior to pregnancy outcome. Most women were enrolled via active recruitment strategies from obstetrical clinics that used QIV in their seasonal influenza vaccination campaigns during routine prenatal care; study data were provided after giving consent. Primary endpoints included preterm birth (PTB), low birthweight (LBW) and major congenital malformations (MCM). A teratologist/geneticist reviewed all reported malformations and classified them using the Center for Disease Control Metropolitan Atlanta Congenital Defects Program's (CDC MACDP) coding system and a Scientific Advisory Committee periodically reviewed data and recommended coding and classification of MCMs and other outcomes of interest.

Result

The study enrolled 494 women who had received QIV as part of routine care during four US influenza seasons (2017-2021). 483 women were evaluable and 1.4% were lost to follow-up. The study population was diverse and key risk groups for adverse pregnancy outcomes were represented. In this study, 98.8% of pregnancies resulted in live birth. The prevalence of PTB, LBW and MCM are shown in the table.

Conclusion

With no safety concerns demonstrated in this contemporary pregnancy registry and consistency with published safety data, the study data reassure that QIV may be safely used in pregnant women.

Poster Reception II

Marlies Ballegeer - AOXI0141

Can the M2 ectodomain (M2e) stabilize neuraminidase (NA) tetramers and broaden its immune protective potential?

Marlies Ballegeer[1], Mirte N. Pascha[2], Sarah Creytens[3], Kenny Roose[3], Cornelis A. M. De Haan[2], Xavier Saelens[3]

[1]Center for Medical Biotechnology, [2]Section Virology, Division Infectious Diseases & Immunology, Department of Biomolecular Health Sciences, Utrecht University, 3584 CL Utrecht, The Netherlands., [3]VIB-UGent Center for Medical Biotechnology, VIB, 9052 Ghent, Belgium;Department of Biochemistry and Microbiology, Ghent University, 9000 Ghent, Belgium

Background

The neuraminidase (NA) protein is a tetrameric type II membrane protein on the surface of influenza virions. Next to hemagglutinin (HA), NA also has immune-protective potential and anti-antibodies are a correlate of protection. When expressed in a soluble form, NA is unstable and dissociates into dimers and monomers which are less enzymatically active. Addition of a tetramerizing zipper such as the tetrabrachion (TB) from Staphylothermus marinus to the NA head domain stabilizes NA tetramers which are important for the induction of protective NA inhibitory antibodies. Here, we evaluate if M2e, the ectodomain of a type III homo-tetrameric membrane protein, can replace (in part or completely) a heterologous tetramerizing leucine zipper to generate stable, enzymatically active formats of N1 and N2 neuraminidase. In addition, we investigate whether addition of 2xM2e copies to an already stabilized TB-NA could broaden its protective potential since anti M2e antibodies are important for M2e-based immunity, can reduce virus replication and protect against challenge with any influenza A virus subtype.

Method

Different 2xM2e-N1 and N2 fusion proteins were produced in ExpiCHO cells and purified. NA activity, stability and tetramerization was studied. The stable and active proteins were adjuvanted with the Sigma adjuvant system (SAS) and used for vaccination of Balb/c mice. After a prime/boost regime, the mice were challenged with a homologous or heterologous influenza challenge. Mice sera was collected after the boost and used for ELISA and Neuraminidase Inhibition Assays (NAIs).

Result

2xM2e-NA fusions without stabilizing zipper were not enzymatically active and tetramers could not be purified. Addition of 2xM2e to already stabilized TB-NA did not drastically impact NA activity but the stability of NA tetramers was slightly improved. Prime followed by boost vaccinations with TB-NA or 2xM2e-TB NA induced similar high NAI titers. In a preliminary in vivo experiment, no difference in protection against homologous and heterologous challenge could be seen between TB-NA and 2xM2e-TB-NA vaccinated mice. The lack of broad protection could be explained by the fact that vaccination with 2xM2e-TB-NA did not result in high anti M2e antibody titers.

Conclusion

Unfortunately, addition of 2 copies of M2e could not replace a tetramerizing leucine zipper and stabilize NA tetramers. Preliminary in vivo data showed that the addition of 2xM2e copies to TB stabilized NA did not broaden the protective potential probably because the lack of protective anti-M2e antibodies. In the future, the role of cysteine residues and bridges in M2e will be further explored to stabilize NA without TB.

Poster Reception II

Sara Khaleeq - AOXI0159

Design, characterization, and immunogenic profile of Influenza HA stem nanoparticles

Sara Khaleeq[1], Uddipan Kar[2], Priyanka Garg[1], Madhuraj Bhat[3], Poorvi Reddy[3], Venkada Subramanian Vignesh[1], Aditya Upadhyaya[3], Mili Das[3], Ghadiyaram Chakshusmathi[3], Suman Pandey[3], Somnath Dutta[1], Raghavan Varadarajan[1]

[1]Indian Institute of Science, [2]Indian Institute of Science; Massachusetts Institute of Technology, [3]Mynvax Private Limited

Background

Current influenza vaccines show sub-optimal efficacy due to circulating and vaccine strain mismatch, arising from escape mutations in the globular head of the viral hemagglutinin (HA), with particularly calamitous consequences in outbreaks. To address this, universal vaccine candidates have been designed from the relatively conserved HA stem domain and have shown protective efficacy in animal models. Oligomerization of the antigens, through display on self-assembling nanoparticle scaffolds, can induce more potent immune responses compared to the corresponding monomeric antigen due to multivalent engagement of B-cells. However, most nanoparticle-based immunogens described to date use mammalian cell expression. A cost effective, universally neutralizing vaccine with rapid scalability in an epidemic/pandemic is urgently needed.

Method

We explored bacterially expressible, self-assembling proteins with a 3-fold axis of symmetry for spontaneous trimerization of a rationally designed stem antigen on the nanoparticle surface. Additionally, we displayed multiple monomeric HA stems on a 180-meric protein to compare immunogenicity between nanoparticles displaying trimeric versus monomeric stems. We also designed mammalian-expressed nanoparticle for comparison. We evaluated the nanoparticle assembly, thermal stability, and antigenic characteristics of the stem-nanoparticles. Protective efficacy of the nanoparticles was evaluated in mice and immunogenicity was also compared with a soluble trimeric version of the HA stem.

Result

We demonstrated bacterially expressed, differently sized particles displaying trimeric or monomeric copies of an H1N1 pdmCal09 derived HA stem. Designed antigens are purified to high yields and retain thermally stable epitopes in prefusion conformation. Both soluble trimer and nanoparticle displayed antigens confer protection against lethal dose of homologous and heterologous mouse adapted virus challenge. Nanoparticles confer a small yet statistically significant benefit over soluble trimer in homologous challenge, while offering similar heterologous protection. 180-mer particles afford equivalent protection to HA trimer displaying particles. Immunogenicity of the mammalian construct is being evaluated.

Conclusion

We expressed nanoparticle-displayed HA stem immunogens in bacteria. These immunogens are cheap and rapidly producible and elicit antibodies with CR6261 overlapping epitopes, that protect mice from homologous and heterologous challenge. We are currently evaluating protective efficacy of a low dose mammalian expressed nanoparticle to assess dose sparing advantage of nanoparticle vaccine platforms.

Poster Reception II

Daria Mezhenskaya - AOXI0172

Immunogenicity and cross-protection of universal live-attenuated influenza vaccine candidates expressing multiple M2e epitopes in preclinical ferret study

Daria Mezhenskaya[1], Irina Isakova-Sivak[1], Victoria Matyushenko[1], Svetlana Donina[1], Polina Prokopenko[1], Andrey Rekstin[1], Larisa Rudenko[1]

[1]Institute of Experimental Medicine, St.Petersburg

Background

The development of a universal influenza vaccine with a wide spectrum of protection and durability is a serious public health problem. Highly conserved extracellular domain of matrix 2 protein (M2e) is an attractive target for the induction of cross-protective immune response. We studied two recombinant live attenuated influenza vaccines (LAIVs) expressing additional four M2e-epitopes within HA (LAIV/HA+4M2e) or NS (LAIV/NS+4M2e) molecules in preclinical ferret study.

Method

Male ferrets were intranasally immunized with two doses of either LAIV/HA+4M2e or LAIV/NS+4M2e recombinant viruses, or with the H3N2 LAIV control virus. Shedding of the LAIV viruses was determined by titration of nasal wash samples collected during 4 days after each vaccination in eggs. Safety of vaccines was monitored by the clinical signs of infection during the course of immunization. Immune response was determined using a standard ELISA against H3N2 whole virus and against 3M2e recombinant protein. Cross-protective effect of the vaccines was assessed by infecting immunized ferrets with high dose of pandemic H1N1 virus. An indirect protection of immune sera was assessed in mice against a panel of PR8-based viruses encoding M genes of different origin.

Result

After first immunization all the LAIV-based viruses efficiently replicated in upper respiratory tracts of vaccinated ferrets, and there were no signs of viral shedding after the second dose. During the course of immunization no signs of disease were detected in any studied animal group. All LAIV immunized ferrets developed high levels of serum anti-H3N2 antibodies, whereas only recombinant vaccines induced significant level of anti-M2e IgGs with notable boost effect. It should be noted, that after immunization with LAIV/HA+4M2e anti-M2e IgGs were at significant level even after first immunization, when corresponding antibodies after LAIV/NS+4M2e vaccination could be detected only after second vaccine dose.

Level of induced anti-M2e IgGs correlated with demonstrated further level of protection against Ð/South Africa/3626/2013 (H1N1). Vaccinated with LAIV/HA+4M2e ferrets had lower viral shedding in respiratory tissues and demonstrated less symptoms of disease.

Further in vivo protection study also revealed advantage of M2e-based vaccines compared to unmodified LAIV.

Conclusion

LAIVs expressing four M2e tandem repeats within HA molecule demonstrated higher immunogenicity and protective effect compared to other studied LAIVs. Therefore, LAIV/HA+4M2e is the promising prototypes of universal influenza vaccine. Further investigation of mechanisms of protection afforded by M2e-specific antibodies is needed.

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Poster Reception II

Daniel Stadlbauer - AOXI0114

Preclinical development of seasonal influenza mRNA vaccine candidates

Daniel Stadlbauer[1], Angela Choi[1], Ling-Zhi Ma[1], Charis Palandjian[1], Angela Woods[1], Isabella Renzi[1], Patricia Jorquera[1], Christy Shaw[1], Sachin Mani[1], Andrea Carfi[1], Raffael Nachbagauer[1], Carole Henry[1]

[1]Moderna, Inc.

Background

Currently licensed seasonal influenza vaccines are either virus- or protein-based vaccines. The success of messenger RNA (mRNA) vaccines against coronavirus disease 2019 (COVID-19) has led to an acceleration of the development of mRNA-based vaccines targeting other infectious diseases. In the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mRNA vaccines have been shown to elicit potent humoral and cellular immune responses, including in older adults, a group that could substantially benefit also from improved influenza vaccines.

Method

We have developed novel lipid-encapsulated mRNA-based vaccine candidates that encode for the surface glycoproteins of seasonal influenza viruses. Mice and ferrets were intramuscularly immunized with 1 or 2 doses of our mRNA vaccine candidates. Animals were then challenged with live virus 3 weeks after the last vaccination. Serology was performed after vaccination and challenge. Weight loss and viral titers were assessed after challenge.

Result

Immunization of mice and ferrets with our mRNA vaccine candidates resulted in functional antibody responses after dose 1. Antibody responses were further boosted after a second dose in ferrets. Upon live virus challenge, animals that received the mRNA-based vaccines were protected.

Conclusion

In summary, we have generated preclinical proof-of-concept data that support further clinical development of mRNA-based seasonal influenza vaccine candidates.

Poster Reception II

Maryann Giel-Moloney - AOXI0117

Influenza QIV mRNA formulated in a LNP is highly immunogenic in the ferret model

Maryann Giel-Moloney[2], Svetlana Pougatcheva[2], Katherine Roebke[2], Bianca Baum[3], John Hamberger[2], Paul Stirba[3], Siré N'DIAYE[1], Aseem Pandey[2], Samuel Simons[2], Stephanie Pepin[2], Ana Goncalvez[2], William Warren[2], Tim Alefantis[2], Raul Gomila[2]

[1]IVIDATA, [2]Sanofi, [3]YOH Services LLC

Background

Influenza is a highly contagious, acute respiratory disease that affects all age groups and evidence suggests that flu also causes additional burden with health impacts including cardiovascular events and the exacerbation of chronic underlying conditions. Vaccination is the most effective strategy to protect against seasonal influenza infection and protecting beyond flu meaning preventing further complications. Current licensed vaccines protect individuals predominantly through the induction of protective antibody responses against the major viral surface glycoprotein, hemagglutinin (HA). The influenza virus regularly mutates through antigenic drift and requires seasonal vaccine composition updates to better match circulating strains annually in the northern and southern hemisphere. Current quadrivalent (QIV) influenza vaccines contain 2 type A strains (H1 and H3) and 2 type B strains (Yamagata and Victoria lineages).

Method

Sanofi is developing a promising alternative to the conventional vaccine platforms, a QIV influenza vaccine based on delivery of the HA antigens for H1, H3, B-Yamagata, and B-Victoria as modified messenger ribonucleic acid (mRNA) in a lipid nanoparticle (LNP). In addition to the humoral response induced by the in vivo expressed HA proteins, cellular responses as well as the LNP activating adjuvant-like immune signals may improve the overall vaccine effectiveness. In this study, the immunogenicity of a QIV mRNA formulated in a LNP was assessed in the naïve ferret model, which is a long-standing accepted animal model for influenza research and vaccine development. Humoral responses were evaluated after second immunization using the hemagglutination inhibition (HAI) assay for binding or microneutralization (mNT) assay for functional antibody responses.

Result

All ferrets immunized with QIV mRNA formulations elicited HA responses to all subtypes as measured by HAI and mNT. In addition, local reactogenicity at the injection site scored as mild and no adverse observations were observed for ferrets receiving different doses of the QIV mRNA formulations and overall were no different from control groups.

Conclusion

The observed responses in the naïve ferret model post two immunizations may not be representative of the responses expected in individuals that have already been exposed to influenza. To mimic the human population that has pre-existing immunity to flu, we have developed a ferret pre-immune model to all 4 subtypes and currently evaluating the QIV mRNA vaccine formulations as a single dose schedule. Overall, our immunogenicity study in the naïve ferret model has demonstrated that the QIV mRNA formulated in a LNP is a robust platform for the development of an alternative influenza seasonal vaccine.

Poster Reception II

Mahrukh Imran - AOXI0123

Real-world relative effectiveness of MF59-adjuvanted influenza vaccine vs. high-dose or vs. standard dose influenza vaccines to prevent hospitalizations in older adults during the 2019-2020 U.S. influenza season

Mahrukh Imran[3], Joan Puig-Barberà[1], Justin R. Ortiz[5], Lorena Lopez-Gonzalez[6], Alex Dean[6], Machaon Bonafede[6], Daniel Dudman[2], Mendel Haag[4]

[1]FISABIO, Valencia, ES, [2]Seqirus Inc., Cambridge, US, [3]Seqirus Inc., Kirkland, Quebec, CA, [4]Seqirus Netherlands B.V, Amsterdam, NL, [5]University of Maryland School of Medicine, Baltimore, MD, US, [6]Veradigm, US

Background

Vaccination with standard, egg-derived quadrivalent inactivated influenza vaccines (QIVe) is less effective in adults ≥65 years. Two vaccines were specifically developed to enhance protection in older adults: MF59-adjuvanted trivalent influenza vaccine (aTIV) and high-dose trivalent influenza vaccine (HD-TIV). This study estimated the relative vaccine effectiveness (rVE) of aTIV vs. HD-TIV or QIVe in preventing cardio-respiratory related hospitalizations, during the 2019-20 influenza season among adults ≥65 years in the United States.

Method

We conducted a retrospective cohort study using electronic medical records linked to pharmacy and medical claims data during the influenza season, defined as September 30, 2019 - March 7, 2020. Since influenza is associated with adverse cardiovascular-respiratory events, the outcomes evaluated were cardio-respiratory-related hospitalizations and respiratory-related hospitalizations, and specifically influenza-related and pneumonia-related hospitalizations as well as hospitalizations related to myocardial infarction and ischemic stroke. Outcomes were defined as a diagnosis in any position of the claim and separately in the first position (regardless of the diagnoses in the subsequent positions). A doubly robust, inverse probability of treatment weighting methodology was used to obtain odds ratios (ORs) adjusted for age, sex, race, ethnicity, geographic region, vaccination week, health status, frailty, and healthcare resource utilization. rVE was determined using the formula (1-ORadjusted)*100.

Result

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

Conclusion

The results from this large real-world study demonstrated the benefit of aTIV over QIVe or HD-TIV for the prevention of cardio-respiratory related hospitalizations during the 2019-20 season, including influenza-related hospitalizations.

Poster Reception II

Mahrukh Imran - AOXI0124

Real-world relative effectiveness of cell-based quadrivalent influenza vaccine vs. egg-based quadrivalent influenza vaccine to prevent hospitalizations in adults 18-64 years of age during the 2019-2020 U.S. influenza season

Mahrukh Imran[3], Joan Juan Puig-Barberà[1], Justin R. Ortiz[5], Lorena Lopez-Gonzalez[6], Alex Dean[6], Machaon Bonafede[7], Daniel Dudman[2], Mendel Haag[4]

[1]FISABIO, Valencia, ES, [2]Seqirus Inc., Cambridge, US, [3]Seqirus Inc., Kirkland, Quebec, CA, [4]Seqirus Netherlands B.V, Amsterdam, NL, [5]University of Maryland School of Medicine, Baltimore, MD, US, [6]Veradigm, US, [7]Veradigm, USA

Background

Recent studies have demonstrated the improved effectiveness of mammalian cell-based quadrivalent influenza vaccine (QIVc) compared to egg-based quadrivalent influenza vaccines (QIVe) as production using cell-derived candidate viruses eliminates the opportunity for egg-adaptation. This study estimated the adjusted relative vaccine effectiveness (rVE) of QIVc compared to QIVe in preventing cardio-respiratory related hospitalizations during the 2019-2020 influenza season in US adults.

Method

We conducted a retrospective cohort study using electronic medical records linked to claims data during the influenza season, defined as September 30, 2019 - March 7, 2020. Adults 18-64 years with a record of vaccination with QIVc or QIVe were included in the analysis. Since influenza is associated with adverse cardio-respiratory events, the outcomes evaluated included influenza related hospitalizations, as well as cardio-respiratory- and respiratory-events overall, and specifically hospitalizations related to pneumonia, myocardial infarction and ischemic stroke. Outcomes were defined as a diagnosis in any position of the claim and the first position (regardless of the diagnoses in the subsequent positions). A doubly robust, inverse probability of treatment weighting methodology was used to obtain odds ratios (ORs) adjusted for age, sex, race, ethnicity, geographic region, vaccination week, health status, frailty, and healthcare resource utilization. rVE was determined using the formula (1-ORadjusted)*100.

Result

Among adults 18-64 years, 1,491,097 (25.2%) individuals and 4,414,758 (74.8%) individuals received the QIVc and QIVe vaccines, respectively. QIVc was more effective compared to QIVe in preventing cardio-respiratory-related and respiratory-related hospitalizations, including influenza-related hospitalizations (Figure 1). When restricting to the first diagnosis position, estimates were similar for influenza-related hospitalizations, but included the null. No difference was observed between QIVc versus QIVe for the outcomes of pneumonia, myocardial infarction or ischemic stroke hospitalizations.

Conclusion

Results from 2019-2020 season support the greater vaccine effectiveness of QIVc compared to QIVe in preventing cardio-respiratory, respiratory, and influenza-related hospitalizations among adults 18-64 years.

Poster Reception II

Jennifer King - AOXI0130

Antibody response to influenza A following sequential vaccination with egg-based, cell culture-based, and recombinant quadrivalent influenza vaccines among adults aged 18-64 years: a randomized open-label trial, 2018-19 and 2019-20

Jennifer King[2], Min Levine[4], David McClure[1], Thomas Boyce[1], Brendan Flannery[3], Huong McLean[1], Edward Belongia[1]

[1]Center for Clinical Epidemiology & Population Health, Marshfield Clinic Research Institute, [2]Center for Clinical Epidemiology and Population Health, Marshfield Clinic Research Institute, [3]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control & Prevention, [4]Pandemic Preparedness Team, Influenza Division, Centers for Disease Control & Prevention

Background

Traditional influenza vaccines contain antigens from viruses grown in eggs, a process that might result in mutations that alter glycosylation, impair neutralizing antibody response, and reduce vaccine effectiveness (VE). Some licensed influenza vaccines are manufactured without eggs, but sequential vaccination effects have not been compared for egg and non-egg vaccines. We assessed the immunogenicity of sequential vaccination with quadrivalent egg-based inactivated (IIV), cell culture-based inactivated (ccIIV), and recombinant (RIV) influenza vaccine.

Method

This randomized open-label trial was conducted in Wisconsin, United States, across two influenza seasons. Adults (18-64 years) were randomized to receive the same vaccine, ccIIV, RIV, or IIV, in both 2018-19 and 2019-20. Sera were obtained before and ~28 days after vaccination each season to measure hemagglutination inhibition titers against egg- and cell culture-propagated H1N1 and H3N2 vaccine reference (or antigenically similar) viruses. Geometric mean titer (GMT) and mean fold rise (MFR) from pre to post vaccination were estimated using back-transformed model means and differences, respectively, from general linear mixed model regressions with log2-transformed titers.

Result

Analysis included 348 adults (115 received ccIIV, 115 received RIV, 118 received IIV). Patterns of response for each vaccine type were similar for both H1N1 and H3N2 egg- and cell-propagated viruses. MFR in season 2 ranged from 2.3 to 3.1 against the egg-propagated (A/Brisbane/02/2018) and 2.1 to 3.7 against the cell-propagated (A/Idaho/07/2018) H1N1 vaccine viruses. Postvaccination GMT against the egg-propagated H1N1 virus in season 2 did not differ by vaccine type, but GMT against the cell-propagated virus was significantly higher for RIV than IIV recipients (GMT [95% CI]: RIV 86 [67-111], IIV 55 [43-70]; p=0.01). For H3N2, MFR in season 2 ranged from 2.7 to 4.3 and 2.4 to 4.9 against the egg- and cell-propagated vaccine (A/Kansas/14/2017) viruses, respectively. Postvaccination GMT against the egg-propagated H3N2 virus in season 2 was significantly higher for RIV and IIV vs ccIIV recipients (GMT [95% CI]: RIV 177 [146-214], IIV 139 [115-167], ccIIV 100 [82-121]; p<0.001 and p=0.02). Postvaccination GMT against the cell-propagated H3N2 virus was significantly higher for RIV vs IIV and ccIIV recipients (GMT [95% CI]: RIV 145 [120-176], IIV 107 [89-130], ccIIV 79 [64-95], p=0.03 and p<0.001).

Conclusion

In this two-year immunogenicity trial, RIV in consecutive seasons elicited higher antibody titers, particularly against H3N2. Future studies should directly compare clinical VE against influenza virus infection between repeated recombinant HA or cell culture-based vaccines and egg-based vaccines.

Poster Reception II

Margarita Mishina - AOXI0132

Humoral and cell-mediated responses to A(H3N2) component of cell culture-based and recombinant quadrivalent influenza vaccines compared to conventional egg-based quadrivalent influenza vaccines among healthcare personnel aged 18-64 years

Margarita Mishina[4], Weiping Cao[4], Sean Ray[4], Zachary Ende[6], Suresh Sharma[4], Rashmi Kumari[5], Amrita Kumar[4], Uma Shanmugasundaram[4], Caitlin Bohannon[4], Priya Ranjan[4], Paul Knight[3], Jessie Chang[4], Paul Carney[4], James Stevens[4], Min Z. Levine[4], Sara Kim[4], Meredith Wesley[1], Sarah Ball[10], Fatimah Dawood[4], Mark Thompson[4], Raghavan Varadarajan[7], Allison Naleway[9], Manjusha Gaglani[2], Marcelo Jorge Pando[2], Sheila Dobin[2], Shivaprakash Gangappa[8], Suryaprakash Sambhara[4]

[1]Abt Associates, 2200 Century Pkwy NE Ste 950, Atlanta, GA, [2]Baylor Scott & White Health and Texas A & M University College of Medicine, Temple, TX, [3]Department of Anesthesiology, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY, USA, [4]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA, [5]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA; Department of Anesthesiology, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY, USA, [6]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA; Oak Ridge Institute for Science and Education (ORISE), CDC Fellowship Program, Oak Ridge, TN, USA, [7]Molecular Biophysics Unit, Indian Institute of Science, Bangalore, Karnataka, India, [8]Research Biologist, [9]The Center for Health Research, Kaiser Permanente Northwest, Portland, OR, [10]Westat, 1600 Research Blvd, Rockville, MD

Background

Influenza results in substantial morbidity and mortality. Annual vaccination remains the most effective method to prevent influenza and its complications, but it is unclear whether some licensed influenza vaccines provide better protection than others. We assessed humoral and cell-mediated immune (CMI) responses to cell culture-based inactivated (ccIIV) and recombinant-hemagglutinin (RIV) influenza vaccines compared to conventional egg-based inactivated influenza vaccine (IIV) among a subset of healthcare personal with extended flu vaccination history and enrolled in a larger randomized trial.

Method

Eligible participants (N=100) were enrolled within age strata (18-44 years, 45-64 years) to receive a single dose of ccIV (Flucelvax™ Quadrivalent by Seqirus, Inc., 15µg of HA per strain) versus RIV (Flublok® Quadrivalent by Sanofi Pasteur, 45µg of HA per strain) versus standard dose IIV (Fluzone® Quadrivalent by Sanofi Pasteur or Fluarix Quadrivalent by GSK, 15µg of HA per strain) during 2018-19 season. Participants had sera collected just prior to vaccination and at approximately 28 days and 6 months post-vaccination to evaluate humoral immune responses to vaccination by microneutralization (MN) assays against cell-grown A(H3N2) vaccine reference virus, and whole blood at pre-vaccination and at approximately 7 days, 28 days, and 6 months post-vaccination for peripheral blood mononuclear cells to evaluate CMI responses. CMI responses were evaluated by multiparametric flow cytometry for circulating follicular T helper cells (cTfh) and HA-specific B cells using recombinant receptor-binding site (RBS)-mutated hemagglutinin probes (rHA) derived from the 2018-19 influenza vaccine viruses.

Result

The RIV induced more robust anti-HA antibody and HA-specific B cell responses to A(H3N2) on day 28 post-vaccination compared to ccIIV4 and IIV. Pre-vaccination MN geometric mean titers (GMTs) against A(H3N2) were similar between the vaccine arms. The MN GMT fold rise from pre-to post- vaccination for A(H3N2) was 8.5 (95% confidence interval [CI] 4.1 -12.8) for RIV, and 3.2 (95% CI: 1.2-5.1) and 1.2 (95% CI: 1-1.4) for ccIIV and IIV respectively. Only RIV induced A(H3N2) HA-specific B cells: cell percentage fold rise [FR] was 1.7 (95% CI: 1.3-2.2) on day 28. GMTs on day 28 and 6 months correlated with HA-specific B cell FR on day 7 ($p=0.0002$, $r2 = 0.14$ and $p<0.0004$, $r2 = 0.18$) and day 28 ($p=0.0004$, $r2 = 0.12$ and $p=0.003$, $r2 = 0.1$) post-vaccination. Furthermore, only RIV induced cTfh cells (FR 1.4, 95% CI: 1 - 1.8) on day 28 post-vaccination.

Conclusion

In highly vaccinated health care personnel, RIV induced more robust humoral and CMI responses to A(H3N2) component when compared to egg- or cell-culture based influenza vaccines.

Poster Reception II

Eve Versage - AOXI0135

COMPARISON OF SAFETY PROFILES OF FOUR MF59-ADJUVANTED CELL CULTURE-DERIVED MONOVALENT PANDEMIC VACCINES

Eve Versage[1], Esther Van Twuijver[2], Derchieh Hung[3], Oksana Tkach-Motulyak[4]

[1]Seqirus, [2]Seqirus, Clinical Development, Amsterdam, NL, [3]Seqirus, Clinical Development, Parkville, AU, [4]Seqirus, Pharmacovigilance & Risk Management, Maidenhead, UK

Background

Development of effective and safe vaccines manufactured with cell-based technology is a major advance towards meeting the global demand for vaccine in the event of a novel zoonotic influenza pandemic. All commercial pandemic preparedness vaccines contain H5N1 strains, yet various other influenza subtypes have pandemic risks. We evaluated the safety profile of MF59-adjuvanted vaccines manufactured via cell technology for a variety of zoonotic influenza virus subtypes to support the use of these vaccines during the early stages of an outbreak.

Method

Safety data were integrated from 11 clinical studies evaluating 4 MF59-adjuvanted monovalent cell culture-derived pandemic vaccines for different virus subtypes (H1N1, H3N2, H5N1 & H7N9) made on the same platform. The studies were similar in design, inclusion/exclusion criteria, vaccine dose (7.5 µg HA and 0.25 mL of MF59) and criteria for safety evaluation. Subjects received two doses of vaccine, 3 weeks apart. This analysis focuses on solicited local and systemic reactions collected for 7 consecutive days after each vaccination in subjects 18 to <65 yrs of age.

Result

2162 adults, similar in age and gender across studies, received at least one dose of one of the 4 vaccines. Across all 4 vaccines percentages of subjects experiencing solicited adverse events (AEs) from day 1 to 7 following any vaccination were comparable, fewer solicited AEs were reported after the second vaccination than the first. The majority of solicited local and systemic AEs were mild to moderate in nature. The most frequent solicited local AE after any vaccination regardless of vaccine subtype was injection site pain. Fatigue, myalgia and headache were the most often reported solicited systemic AEs after any vaccination. For all vaccines most solicited AEs had onset from 1 to 3 days after vaccination and resolved within a few days.

Conclusion

Integration of safety data from clinical trials representing 4 pandemic vaccines manufactured on the same cell platform and containing the adjuvant MF59 show that solicited local and systemic reactions reported by subjects are similar in nature, regardless of the vaccine's virus subtype. All 4 vaccines were well tolerated, had acceptable safety profiles without clinically relevant differences in nature and severity of solicited reactions. These findings support the use of the adjuvanted cell-based technology for vaccine development in the event of an influenza pandemic.

Poster Reception II

João Paulo Portela Catani - AOXI0160

The antigenic landscape of recent human influenza virus N2 neuraminidases circulating in 2009-2017

João Paulo Portela Catani[4], Anouk Smet[4], Tine Ysenbaert[4], Marnik Vuylsteke[1], Guy Bottu[3], Janick Mathys[3], Alexander Botzki[3], Guadalupe Cortes-Garcia[2], Tod Strugnell[2], Raul Gomila[2], John Hamberger[2], John Catalan[2], Irina V. Ustyugova[2], Timothy Farrell[2], Svetlana Stegalkina[2], Satyajit Ray[2], Lauren LaRue[2], Thorsten U. Vogel[2], Xavier Saelens[4]

[1]Gnomixx, Melle, Belgium, [2]Sanofi, Research North America, Cambridge, Massachusetts, USA, [3]VIB-Bioinformatics Core, VIB, B-9052 Ghent, Belgium, [4]VIB-UGent Center for Medical Biotechnology, VIB, B-9052 Ghent, Belgium; Department of Biochemistry and Microbiology, Ghent University, B-9000 Ghent, Belgium

Background

The overall Influenza virus vaccine effectiveness varies between seasons, and it is estimated that the H3N2 vaccine component frequently has the lowest performance in protection (5-39%). Multiple studies point to the protective potential of influenza neuraminidase (NA) inhibitory antibodies in the clinic. Therefore, the inclusion of a standardized amount of NA antigen has been proposed as a valuable second layer of protection, to potentially increase the breadth of protection, and to compensate for potential HA mismatches of next generation influenza vaccines. However, little is known about the antigenic landscape of NA from circulating human H3N2 strains. Here we determined the inhibition of a large panel of NAs corresponding to H3N2 viruses that circulated between 2009 and 2017 to better understand the mutations that result in antigenic drift of NA.

Method

Anti-NA sera were raised in ferrets and mice using a panel of 44 H1N2 viruses and/or recombinant NAs. The anti-NA response was determined by ELISA and the breadth of NA inhibition (NAI) was determined using H6N2 reassortant viruses by Enzyme-Linked Lectin Assay (ELLA).

Result

Ferrets were primed by infection with H1N2 reassortant viruses and boosted with soluble recombinant N2. The NAI titers of the resulting sera were determined against a panel of 27 distinct H6N2s and revealed a N2 inhibition pattern that agrees with the phylogenetic relatedness of the N2 protein sequences. The 27 tested H6N2s could be classified into at least four major antigenic groups. In addition, the sera tested after H1N2 priming only, displayed the same pattern of cross-inhibition as the N2 protein boost sera. Moreover, NAI titers of sera from mice that had been immunized with recombinant N2 NA, followed the same pattern of breadth and specificity as the ferret sera. We performed an association analysis to rank the probability of each amino acid residue change to impact on NAI. This analysis revealed that 9 to 24 residues may impact on NAI in each of the evaluated H6N2s. The results were consistent within each antigenic group. Furthermore, amino acids in close proximity of the catalytic site are most likely impacting on NAI.

Conclusion

N2 NAs from 2009 until 2017 can be classified in at least 4 distinct antigenic groups based on the cross-inhibiting NAI response. This pattern is similar in ferrets and mice. The NAI breadth of the immune response induced by H1N2 infection of ferrets correlates very well with that obtained from subsequently NA protein-boosted sera. Finally, amino acid substitutions that dictate the antigenic landscape of our H3N2 breadth panel are most likely to be located in close proximity of the NA catalytic site. (Study funded by Sanofi)

Poster Reception II

Shuyi Zhong - AOXI0174

The association of prior-year vaccination on antibody response to A(H3N2) with standard-dose, MF59-adjuvanted, high-dose, and recombinant-HA influenza vaccines in older adults.

Shuyi Zhong[3], Tiffany Ng[3], Nancy Leung[2], A.Danielle Iuliano[1], Yuyun Chen[2], Ranawaka Perera[2], Joseph Peiris[2], Mark Thompson[1], Benjamin Cowling[2]

[1]Influenza Division, Centers for Disease Control and Prevention, [2]School of Public Health, The University of Hong Kong, [3]The University of Hong Kong

Background

Older adults are vulnerable to influenza virus infections, but repeat annual influenza vaccination has been linked to reduced immunogenicity and lower clinical effectiveness especially against A(H3N2). Here, we examined whether enhanced influenza vaccines with improved immunogenicity for older adults could overcome blunted antibody responses to A(H3N2) associated with repeat vaccination.

Method

From October 2017 through January 2018, community-dwelling older adults between 65 and 82 years of age were recruited in Hong Kong and were randomly assigned to receive a standard-dose quadrivalent vaccine, MF59-adjuvanted trivalent vaccine, high-dose trivalent vaccine, or recombinant-hemagglutinin quadrivalent vaccine. Serum samples from a subset of 800 participants (200 per vaccine type) collected before and approximately 30 days after vaccination were tested by hemagglutination inhibition (HAI) assay against egg-propagated A(H3N2) antigen and microneutralization (MN) assays against cell-propagated A(H3N2) antigen.

Result

Older adults who were not vaccinated in the prior 2016/17 season had higher mean fold rise (MFR) and achieved higher geometric mean titers (GMT) following vaccination with 2017/18 vaccine compared to those vaccinated in both 2016/17 and 2017/18. This was observed with both HAI and MN against egg-propagated A(H3N2) antigen. This blunting of antibody response among previously vaccinated adults was observed with the standard-dose vaccine as well as the 3 enhanced vaccines. The blunted antibody response was less pronounced using cell-propagated antigen.

Conclusion

Our study found that blunted antibody responses to A(H3N2) vaccine strain occurred among previously vaccinated older adults. Blunting was not lower among those who received a high-dose, adjuvanted, or recombinant-hemagglutinin vaccine.

Poster Reception II

Carolyn Cohen - AOXI0182

SARS-CoV-2 vaccines induce equivalent or greater antibody responses in adolescents compared with adults

Carolyn A Cohen[3], Daniel Leung[1], Jaime S Rosa Duque[1], Samuel MS Cheng[4], Malik Peiris[4], Yu-Lung Lau[1], Sophie Valkenburg[2]

[1]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, [2]HKU-Pasteur Research Pole, The University of Hong; Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, University of Melbourne, [3]HKU-Pasteur, University of Hong Kong, [4]School of Public Health, The University of Hong Kong

Background

SARS-CoV-2 vaccines, Spike mRNA (BNT162b2) and Alum adjuvanted whole inactivated virion (CoronaVac) are available for use in those aged 5 or 3 years and above respectively in Hong Kong. Whilst children and adolescents experience lower COVID-19 mortality and morbidity than adults, complications, hospitalisations and death do still occur. This age group can also further contribute to virus transmission within a community and increase the probability of future variants arising. Therefore, vaccination of children and adolescents can mitigate the impact of COVID-19. Assessment of neutralising antibodies has been carried out in adolescents following vaccination with both BNT162b2 and CoronaVac, however other assessments of antibody quality have not been made. The potential benefits of intradermal CoronaVac vaccination for children as a way of targeting larger numbers of antigen presenting cells and improving the antibody response to this vaccine has also not yet been explored.

Method

Antibody effector function such antibody dependent cell cytotoxicity (ADCC) via FcγRIIIa binding and antibody avidity by the Fab region are markers protection from severe disease and long-term neutralisation respectively. In this study, adolescents (aged 11-17 years) donated plasma at 3 time points before and after receiving a 2 dose-regime of BNT162b2 or CoronaVac. BNT162b2 was delivered via the intramuscular route, while CoronaVac was delivered intradermally or intramuscularly. Plasma was then used in ELISA assays to compare quality of antibody responses between vaccines and with adults for Spike specific avidity and FcγRIIIa binding.

Result

Here we show that both vaccines induce Spike IgG and FcγRIIIa-binding antibodies in adolescents. These antibodies are equivalent in vaccinated adolescents and adults, and similarly to adults, are significantly higher following BNT162b2 vaccination compared with CoronaVac. Antibody avidity following vaccination was higher in adolescents than adults. These responses are further maintained against the Omicron BA.1 variant.

Conclusion

Vaccinated adolescents mount anti-Spike antibody responses that are equivalent to or greater than vaccinated adults. These vaccine-induced responses are cross reactive with variants of concern and so may provide significant protection to adolescents, supporting arguments for the vaccination of adolescents.

Poster Reception II

Serena Marchi - AOXI0184

Antibody avidity and neutralizing response against SARS-CoV-2 Omicron variant after infection or vaccination

Serena Marchi[1]

[1]University of Siena

Background

Since its first isolation, SARS-CoV-2 has continuously mutated with the emergence of several variants. The recently emerged SARS-CoV-2 Omicron variant exhibits several mutations on the spike protein, enabling it to escape the immunity elicited by natural infection or vaccines.

Avidity is defined as the strength of binding between an antibody and its specific target epitope, and is established during affinity maturation. The absence of high avidity IgG may result in a lack of protective immunity towards infection. The SARS-CoV-2 spike protein, via the receptor-binding site, binds to its cellular receptor with high affinity, and is the primary target of neutralizing antibodies. Therefore, protective antibodies should show high avidity.

This study aimed at investigating the avidity of receptor-binding domain (RBD) binding antibodies and their neutralizing activity against the Omicron variant in COVID-19 patients and vaccinated subjects.

Method

Serum samples were collected from hospitalized COVID-19 patients and from subjects who had received two doses of mRNA vaccine, three doses of mRNA vaccine, or two doses of adenovirus-based vaccine and a booster dose of mRNA vaccine, and were tested for RBD-binding IgG, RBD-binding IgG avidity and neutralizing antibodies against the wild-type SARS-CoV-2 virus and the Omicron variant.

Result

In COVID-19 patients, RBD-binding IgG titres and avidity indexes against the SARS CoV-2 wild-type virus increased with time, but remained low. High neutralizing antibody titres against the wild-type virus were not matched by high avidity indexes or neutralizing activity against the Omicron variant.

Vaccinated subjects showed higher avidity indexes than patients. Two vaccine doses elicited the production of neutralizing antibodies, but low avidity for the wild-type virus; antibody levels against the Omicron variant were even lower. Conversely, three doses of vaccine elicited high avidity and high neutralizing antibodies against both the wild-type virus and the Omicron variant. No differences were found between subjects who had received three doses of mRNA vaccine and those who had received two doses of adenovirus-based vaccine and a booster dose of mRNA vaccine.

Conclusion

Results from this study showed that repeated vaccination is able to induce higher levels of functional antibodies with higher avidity than those induced by natural infection. Overall, repeated vaccination increases antibody avidity against the spike protein of the Omicron variant, suggesting the idea that antibodies with high avidity and high neutralizing potential can increase cross-protection against variants that carry several mutations on the RBD.

Poster Reception II

Phillip Swanson - AOXI0211

Analysis of initial cellular immune responses to breakthrough SARS-CoV-2 infection following primary series AZD1222 (ChAdOx1 nCoV-19) vaccination

Phillip Swanson 2nd[8], Marcelino Padilla[8], Ann R. Falsey[9], Magdalena E. Sobieszczyk[6], Anne F. Luetkemeyer[10], Grant C. Paulsen[3], Sharon A. Riddler[5], Charlotte-Paige Rolle[7], Beverly E. Sha[4], Himanshu Bansal[1], Nicholas M. Durham[8], Jill Maaske[1], Kathryn Shoemaker[1], Stephanie Sproule[1], Tonya Villafana[2], Elizabeth J. Kelly[8]

[1]Biometrics, Vaccines & Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA, [2]Clinical Development, Vaccines & Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA, [3]Department of Pediatrics, University of Cincinnati College of Medicine, Division of Pediatric Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [4]Division of Infectious Diseases, Department of Internal Medicine, Rush University Medical Center, Chicago, IL, USA, [5]Division of Infectious Diseases, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA, [6]Division of Infectious Diseases, Department of Medicine, Vagelos College of Physicians and Surgeons, New York-Presbyterian Columbia University Irving Medical Center, New York, NY, USA, [7]Orlando Immunology Center, Orlando, FL, USA, [8]Translational Medicine, Vaccines & Immune Therapies, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA, [9]University of Rochester School of Medicine and Dentistry, Rochester, NY; Rochester Regional Health, Rochester, NY, USA, [10]Zuckerberg San Francisco General, University of California, San Francisco, CA, USA

Background

Breakthrough SARS-CoV-2 infection in COVID-19 vaccinees typically results in less severe disease. We analysed initial immune responses to breakthrough infection in adult participants from a 2:1 randomised, double-blind, placebo-controlled Phase 3 study of 2-dose primary series AZD1222 (ChAdOx1 nCoV-19) vaccination (NCT04516746) to investigate if vaccinated individuals had enhanced cellular responses that may attenuate the severity of COVID-19.

Method

Study participants who experienced US CDC COVID-19 symptoms for ≥2 days, or any duration of fever, shortness of breath, or difficulty breathing, initiated illness visits. We analysed PBMCs, sera, and nasopharyngeal swabs from participants who had PCR-confirmed SARS-CoV-2 infection ≥15 days after dose 2 of AZD1222 or placebo and provided samples during their first illness visit. CD4+ and CD8+ T cell response rates were assessed using intracellular cytokine staining assays and flow cytometry. Neutralising antibody titres were assessed using a SARS-CoV-2 pseudovirus assay. Viral shedding and viral load were assessed using quantitative RT-PCR.

Result

AZD1222 vaccinees had significantly higher levels of SARS-CoV-2 spike-specific CD4+ and CD8+ T cells than placebo participants (figure). The proportion of participants generating spike-specific T cells was higher in AZD1222 vaccinees. Neutralising antibody responses in AZD1222 vaccinees correlated with CD4+ (Spearman rank 0.65; p=0.02) but not CD8+ (Spearman rank 0.05; p=0.85) T cell responses. A greater proportion of T cells from AZD1222 vaccinees displayed polyfunctional markers vs those from placebo recipients. Correlations between CD4+ and CD8+ T cell responses with viral shedding and viral load in AZD1222 vaccinees and placebo participants will be presented.

Figure. CD4+ and CD8+ T cell responses to breakthrough infection in AZD1222 vaccinees and placebo recipients at first illness visit.

Not significant (NS), p>0.05; *p≤0.05; **p≤0.01; ***p≤0.001.

†Any combination of CD154, interferon gamma (IFNγ), interleukin-2 (IL-2) and tumour necrosis factor alpha (TNFα) for CD4+ T cells and IFNγ, IL-2, and TNFα for CD8+ T cells; ‡Any response above the lower limit of quantitation [LLoQ]).

Conclusion

AZD1222 vaccinees had higher spike-specific T cell responses than placebo participants to early symptomatic SARS-CoV-2 infection, with greater proportions with polyfunctional markers, indicating robust cellular recall responses to vaccination.

This study is funded by AstraZeneca.

Poster Reception II

Jutte J.C. De Vries - AOXI0205

Absence of rapid T cell control corresponds with delayed viral clearance in hospitalised COVID-19 patients

Mihaela Zlei[1], Igor A. Sidorov[1], Simone A. Joosten[1], Mirjam H.M. Heemskerk[1], Sebenzile K. Myeni[1], Cilia R. Pothast[1], Caroline S. De Brouwerq[1], A. Linda Boomaars-van der Zanden[1], Krista E. Van Meijgaarden[1], Shesssy T. Morales[1], Els Wessels[1], Jacqueline J. Janse[1], Jelle J. Goeman[1], Christa M. Cobbaert[1], Aloys Kroes[1], Suzanne C. Cannegieter[1], Meta Roestenberg[1], Leonardus G. Visser[1], Marjolein Kikkert[1], Mariet C.W. Feltkamp[1], Sesmu M. Arbous[1], Frank J.T. Staal[1], Tom H.M. Ottenhoff[1], Jacques J.M. Van Dongen[1], Anna H.E. Roukens[1], Jutte J.C. De Vries[1]

[1]Leiden University Medical Center, the Netherlands

Background

Mechanisms underlying SARS-CoV-2 clearance are poorly understood and a better understanding is crucial to guide clinical management.

Method

Here, we studied the timing of viral clearance in relation to 122 immune parameters in 102 hospitalized patients with moderate and severe COVID-19 in a longitudinal design.

Result

Delayed viral clearance was associated with more severe disease, which occurred after the virus had been cleared in most cases. Apparent paradoxically, delayed viral clearance was associated with over time higher levels of SARS-CoV-2 specific IgG, IgA, and neutralizing antibodies, increased numbers of neutrophils, monocytes, basophils, and a wide range of pro-inflammatory cyto-/chemokines, including IL-4, IL-6, sIL-6Rbeta, LIF, HGF, SCGF-beta, and sCD163. In contrast, early viral clearance and less critical illness correlated with higher levels of naïve CD4+ T cells, suggesting their role in early control of SARS-CoV-2. The timing of viral clearance coincided with peaks of effector T and B cells.

Conclusion

Collectively, our data show that absence of rapid T cell control corresponds with delayed clearance, followed by aberrant antibody and cytokine profiles and disease deterioration. Viral clearance often precedes critical illness, which supports immunopathology as underlying mechanism, including the enhanced innate response related to the prolonged virus-induced tissue damage.

Poster Reception II

Allison McGeer - AOXI0287

Frailty, age and outcomes of hospitalized adults differ across waves of the COVID-19 pandemic; a report from the CIRN Serious Outcomes Surveillance (SOS) Network

Melissa Andrew[9], Jason LeBlanc[11], Kevin Wilson[2], Hanan Elawadi[2], Allison McGeer[14], Janet E. McElhaney[13], Todd F. Hatchette[11], May Elsherif[1], Donna MacKinnon-Cameron[1], Judith Godin[12], Ardith Ambrose[1], Guy Boivin[3], Louis Valiquette[4], Sylvie Trottier[7], Mark Loeb[8], Stephanie Smith[5], Kevin Katz[15], Anne McCarthy[6], Shelly McNeil[10]

[1]Canadian Center for Vaccinology, Halifax, Canada, [2]Canadian Centre for Vaccinology, Halifax, Canada, [3]CHU de Québec-Université Laval, Québec, Québec, [4]Département de microbiologie et d'infectiologie, Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Sherbrooke, Québec, [5]Department of Medicine (Infectious Disease), University of Alberta, Edmonton, Alberta, Canada, [6]Department of Medicine (Infectious Disease), University of Ottawa, Ottawa, Ontario, Canada, [7]Department of Microbiology-Infectology and Immunology, Université Laval, Québec, [8]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada, [9]Dept of Medicine (Geriatrics) Dalhousie University; Canadian Centre for Vaccinology, Halifax, Canada, [10]Dept of Medicine (Infectious Disease), Dalhousie University; Canadian Center for Vaccinology, Halifax, Canada, [11]Depts of Medicine (Infectious Diseases) and Pathology, Dalhousie University; Canadian Centre for Vaccinology, Halifax, Canada, [12]Geriatric Medicine Research, Dalhousie University, Halifax, Canada, [13]Health Sciences North Research Institute, Sudbury, Canada, [14]Mount Sinai Hospital, Toronto, Ontario, Canada, [15]North York General Hospital, Toronto, Ontario, Canada

Background

Frailty is a holistic measure of health status which influences risk, disease expression, and outcomes of illnesses including COVID-19. Here we report characteristics, including frailty, and outcomes of adults admitted to Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) Network hospitals with COVID-19 during pandemic waves 1-5.

Method

Patients with laboratory-confirmed COVID-19 admitted to eleven sites in Ontario, Quebec, Alberta and Nova Scotia were enrolled in this prospective observational cohort study. Waves varied slightly by jurisdiction, but were defined by admission date as W1:Mar 1-Aug 31,2020, W2:Sept 1,2020-Feb 28,2021, W3:Mar 1,2021-Aug 31,2021, W4:Sept 1,2021-Nov 30 2021, W5:Dec 1,2021-Feb 28, 2022. Key measures included age, Clinical Frailty Scale (CFS 1-3=fit, 4=vulnerable, 5=mildly frail, 6=moderately frail, 7=severely frail), demographics, and vaccination status. Outcomes of interest included intensive care unit admission and survival (data collection is ongoing and outcomes are not yet confirmed for some patients).

Result

Among 9432 patients, mean age by wave was W1:68.8 (95%CI:67.6-70.1), W2:71.4(70.8-72.0), W3:59.7(59.0-60.4), W4:59.8(58.5-61.2), and W5:66.9(66.2-67.6). The full spectrum of frailty was represented in both younger and older age groups. Frailty was highest in W2[CFS 4.4(4.4-4.5)] and W5[CFS 4.3(4.2-4.4)], and lowest in W3[CFS 3.7(3.6-3.8)] and W4[CFS 3.9(3.7-4.1)]. Mortality was higher in W1(20.8%) and W2(23.0%) compared with W3(12.0%), W4(10.2%), and W5(3.5%). Patients who died were older and frailer than the mean in each wave, though in W3-4 the mean CFS of those who died (4.7 and 4.8) was < mildly frail.

Conclusion

Frailty and age of patients admitted with COVID-19 to Canadian hospitals decreased in W3 and W4, and outcomes have varied across waves. This is likely due to multiple factors including vaccination program targeting (in the earliest phases of programmatic roll-out), higher vaccine uptake in older age groups and among those with multiple medical conditions, introduction of therapeutics, and emergence of Variants of Concern associated with severe illness in younger, less frail, individuals in later waves. Frailty is a critical clinical factor in predicting outcomes of COVID-19, which should be considered in research and clinical settings.

Poster Reception II

Pete C. Schmidt - AOXI0233

Validation of a Predictive Model to Correlate Neutralization Titers and Efficacy for the Prevention of COVID-19

Laura Walker[2], Xia Pu[1], Jean Gong[1], Pamela Hawn[1], Pete Schmidt[1]

[1]Adagio Therapeutics, Inc., [2]Adagio Therapeutics, Inc.; Adimab

Background

Most anti-viral vaccines, including COVID-19 vaccines, induce neutralizing antibodies as a correlate of protection (CoP). Here we describe a novel model to predict the absolute serum neutralizing antibody titer required for prevention of symptomatic COVID-19, and its validation from Phase 2/3 clinical trial of adintrevimab (ADI) for prevention.

Method

To determine neutralizing antibody (nAb) titers that were associated with protection against symptomatic COVID-19, a literature search was conducted to evaluate efficacy data from vaccines and monoclonal antibodies (mAb). Median authentic virus serum neutralizing titers induced by vaccination or passive mAb therapy were measured experimentally or projected based on mAb pharmacokinetic (PK) and neutralization IC50 data. From previous FIH study of ADI, PK and neutralizing titers correlate in a predictable manner. Therefore, to validate the CoP, serum concentrations from population PK model based on Phase 2/3 data of ADI on days 55 and 76 (Omicron BA.1/BA1.1), and 90 (Delta) were used to calculate predictive nAb titers and corresponding efficacy for the Delta and Omicron variants and then compared to clinical efficacy results from the EVADE clinical trial in prevention of COVID-19.

Result

A CoP was identified as an authentic virus serum neutralizing titer of 1:100 which would provide approximately 70% protection against development of symptomatic COVID-19. Population PK median serum concentrations of ADI at 55, 76, and 90 days were 29.8 mg/L, 26.7 mg/L, and 24.6 mg/L, respectively. The neutralizing titer against Delta was extrapolated to be 1:4100 at day 90, predicting ADI would have at least 70% protection. This was consistent with the observed clinical outcome from the EVADE trial where patients taking ADI experienced a 71% reduction in development of symptomatic COVID-19 through 3 months. Neutralizing titers against Omicron were extrapolated to be 1:29 and 1:26, at days 55 and 76, respectively. The model predicted an efficacy of approximately 50% and 46.6% for ADI against Omicron given a higher IC50. This was in range of the observed efficacy of 62.3% and 50.9% at a median follow-up of 55 and 76 days in EVADE.

Conclusion

An authentic virus serum neutralizing titer of 1:100 was established as a CoP for the prevention of symptomatic COVID-19 and validated using Phase 2/3 clinical data in a model that could be used to predict expected outcomes and redosing strategy based on IC50 of the circulating variant.

Poster Reception II

Masafumi Seki - AOXI0255

Clinical use of molnupiravir and the combination with sotrovimab for SARS-CoV-2 infected (COVID-19) patients in a tertiary hospital of Japan

Masafumi Seki[1]

[1]Saitama Medical University

Background

New antiviral agents for COVID-19, including molnupiravir for the oral treatment and sotrovimab as the monoclonal antibody for the intravenous treatment are currently authorized and available in Japan.

Method

We investigate the clinical use of molnupiravir for COVID-19 patients in our tertiary hospital from January to May 2022, which was the omicron strains dominant term.

Result

35 patients received the molnupiravir administration. 32/35 patients were used combined with sotrovimab. The patients were 67.3 years old (26-90 y.o) and all survived. In the same term, the patients treated by sotrovimab alone were 14 cases of 79.0 (63-92) y.o. Furthermore, the mild/moderate patients treated by molnupiravir were 15/20 cases although all patients with sotrovimab alone were mild. However, one patient treated by sotrovimab alone was died.

Conclusion

Most of the molnupiravir were used in the combination with sotrovimab. Molnupiravir may be useful for the COVID-19 patients who could accept oral administration of antiviral agents in the clinical setting.

Poster Reception II

Akira Ueno - AOXI0297

Functional analysis of polymeric monoclonal anti-SARS-CoV-2 IgA antibodies

Akira Ueno[1]

[1]National Institute of Infectious Diseases

Background

Neutralizing antibodies (Abs) against SARS-CoV-2 mainly target its spike protein, a viral glycoprotein that mediates binding to ACE2. Although the neutralizing Abs against SARS-CoV-2 have been well characterized, majority of studies have been limited to analyses on monomeric IgG Abs. The mucosal barrier including secretory IgA Abs (SIgAs) with polymeric forms plays as the first line of protection against SARS-CoV-2 infection on respiratory mucosa. It was reported that early and intense induction of SARS-CoV-2 spike-specific IgA Abs on nasal mucosa linked to a rapid decrease in viral road. However, it is not obvious which quaternary structures or paratopes of IgA Abs contribute to this high antiviral activity. In this study, we generated recombinant monoclonal human anti-SARS-CoV-2 polymeric SIgAs based on the well-characterized anti-SARS-CoV-2 IgG Abs and evaluated the potency of the polymeric SIgAs on inhibition against SARS-CoV-2 infection.

Method

Seven clones of recombinant monoclonal polymeric SIgAs against SARS-CoV-2 S protein were generated, which were originally identified as binding Abs as IgG and are classified according to the binding epitopes on the spike protein: four classes for receptor binding domain and a class for N-terminal domain. The antigen binding abilities and antiviral activities of these polymeric SIgAs were compared with those of monomeric IgG or IgA by ELISA and biolayer interferometry, and by pseudotyped and authentic virus neutralization assay against variants of concern respectively.

Result

All seven clones of the polymeric SIgAs showed higher binding abilities and antiviral activities against strain A (Wuhan) than monomers, partly because polymeric SIgAs dissociated less well from spike protein than monomers. Although, the degree of the increase in binding abilities did not necessarily correlate with that in antiviral activities, class 4 clones, which interact with the core region of receptor-binding domain (RBD), showed increased neutralizing activities against alpha, beta, delta, Omicron BA.1, and BA.2 variants by IgA polymerization, especially in IgA1 subclass.

Conclusion

These results suggested that the conversion of monomeric IgG or IgA to polymeric SIgAs may be advantageous against SARS-CoV-2 infection, but the degree of increase in binding and antiviral activities by conversion to polymeric SIgAs varied from clone to clone. Notably, IgA1 Abs targeting the core region of RBD efficiently increase binding and antiviral activity upon multimerization, suggesting the importance of SIgA1 in mucosal Abs. Further studies are needed for better understanding the role of polymeric SIgAs in protection against SARS-CoV-2 infection in respiratory mucosal tissues.

Poster Reception II

Kriengkrai Prasert - AOXI0312

Antibody responses after two-doses of inactivated vaccine followed by a booster dose of either viral-vector or mRNA COVID-19 vaccine in healthcare workers in Thailand

Kriengkrai Prasert[7], Sutthichai Nukphook[1], Sutthinan Chavalchitiporn[4], Hatairat Lerdsamran[3], Somrak Sriketkorn[6], Tanasit Praipong[8], Nuddaporn Sripradit[8], Piyapong Sirinapakul[8], Darunee Ditsungneon[9], William Davis[5], Pilaipan Puthavathana[2], Prabda Praphasiri[5]

[1]Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand., [2]Faculty of Medical Technology, Mahidol University, Salaya, Nakhon Pathom, Thailand, [3]Faculty of Medical Technology, Mahidol University, Salaya, Nakhon Pathom, Thailand., [4]Faculty of medicine, Thammasat University, Thailand, [5]Influenza Program, Thailand Ministry of Public Health-U.S. Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand, [6]Institute of Urban Disease Control, Bangkok, Thailand, [7]Nakhon Phanom Hospital, [8]Nakhon Phanom Provincial Hospital, Nakhon Phanom Thailand, [9]Thailand Ministry of Public Health-U.S. Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand

Background

In response to the wave of SARS CoV-2 Delta(B1.671.2)variant in Thailand, the Ministry of Public Health recommended that healthcare workers(HCWs) receive a booster dose of COVID-19 vaccine. HCWs had previously received two doses of Sinovac and were offered either AZD1222(ChAdOx1 nCoV19 vaccine, Oxford-AstraZeneca) or BNT162b2(BNT162b2 vaccine, Pfizer-BioNTech) as boosters. We report on the effect of the booster on binding and neutralizing antibodies specific to the Delta(B1.671.2) variant among HCWs in Nakhon Phanom province, Thailand.

Method

In June 2021, we collected blood from 106 HCWs 4 weeks after the second SARS CoV-2 vaccination and then 4-6weeks after the booster vaccination. Serum was screened for SARS-CoV-2 total Ig by sandwich qualitative ELISA(Wantai Biological Pharmacy, Beijing) using the receptor-binding domain(RBD) as the test antigen. Positive samples were further investigated for SARS-CoV-2 neutralizing(NT) antibodies with cytopathic effect based-microneutralization(microNT) assay using Delta variant as the test antigen. We compared the proportion of each group that had at least a fourfold increase in NT titers(a common assumption for seroconversion) with the exact probability test, and we compared the geometric mean of NT antibody titers(GMNT) with the t-test.

Result

Among 106 healthcare providers who received two doses of Sinovac, 50 received AZD1222, and 56 received BNT162b2 boosters. Females comprised 43/50 (86%) participants in the AZD1222 group and 45/56 (80%) in the BNT162b2 group. The median ages were 45 years (IQR 34 - 52) and 36 years (IQR 31 - 42) ($p < 0.001$) in the AZD1222 and BNT162b2 groups, respectively. In baseline sera, 100% of both groups were positive for SARS-CoV-2 antibodies by ELISA; at 4 weeks after the booster, the mean total Ig values were 16.5±0.4and 16.7±0.5 in the AZD1222 group and BNT162b2 group, respectively ($p=0.75$). In baseline sera, the GMNT were 5.75 (1, 6.4) and 6.1 (5.3, 7.0) ($p = 0.61$); 4 weeks after booster vaccination, GMNT increased to 54.26 (42.18, 68.8) and 190.3 (153.8, 235.5) ($p < 0.001$) with proportions of 4-fold rise in antibody titers of 90% (78.2, 97.2) and 100% (93.6, 100.0) ($p = 0.68$) in the AZD1222 group and BNT162b2 group, respectively.

Conclusion

Booster doses of AZD1222 and BNT162b2 both elicited a 4-fold increase in NT antibody titers in ≥90% of HCWs, although BNT162b2 elicited a higher overall response. This study demonstrated neutralizing antibody activity against Delta variant in HCWs who completed two doses of inactivated vaccine and one booster dose with either viral-vectored or mRNA vaccine. Further study is needed to determine the effect of the booster dose on clinical outcomes and with other variants.

Poster Reception II

Daniel R. Perez - AOXI0283

Antigenic map of the hemagglutinin of influenza A virus of the H9 subtype

Silvia Carnaccini[2], C. Joaquin Caceres[2], L. Claire Gay[2], Lucas Ferreri[2], Eugene Skepner[4], David Burke[4], Ian Brown[1], Stivalis Cardenas-Garcia[2], Ginger Geiger[2], Adebimpe Obadan[2], Daniela S Rajao[2], Ron A.M Fouchier[3], Nicola S Lewis[1], Daniel R Perez[2]

[1]Department of Pathobiology and Population Sciences, Royal Veterinary College, London, United Kingdom, [2]Department of Population Health, College of Veterinary Medicine, University of Georgia, Athens, Georgia, USA, [3]Department of Viroscience, Erasmus Medical Center, 3015 GD Rotterdam, the Netherlands, [4]Department of Zoology, University of Cambridge, Cambridge, United Kingdom

Background

Influenza A viruses (IAVs) of the H9N2 subtype are enzootic in poultry in Asia, the Middle East, and Africa, causing significant economic damage to the poultry industry due to high morbidity and associated mortality. Due to their zoonotic potential, the World Health Organization (WHO) places H9N2 IAVs among those with pandemic concern. To determine molecular signatures of antibody recognition of the hemagglutinin (HA) of the H9 subtype IAVs, phylogenetics, and antigenic cartography were combined.

Method

Analyzing the HA1 portion of H9 IAVs, 11 consensus sequences were produced to capture the potential antigenic diversity of these viruses on a global scale. We created 11 chimeric HA sequences containing the HA1 of these consensus sequences on a constant HA2 portion from a prototypic H9 strain. Nine chimeric HAs were successfully rescued by reverse genetics, and the resulting viruses were used to generate antibodies in quails.

Result

Antigenic cartography maps were generated, plotting the cross-hemagglutination inhibition (HI) data from the panel of sera against the chimeric constructs. ACMACS k-cluster analysis implemented with the Ward hierarchical-clustering approach allowed the identification of 4 H9 HA antigenic clusters. Furthermore, few amino acid positions of putative antigenic relevance allowed two-way complete antigenic cluster transitions. Although mutations at amino acid positions 150, 180, and 217 (H9 HA numbering) had a relatively significant impact on HI activity, only the mutations E180A, R131K/E180A, and F150L/Q217I led to complete cluster transitions.

Conclusion

These studies suggest that a combination of a few amino acid residues modulates HI activity in the HA of H9 IAVs. Our studies provide significant insights into the antigenic profile of H9 IAVs with essential implications for understanding antigenic drift and for improved vaccine development.

Poster Reception II

Rebecca Gillespie - AOXI0249

Versatile virus microneutralization assay for high-throughput assessment of influenza antibodies

Rebecca Gillespie[1], Adrian Creanga[1], Masaru Kanekiyo[1]

[1]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Background

An integral step in vaccine development and antibody discovery is the ability to test serum or antibodies for their functional activity such as virus neutralization. Standard neutralization assays, for example the plaque reduction neutralization test (PRNT), the hemagglutination inhibition (HAI) assay, and the ELISA based microneutralization assay (MNA) are limiting and pose challenges to laboratories without high containment facilities, restricting research on influenza viruses with pandemic potential (e.g., H5N1 and H7N9). We set out to create an influenza MNA that can be performed rapidly and safely in the BSL-2 laboratory, has biological relevance similar to a traditional PRNT, and is comparable in sensitivity to the ELISA-based MNA for influenza standardized by the World Health Organization.

Method

We used reverse genetics techniques to build a panel of representative replication-restricted reporter (R3) influenza viruses carrying a fluorescent reporter gene by replacing an essential viral gene (i.e., HA or PB1). Thus, R3 viruses are restricted to grow only in cells expressing the missing viral gene. These R3 viruses have the internal genes of A/WSN/1933 with HA and NA genes derived from viruses of interest. Using these R3 viruses, we developed a fluorescence-based high-throughput R3 virus MNA for in-depth profiling of influenza antibodies and serum which is safely performed in a biosafety level 2 environment.

Result

The R3 virus MNA has facilitated significant improvements in our ability to characterize anti-influenza antibodies and advance improved influenza vaccines. Our current panel represents 50+ R3 influenza A viruses including group 1 H1, H2, H5, H6, H9 and group 2 H3, H7 and H10 subtypes as well as influenza B lineages. Recent and upcoming studies have included deep profiling of broadly neutralizing antibodies, detailed evaluation of vaccine-induced responses for pre-clinical and clinical samples, and characterization of the virus inhibitory activity of antibodies to viral NA.

Conclusion

The improved R3-based influenza virus MNA is a powerful tool that has had a profound impact on our capability to analyze vaccine-induced antibody responses and monoclonal antibodies. It has been used in multiple discovery, preclinical, and clinical studies. As we evolve the panel of influenza viruses and improve throughput, the assay continues to be an indispensable tool not only to assess immune responses but also to study virus-antibody interactions that would not have been reliably possible with the traditional assays. New technologies such as this are essential in our pursuit to develop broadly protective vaccines and therapeutics.

Poster Reception II

Luca Giurgea - AOXI0273

Mucosal Antibody Responses Against Influenza Antigens do not Correlate with Serum Antibody Responses in Healthy Volunteers undergoing Influenza Viral Challenge

Luca Giurgea[3], Rachel Bean[3], Alison Han[3], Lindsay Czajkowski[3], Adriana Cervantes-Medina[3], Monica Gouzoulis[3], Holly Ann Baus[3], Susan Reed[3], Rani Athota[3], Allyson Mateja[2], Sally Hunsberger[1], John Kash[4], Jeffery Taubenberger[4], Matthew Memoli[3]

[1]Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, [2]Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, [3]LID Clinical Studies Unit, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, [4]Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Background

The relationship between mucosal humoral immunity and systemic humoral immunity, measured against specific antigens, and its evolution over time is not well understood.

Method

We examined the correlation of antibody titers against different antigens and at different timepoints from serum and nasal mucosal samples collected during a human influenza A (H1N1) intranasal (IN) challenge in vaccinated and unvaccinated individuals.

Result

Most systemic antibody titers were boosted following challenge, but participants with relatively higher titers pre-challenge also had higher titers post-challenge. There were strong correlations between systemic hemagglutinin (HA) inhibition (HAI) and both HA IgG and HA Stalk IgG titers pre-challenge and 7 days post-challenge; at 8 weeks post-challenge HAI and HA IgG were moderately correlated. There were significant moderate correlations between systemic neuraminidase (NA) inhibition (NAI) and NA IgG titers pre-challenge and 7 days post-challenge. However, serum antibody responses against HA had no significant correlation with serum antibody responses against NA at pre-challenge and 7 days post-challenge timepoints and had a modest correlation at the 8-week post-challenge timepoint. At all timepoints, systemic antibody titers against each specific antigen did not correlate significantly with mucosal titers against the same antigen. Similarly, there were no significant correlations between total serum IgA or IgG titers and any other antibody levels.

Conclusion

These results suggest that there were no strong relationships between the systemic levels of antibodies against HA and those against NA. Furthermore, the levels of serum IgG antibodies against a particular antigen were not predictive of the levels of nasal IgA antibodies against the same antigen, suggesting an independence in immune responses across systemic and mucosal compartments.

Poster Reception II

Shivaprakash Gangappa - AOXI0288

Impact of dietary calories restriction on protective immunity to influenza infection

Andrew Taylor[1], Caitlin Bohannon[1], Weiping Cao[1], Amrita Kumar[1], Suryaprakash Sambhara[1], Shivaprakash Gangappa[1]

[1]Centers for Disease Control and Prevention

Background

Dietary protein plays an important role in immunity against microbial infections. Previously, several studies have established a positive correlation between calorie restriction and immunity to influenza. In our earlier studies in mice fed with different levels of dietary protein, when compared with adequate protein (AP; 18%), we found that mice maintained on very low protein (VLP; 2%) show significant defects in immune responses and protective immunity to influenza.

Method

In the current study, by increasing the protein-derived energy from VLP to low protein (LP; 5%), we investigated the effects of low protein diet when compared with AP diet in the mouse model of influenza infection.

Result

We found that virus-induced disease severity, based on virus-induced morbidity, mortality, and trafficking of inflammatory cell types to the lung tissue, was comparable between AP and LP groups. Several virus-induced cytokines (IL-6, IL-12p40) and chemokines (KC, GM-CSF, MCP-1, MIP-beta) were decreased in the lung tissue of LP diet fed mice. Also, early antiviral response (IFN-beta) in the LP group was significantly decreased leading to a relative increase in lung virus titer. Furthermore, despite a relative increase in percent pro-B cells (LP; 12.4 vs. AP; 8.6) and a decrease in immature B cells (LP; 3.8 vs. AP; 5.4) in the bone marrow, mice maintained on the LP diet showed comparable virus-specific antibody response. Unexpectedly, when compared with AP group, influenza-infected LP group of mice showed increase in percent IFNgamma+CD4+ T cells (Day 15: LP; 2.3 vs. AP; 0.7) and percent influenza nuclear protein-specific CD8+ T cells (Day 15: LP; 4.1 vs. AP; 1.2) in the spleen. Moreover, transfer of either immune serum or immune splenocytes from LP diet fed mice to naïve mice conferred protective immunity to viral challenge at levels comparable to transfer of immune mediators from AP group of mice.

Conclusion

Our results demonstrate the effect of lowering dietary protein on innate and adaptive immune responses to influenza infection in mice and underscore the need to understand the different effects of protein-derived calorie restriction to boost immunity against influenza virus infection.

Poster Reception II

Evan Anderson - AOXI0242

Influenza Vaccine Effectiveness among Hospitalized Adults Age 50 or Greater with ARI and among Hospitalized Adults 18 Years or Greater with Chronic Obstructive Pulmonary Disease (COPD) or Congestive Heart Failure (CHF) Exacerbations

Ashley Tippett[2], Laila Hussaini[2], Mary Kelly[5], Meg Taylor[5], Olivia Reese[2], Inci Yildirim[2], Theda Gibson[2], Luis Salazar[2], Laurel Bristow[1], Caroline Ciric[5], Andrew Chang[1], Kieffer Hellmeister[1], Zayna Al-Husein[1], Wensheng Li[5], Hui-Mien Hsiao[5], Robin Hubler[6], Elizabeth Begier[6], Qing Liu[6], Bradford Gessner[6], Amy Keane[2], Christina Rostad[3], Carol Kao[4], Nadine Rouphael[1], Evan Anderson[4]

[1]Emory University School of Medicine Department of Medicine, Hope Clinic, [2]Emory University School of Medicine Department of Pediatrics, [3]Emory University School of Medicine Department of Pediatrics, Children's Healthcare of Atlanta, [4]Emory University School of Medicine Departments of Pediatrics and Medicine, Children's Healthcare of Atlanta, [5]Emory University School of Medicine, Department of Pediatrics, [6]Pfizer

Background

Influenza (Flu) vaccine effectiveness (VE) varies from year-to year against outpatient influenza-like illness (ILI). Data are limited about Flu VE in prevention of Flu-related hospitalizations.

Method

We conducted Flu surveillance at two US hospitals from Oct 2018 - Mar 2020 among adults age >=50 years hospitalized with acute respiratory tract infections (ARI) and adults age ≥18 years with COPD or CHF-related admissions. Adults were eligible if they resided in 1 of 8 counties around Atlanta, GA. Persons with symptoms >14 days were excluded. Nasopharyngeal and oropharyngeal swabs were tested for Flu using BioFire® FilmArray® respiratory panel and standard of care molecular results were included (when available). Influenza vaccination history was determined by Georgia vaccine registry review and review of inpatient and outpatient medical records. We compared the demographic features and past medical history of Flu+/Flu- and vaccinated/nonvaccinated patients (confirmed Flu vaccination history). We used a test-negative case-control design to determine Flu VE by comparing the odds that the Flu+ group received vaccine to the odds that the Flu- group received vaccine. Multivariable logistic regression was used to control for potential confounders.

Result

Among 3,090 eligible adults, 1607 (52%) were enrolled. Of the 1562 meeting the final case definition, 116 (7.4%) were Flu+; 1516 had verified vaccination history of whom 701 (46.2%) were vaccinated. Of those vaccinated, 37 (5.3%) were Flu+. The unadjusted VE for the 2 seasons was 44.3% (95% CI:16, 62); Season 1 VE=47.8% (95% CI: -5.8, 74.2) and Season 2 VE=40.2% (95% CI: 1.2, 63.8). After adjustment for age, race/ethnicity, blood disorders, diabetes, chronic kidney disease, transplantation, and other immunocompromising conditions, Flu VE for the 2 seasons was 43.7% (95% CI: 14, 63).

Conclusion

The adjusted Flu VE was 43.7% (95% CI: 14, 63) during the 2018 - 2020 influenza seasons in prevention of influenza-related hospitalizations in this population.

Poster Reception II

Ian McGovern - AOXI0244

Relative Vaccine Effectiveness of the MF59-Adjuvanted Trivalent Seasonal Influenza Vaccine Compared to High-Dose Trivalent Seasonal Influenza Vaccine Among Adults 65 Years of Age or Older, a Systematic Literature Review and Meta-Analysis

Ian McGovern[1], Brenda Coleman[3], Mendel Haag[2]

[1]Seqirus Inc., Cambridge, MA, United States, [2]Seqirus Netherlands BV, Amsterdam, The Netherlands, [3]Sinai Health System, Toronto; Dalla Lana School of Public Health, University of Toronto

Background

Immunosenescence in older adults results in a lower immune response to vaccination, and sub-optimal effectiveness of non-enhanced vaccines. The MF59-adjuvanted trivalent influenza vaccine (aTIV) and high-dose influenza vaccine (HD-TIV) were both developed to improve response to influenza vaccination for older adults. This systematic review and meta-analysis evaluated the relative vaccine effectiveness (rVE) of these two enhanced vaccines.

Method

Peer-reviewed and grey literature published between 01-January-1997 and 17-September-2021 were included. Observational studies evaluating the rVE of aTIV vs HD-TIV among adults ≥65 years of age were eligible. Paule-Mandel random-effects meta-analysis was used for all analyses in anticipation of variable rVE due to viral, vaccine, and host factors.

Result

After removal of duplicates, 4,627 publications were screened for eligibility and a total of 11 publications reporting the rVE of aTIV vs HD-TIV were identified, 9 of which were included in at least one meta-analysis. Of the two publications that were not included in any meta-analysis, one reported rVE among high-risk patients while the other evaluated rVE against any respiratory outcome. The remaining 9 studies reported rVE estimates for prevention of influenza-related medical encounters in different clinical settings over a 4-season period in the US. The pooled rVE of aTIV vs HD-TIV for prevention of influenza-related medical encounters was 8.5% (95%CI: -3.0 to 18.8) for outpatient encounters and 1.2% (95% CI: -1.3 to 3.8) for hospital/emergency department (ED) encounters (Figure 1), with high heterogeneity for both analyses.

Conclusion

Pooled estimates from multiple real-world evidence studies suggest that aTIV and HD-TIV have comparable performance for prevention of influenza-related outpatient and hospital/ED encounters.

Poster Reception II

Roberta Vaikutytė - AOXI0270

Influenza Vaccine Effectiveness in Patients Hospitalized with Severe Acute Respiratory Infection in Lithuania During the 2019/2020 Influenza Season

Roberta Vaikutytė[3], Monika Kuliese[3], Aukse Mickiene[3], Ligita Jancoriene[1], Birute Zablockiene[1], Giedre Gefenaite[2]

[1]Clinic of Infectious Diseases and Dermatovenerology, Institute of Clinical Medicine, Faculty of Medicine; Center of Infectious Diseases, Vilnius University Hospital Santaros Clinics, [2]Department of Health Sciences, Faculty of Medicine, Lund University, [3]Department of Infectious Diseases, Lithuanian University of Health Sciences

Background

Influenza is a contagious viral airborne disease that adds to the clinical and economic burden on the healthcare system that could be prevented substantially by seasonal influenza vaccination. Seasonal influenza vaccine effectiveness (SIVE) varies a lot and should therefore be monitored. This report aims to update age-stratified SIVE estimates among patients hospitalized due to severe acute respiratory infection (SARI) during the 2019-2020 influenza season.

Method

We performed a test-negative case-control study between December, 2019 and April, 2020 influenza season. We estimated SIVE and its 95% confidence intervals (95% CI) with logistic regression as (1-odds ratio)*100%. The models were adjusted for covariates that changed the unadjusted SIVE by ≥10%.

Result

Among 84 participants, 32 (38.1%) were influenza positive, mostly with A(H1N1)pdm09. SIVE against any influenza adjusted for age and heart disease was 60.8% (95% CI: 13.2%, 86.3%). Age-stratified point estimates adjusted for heart diseases indicated different SIVE, and was 36.0% (95% CI: 3.2%, 409.2%) and 78.4% (95% CI: 17.4%, 352.2%) for ≥ 65 and 18-64 year-old participants, respectively.

Conclusion

The point estimates suggested high SIVE against any influenza among hospitalized 18-64-year-old SARI participants, while lower estimates were found in the ≥65-year-old group. Although SIVE estimates confidence intervals are broad and results can serve only as indicatory due to lacking sample size and therefore statistical power, they are in line with the estimates reported by other studies during the 2019-2020 season.

Poster Reception II

Md. Zakiul Hassan - AOXI0295

Cost-effectiveness of seasonal influenza vaccination in WHO defined- high-risk population in Bangladesh

Md. Zakiul Hassan[5], Md Abdullah Al Jubayer Biswas[5], Tahmina Shirin[3], Mahmudur Rahman[1], William W. Davis[2], Fahmida Chowdhury[5], Mofakhar Hussain[4]

[1]Global Health Development/the Eastern Mediterranean Public Health Network (EMPHNET), [2]Influenza Division, Centers for Disease Control and Prevention Regional Influenza Program, Bangkok, Thailand, [3]Institute of Epidemiology, Disease Control and Research (IEDCR), Dhaka, Bangladesh, [4]Institute of Health Policy, Management and Evaluation, University of Toronto, Canada, [5]Program for Emerging Infections, Infectious Disease Division, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Mohakhali, Dhaka, Bangladesh

Background

Bangladesh carries substantial health and economic burden of seasonal influenza, particularly among the World Health Organization (WHO)-defined high-risk population: children under five years, the elderly (≥60), adults with co-morbid conditions, pregnant women and healthcare workers (HCWs). We implemented a modelling study to determine the cost-effectiveness of influenza vaccination in each of these five groups to inform policy decisions on risk group prioritization for influenza vaccination in Bangladesh.

Method

We implemented a Markov decision-analytic model to estimate the impact of influenza vaccination for each target risk group. We obtained model inputs from hospital-based influenza surveillance data, unpublished surveys, and published literature preferentially from studies in Bangladesh, followed by regional and global literature. We used Quality-Adjusted Life Years (QALY) as the health outcome. We estimated incremental cost-effectiveness ratios (ICERs) for each risk group by comparing the costs and QALY of immunizing each group compared to no vaccination. We considered a willingness to pay (WTP) threshold (ICER) of less than one GDP per capita as highly cost-effective and of one to three times GDP per capita as cost-effective (per WHO standard); for Bangladesh, this threshold ranges between $2,462 and $7,386. We performed a multivariable probabilistic sensitivity analysis using Monte Carlo simulations to address uncertainty in the model inputs.

Result

The estimated annual number of outpatient cases (range:6,610-375,8076), hospitalization (range:2,179-127,796) and deaths (range: 14-508,439) averted for each group by vaccinating everyone in the group was highest for the elderly and the lowest for HCWs. Direct vaccine program cost ranged between $281,198 (for HCWs) to $226 million (for adults with co-morbid conditions), and total direct health care incremental cost (versus no vaccine) ranged from $80,710 (for HCWs) to $18 million (for adults with co-morbid conditions). ICERs were -$86.34, -$34.50, -$12.15, $47.17, and $248.97 per QALY gained for HCWs, the elderly, children under five years, adults with co-morbid conditions, and pregnant women, respectively. For all risk groups, ICER were below the WHO willingness-to-pay threshold for Bangladesh and were thus cost-effective; pregnant women and adults with co-morbid conditions were highly cost-effective per additional life gained. Vaccinating children under five years, adults with a co-morbid condition, and HCWs was cost-saving per additional life gained.

Conclusion

Influenza vaccination to all target risk groups in Bangladesh would be highly cost-effective, per WHO standards. However, vaccinating HCWs, the elderly and children under five years would be cost-saving to society and could be prioritized.

Poster Reception II

Ashley Fowlkes - AOXI0309

Evaluating COVID-19 mRNA vaccine effectiveness in preventing asymptomatic and symptomatic SARS-CoV-2 infection in a prospective cohort of frontline workers in the United States, December 2020 - February 2022

Ashley Fowlkes[4], Jeffrey Burgess[7], Alberto Caban-Martinez[8], Manjusha Gaglani[1], Allison Naleway[5], Lauren Olsho[2], Harmony Tyner[6], Mark Thompson[3]

[1]4Baylor Scott and White Health, Texas A&M University College of Medicine, [2]Abt Associates, Inc., [3]Centers for Disease Control and Prevention, [4]Epidemiology and Prevention Branch, Influenza Division, Centers for Disease Control and Prevention, [5]Kaiser Permanente Northwest Center for Health Research, [6]St. Luke's Regional Health Care System, [7]University of Arizona, [8]University of Miami

Background

Since emergence of the SARS-CoV-2 virus, frontline workers have faced a disproportionally high risk of SARS-CoV-2 infection while ensuring continuity of essential services during the COVID-19 pandemic. Using data from a prospective occupational cohort study of frontline workers, we evaluated COVID-19 mRNA vaccine effectiveness (VE) in preventing symptomatic and asymptomatic SARS-CoV-2 infections.

Method

The ongoing HEROES-RECOVER cohort of over 5,000 health care personnel, first responders, and other essential and other frontline workers was initiated in July 2020, in 6 states. Participants provide self-collected nasal swabs weekly and upon the onset of COVID-19-associated illness symptoms for SARS-CoV-2 and influenza virus testing by reverse transcription-polymerase chain reaction (RT-PCR) and whole genome sequencing. Socio-demographic information and medical, occupational and COVID-19 and influenza vaccination history are collected throughout the study. From December 2020 through January 2022, COVID-19 VE was estimated using Cox proportional hazards model with time-varying vaccination status and adjusted by covariates for confounders and inverse propensity to be vaccinated weights.

Result

The 2-dose VE against SARS-CoV-2 infections prior to B.1.617.2 (Delta) variant circulation was 91% (95% Confidence Interval [CI]: 81%-96%, median 192 days since dose 2 [IQR: 135-209]), falling to 65% (95% CI: 49%-76%, median 267 days [IQR: 248-301]) against Delta infection and 46% (95% CI: 25%-61%, median 330 days [IQR: 272-357]) against B.1.1.529 (Omicron) infection. A third (booster) dose increased VE against Delta infection to 91% (95% CI: 84%-95%, median 74 days since dose 3 [IQR: 52-93]) and 60% (95% CI: 42%-72%, median 93 days [IQR: 70-113]) against Omicron.

Conclusion

Systematic testing of frontline workers at increased risk for exposure to SARS-CoV-2 provided estimates of COVID-19 mRNA VE against infection. VE declined over time for both the 2-dose and 2-dose plus booster regimens during multiple variant predominance waves, demonstrating the importance of remaining up to date with recommended COVID-19 vaccine doses. The HEROES-RECOVER platform will allow for future evaluations of COVID-19 and influenza VE.

Poster Reception II

Delphine Guyon-Gellin - AOXI0232

RESULTS OF A PHASE 2 STUDY WITH OVX836 SUGGEST EFFECTIVENESS IN PREVENTING INFLUENZA-LIKE ILLNESS AND CONFIRM GOOD SAFETY PROFILE

Isabel Leroux-Roels[1], Jessika Tourneur[2], Geert Leroux-Roels[1], Delphine Guyon-Gellin[2], Florence Nicolas[2], Paul Willems[2], Alexandre Le Vert[2]

[1]Ghent University, [2]Osivax

Background

OVX836 is an unadjuvanted subunit vaccine composed of a recombinant version of the Influenza A Nucleoprotein (NP), designed to trigger strong cellular immunity to the well-conserved NP. Such T-cell immunity against NP is associated with protection against influenza disease, providing strong rationale for NP-based influenza universal vaccine. OVX836 was safe and immunogenic in two clinical trials. In a previous phase 2a study, we observed a potential protective effect of OVX836 at 180µg, not observed with 90µg. Here, we share the results of a third study evaluating higher dose-levels of OVX836.

Method

OVX836-003 is a Phase 2a, randomized, double-blind, controlled study in 137 healthy adults (<50 years old) comparing immunogenicity and safety of one intramuscular immunization of OVX836 at 300µg or 480µg, to OVX836 at 180µg and placebo. Monitoring of PCR-confirmed Influenza-Like Illness in vaccinated subjects (104 subjects) vs unvaccinated subjects allowed to explore vaccine efficacy. The placebo group of 33 subjects was complemented by a cohort of 66 matched unvaccinated subjects recruited in parallel at the same center under an observational study protocol (OVX-FLU-001).

Result

Efficacy: Two cases of PCR-confirmed symptomatic Influenza (ILIs) were reported in the OVX836 groups (all dose-levels pooled) vs 9 cases for the placebo + untreated cohorts, reflecting an Observed Efficacy of 79% [4.5%; 95.3%] (p=0.030; Fisher's exact test). Absence of differences in PCR-confirmed symptomatic COVID-19 between groups supported the validity of the pooled analysis between the OVX836-003 and OVX-FLU-001 studies, by allowing to eliminate a placebo effect between vaccinated and unvaccinated cohorts as a possible confounder.

Safety: All dose-levels of OVX836 were found safe and well-tolerated. Incidence of "severe" (Grade 3 as per FDA toxicity scale for vaccine clinical trials) or higher intensity adverse events remained low without apparent dose-limiting effects.

Conclusion

This is the second study suggesting efficacy of OVX836 in decreasing symptomatic influenza. This observation, made during the 2021-22 flu season with circulating strains differing from those of the 2019-20 flu season, tends to confirm the potential of OVX836 to provide a broad-spectrum protection against different strains of influenza virus. These results warrant further evaluation of this universal vaccine candidate in larger efficacy clinical trial(s).

Poster Reception II

Amelia Hofstetter - AOXI0314

Influenza hemagglutinin stem nanoparticle vaccine (H1ssF) induces cross-reactive neutralizing antibodies against group 1 influenza: a phase 1 trial in healthy adults

Amelia Hofstetter[1], Alicia T. Widge[3], Katherine V. Houser[3], Seemal Awan[3], Grace L. Chen[3], Maria Claudia Burgos Florez[3], Nina M. Berkowitz[3], Floreliz Mendoza[3], Cynthia S. Hendel[3], LaSonji A. Holman[3], Ingelise J. Gorgon[3], C. Jason Liang[2], Michelle Crank[3], Rebecca A. Gillespie[3], Adrian Creanga[3], Sarah F. Andrews[3], Sandeep R. Narpala[3], Christian Hatcher[3], Mike Castro[3], Manjula Basappa[3], Bob C. Lin[3], Sarah O'Connell[3], Masaru Kanekiyo[3], Adrian B. McDermott[3], Lesia K. Dropulic[3], Richard A. Koup[3], Barney S. Graham[3], John R. Mascola[3], Julie E. Ledgerwood[3]

[1]United States National Institutes of Health, [2]United States National Institutes of Health, Division of Clinical Research, [3]United States National Institutes of Health, Vaccine Research Center

Background

Immune responses resulting from current influenza vaccines are biased toward the immunodominant and variable hemagglutinin (HA) head. We found this dominant head region limited stem-directed responses in H2N2-immune adults in a prior clinical trial evaluating a full-length H2 HA ferritin-based nanoparticle vaccine. A vaccine designed without the variable HA head domain has the potential to focus the immune response on the highly conserved HA stem region, which could generate broader cross-reactive immunity across diverse influenza viruses.

Method

At the National Institutes of Health Clinical Center in Bethesda, MD, USA, we conducted a first-in-human dose-escalation open-label phase 1 clinical trial (NCT03814720) evaluating a novel influenza H1 hemagglutinin (HA) stabilized stem ferritin-based nanoparticle vaccine (H1ssF) derived from the stem of A/New Caledonia/20/1999 (H1N1). Fifty-two healthy adults aged 18-70 years old enrolled to receive either unadjuvanted 20 mcg H1ssF once (5 participants) or 60 mcg H1ssF twice (47 participants) with a prime-boost interval of 16 weeks. The participants who received 60 mcg doses were stratified by age. The primary objective of this trial was to evaluate the safety and tolerability of H1ssF, and the secondary objective was to evaluate antibody responses after vaccination.

Result

We found this vaccine to be safe and well tolerated. Solicited local and systemic reactogenicity was mild when reported. The most common symptoms included pain/tenderness at the injection site (n=10, 19%), headache (n=10, 19%) and malaise (n=6, 12%). We found that H1ssF elicited cross-reactive neutralizing antibodies targeting the conserved HA stem of group 1 influenza viruses in immune adults by two weeks after vaccination to a level 2.3-, 2.6- and 5.5-fold higher than the baseline for H1, H2 and H5, respectively. Neutralizing antibody responses remained elevated over a year after vaccination.

Conclusion

H1ssF is safe and immunogenic; resulting in cross-reactive neutralizing antibodies targeting the conserved HA stem for group 1 influenza viruses. Our results support this platform as a step forward in the search for a universal influenza vaccine.

Poster Reception II

Melanie Möller-Arendt - AOXI0220

Results from the Enhanced Passive Safety Surveillance for the influenza vaccine Influvac Tetra in Germany during 2021/2022 vaccination season

Melanie Möller-Arendt[4], Serge Van de Witte[1], Jos Nauta[1], Laura Colombo[2], Jutta Rogoll[3]

[1]Abbott Healthcare Products B.V., Weesp, The Netherlands, [2]Global Medical Affairs, Viatris, Monza, Italy, [3]Global Pharmacovigilance, Abbott Laboratories GmbH, Hannover, Germany, [4]Viatris Healthcare GmbH

Background

Since 2014, an Enhanced Passive Safety Surveillance (EPSS) has been run successfully for Influvac®/ Influvac® Tetra, fulfilling the Interim guidance's objectives on enhanced safety surveillance for seasonal influenza vaccines in the European Union. Results from seven consecutive seasons confirmed the favorable safety profile of both vaccines. This abstract summarizes the data obtained from the EPSS conducted in the 2021/2022 vaccination season.

Method

After immunization with Influvac® Tetra as per routine medical practice, vaccinees were asked to complete response cards with pre-specified local and systemic Adverse Events of Interest (AEIs) and to return within seven days. In addition, the response cards contained a call center number enabling to report any other than the pre-defined AEs. The EPSS aimed to include 1,000 vaccinees across all age groups.

Result

In the EPSS 2021/2022, a total of 805 vaccinees were exposed, of which 255 (31.7%) reported at least one AEI. Overall, headache and muscle/joint pain were the most frequent systemic AEIs and injection site pain was the most frequent local AEI reported (Table 1). Local AEIs were generally mild to moderate in severity and mostly resolved within 3 days. Reporting rates in elderly tended to be lower than in adults. Overall, data from this year´s EPSS in terms of reporting rates, severity and duration were comparable to previous seasons´ data. Four non-serious AEs were reported via the call center. No new safety concern was identified from this data set.

Conclusion

Results from the EPSS 2021/2022 in any of the age groups are comparable to the previous years' data and confirm the favorable safety profile of Influvac® Tetra.

Poster Reception II

Jason Lee - AOXI0224

Efficacy and Effectiveness of High-Dose Influenza Vaccine in Older Adults by Age and Seasonal Characteristics: An Updated Systematic Review and Meta-Analysis

Jason Lee[1], Gary Lam[6], Rolan Vaisman[6], Kevin Yin[3], Bruce Seet[5], Matthew Loiacono[4], Sandrine Samson[2]

[1]Sanofi, [2]Sanofi, Lyon, France, [3]Sanofi, Singapore; University of Sydney, Camperdown, NSW, Australia, [4]Sanofi, Swiftwater, PA, USA, [5]Sanofi, Toronto, ON, Canada, [6]Sanofi, Toronto, ON, Canada; Leslie Dan School of Pharmacy, University of Toronto, Toronto, ON, Canada

Background

Since its initial approval in 2009, high-dose inactivated influenza vaccine (HD-IIV) has been used in older adults in 31 countries. Many studies comparing HD-IIV to standard-dose influenza vaccines (SD-IIV) have demonstrated protection beyond influenza illness, including reduction of outcomes such as cardiorespiratory and all-cause hospitalizations. This study is an update of previously-conducted reviews of the relative vaccine efficacy/effectiveness (rVE) of HD-IIV compared to SD-IIV in adults ≥65 years against influenza-associated outcomes from 2009/10 - 2019/20 influenza seasons, with additional sub-analyses by both seasonal and recipient characteristics.

Method

An updated systematic review and meta-analysis was conducted for studies assessing the rVE of HD-IIV against probable/laboratory-confirmed influenza-like illness (ILI), emergency department (ED) and/or hospital admissions in adults ≥65 years. Results from individual seasons were extracted from the identified studies, and stratified based on clinical outcomes, characteristics of study subjects, and influenza season. Meta-analyses were then performed to estimate pooled rVEs of HD-IIV.

Result

19 studies (4 randomized and 15 observational studies) were meta-analyzed, providing data from 11 consecutive influenza seasons and over 45 million individuals receiving either HD-IIV or SD-IIV. Across all influenza seasons and age groups, HD-IIV demonstrated improved protection compared to SD-IIV against ILI (rVE=14.3%, 95% CI: 4.2-23.3%). HD-IIV was also more effective at preventing hospital/ED visits due to influenza (rVE=10.4%, 95% CI: 6.8-13.9%), as well as hospital admissions due to influenza (rVE=11.2%, 95% CI: 7.4-14.8%), pneumonia (rVE=27.3%, 95% CI: 15.3-37.6%), pneumonia and influenza (rVE=13.4%, 95% CI: 7.3-19.2%), respiratory events (rVE=14.3%, 95% CI: 8.5-20.0%), cardiovascular events (rVE=13.1%, 95% CI: 10.5-15.7%), cardiorespiratory events (rVE=17.9%, 95% CI: 15.0-20.8%), and all-causes (rVE=8.4%, 95% CI: 5.7-11.0%). Pooled rVEs were similar in sub-analyses by predominant circulating strains, match of the vaccine to circulating strains, study type, and study setting. While all adults 65+ benefited from the use of HD-IIV, age-stratified sub-analyses of the rVE of HD-IIV against ILI and influenza hospitalizations suggested additional relative benefit by HD-IIV with increasing age.

Conclusion

Evidence over 11 consecutive influenza seasons from both randomized and observational studies suggests that HD-IIV was consistently more effective than SD-IIV at reducing influenza and associated serious outcomes irrespective of recipient age and characteristics of the influenza season.

Poster Reception II

Othmar Engelhardt - AOXI0234

Assay Harmonisation and Use of Biological Standards to Improve the Reproducibility of the Haemagglutination Inhibition Assay: A FLUCOP collaborative study

Joanna Waldock[4], Lingyi Zheng[7], Edmond Remarque[1], Alexandre Civet[5], Branda Hu[7], Sarah Lartey Jalloh[3], Rebecca Cox[3], Sammy Ho[8], Katja Hoschler[8], Thierry Ollinger[2], Claudia Trombetta[9], Catherine Caillet[6], Othmar Engelhardt[4]

[1]Biomedical Primate Research Center, Rijswijk, The Netherlands, [2]GSK, Wavre, Belgium, [3]Influenza Centre, Department of Clinical Sciences, University of Bergen, Norway, [4]MHRA, Potters Bar, UK, [5]Quinten, Paris, France, [6]Sanofi Pasteur, Lyon, France, [7]Sanofi Pasteur, Swiftwater, Pennsylvania, USA, [8]UK Health Security Agency, London, UK, [9]University of Siena, Department of Molecular and Developmental Medicine, Italy

Background

The haemagglutination inhibition (HAI) assay is an established technique for assessing influenza immunity, through measurement of anti-haemagglutinin antibodies. Improved reproducibility of this assay is required to provide meaningful data across different testing laboratories. This study assessed the impact of harmonising the HAI assay protocol/reagents and using standards on inter-laboratory variability.

Method

Human pre- and post-vaccination sera from individuals (n=30) vaccinated against influenza were tested across six laboratories. We used a design of experiment (DOE) method to evaluate the impact of assay parameters on inter-laboratory HAI assay variability. Statistical and mathematical approaches were used for data analysis. We developed a consensus protocol and assessed its performance against in-house HAI testing. We additionally tested the performance of several potential biological standards.

Result

In-house testing with four reassortant viruses showed considerable inter-laboratory variation (geometric coefficient of variation (GCV) range of 50%-117%). The age and concentration of turkey red blood cells, incubation duration and temperature were key assay parameters affecting variability. Use of a consensus protocol with common reagents, including viruses, significantly reduced GCV between laboratories to 22%-54%. Pooled post-vaccination human sera from different vaccination campaigns were effective as biological standards.

Conclusion

Our results demonstrate that the harmonisation of protocols and critical reagents is effective in reducing inter-laboratory variability in HAI assay results, and that pools of post-vaccination human sera have potential as biological standards that can be used over multiple vaccination campaigns. Moreover, the use of standards together with in-house protocols is as potent as the use of common protocols and reagents in reducing inter-laboratory variability.

Poster Reception II

Guadalupe Cortes-Garcia - AOXI0263

Influenza virus neuraminidase delivered as recombinant protein or mRNA is highly immunogenic in ferrets.

Guadalupe Cortes-Garcia[2], Mithila Ferdous[4], Justin Lagraff[5], Timothy Farrell[4], Karolyne Warny[5], Lisa Beppu[4], Siré N'Diaye[1], Lingyi Zheng[3], Satyajit Ray[4], Raul Gomila[4], Liqun Han[4], Svetlana Stegalkina[4], Jianxin Zhang[4], Irina Ustyugova[4], Mario Barro[4]

[1]IVIDATA Lyon, France, [2]Sanofi, [3]Sanofi, Non-clinical Biostatistics, Swiftwater PA, [4]Sanofi, Research North America, Cambridge MA, [5]Yoh Services LLC, Philadelphia PA

Background

Influenza causes significant respiratory morbidity and broader health impacts, including cardiovascular events and the exacerbation of chronic underlying conditions. Vaccination against influenza prevents or limits influenza like illness, and in the case of some established flu vaccines it also provides protection beyond flu, meaning demonstrated protection against flu complications. Next generation influenza vaccines that improve vaccine effectiveness are being investigated.

Neuraminidase (NA) is the second-most abundant glycoprotein on the surface of the influenza virus and an emerging target for next-generation influenza vaccines. In humans, NA-inhibiting (NAI) antibodies correlate with protection against disease caused by natural or experimental influenza virus infections and can be boosted by vaccination with seasonal inactivated influenza vaccines. However, NA content in current licensed vaccines is not standardized and NAI induction achieved through vaccination is often low compared to natural infection.

Method

To investigate the potential of NA antigen as a vaccine candidate, we developed the following platforms for NA vaccine production: 1) a recombinant protein vaccine based on a truncated soluble NA protein including the intact globular head domain in tetrameric conformation (rNA), and 2) an mRNA vaccine encoding full length neuraminidase protein and encapsulated in a lipid nanoparticle (mRNA-LNP).

A ferret model was used to assess the pathogenicity of influenza virus isolates due to their natural susceptibility to infection with human influenza isolates and the influenza-like symptoms displayed by infected ferrets. In this study, naïve ferrets were immunized twice with either a rNA vaccine (with or without squalene-based adjuvant) or a NA mRNA-LNP vaccine, prior to intranasal challenge with a clinical H3N2 influenza isolate expressing the homologous NA protein.

Result

Both rNA antigen given with adjuvant and NA mRNA-LNP vaccines induced NAI antibodies of similar magnitude as those induced with wild-type viral infection after two immunizations. A dose-dependent response was observed for NA mRNA-LNP, while adjuvant greatly boosted immunogenicity of rNA.

Ferrets vaccinated with rNA and NA mRNA-LNP were evaluated for viral shedding in nasal wash and severity of influenza-like symptoms (i.e., body weight loss and fever) compared to placebo, standard-of-care prophylactic (HA vaccine) and therapeutic (oseltamivir) interventions.

Conclusion

Our study supports the use of recombinant protein and mRNA-LNP vaccine platforms to selectively target NA based on the immunogenicity data. Protectivity of the NA vaccine variants, even in the absence of HA, will be reported.

(Study funded by Sanofi)

Poster Reception II

Nidhi Mittal - AOXI0274

Protective Efficacy of Recombinant Influenza Hemagglutinin Ectodomain fusions

Nidhi Mittal[1], Nayanika Sengupta[1], Sameer Kumar Malladi[1], Poorvi Reddy[2], Madhuraj Bhat[2], Raju S. Rajmani[1], Koyen Sedeyn[3], Xavier Saelens[3], Somnath Dutta[1], Raghavan Varadarajan[1]

[1]Molecular Biophysics Unit (MBU), Indian Institute of Science, Bengaluru 560012, India., [2]Mynvax Private Limited, Brigade MLR centre, Basavanagudi, Bengaluru 560004, India, [3]VIB-UGent Center for Medical Biotechnology, VIB, 9052 Ghent, Belgium; Department of Biochemistry and Microbiology, Ghent University, 9052 Ghent, Belgium.

Background

In current seasonal influenza vaccines, neutralizing antibody titers directed against the variable globular head of hemagglutinin surface protein are the primary correlate of protection. Given the requirement to provide broad protection, the focus of immunogen design in recent years has been to target conserved epitopes in the hemagglutinin stem, hemagglutinin receptor binding site, and alternative antigens such as neuraminidase (NA), and an extracellular domain (M2e). One significant barrier to including these antigens is the technical difficulty of adding additional components to current quadrivalent vaccine formulations. Since each component needs to be separately manufactured, this would come with increased manufacturing complexity and cost. To address this issue, as a proof of principle, we have designed genetic fusions of hemagglutinin ectodomains from influenza A subtype (H3 and H1) and influenza B subtype (HV and HY).

Method

We designed genetic fusions of hemagglutinin ectodomains from influenza A subtypes, and influenza B subtypes, containing either a single foldon trimerization motif or two foldons. The designed hemagglutinin ectofusion immunogens were recombinantly expressed in Expi293F cells and characterized. Immunogenicity and protective efficacy of designed hemagglutinin ectofusions, formulated with the MF59 equivalent adjuvant squalene-in-water emulsion (SWE), were evaluated in mice.

Result

Designed HA ectofusion immunogens were expressed as soluble trimers in Expi293F cells. Ectofusions were correctly folded and as thermostable as individual HA ectodomains. Interestingly, the ectofusion immunogens were equivalent to individual H1 and H3 ectodomains mixed in equimolar amounts in terms of immunogenicity and protective efficacy, although in the latter case, the immunogen concentration was double that in the ectofusion groups. Ectofusion immunogens elicited subtype-specific humoral immune responses in mice and protected against challenge with heterologous H1N1 and H3N2 mouse-adapted challenge viruses with higher neutralizing antibody titers against the H1N1 virus.

Conclusion

Our results demonstrate that hemagglutinin ectodomain fusions are viable immunogens that can be tolerated without loss of immunogenicity. The use of such ectodomain fused immunogens would reduce the number of components in a formulation and allow for the inclusion of other protective antigens to increase influenza vaccine efficacy.

Poster Reception II

Clotilde EL GUERCHE-SEBLAIN - AOXI0251

Comparison of the evolution of SARS-COV 2 variant distribution and seroprevalence estimates during the Sanofi Adjuvanted Recombinant Protein Vaccine efficacy trial: an epidemiology perspective.

Clotilde EL GUERCHE-SEBLAIN[1], Myint Aung-Pone, Nabila Shaikh[1], Christophe Grégoire, Carlos Guzman, Valentine Delore

[1]Sanofi Vaccines

Background

Globally, the first SARS-CoV-2 variant of concern (VOC) appeared at the end of 2020. Since then, several new variants have raised, some co-circulating, with unpredictability on the timing of their appearance. A phase III placebo-controlled clinical trial (VAT08) was conducted in several regions to evaluate the efficacy, immunogenicity, and safety of the Sanofi/GSK monovalent and bivalent recombinant protein vaccines. We compared epidemiology distribution of VOCs and seroprevalence estimates during the trial to help interpret preliminary seroprevalence rates and clinical trial results.

Method

The epidemiological monitoring of SARS-CoV-2 VOC circulation was performed between August 2021 and January 2022 for the 8 countries (United States, Colombia, Honduras, Kenya, Ghana, Nepal, India, Japan) where the trial was conducted, spanning across 4 continents. The GISAID platform was used to extract sequencing data from the different countries on a weekly basis. Information was crossed with national surveillance when available. SeroTracker dashboard (serotracker.com) was used to monitor the evolution of seroprevalence estimates. Data were compared to preliminary data available from the clinical trial.

Result

Based on published data, the circulation of VOCs was dominated by Delta from September 2021 until the first half of December 2021 (except in Colombia where Mu dominated until September 2021 and in the US at the start of the trial with Alpha predominating until mid-June 2021). From December 2021, Omicron has progressively become predominant in all countries. This epidemiological trend is consistent with what we observed in the preliminary data of the clinical trial. In parallel, a progressive increase of seroprevalence in all populations and all regions has been observed from 0% in early 2020 to over 95% in October 2021. While seroprevalence estimates were not available for all study countries, preliminary results from the clinical trial are consistent with published seroprevalence estimates.

Conclusion

Despite the limitation of non-availability of published epidemiological seroprevalence estimates for several study countries, overall similar high value ranges were observed compared to the clinical trial rates. The progressive increase of seroprevalence was initially observed with Delta variant predominating, followed by Omicron emerging at the end of 2021 presenting similar trend to the preliminary results from the clinical trial.

Poster Reception II

Claudia Maria Trombetta - AOXI0311

HUMORAL IMMUNE RESPONSE AGAINST SARS-CoV-2 VARIANTS AFTER TWO DOSES OF mRNA VACCINE IN AN ITALIAN CORRECTIONAL FACILITY

Claudia Maria Trombetta[3], Serena Marchi[3], Angela Stufano[2], Nicola Buonvino[1], Eleonora Lorusso[2], Emanuele Montomoli[3], Nicola Decaro[2], Piero Lovreglio[2]

[1]U.O.C. Penitentiary Medicine - Bari Local Health Authority, [2]University of Bari, [3]University of Siena

Background

Since the first isolation of SARS-CoV-2 in 2020, several variants have been detected worldwide, some of which designated as "variants of concern" (VOCs).

Correctional and detention facilities are not closed systems, representing a source of infection for the whole community. The prisoner population is a highly vulnerable population, at higher risk for the SARS-CoV-2 spread, also due to overcrowding, poor air ventilation and less healthcare provisions.

The available vaccines offer protection against SARS-CoV-2.

This study aimed to assess the humoral immune response against the original wild-type (WT) SARS-CoV-2 virus and four VOCs after two doses of mRNA vaccine in an Italian correctional facility for inmates affected by chronic diseases.

Method

A total of 342 serum samples were collected at the Bari correctional facility (Apulia, Italy) 21 days after the 2nd dose of mRNA vaccine (BNT162b2). One hundred forty-seven (147) serum samples were from correctional officers (CO) and 195 from inmates. Samples were tested by ELISA for the detection of antibodies against the nucleoprotein (NP) and by the virus neutralization assay against the original WT SARS-CoV-2 virus (2019-nCov/Italy-INMI1 strain) and some VOCs (Alpha, Beta, Gamma, and Omicron).

The research protocol was approved by the Ethics Committee of the University Hospital of Bari (n. 6955, prot. N. 0067544-02082021).

Result

Samples were tested for their ability to neutralize the original WT SARS-CoV-2 virus and Alpha, Beta, Gamma and Omicron variants.

After two doses of mRNA vaccine, 139 (94,56%) CO and 181 (92,82%) inmates were positive for neutralizing antibodies against the WT virus.

When tested against the VOCs, the most dramatic reduction in neutralizing antibodies was observed against the Omicron variant with 138 (93,88%) CO and 181 (92,82%) inmates having a ≥2-fold decrease, followed by the Beta variant (91,16% and 85,13%). When tested against Alfa and Gamma variants, 83 (56,46%) CO and 102 (52,31%) inmates and 83 (56,46%) CO and 124 (63,59%) inmates retained their neutralizing activity, respectively. Notably, N-positive subjects showed the highest geometric mean titers.

Conclusion

Overall, our results showed that two doses of mRNA vaccine induce a good antibody response against the WT virus even in subjects with chronic diseases and that natural infection seems to boost vaccine immunity. Against Omicron and Beta variants, neutralizing antibody response drops dramatically, underlining that two doses may not provide sufficient protection against variants characterized by some S mutations. These results support the strategy of administering an mRNA vaccine booster to enhance antibody-based cross-protection.

Poster Reception II

Takuya Hemmi - AOXI0371

Intranasal vaccine with ODN2006 as an adjuvant protects against viral infection with reducing the potential risk of lung eosinophilic immunopathology.

Takuya Hemmi[3], Akira Ainai[3], Takao Hashiguchi[6], Minoru Tobiume[2], Sho Miyamoto[2], Takayuki [2], Akira Ueno[4], Kaori Sano[2], Koji Tamura[1], Ryosuke Suzuki[5], Tadaki Suzuki[2]

[1]Department of Biological Science and Technology, Tokyo University of Science, [2]Department of Pathology, National Institute of Infectious Diseases, [3]Department of Pathology, National Institute of Infectious Diseases; Department of Biological Science and Technology, Tokyo University of Science, [4]Department of Pathology, National Institute of Infectious Diseases; Department of Life Science and Medical Bioscience, Waseda University, [5]Department of Virology II, National Institute of Infectious Diseases; Department of Biological Science and Technology, Tokyo University of Science, [6]Laboratory of Medical Virology, Institute for Frontier Life and Medical Sciences, Kyoto University

Background

For the control of the COVID-19 pandemic, development of vaccines that enable protection against infection with SARS-CoV-2 is considered to be important. One candidate would be a nasal vaccine that could induce mucosal immunity, including secretory IgA antibodies. Meanwhile, it is recommended to address the potential risk of vaccine-associated enhanced respiratory disease (VAERD), that is lung eosinophilic immunopathology induced by post-vaccination infection, in the case of COVID-19 vaccines. VAERD is considered to be caused as a result of Th2-dominant adaptive immune response by vaccination. In this study, we analyzed the immune response as well as the protective effect against viral infection induced by intranasal vaccination with recombinant trimeric SARS-CoV-2 spike (S) protein adjuvanted with the CpG oligonucleotide ODN2006 in a mouse model.

Method

Mice were vaccinated either intranasally or subcutaneously with recombinant S protein 3 times at 2-week intervals. ODN2006 and Alum were used as mucosal adjuvant and a classical Th2 adjuvant, respectively. One week after the last vaccination, serum, nasal, and lung washes were collected from mice to evaluate S-specific antibody responses. S-specific IgG1 and IgG2a subclasses were quantified as the indicator of Th2 and Th1 responses, respectively. In addition, vaccinated mice were intranasally challenged with mouse adapted SARS-CoV-2 QHmusX, and viral load in nasal and lung samples at 3 days post-infection (dpi) as well as body weight changes for 10 days were evaluated. Eosinophilic infiltration into lungs were evaluated by flow cytometry at 6 dpi.

Result

Nasal vaccine combined with ODN2006 induced not only serum neutralizing IgG antibodies but also nasal and lung S-specific IgA antibodies, resulting in the survival of mice without a significant decrease in body weight. When the S-specific serum IgG1/IgG2a ratio was evaluated, mice intranasally vaccinated together with ODN2006 presented significantly lower values compared to those subcutaneously vaccinated with alum as an adjuvant. The degree of eosinophil infiltration in lungs correlated with IgG1/IgG2a ratio. Accordingly, the infiltration of eosinophils was suppressed in mice intranasally vaccinated with ODN2006.

Conclusion

Our results suggest that intranasal vaccines combined with a Th1 adjuvant would be highly effective against infection of SARS-CoV-2 virus while reducing the risk of VAERD.

Poster Reception II

Jason Wilson - AOXI0382

Identification and Characterization of Human Memory B Cell Receptors Targeting Influenza Virus Hemagglutinin Proteins

Jason Wilson[1]

[1]Influenza Division; NCIRD; Centers for Disease Control and Prevention

Background

Influenza remains a significant public health problem, causing annual seasonal epidemics and occasional pandemics. Human B cells can generate a remarkable diversity of B cell receptors (BCR) due to V(D)J recombination of immunoglobulin gene segments and the subsequent process of affinity maturation through somatic hypermutation (SHM) to combat infectious disease. Repeated exposure to influenza during one's lifetime via infection and/or vaccination drives the immune system to build a repository of memory B cells bearing a diverse array of antigen-experienced BCRs that are potentially available for rapid recall during a subsequent immune response.

Method

Here we use single-cell technology to dissect the antigen-experienced BCR repertoire targeting influenza surface proteins in a healthy individual to identify strain-specific versus broadly protective BCR signatures.

Result

Using a single-cell sequencing approach, we identify, validate, and characterize the BCRs of 67 memory B cells from a healthy donor that specifically bind to hemagglutinin (HA) probes from different influenza subtypes. BCR specificity was validated by demonstrating that the cloned and expressed antibodies recognize recombinant HA protein. Interestingly, all of the cloned antibodies show some degree of cross-reactivity, including some that bind both Influenza group 1 and group 2 HA's. Sequence analysis reveals that these BCRs represent several clonotypic families, many of which have gone through detectable clonal expansion and significant SHM.

Conclusion

Identification of baseline anti-influenza memory B cell diversity within individuals may help predict their level of protection against future infections and will better inform the rational design of broadly protective influenza vaccines.

Poster Reception II

Walter Harrington - AOXI0409

Characterization of three human monoclonal influenza NP antibodies

Walter Harrington[1], Aaron Schmitz[2], Ali Ellebedy[2], Richard Webby[1]

[1]St. Jude Children's Research Hospital, [2]Washington University School of Medicine

Background

The influenza virus causes seasonal epidemics and occasional pandemics that take a significant toll on both lives and economies. Many studies have focused on developing universal influenza vaccines that can provide protection not only against seasonal viruses but also confer at least a measure of protection against potential pandemic viruses. One method of making a universal or broadly cross-reactive vaccine is to immunize with an antigen that is relatively conserved across influenza strains. Influenza NP has been explored as a possible conserved antigen that has shown promise in vaccine studies, but results from passive immunity studies with NP antibodies have been mixed.

Method

Here, we characterize three NP-specific monoclonal antibodies (mAb) derived from patients who had recovered from seasonal H1N1 infection. Binding and competition of the three mAbs were measured using direct and competitive ELISAs. Influenza strains across a wide range of subtypes (including H5, H7, and H9) were tested for binding potential. Possible in vitro effects that these antibodies might have during infection were probed via microneutralization and Antibody-Dependent Cellular Cytotoxicity assays. Membrane binding was visualized using fluorescent microscopy. In vivo therapeutic effects were determined with passive immunity studies in mice.

Result

We show that these mAbs bind a broad range of influenza viruses, as well as bind to the surface of infected cells. Further, we use competitive ELISAs to show that there is a broad set of epitopes on the NP presented to the immune system. Despite their breadth of binding, however, we show that these mAbs were not able to neutralize influenza infection in vitro, nor did we observe a protective effect in passive immunity studies in vivo.

Conclusion

The high cross-reactivity of NP mAbs is attractive in universal vaccine studies; however, despite the strength and breadth of binding, the mAbs characterized in this study did not show clear therapeutic effects in vivo. These results do not support recent studies that demonstrate a protective role for NP antibodies during influenza infection. More research is needed to further our understanding of the role NP antibodies play in the adaptive immune response.

Poster Reception II

Iuliia Desheva - AOXI0423

Establishment of a baculovirus platform for the study of neuraminidase inhibitory antibodies

Iuliia Desheva[1], Igor Losev[1], Nadezhda Petkova[1], Chih-Hsuan Tsai[2], Yu-Chan Chao[2]

[1]Federal State Budgetary Scientific Institution Institute of Experimental Medicine, [2]Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan

Background

Neuraminidase (NA)-based immunity to influenza could be useful for protecting against novel antigenic variants. Detection of neuraminidase-inhibiting (NI) antibodies could be beneficial to the immunological study of influenza vaccines. Baculovirus is a promising vector platform due to its high genome capacity, low cytotoxicity even with a high multiplicity of infection, and a highly specific host range, making them some of the safest eukaryotic vectors.

Method

We evaluated the level of NI serum antibodies by means of enzyme-linked lectin assay (ELLA) using whole influenza virus or baculovirus-based pseudotyped viruses expressing the full-length NA (NA-Bac) of the influenza A/California/07/2009 (H1N1) pdm09 strain. To assess immunogenicity and protection, we vaccinated Balb/c mice intramuscularly twice with NA-Bac and incomplete Freund's adjuvant.

Result

As assessed by cleavage of the high molecular weight fetuin substrate, the N1-Bac pseudoviruses exhibited no less, if not greater, NA activity than that of the whole purified influenza A/H7N1 virus. Since the enzymatic activity of the NA protein depends on its tetrameric structure, these results show that N1-Bac exhibited recombinant N1 proteins with appropriate structure.

NI antibodies were assessed in paired sera from patients with confirmed infection of influenza A. Strong correlation was shown between antibody titers in human sera using influenza A/H7N1 or NA-Bac (rs = 0.978). In mice, parenteral administration of NA-bac provided 100% protection from lethality after infection with 5 LD50 of drifted A/South Africa/3626/13 (H1N1) pdm09 influenza virus.

Conclusion

s. The NA-Bac can be reliably used to evaluate anti-NA antibodies and demonstrates protective efficacy in mice. One of the benefits of using NA-Bac is that it does not require the use of BSL-2 equipment.

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Poster Reception II

Joaquin Mould - AOXI0410

THE IMPACT OF INFLUENZA VACCINE EFFECTIVENESS ON U.S. HOSPITAL SYSTEM RESOURCES WITHIN. AN INFLUENZA AND COVID-19 CO-CIRCULATION SCENARIO.

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

[1]Seqirus USA Inc., [2]VHN Consulting Inc.

Background

Throughout the COVID-19 pandemic, influenza (flu) immunization has been a critical public health tool to protect against flu, reduce the risk of co-infection from both flu and COVID-19, and minimize the burden of flu on the healthcare system. The noted above could be achieved by improving flu immunization with more effective flu vaccines that may relieve the usage of acute hospital beds and intensive care unit (ICU) hospital beds. This study evaluated the hospital system resources impact of using more effective flu vaccines within a flu and COVID-19 co-circulation scenario.

Method

The impact of more effective flu vaccines on hospital system resources was estimated using a dynamic age-stratified transmission model. Two U.S. flu seasons (2011-2012 for low incidence and 2017-2018 for high incidence) were used in the analysis to simulate the variation of flu epidemic. Outcome measures include the number of acute hospital beds and ICU hospital beds. The COVID-19 variants (Alpha, Delta and Omicron) were used to create an average scenario of the impact on acute bed and ICU bed utilization from COVID-19. This assessment compares a scenario in which all subjects are immunized with standard-dose, egg-based, quadrivalent flu vaccine (QIVe) against a scenario of subjects 6 months through 64 years are immunized with cell-based, quadrivalent flu vaccine (QIVc) and those 65 years and above with adjuvanted, quadrivalent flu vaccine (aQIV). Based in U.S. literature, vaccine effectiveness for QIVc and aQIV is significantly higher to QIVe. Total number of acute hospital and ICU hospital beds was assumed in the U.S. at 1,000,000 and 100,000, respectively; with a regular occupancy rate of 70% related to other diseases.

Result

At the current U.S. flu immunization rate (45%), vaccinating with more effective vaccines (QIVc + aQIV) compared to QIVe will prevent utilization of 24,010 acute hospital beds and 3,601 ICU hospital beds within a high incidence flu season; and 17,329 acute hospital beds and 2,659 ICU hospital beds within a low incidence flu season. This reduction of inpatient services will provide relief but will not be enough to avoid saturation of ICU hospital resources due to COVID-19 hospital beds demand during a co-circulation scenario. Therefore, an increase in the flu immunization rate to 60% or higher with more effective, enhanced vaccines (QIVc + aQIV) will be needed to prevent ICU beds saturation in the U.S.

Conclusion

This analysis demonstrates increasing flu immunization rates should be combined with more effective influenza vaccines for all ages in the U.S. to avoid ICU hospital bed saturation during a co-circulation scenario.

Poster Reception II

Sarah Larteley Lartey Jalloh - AOXI0416

Comparison of live attenuated and inactivated influenza vaccine induced hemagglutinin and neuraminidase inhibiting antibody responses in children

Sarah Lartey Jalloh[1], Kristin G-I Mohn[4], Kristin Risa[3], Fan Zhou[3], Anders Madsen[3], Haakon Amdam[3], Camilla Tøndel[2], Karl A Brokstad[5], Rebecca J Cox[3]

[1]Department of Clinical Science, University of Bergen, [2]Department of Clinical Science, University of Bergen, The Pediatric Clinical Trial Unit, Haukeland University Hospital, Bergen, Norway, [3]Influenza Centre, [4]Influenza Centre, Department of Medicine, [5]Influenza Centre,Department of Safety, Chemistry and Biomedical Laboratory Sciences, Western Norway University of Applied Sciences; Bergen, Norway on behalf of the European Union-INCENTIVE

Background

Influenza is a major public health concern especially among venerable individuals such as young children under 5 years old. Young children experience high rates of influenza infection during seasonal epidemics. As children are the main transmitters of influenza, vaccinating them against seasonal influenza has the potential to reduce the burden of disease in both vaccinated and unvaccinated individuals. Vaccination remains the most effective prophylaxis against seasonal influenza illness. Annual seasonal vaccination is recommended for high-risk groups including infants >6 months, young children under 5 years old and the elderly. Two main type of influenza vaccine are recommended for use in children: the inactivated influenza vaccines (IIVs) and the live attenuated influenza vaccine (LAIV). IIVs has been licenced for use in children >6 months for many decades, whereas LAIV was licensed for use Europe in 2012 and it is recommended for children (2-17 years old). Both vaccines have good safety records in this age group. We evaluated and compared the immune responses induced by IIV and LAIV vaccination in children.

Method

Thirty-four children scheduled for elective tonsillectomy were recruited and vaccinated with trivalent LAIV, furthermore fifty children were enrolled and vaccinated with quadrivalent IIV (QIV). Blood samples were collected prior to vaccination at day 0 (D) and 3 consecutive timepoints at days 3-14, 28 and 58 after vaccination from all the study participants. We used hemagglutination inhibition (HI) and microneutralization assays to assess hemagglutinin-specific neutralizing and function antibody responses induced by both vaccines against the vaccine strains. Enzyme-linked immunosorbent assay (ELISA) was used to quantify influenza-specific binding antibody response, whereas the enzyme-linked lectin assay (ELLA) was used for the assessment of neuraminidase inhibiting (NI) antibody response.

Result

The trivalent LAIV induced significant increases in influenza-specific HI antibody responses against A/H3N2 and influenza B strains 14 days post-vaccinations and increased only slightly to A/H1N1. LAIV boosted functional antibody responses and elicited high levels of IgG and NI antibody responses at 28 days post-vaccination. The QIV rapidly elicited significant increases in HI and NI antibody titres against all the vaccines strains tested as early as 3-7 days post-vaccination.

Conclusion

The collectively the result from the clinical trials showed that both vaccines are capable of rapidly induing HA and NA-specific antibody responses in children and will help better understanding the immunogenicity and effectiveness of influenza vaccination in this age groups.

Poster Reception II

Anna-Polina Shurygina - AOXI0438

Influenza vaccine immunogenicity in hemodialysis patients

Anna-Polina Shurygina[2], Kirill Vasilyev[2], Ekaterina Romanovskaya-Romanko[2], Vera Krivitskaya[2], Janna Buzitskaya[2], Maria Sergeeva[2], Marina Shuklina[2], Maria Ladygina[2], Konstantin Vishnevskii[1], Marina Stukova[2]

[1]North-Western State Medical University named after I.I. Mechnikov, [2]Smorodintsev Reseaech Institute of Influenza

Background

Patients with End-Stage Renal Disease (ESRD) receiving hemodialysis (HD) are at high risk of severe influenza infection. The efficacy of influenza vaccines in this population is believed to be insufficient due to immune deficiency predisposition.

During the 2019-2020 epidemic season, 22 HD patients were vaccinated with one standard dose of a trivalent inactivated influenza vaccine (TIV). The median age of the patients was 63 years; all patients received dialysis therapy three times a week for 4-4.5 hours in sufficient dose.

Method

Post-vaccination immune response was assessed by measuring hemagglutination inhibition and neutralizing antibody titers, frequencies of T-follicular helper cells, and CD4 and CD8 effector T cells. Blood samples were collected pre-vaccination, 7 and 21 days, 3, 6, and 12 months after vaccination. The results were compared with the data obtained for healthy volunteers of two age groups: 18-60 years old (n=47) and over 60 years old (n=42).

Result

Before vaccination, the percentage of individuals seronegative to seasonal influenza viruses was higher in the HD group than in the control groups of healthy subjects. The post-vaccination HI and MN titres and the duration of the antibody response in the group of HD patients were similar to those obtained for the general human population. However, HD patients responded better to the B/Victoria vaccine component: significant differences were shown for both age groups ($p<0.0001$). Moreover, the pronounced increase in the relative content of Th1-type follicular T cells (PD1 + ICOS +) in the group of hemodialysis patients was observed on Day 7 ($p < 0.05$). Vaccination led to the formation of a T-cell response, accompanied by the formation of polyfunctional CD4+ and CD8+ effector memory cells. When comparing the T-cell response (cumulative IFN-γ, TNF-α and IL-2 production) in the HD group and two age groups of healthy volunteers, it was found that despite a reduced level of T-cell response at all time points of observation, an increase in the number of antigen-specific T-lymphocytes relative to baseline values in HD patients was higher than that of healthy study participants.

Conclusion

The results obtained confirm the expediency of vaccination for dialysis patients and suggest that modern effective dialysis therapy contributes to the compensation not only of renal failure but also of the concomitant immunodeficiency of ESRD.

Poster Reception II

Mark Katz - AOXI0339

The European Severe Acute Respiratory Infection Vaccine Effectiveness (Euro-SAVE) Network: a new network for evaluating the effectiveness of COVID-19 and Influenza vaccines in preventing severe illness in countries in the European Region of the World Health Organization

Mark Katz[9], Sandra Cohuet[2], Silvia Bino[3], Olgha Tarkhan-Mouravi[5], Ariana Kalaveshi[6], Dinagul Otorbayeva[1], Kristina Stavridis[4], Maja Stosic[7], Iris Finci[9], Kasper Amelia[9], Oksana Artemchuk[9], Kirill Stolyarov[9], Alina Guseinova[9], Karen Nahapetyan[9], Iris Hasibra[3], Giorgi Chakhunashvili[5], Besfort Kryeziu[6], Kalila Zhumaliyeva[8], Elizabeta Jancheska[4], Dragana Plavsa[7], Angie Rose[2], Richard Pebody[9]

[1]Department for Disease Prevention, State Sanitary and Epidemiological Surveillance, Kyrgyzstan, [2]Epiconcept, [3]Institute of Public Health, Albania, [4]Institute of Public Health, Republic of North Macedonia, [5]National Center for Disease Control and Public Health, Georgia, [6]National Institute of Public Health, Kosovo, [7]National Institute of Public Health, Serbia, [8]National Virology Laboratory, Kyrgyzstan, [9]World Health Organization, European Regional Office

Background

Countries in the WHO European region have deployed a variety of COVID-19 and influenza vaccines with evolving schedules to reduce morbidity and mortality in key target groups. Understanding the effectiveness of COVID-19 and influenza vaccine interventions in preventing severe disease is critical to inform optimal guidance about national, regional and global vaccine use.

Method

We supported the establishment of a network of countries, Euro-SAVE, monitoring COVID-19 and influenza vaccine effectiveness against hospitalized severe acute respiratory infection (SARI). Studies leverage existing integrated SARI sentinel surveillance platforms to obtain vaccine effectiveness (VE) estimates and follow a standard WHO-defined methodology. All studies use the WHO SARI case definition, collect similar core data on enrolled patients, conduct testing by RT-PCR, including multiplex testing), and conduct genomic sequencing for influenza and SARS-CoV-2 in-country or at regional COVID-19 reference laboratories. In addition to country-level VE analyses, network-wide pooled analyses will allow for more precise VE estimates by vaccine type; number of doses; variants of concern; time since vaccination; age group; and underlying comorbidities. For pooled analysis, VE will be calculated as 1 - Odds Ratio using a one-stage analysis of pooled individuals. All study protocols were appro¬ved or given a waiver by the WHO Ethical Review Committee (ERC) ¬and in-country ERCs.

Result

To date, six countries and areas, including Albania, Georgia, Kyrgyzstan, North Macedonia and Serbia, as well as Kosovo, participate in the network. Patient recruitment began in November 2021. Four studies use the REDCap data management platform; one study uses Kobo Toolbox; and one study uses the Electronic Database Management System. As of May 15, 2022, 373 SARI patients had been recruited by studies in the network; 72/373 (19.3%) had positive samples for SARS-CoV-2 and 10/285 (3.5%) had positive samples for influenza. The mean age was 61 years (IQR: 46-71) and half (n=189 (50.7 %)) were female. Patients had received seven different COVID-19 vaccines. The first pooled VE analysis is planned for June 2022, and analyses will be conducted on a monthly or bimonthly basis thereafter.

Conclusion

The Euro-SAVE network will allow for VE estimates against severe disease for multiple influenza and COVID-19 vaccines. The pooling approach will allow us to obtain precise VE estimates for multiple subgroup analyses. The network could be expanded to include additional countries that are part of the WHO European region and are undertaking comparable SARI VE monitoring.

*For the purposes of this abstract, all references to "Kosovo" should be understood as "Kosovo (in accordance with security council resolution 1244 (1999)."

Poster Reception II

Angela Rose - AOXI0353

Vaccine effectiveness against hospitalisation with COVID-19 prior to and during Delta circulation in Europe in adults aged 30 yrs and over: I-MOVE-COVID-19 and ECDC hospital networks, January-December 2021

Angela Rose[11], Nathalie Nicolay[38], Virginia Sandonis Martín[15], Clara Mazagatos[30], Goranka Petrovic[22], Odile Launay[36], Sarah Denayer[33], Lucie Seyler[35], John Paul Cauchi[17], F Annabel Niessen[27], Ausenda Machado[31], Cristina Burgui[25], Isabela Loghin[16], Lisa Domegan[19], Roberta Vaikutyte[5], Petr Husa[9], Nassera Aouali[29], George Panagiotakopoulos[32], Jennifer Howard[12], Francisco Pozo[28], Amparo Larrauri[30], Diana Nonkovic[4], Liem binh Luong Nguyen[23], Nathalie Bossuyt[21], Thomas Demuyser[35], Ausra Dziugyte[17], Mirjam J Knol[27], Irina Kislaya[31], Ivan Martinez-Baz[25], Corneliu Popescu[2], Roisin Duffy[19], Geidre Gefenaite[6], Lenka Souckova[14], Marc Simon[3], Stella Michelaki[32], Ana Gandarillas[34], Zvjezdana Lovric Makaric[10], Zineb Lesieur[24], Cyril Barbezange[37], Els Van Nedervelde[26], Maria-Louise Borg[17], Patricia CJL Bruijning-Verhagen[27], Veronica Gomez[31], Jesus Castilla[25], Mihaela Lazar[1], Joan O'Donnell[18], Aukse Mickiene[8], Regina Demlova[7], Gil Wirtz[3], Sabrina Bacci[38], Esther Kissling[12], I-MOVE-COVID-19 Hospital study team[20], ECDC Hospital study team[13]

[1]Cantacuzino, National Military Medical Institute for Research-Development, Bucharest, [2]Carol Davila University of Medicine and Pharmacy; Dr Victor Babes Clinical Hospital of Infectious and Tropical Diseases, Bucharest, [3]Centre Hospitalier de Luxembourg, Luxembourg City, [4]Croatian Institute of Public Health, Zagreb, [5]Department of Infectious Diseases, Lithuanian University of Health Sciences, Kaunas, [6]Department of Infectious Diseases, Lithuanian University of Health Sciences, Kaunas; Department of Health Sciences, Faculty of Medicine, Lund University, Lund, [7]Dept f Pharmacology, Masaryk University, [8]Dept of Infectious Diseases, Lithuanian University of Health Sciences, Kaunas, [9]Dept of Infectious Diseases, University Hospital Brno, Brno, [10]Division for Epidemiology of Communicable Diseases, Croatian Institute of Public Health, Zagreb, [11]Epiconcept, [12]Epiconcept, Paris, [13]European Centre for Disease Prevention and Control, [14]Faculty of Medicine, University Hospital Brno, [15]Flu and Respiratory Virus Reference Laboratory, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, [16]Grigore T. Popa University of Medicine and Pharmacy, Iasi; St. Paraschiva Clinical Hospital of Infectious Diseases, Iasi, [17]Health Promotion and Disease Prevention Directorate, Ministry for Health, [18]HSE Health Protection Surveillance Centre (HPSC), Dublin, [19]HSE-Health Protection Surveillance Centre (HPSC), Dublin, [20]I-MOVE COVID-19, [21]Infectious Disease Epidemiology Unit, Sciensano, Brussels, [22]Infectious Diseases Epidemiology Service, Croatian Institute of Public Health, Zagreb, [23]Inserm, CIC 1417, Hopital Cochin, AP-HP, Paris, [24]Inserm, F-CRIN, Innovative Clinical Research Network in Vaccinology (I-REIVAC), Hospital Cochin, Paris, [25]Instituto de Salud Publica de Navarra-IdiSNA; CIBER-Epidemiologia y Salud Publica (CIBERESP), Pamplona, [26]Internal Medicine - Infectiology, Universitair Ziekenhuis Brussel, Brussels, [27]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht; Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, [28]Laboratorio de Referencia de Gripe y Virus Respiratorios Centro Nacional de Microbiología Instituto de Salud Carlos III, Madrid, [29]Luxembourg Institute of Health, Luxembourg City, [30]National Centre for Epidemiology, Institute of Health Carlos III, Madrid; Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP), Institute of Health Carlos III, Madrid, [31]National Institute of Health Dr Ricardo Jorge, Lisbon, [32]National Public Health Organisation (EODY), Athens, [33]Respiratory Viruses Unit, Viral Diseases Service, Sciensano, Brussels, [34]Subdireccion General de Epidemiologia, Direccion General de Salud Publica, Comunidad de Madrid, [35]Universitair Ziekenhuis Brussel, Brussels, [36]University of Paris City, Faculty of Medecine; AP-HP, Hopital Cochin; Inserm, CIC Cochin-Pasteur, Paris, [37]Viral Diseases - Respiratory Viruses Unit, Belgian National Reference Centre for Influenza & WHO-recognised National Influenza Centre (BELNIC); Sciensano, Brussels, [38]VPD and Immunisation, DPR, European Centre for Disease Prevention and Control

Background

Severe acute respiratory illness (SARI) surveillance platforms have been implemented in Europe, providing a system to measure vaccine effectiveness (VE) against hospitalised, PCR-confirmed influenza and SARS-CoV-2. Data were pooled from two European hospital networks. In 2021, circulation of influenza in Europe was too low to estimate influenza VE. We estimated VE against PCR-confirmed SARS-CoV-2 in hospitalised SARI patients aged 30+ years by vaccine product in order to further guide adaptation of COVID-19 vaccine policy in Member States.

Method

Hospitals follow a similar generic protocol for measuring COVID-19 VE, adapted from the influenza VE test-negative design. SARI patients are defined clinically using the ECDC definition (at least one of fever, cough, shortness of breath, or sudden onset of anosmia/ageusia). Complete vaccination is defined as two doses of mRNA

(Comirnaty, Spikevax) or Vaxzevria, or one dose of Janssen vaccine, received ≥14 days before symptom onset. Those receiving a booster/third dose were excluded. VE was estimated as 1 minus the odds ratio of vaccination among cases and controls. VE was calculated overall, by vaccine product/category, age-group (30-59, 60-79, 80+ years), and presence/absence of at least one of four commonly collected chronic conditions (asthma, diabetes, heart disease, lung disease). VE was estimated for two periods: January-May 2021 (pre-Delta) and July-December 2021 (Delta-dominant).

Result

There were 2544 hospitalised SARI patients included in the pre-Delta and 3438 in the Delta-dominant period. Most vaccinated cases (65%) and controls (75%) received an mRNA vaccine. For this vaccine type, overall adjusted COVID-19 VE for complete vaccination during pre-Delta was 93% (95%CI: 87-96); 99% (95%CI: 92-100) in those 60-79 years, 87% (95%CI: 71-94) in 80+ years. (In the 30-59 age-group, <20 vaccinated patients precluded a VE estimate). In the Delta-dominant period, adjusted VE was 83% (95%CI: 79-87) overall; 92% (95%CI: 88-95), 86% (95%CI: 80-91) and 54% (95%CI: 26-71) in those aged 30-59, 60-79 and 80+ years, respectively.

Conclusion

High overall vaccine effectiveness against hospitalisation was observed during both pre-Delta and Delta-dominant periods. For mRNA vaccines, protection against hospitalisation with COVID-19 during dominant circulation of the Delta variant was lower than pre-Delta, particularly in the 80+ age-group. During the Delta period, the reduced effectiveness provides justification for administration of a booster dose in this oldest age-group to improve protection against severe outcomes. Further work will investigate VE for subsequent variant periods, booster doses and expanded age-groups.

Poster Reception II

Sneha Vishwanath - AOXI0335

ITERATIVELY DESIGNED HEMAGGLUTININ BASED H5Nx ANTIGENS GENERATE A BROAD NEUTRALISING IMMUNE RESPONSE IN MICE

Sneha Vishwanath[1], George Carnell[1], Joanne Marie M. Del Rosario[3], Kelly A.S. da Costa[7], Maria Suau Sans[1], Charlotte George[1], Benedikt Asbach[5], Nigel J Temperton[7], Ralf Wagner[6], Rebecca Kinsley[2], Simon Frost[4], Jonathan L Heeney[2]

[1]Department of Veterinary Medicine, University of Cambridge, Cambridge, UK, [2]Department of Veterinary Medicine, University of Cambridge, Cambridge, UK; DIOSynVax, Cambridge, UK, [3]DIOSynVax, Cambridge, UK, [4]DIOSynVax, Cambridge, UK; London School of Hygiene and Tropical Medicine, London, United Kingdom; Microsoft Health Futures, Redmond, United States., [5]Institute of Medical Microbiology and Hygiene, University of Regensburg, Regensburg, Germany, [6]Institute of Medical Microbiology and Hygiene, University of Regensburg, Regensburg, Germany; Institute of Clinical Microbiology and Hygiene, University Hospital Regensburg, Regensburg, Germany, [7]Viral Pseudotype Unit, Medway School of Pharmacy, The Universities of Kent and Greenwich at Medway, Chatham, UK

Background

Yearly outbreaks of avian influenza (H5Nx) have a huge socio-economic impact worldwide and represent a constant threat of zoonotic spill overs causing human epidemics or pandemics. Constant antigenic drift of hemagglutinin surface glycoprotein and recombination with different neuraminidase subtypes, add a complex dimension to design of universal H5 influenza vaccine antigens that can provide broad protection from H5Nx. Here we present data on novel hemagglutinin based H5Nx antigen designs that have been iteratively optimised to increase the antigenic coverage of H5Nx clades.

Method

Available hemagglutinin H5Nx sequences from the NCBI virus database were downloaded, cleaned, and trimmed to generate a non-redundant dataset of H5 sequences. Phylogenetic relationship between these sequences were estimated and a phylogenetically optimised sequence was designed as a first DIOS vaccine candidate (DIOS-T2_HA_9). Immunogenicity of the vaccine design was confirmed by DNA immunisation of BALB/c mice. Mouse sera were tested for neutralisation using pseudotype neutralisation assays against a diverse panel of H5 hemagglutinin. Based on these results, DIOS-T2_HA_9 was further optimised to generate a panel of next tier DIOS vaccine designs (DIOS-T3_HA_1/2/3/4/5) using epitope optimisation and receptor binding site modification to achieve broad neutralisation.

Result

The DIOS-T2_HA_9 vaccine candidate generated broader immune responses to different H5Nx compared to the wild-type controls (H5_WSN and H5_GYR). We then improved DIOS-T2_HA_9 to broaden the immune response to those H5Nx clades missed by previous immunisations. The improved designs (DIOS-T3_HA_1/2/3/4/5) showed better neutralisation profiles against a panel of pseudotype expressing 9 antigenically diverse H5 hemagglutinin.

Fig. 1| Neutralisation by mice sera immunised with different H5 vaccine candidates. Each panel represents neutralisation data for the H5 HAs belonging to the clade listed on the top of each panel. The X-axis represents different vaccine candidates, and the Y-axis represents the log10IC50 values of the neutralisation curves.

Conclusion

A promising panel of hemagglutinin based H5 vaccine antigen candidates was developed, that upon immunisation induced broad neutralisation against multiple antigenically distinct H5Nxs. This novel broadly neutralising H5 based vaccine candidates (either in combination or individually) could be utilised pre-pandemically in poultry to keep in check the recurrent yearly avian influenza outbreaks, and/or prophylactically in the human population in years of high risk.

Poster Reception II

Fan Zhou - AOXI0340

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

Fan Zhou[2], Lena Hansen[2], Gabriel Pedersen[4], Gunnveig Grødeland[1], Rebecca J. Cox[3]

[1]Department of Immunology, University of Oslo and Oslo University Hospital, [2]Influenza Center, Department of Clinical Science, University of Bergen, [3]Influenza Center, Department of Clinical Science, University of Bergen; Department of Microbiology, Haukeland University Hospital, Bergen, Norway., [4]Influenza Center, Department of Clinical Science, University of Bergen;Center for Vaccine Research, Statens Serum Institut, Copenhagen, Denmark

Background

The highly pathogenic avian influenza H5N1 viruses constantly evolve and give rise to novel variants that have caused widespread zoonotic outbreaks and sporadic human infections. 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 animal models and clinical trials.

Method

We conducted a dose escalating study 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 at multiple time points. 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 protective antibody responses against HPAI H5N1 virus.

Result

An evaluation of sera from vaccinees against pseudotyped viruses covering all (sub)clades isolated from human H5N1 infections demonstrated that the adjuvanted vaccines (7.5µg and 30µg) could elicit 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.

Poster Reception II

Sebastian Giese - AOXI0343

Generation of an attenuated chimeric bat influenza A virus live vaccine prototype

Ran Wei[2], Jacob Schön[1], Kevin Ciminski[2], Julian Kraft[2], Susanne Kessler[2], Sophie Euchner[2], Donata Hoffmann[1], Anne Pohlmann[1], Martin Beer[1], Martin Schwemmle[2], Sebastian Giese[2]

[1]Institute of Diagnostic Virology, Friedrich Loeffler Institut, Federal Research Institute for Animal Health, Greifswald-Insel Riems, Germany, [2]Institute of Virology, University Medical Center Freiburg, Freiburg, Germany; Faculty of Medicine, University of Freiburg

Background

Influenza A virus (IAV) infections in swine and poultry pose a constant threat to humans. Universally applicable and safe animal vaccines are therefore urgently needed as they could help to prevent epizootic outbreaks and resulting zoonotic spillovers. We recently demonstrated that a reassortment-incompatible chimeric bat H17N10 virus equipped with the surface glycoproteins of an avian IAV can be efficiently used as a modified live influenza vaccine (MLIV) for poultry.

Method

We generated a chimeric bat IAV containing six internal gene segments of H17N10, together with the two surface glycoproteins HA and NA of an avian H5N1 virus by reverse genetics and subsequently performed consecutive passaging in eggs and chicken. Avian adaptive mutations were identified via deep sequencing. Mutations were then characterized in avian and mammalian cell cultures as well as in mice.

Result

To ensure vaccine safety and thus improve the applicability of this novel MLIV for mammalian usage, we performed consecutive passaging in eggs and chicken. Following passaging, we identified mutations in the viral polymerase subunits PB2 (I382S), PB1 (Q694H, I695K), and PA (E141K). Strikingly, recombinant chimeric viruses encoding these mutations showed no growth deficiencies in avian cells, but displayed impaired growth in human cells and mice. Homologous prime-boost immunization of mice with one of these avian-adapted chimeric viruses elicited a strong neutralizing antibody response and conferred full protection against lethal HPAIV H5N1 challenge infection. Importantly, insertion of the avian-adaptive mutations into conventional avian-like A/SC35M/1980 (H7N7) and prototypic human A/PR/8/34 (H1N1) led to attenuated viral growth in human cells and mice.

Conclusion

In summary, we show that the polymerase mutations identified here can be utilized to further improve the safety of our novel H17N10-based MLIV candidates for future mammalian applications.

Poster Reception II

Jeonghun Kim - AOXI0357

Development of the H3N2 influenza microneedle vaccine for cross-protection against antigenic variants

Jeonghun Kim[4], Yura Shin[1], Jong Hyeon Seok[3], Heedo Park[3], Hye-Ran Cha[2], Si Hwan Ko[2], Jae Myun Lee[2], Jung-Hwan Park[1], Man-Seong Park[3]

[1]Department of BioNano Technology, Gachon University, [2]Department of Microbiology and Immunology, Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, [3]Department of Microbiology, Institute for Viral Diseases, Chung Mong-Koo Vaccine Innovation Center, College of Medicine, Korea University, [4]Department of Microbiology, Institute for Viral Diseases, College of Medicine, Korea University

Background

Due to the continuously mutating nature of the H3N2 virus, two aspects were considered when preparing the H3N2 microneedle vaccines: (1) rapid preparation and (2) cross-protection against multiple antigenic variants. Previous methods of measuring hemagglutinin (HA) content required the standard antibody, thus rapid preparation of H3N2 microneedle vaccines targeting the mutant H3N2 was delayed as a result of lacking a standard antibody. In this study, H3N2 microneedle vaccines were prepared by high performance liquid chromatography (HPLC) without the use of an antibody, and the cross-protection of the vaccines against several antigenic variants was observed.

Method

The HA content measured by HPLC was compared with that measured by ELISA to observe the accuracy of the HPLC analysis of HA content. The cross-protection afforded by the H3N2 microneedle vaccines was evaluated against several antigenic variants in mice. Microneedle vaccines for the 2019-20 seasonal H3N2 influenza virus (19-20 A/KS/17) were prepared using a dip-coating process. The cross-protection of 19-20 A/KS/17 H3N2 microneedle vaccines against the 2015-16 seasonal H3N2 influenza virus in mice was investigated by monitoring body weight changes and survival rate. The neutralizing antibody against several H3N2 antigenic variants was evaluated using the plaque reduction neutralization test (PRNT).

Result

HA content in the solid microneedle vaccine formulation with trehalose post-exposure at 40℃ for 24h was 48% and 43% from the initial HA content by HPLC and ELISA, respectively. The vaccine was administered to two groups of mice, one by microneedles and the other by intramuscular injection (IM). In vivo efficacies in the two groups were found to be similar, and cross-protection efficacy was also similar in both groups.

Conclusion

HPLC exhibited good diagnostic performance with H3N2 microneedle vaccines and good agreement with ELISA. The H3N2 microneedle vaccines elicited a cross-protective immune response against the H3N2 antigenic variants. Here, we propose the use of HPLC for a more rapid approach in preparing H3N2 microneedle vaccines targeting H3N2 virus variants.

Poster Reception II

Pauline van Diemen - AOXI0385

Immunogenicity and efficacy of a broadly reactive H1N1 Influenza vaccine in pigs

Pauline Van Diemen[1], Andrew Ramsay[1], Joanne Del Rosario[2], Sneha Wishwanath[6], Simon Frost[2], Benjamin Mollett[1], Benedikt Asbach[7], Nigel Temperton[5], Ralf Wagner[4], Rebecca Kinsley[3], George Carnell[6], Jonathan Heeney[3], Helen Everett[1]

[1]APHA-Weybridge, [2]DIOSynVax Ltd, [3]DIOSynVax Ltd; University of Cambridge, [4]DIOSynVax Ltd; University of Regensburg, [5]The Universities of Greenwich and Kent at Medway, [6]University of Cambridge, [7]University of Regensburg

Background

The continued antigenic change (drift) of influenza A virus strains over time in the human population necessitates twice-yearly updates to the human seasonal vaccine composition. Development of a broadly cross-reactive 'universal' vaccine that does not require such frequent updates would be a considerable advantage. The aim of this study was to assess a novel broadly cross-reactive vaccine technology in the pig model of influenza.

Method

The test vaccine in this study was a structure-based computational synthetic multi-gene antigen of human-origin H1N1 influenza A virus (DIOSynVax-H1N1). It was administered intradermally (ID) to 5 pigs as DNA using the PharmaJet® Tropis® needle-free system. Two control whole, inactivated virus (WIV) vaccines of the same H1N1 pandemic 2009 1A3.3.2 lineage, A/swine/England/1353/2009 (WIV1353) and A/Victoria/2454/2019 (WIVVic) in oil-in-water adjuvant were administered intramuscularly to 5 pigs each at the same 4-week interval. Six weeks following the second immunisation all groups were challenged with the swine-origin 1A3.3.2 strain A/swine/England/1353/2009 (1.7 x10^6 TCID50 per pig intranasally). Pigs were monitored daily post-inoculation (dpi) until study completion on 8 or 9dpi.

Result

Nasal shedding of viral RNA was monitored daily by RRT-qPCR. All challenged animals shed viral RNA, reaching a peak between 2 to 5dpi. Area under the curve analysis (Figure) showed significant reduction in the nasal shedding of viral RNA in the animal groups vaccinated with the broadly reactive DIOSynVax-H1N1 (P=0.0012) or WIV1353 (P=0.0003) vaccines when compared to the naïve control or WIVVic vaccinated groups. All pigs resolved the infection by 8-9dpi.

Influenza virus-specific serum antibody levels were monitored longitudinally by Haemagglutinin inhibition Assay (HAI), and nucleoprotein (NP) ELISA. Both assays revealed significant antibody levels in the WIV-vaccinated groups, even after a single vaccination. The DIOSynVax-H1N1 immunised pigs mounted an equivalent HA antibody response to the WIV vaccines after the boost vaccination. In the groups where RNA shedding was decreased, high neutralising antibody titres to the challenge virus were detected.

Conclusion

Importantly this study demonstrated proof-of-concept that pigs immunised with the DIOSynVax-H1N1 vaccine were protected as well as pigs immunised with the WIV vaccine homologous to the challenge strain. In contrast, a WIV vaccine antigen from a human-origin strain from the same pH1N1 1A.3.3.2 lineage, did not afford equivalent protection against challenge, despite eliciting high hemagglutinating antibody levels.

Poster Reception II

Giuseppe Sautto - AOXI0388

Characterization fo the human pre-existing COBRA HA-reactive antibody response following influenza vaccination.

***Ileia Scheibe*[1], *Robert Richardson*[1], *Ted Ross*[1]**

[1]Center for Vaccines and Immunology, University of Georgia

Background

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

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

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

Method

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

Result

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

Conclusion

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

Poster Reception II

Lora Thomas - AOXI0398

Immunogenicity and Safety of High-Dose Versus Standard-Dose Influenza Vaccine in Adult Hematopoietic Stem Cell Transplant Recipients

Lora Thomas[8], Einas Batarseh[4], Lubna Hamdan[6], Zaid Haddadin[1], Daniel Dulek[7], Laura Stewart[7], Herdi Rahman[7], Anna Stahl[7], Andrew Spieker[7], Michael Ison[3], Edgar Turner Overton[5], Steven Pergam[2], Natasha Halasa[7], Spyros Kalams[7]

[1]Albert Einstein Medical Center, [2]Fred Hutchinson Cancer Research Center, [3]Northwestern University Feinberg School of Medicine, [4]University at Buffalo- SUNY, [5]University of Alabama-Birmingham, [6]University of Cincinnati, [7]Vanderbilt University Medical Center, [8]Virginia Commonwealth University Medical Center

Background

Adult hematopoietic stem cell transplant (HCT) recipients are at high risk for influenza-related morbidity and mortality and have suboptimal influenza vaccine immune responses compared to healthy adults. A prior phase I study demonstrated high-dose (HD) influenza vaccination to be safe in adult HCT recipients.

Method

This phase II, randomized, controlled, double-blind, multicenter trial compared two doses of either HD trivalent (HD-TIV) or standard-dose quadrivalent (SD-QIV) influenza vaccine administered one month apart in adults who were 3-23 months post-allogeneic HCT. Injection site and systemic reactions were assessed for 7 days post-vaccination, and hemagglutinin antibody inhibition (HAI) geometric mean titers (GMTs) were calculated at baseline, four weeks following each vaccine dose, and approximately six months post-second vaccination. The primary immunogenicity endpoint was the visit 3 HD/SD GMT ratio (GMR).

Result

From 2017-2019 we enrolled and randomized 124 adults (64 SD-QIV and 60 HD-TIV) at 4 sites (Table 1). Adjusted GMR for A/H1N1, A/H3N2, and B-Victoria at visit 3 were 1.16 (CI: 0.67, 2.02), 2.09 (CI:1.19, 3.68), and 1.61 (CI: 1.00, 2.58), respectively. Any injection site reactions (Figure 1) at visits 1 and 2 were 48% vs.36%, p=0.5 and 48% vs. 32%, p=0.10 for HD-TIV vs. SD-QIV, respectively. Any systemic reactions at visits 1 and 2 were 52% vs. 44%, p=0.9 and 44% vs.46%, p=0.7 for HD-TIV vs. SD-QIV, respectively. Four serious adverse events occurred in the HD-TIV group; none were deemed related to the vaccine.

Conclusion

In adult HCT recipients, two doses of HD-TIV produced higher HAI antibody responses for H3N2 and B/Victoria compared with SD-QIV, with no statically significant difference in injection site and systemic reactions.

Poster Reception II

Nigel Temperton - AOXI0408

An ABCD Influenza virus pseudotype library: generating a globally accessible resource for immunogenicity studies of universal vaccines

Nigel Temperton[1]

[1]University of Kent

Background

With the rapid expansion of new universal influenza vaccine technologies, there is an acute need to match this with evaluation of immunogenicity broadly against multiple subtypes and strains.

Method

A best-in-class influenza hemagglutinin (HA) pseudotype library encompassing Influenza A subtypes HA1-18, Influenza B (both lineages), Influenza C and Influenza D has been developed using lentiviral vector platform technologies and co-expressed proteases. These viruses have been evaluated in influenza pseudotype microneutralization (pMN) assays with post-vaccine sera and HA2-directed mAbs.

Result

The pMN is highly sensitive and specific for detecting virus-specific neutralizing antibodies against influenza viruses and can be used to safely assess antibody functionality in vitro. and in high-throughput systems. We demonstrate their utility in detecting serum responses to infection and vaccination with the ability to evaluate cross-subtype neutralizing responses elicited by specific vaccinating antigens.

Conclusion

Our findings will inform further preclinical studies involving (universal, pan-subtype) immunization dosing regimens in animal models and may help in the creation and selection of better antigens for vaccine design. This library is the most comprehensive available globally and can be harnessed to meet strategic objectives that contribute to the strengthening of global influenza surveillance, expansion of seasonal and zoonotic influenza prevention and control policies, and strengthening pandemic preparedness and response.

Poster Reception II

Weiwen Liang - AOXI0325

Egg-adaptation pathway of human influenza H3N2 virus is contingent on natural evolution

Weiwen Liang[1]

[1]HKU-Pasteur

Background

Egg-adaptive mutations in influenza hemagglutinin (HA) often emerge during the production of egg-based seasonal influenza vaccines, which contribute to the largest share in the global influenza vaccine market. Since the receptor-binding site on hemagglutinin (HA) partially overlaps with several major antigenic sites, some egg-adaptive mutations can alter the antigenicity of HA (e.g. L194P) while some mutations (e.g. G186V) have minimal impact on the antigenicity. It is possible that different strains have different preferences of egg-adaptation pathways. However, it remains to be explored whether such differential preference exists.

Method

Sequence analysis and mutagenesis experiments were performed to identify amino acid variants on human H3N2 HA that can affect the viral replication and preference of egg-adaptation pathway. We also performed a structural modeling to give insights on the mechanism of such preference.

Result

We show that the preference of egg-adaptation pathway in human H3N2 HA is strain-dependent. In particular, Thr160 and Asn190, which are found in many recent H3N2 strains, restrict the emergence of L194P but not G186V. Our results further suggest that natural amino acid variants at other HA residues also play a role in determining the egg-adaptation pathway. Consistently, recent human H3N2 strains from different clades acquire different mutations during egg passaging.

Conclusion

Our study demonstrates that natural mutations in human H3N2 HA can influence the egg-adaption pathway, which has important implications in seed strain selection for egg-based influenza vaccine.

Poster Reception II

Christine Wadey - AOXI0355

USE OF THE NF-KB ACTIVATION ASSAY ENSURES INFLUENZA VACCINE SAFETY

Christine Wadey[1], Steve Rockman[2], Chi Ong[1]

[1]Seqirus, [2]Seqirus, The University of Melbourne

Background

As part of the influenza vaccine redevelopment program associated with the introduction of quadrivalent influenza vaccine (QIV), Seqirus has developed a process for the biannual introduction of new influenza strains to meet WHO recommendations, which involves ensuring adequate virus splitting conditions to eliminate potential cytokine induction.

This report demonstrates the utility of the NF-kB cytokine activation assay for detection of cytokine activation to ensure virus is sufficiently split to ensure an appropriate safety profile.

Method

The NF-kB Activation Assay is an in vitro method to screen for the ability to induce cytokine responses, a surrogate measure for potential vaccine pyrogenicity. The assay assesses the uptake of either double stranded (ds)RNA or single stranded (ss)RNA by Toll-like receptors (TLR-3) and TLR-8 respectively, and the subsequent activation of NF-kB, a key cellular transcription factor. Toll-like receptors are a class of pattern recognition receptors whose role in vivo is to detect danger signals associated with pathogens, and when activated, to drive cytokine production and the innate immune response. Thus, assessing NF-kB activation in this assay provides a direct measure of potential cytokine induction, and thus pyrogenic potential of vaccine drug substance and drug product.

Result

The report analyses the sensitivity of the TLR/NF-kB activation assay using data generated through the QIV development program, post marketing commitments, as well as characterisation data generated to support the introduction of new strains, demonstrating that the assay to be a sufficiently sensitive marker to detect low levels of pyrogenic signal. Once an optimised TDOC concentration has been established for an influenza strain, the concentrated and formulated vaccine remains pyrogenically inert in the NF-kB activation assay.

Conclusion

The report highlights the importance of optimisation of the influenza virus splitting process as assessed by the NF-kB activation assay in controlling the pyrogenic potential of new virus strains and in ensuring the production of vaccine with an appropriate product quality safety profile.

Poster Reception II

Sohwa Kim - AOXI0361

Recombinant HA protein vaccine fused with RNA interaction domain induce significant humoral and cellular immune response against influenza virus

Sohwa Kim[1], Jae Min Song[1], Yeh Eun Kim[1], Yong Chan Park[1]

[1]Sungshin Women's University

Background

It is challenging to produce high quality recombinant proteins using prokaryotic expression systems, like Escherichia coli (E. coli) even though this system can save a great time and expense. To overcome this problem, RNA was used as molecular chaperon for effective protein folding in previous study. In this study, recombinant H9 or H5 HA globular domain (HAgd) fused with RNA interaction domain (RID) were produced in E. coli system and immunogenicity of these vaccines were verified by animal experiments. Also, different band pattern in western blot results showed that RID could be used as a marker to differentiate infected animals from vaccinated animals. (DIVA)

Method

H9 HAgd or H5 HAgd fused with RID were produced in E. coli system respectively. BALB/C mice(n=6) were vaccinated with RID H9 formulated with Alhydrogel adjuvant 2 times with 2 weeks intervals by intramuscular injection (IM). Mice sera were collected 2 weeks after each immunization and used for Enzyme-Linked Immunosorbent Assay (ELISA). 3 mice of each of groups were sacrificed for Enzyme-Linked ImmunoSpot (ELISPOT) assay. Vaccinated mice were challenged with H9 virus to test protection against wildtype virus. Also, DIVA strategy of RID H9 vaccine was confirmed with different band pattern against H9 inactivated virus immunized group by western blot. To demonstrate immunogenicity in chicken experiment, RID H9 protein formulated with ISA70 were injected to SPF chickens (n=8) 2 times 3 weeks apart by IM route. In ELISA, IgY antibody titers were measured with Chicken sera which were collected 3 weeks after each vaccination.

For RID H5 HAgd vaccine, BALB/C mice(n=6) were immunized with RID H5 formulated with Alhydrogel adjuvant 3 times with 2 weeks intervals by IM route. ELISA and virus challenge were also conducted for RID H5 vaccine.

Result

In mouse experiment results, the specific IgG antibody titers against RID HAgd were induced significantly. Also, specific IgY antibody titers against RID H9 were detected in chicken experiment. For T cell responses, there were considerable induced level of interferon gamma and interleukin 4. In virus challenge results, there were no significant loss in mice body weight and all immunized mice could survive from virus infection. With western blot results, recombinant RID H9 immunized sera could detect RID protein, on the other hand H9 inactivated virus immunized sera could not detect RID protein.

Conclusion

Recombinant RID H9 or H5 HAgd vaccine could induce significant humoral and cellular responses in animal experiments. Also, different band pattern using RID H9 vaccinated sera which interact with RID protein in western blot, shows promise as a DIVA vaccine. With these results, RID H9 or H5 HAgd DIVA vaccine can be a desirable influenza vaccine candidate.

Poster Reception II

Jong Hyeon Seok - AOXI0433

Modification of HA glycosylation for the generation of efficacious vaccines against avian influenza viruses

Jong Hyeon Seok[4], Jin Il Kim[2], Joon-Yong Bae[1], Jeonghun Kim[1], Heedo Park[1], Jineui Kim[1], Jaehwan You[1], Ho Young Lee[1], Kisoon Kim[3], Man-Seong Park[2]

[1]Department of Microbiology, the Institute of Viral Diseases, Korea University College of Medicine, Seoul, 02841, Republic of Korea, [2]Department of Microbiology, the Institute of Viral Diseases, Korea University College of Medicine, Seoul, 02841, Republic of Korea; Biosafety Center, Korea University College of Medicine, Seoul, 02841, Republic of Korea; Vaccine Innovation Center, Korea University College of Medicine, Seoul, 02841, Republic of Korea, [3]Department of Microbiology, the Institute of Viral Diseases, Korea University College of Medicine, Seoul, 02841, Republic of Korea;Vaccine Innovation Center, Korea University College of Medicine, Seoul, 02841, Republic of Korea, [4]Korea university

Background

Zoonotic avian influenza viruses (AIVs) pose a severe health threat to humans. Of several viral subtypes that have been reported, a H7N9 virus has been responsible for more than 1,500 cases of human infection nearing a 40% case-fatality rate. Vaccination of poultry appears to reduce risk of human infections, yet the emergence of AIVs has increased concerns over the occurrence of avian influenza pandemics. To combat this issue, we set out to develop a vaccine by utilizing N-linked glycosylation (NLG) pattern changes on the viral hemagglutinin (HA) protein based on evolutionary patterns of HA NLG changes of AIVs.

Method

Complete HA genomic sequences of AIVs were downloaded from the NCBI database and used for NLG pattern analysis. Target residues for NLG modification were then selected, and NLG-mutant HA viruses (7:1 recombinant) were generated on the genetic backbone of A/Puerto Rico/8/1934 (PB2, PB1, PA, NP, NA, M, and NS genes) carrying an NLG-mutant HA gene by plasmid-based reverse genetics. For animal model study, BALB/c mice and ferrets were either primed or boosted intramuscularly at a 2-week interval, with the inactivated virus antigen containing or without alum adjuvant. Two weeks after the final immunization, the mouse and ferret antisera were collected for use in serological assays.

Result

The virus containing NLG modification to HA (H2, H4, H5, and H6 subtypes) displayed higher growth rates in cell culture and elicited more cross-reactive antibodies when compared with the vaccine viruses harboring wild-type HA with no change in the viral antigenicity. In the inactivated vaccine formulation, the vaccine virus with NLG additions exhibited noticeably improved protective efficacy in lethally challenged mice and resulted in the reduction of viral replication in the lungs. In ferrets, the NLG-added vaccine viruses also induced hemagglutination-inhibiting antibodies and significantly suppressed viral replication in the upper and lower respiratory tracts compared with the wild-type HA vaccines.

Conclusion

As presented in the H7N9 vaccine study, HA NLG modification protected animals from lethal challenge of H2, H4, H5, and H6 subtypes. These results strongly suggest the potential of HA NLG modifications when designing avian influenza vaccines.

Poster Reception II

Yeh Eun Kim - AOXI0444

Inactivation of antigen-displayed baculovirus using natural products : a proof-of-concept for influenza vaccine

Yeh Eun Kim[1], Young Chan Park[1], Sohwa Kim[1], Jae Min Song[1]

[1]Sungshin Women's university

Background

The most common egg-based inactivated Influenza vaccine has several limitations, such as residual allergenicity of egg protein and the use of toxic chemical agents for pathogen inactivation. In this study, we develop new vaccine platforms using antigen displayed baculovirus with inactivation by catechin component to overcome disadvantages of traditional vaccine platform. This vaccine platforms produced in insect cells and inactivated by natural material have shown the possibility for safe and expeditious production. In addition, catechin inactivation minimize side effects caused by the remaining chemical substances such as formalin and no chemical removal step is required in vaccine produce.

Method

The antigen expressed recombinant baculovirus were generated in sf9 cells using Bac-to-Bac system and quantified by hemagglutination assay and baculovirus titration. Also, the inactivation effect of catechin against to antigen displayed baculovirus were quantified by baculovirus titration. In vivo test, the specificity of antibody responses was tested by ELISA and mice were survived from lethal influenza virus challenge.

Result

Our study demonstrated the safety, immunogenicity and protective efficacy of inactivated recombinant baculovirus(egcg-rBV). It was not replicated in mice through real-time quantitative PCR using homogenized infected lung. This egcg-rBV induced neutralizing antibodies in mice and survived against lethal PR8 virus challenge.

Conclusion

The HA expressed recombinant baculovirus inactivated with egcg as effective novel vaccine platform. We have successfully evaluated the safety, immunogenicity and protective efficacy of HA expressed recombinant baculovirus inactivated with egcg. This novel vaccine platform could be used for the other virus vaccine.

Poster Reception II

Chris Ka Pun Mok - AOXI0324

Comparison of Omicron BA.1-specific T cell responses in adults vaccinated with CoronaVac or BNT162b2 in Hong Kong

Chris Ka Pun Mok[1], Chunke Chen[1], David S Hui[1], Malik Peiris[2]

[1]The Chinese University of Hong Kong, [2]The University of Hong Kong

Background

As COVID-19 vaccines do not efficiently prevent virus transmission of new variants of concern such as Omicron, the primary aim of vaccines is reducing disease severity in high-risk groups, towards which T cell immunity makes significant contributions. There is a paucity of data on vaccine induced T-cell immunity to Omicron especially the CoronaVac. Here we provide a head-to-head comparative study on T cell immune responses to Omicron elicited by CoronaVac and BNT162b2 vaccines.

Method

s: Adults receiving either 2 doses of BNT162b2 (n=214) or CoronaVac (n=214) vaccines as well as subgroups who had received 2 doses of CoronaVac and then a booster dose of either BNT162b2 (n=39) or CoronaVac (n=40) were recruited in Hong Kong. The percentage of IFNγ+CD4+ and IFNγ+CD8+ T cells against SARS-CoV-2 were determined from by flow cytometry using peptide pools of wild type or Omicron.

Result

Two doses of either CoronaVac or BNT162b2 elicited significant number of SARS-CoV-2 specific CD4 and CD8 responses compared to the pre-vaccinated controls. Vaccine induced T cell responses to the wild-type and Omicron viruses were comparable in the two vaccines. However, BNT162b2 induced more potent spike-specific CD4 and CD8 T cell responses in adults compared to CoronaVac. Adults with age ≥60 showed significantly lower numbers of SARS-CoV-2 specific T cells if they received CoronaVac, compared to BNT162b2. Receiving a third dose of either BNT162b2 or CoronaVac boosted waning T cell responses compared to pre-third dose levels, but levels did not exceed those seen 1 month after the second dose.

Conclusion

Two doses of CoronaVac or BNT162b2 provide T cell responses to Omicron in adults but BNT162b2 induces better T cell responses in old adults. A third dose of either vaccine restores waning T cell responses to that seen one month after the second dose.

Poster Reception II

DeokHwan Kim - AOXI0332

Recombinant NDV-vectored SARS-CoV-2 Spike gene Live vaccine protect hACE-2 mouse from Lethal infection of the SARS-CoV-2

DeokHwan Kim[1]

[1]KHAV Co., Ltd

Background

SARS-CoV-2 is a type of beta-corona virus, which occurred in 2019 and has caused many infections and many deaths until 2022, and continues to cause infections and deaths. As the SARS-CoV-2 outbreak caused a worldwide infection, various vaccine platforms were used to create a vaccine against SARS-CoV-2. Newcastle disease virus(NDV) is a poultry-derived Single Strand RNA virus and is a safe virus vector Known to rarely infect humans. In this study, a SARS-CoV-2 vaccine of a novel virus vector platform was created and evaluated using the NDV-vector system.

Method

The whole Spike genome of the beta strain of SARS-CoV-2 was inserted using the NDV- vector system. NDV-SARS-CoV-2(s full; beta) was evaluated for immunogenicity against intranasal and intramuscular route and protective ability against SARS-CoV-2 beta strain through hACE-2 transgenic mouse. After serum separation through blood collection, the antibody titer of NDV was evaluated through HI, and the antibody titer SARS-CoV-2 was evaluated through ELISA. After two vaccinations with NDV-SARS-CoV-2(S full; beta) at 10^6.0EID50, the protection level against the SARS-CoV-2 beta strain was also evaluated.

Result

The HI titer of NDV of the two inoculation methods appeared after the secondary vaccine, and the SARS-CoV-2 antibody titer through ELISA was confirmed from the 4th week after the primary vaccine. The protective ability of the SARS-CoV-2 beta strain was confirmed to be 70% for the intra-muscular vaccine and 85% for the intranasal vaccine.

Conclusion

When 100% survival rate is confirmed by increasing the vaccine concentration, NDV-SARS-CoV-2(S full; beta) can be a candidate for the egg-based SARS-CoV-2 vaccine, vaccination routes can also be used for intramuscular and intranasal routes.

Poster Reception II

Fan Zhou - AOXI0341

Different kinetics of seasonal and pandemic human coronavirus reactive antibodies after repeated vaccination in adults and the elderly

Fan Zhou[2], Juha Vahokoski[2], [1], Nina Langeland[2], Rebecca J. Cox[3]

[1]Bergen COVID- 19 Research Group, [2]Influenza Center, Department of Clinical Science, University of Bergen, Bergen, Norway, [3]Influenza Center, Department of Clinical Science, University of Bergen, Bergen, Norway; Department of Microbiology, Haukeland University Hospital, Bergen, Norway.

Background

Variants of SARS-CoV-2 have been emerging since 2020, often with enhanced transmissibility and/or can escape from pre-existing immunity established by vaccination or earlier infection. Repeated vaccination was recommended to provide protection against severe illness and hospitalization, especially in the elderly and healthcare worker. Human coronaviruses (HCoV), including HKU-1, OC43, NL63, 229E, circulate in humans and cause mild respiratory tract symptoms. However, little is known about the HCoVs specific immunity prior to COVID19 pandemic. It's important to understand whether and how HCoV specific immunity is impacted by repeated SARS-CoV-2 vaccination and infection.

Method

At the Influenza Centre, we have conducted prospective cohort studies in SARS-CoV-2 infected and vaccinated subjects from different ages and collected sequential serum samples before and after repeated mRNA (Comirnaty, BNT162b2 2 doses at 3 week interval, and booster dose 9 months later) vaccination. The SARS-CoV-2 specific and HCoVs-reactive binding antibodies were quantified using ELISA with full length spike proteins. The different magnitude and kinetics of head and stalk domain specific antibodies were assessed with S1 and S2 proteins. The cross-neutralizing antibodies were measured against live SARS-CoV-2 and HCoVs in neutralization assays.

Result

The elderly and young adults had low concentrations of full-length spike and S1 domain specific antibodies, but moderate level of S2 domain specificantibodies prior to vaccination. The initial two doses of mRNA vaccines induced significantly higher SARS-CoV-2 specific antibodies in young adults than in the elderly. Whereas the booster vaccine dose increases SARS-CoV-2 specific antibodies in both age cohorts. S2 domain specific antibodies fold-induction and waning are not as dramatic as S1 specific antibodies after repeated vaccination.OC43 and HKU1 beta-coronaviruses are genetically closer to SARS-CoV-2 compared to 229E and NL63 alpha-coronaviruses. Repeated SARS-CoV-2 vaccination induced higher levels of cross-reactive antibodies against OC43 and HKU1 in young adults than in the elderly, whilst cross-reactive antibodies against 229E or NL63 maintained the same in young adults, but waned over time in the elderly.

Conclusion

Our study shows repeated SARS-CoV-2 vaccination altered the ratio of spike head and stalk domain specific antibody responses, and boosted antibodies cross-reactive towards closely related beta-coronavirus.

Poster Reception II

Wanitchaya Kittikraisak - AOXI0359

Anti-SARS-CoV-2 IgG antibody levels among Thai healthcare providers receiving homologous and heterologous COVID-19 vaccination regimens

Wanitchaya Kittikraisak[8], Taweewun Hunsawong[13], Somsak Punjasamanvong[12], Thanapat Wongrapee[10], Patama Suttha[2], Phunlerd Piyaraj[11], Chaniya Leepiyasakulchai[6], Chuleeekorn Tanathitikorn[9], Pornsak Yoocharoen[4], Anthony R. Jones[13], Duangrat Mongkolsirichaikul[1], Matthew Westercamp[5], Eduardo Azziz-Baumgartner[7], Joshua A. Mott[8], Suthat Chottanapund[3]

[1]Armed Forces Research Institute of Medical Sciences, [2]Bamrasnaradura Infectious Diseases Institute, [3]Bureau of Risk Communication and Health Behavior Development, Department of Disease Control, Ministry of Public Health, [4]Department of Disease Control, Ministry of Public Health, [5]Division of Healthcare Quality Promotion, U.S. Centers for Disease Control and Prevention, [6]Faculty of Medical Technology, Mahidol University, [7]Influenza Division, U.S. Centers for Disease Control and Prevention, [8]Influenza Program, Thailand MOPH - U.S. CDC Collaboration, [9]Institute of Preventive Medicine, Department of Disease Control, Ministry of Public Health, [10]Phaholpolpayuhasena Hospital, [11]Phramongkutklao College of Medicine, [12]Rayong Hospital, [13]Virology Laboratory, Armed Forces Research Institute of Medical Sciences

Background

We examined SARS-CoV-2 anti-spike 1 IgG antibody levels following COVID-19 vaccination (AstraZeneca [AZ], Sinovac [SV], Pfizer-BioNTech [PZ]) among Thai healthcare providers.

Method

Blood specimens were tested using enzyme-linked immunosorbent assay. We analyzed seven vaccination regimens: a) one dose of AZ or SV, b) two doses of homologous (2AZ, 2SV) or heterologous (1AZ+1PZ) vaccines, and c) three doses of heterologous vaccines (2SV+1AZ, 2SV+1PZ). Differences in antibody levels were assessed using Kruskal-Wallis statistic, Mann-Whitney test, or Wilcoxon matched-pairs signed-rank test. Antibody kinetics were predicted using fractional polynomial regression.

Result

The 563 participants had median age of 39 years; 92% were female; 74% reported no underlying medical condition. Antibody levels peaked at 22-23 days in both 1AZ and 2SV vaccinees and dropped below assay's cutoff for positive (35.2 binding antibody units/mL [BAU/mL]) in 55 days among 1AZ vaccinees compared to 117 days among 2SV vaccinees. 1AZ+1PZ vaccination regimen was highly immunogenic (median 2,279 BAU/mL) 1-4 weeks post vaccination. 2SV+1PZ vaccinees had significantly higher antibody levels than 2SV+1AZ vaccinees four weeks post vaccination (3,423 vs. 2,105 BAU/mL; p-value<0.01), and during weeks 5-8 (3,656 vs. 1,072 BAU/mL; p-value<0.01). Antibodies peaked at 12-15 days in both 2SV+1PZ and 2SV+1AZ vaccinees, but those of 2SV+1AZ declined more rapidly and dropped below assay's cutoff in 228 days while those of 2SV+1PZ remained detectable.

Conclusion

1AZ+1PZ, 2SV+1AZ, and 2SV+1PZ vaccinees had substantial IgG levels, suggesting that these individuals likely mounted sufficient anti-S1 IgG antibodies for possible protection against SARS-CoV-2 infection.

Poster Reception II

Raquel Guiomar - AOXI0379

COVID-19 vaccine booster recovered the antibody titers acquired after the primary vaccination scheme

Raquel Guiomar[5], Aryse Melo[7], Ana João Santos[2], Camila Henriques[7], Inês Costa[6], Rita Matos[9], Ana Paula Rodrigues[3], Irina Kislaya[3], Anabela Santos Silva[1], Carla Nunes[1], Carla Roque[4], Joaquim Aguiar[1], Fátima Graça[8], António Silva Graça[8], Ausenda Machado[2]

[1]COVID-19 workgroup of Porto, National Institute of Health Dr. Ricardo Jorge, Portugal, [2]Department of Epidemiology, National Institute of Health Dr. Ricardo Jorge, Portugal, [3]Department of Epidemiology, National Institute of Health Dr. Ricardo Jorge, Portugal., [4]Department of Infectious Diseases, National Institute of Health Dr. Ricardo Jorge, Portugal, [5]National Institute of Health, Portugal 501427511, [6]National Reference Laboratory for Influenza Virus and Other Respiratory Virus, Department of Infectious Diseases, National Institute of Health Dr. Ricardo Jorge, Portugal, [7]National Reference Laboratory to Influenza Virus and Other Respiratory Virus, Department of Infectious Diseases, National Institute of Health Dr. Ricardo Jorge, Portugal, [8]Occupational Health Department, National Institute of Health Dr. Ricardo Jorge, Portugal, [9]Serology Laboratory, Department of Infectious Diseases, National Institute of Health Dr. Ricardo Jorge, Portugal

Background

The waning immunity against COVID-19 was already shown by several studies and constitute the main challenge to adapt the national vaccination program. The Portuguese vaccination campaign recommended the primary vaccination scheme for all population above 5 years old and a booster dose for adults and risk groups. This study aims to report the immunological profile of a health care professional (HCW) cohort of the National Institute of Health (INSA) by the detection of SARS-CoV-2 specific antibodies, including those induced by the vaccine or acquired after natural infection.

Method

Between January 2021 and February 2022 (12 months), a prospective longitudinal study followed-up a cohort of 221 HCW from INSA. All the participants collected nasopharyngeal samples to monitor SARS-CoV-2 infection by RT-PCR, and sera for specifc antibody detection against SARS-CoV-2 (quantitative IgG anti-Spike/RBD) through a Chemiluminescence enzyme immunoassay. Samples were collected at recruitment/before 1st dose (T1), 30 days(d) after 1st dose (T3), 20-70d after 2nd dose (T4), 150-210d after 2nd dose (T5), 240-300d after 2nd dose/before booster(T6) and 20-60d after booster dose(T7). The geometric mean (GMT, 95% CI) of anti-S/RBD IgG was estimated and Wilcoxon's rank sum test was applied to detect statistical differences at different moments of the follow-up period.

Result

From the 221 participants included in the study, 86,9% were women, between 20-49 years old (51,6%) and 50-70 years old (48,4%). The most frequently administered vaccine was Comirnaty (83.8%). 184 participants took the booster dose of COVID-19 vaccine. Although a marked decay was observed in antibody titers along the follow up period, the booster dose increased the GMT antibody 2,2 fold for participants compared to the GMT at 30 days after the primary vaccination scheme (1028,86 [95%IC: 873,70-1211,58] vs. 2309,12 [95%IC: 2010,68-2651,86]. Rise in antibody titers, after booster dose, was markedly higher for the ones without SARS-CoV-2 infection (2,24 fold increase in GMT, 982,42[95%IC: 832,90-1159,69] vs. 2213,14[95%IC: 1912,59-2560,92]) compared to the ones with a SARS-CoV-2 previous infection (1, 01 fold increase in GMT, 1750,48[95%IC: 700,51-4374,21] vs. 1750,48 [95%IC: 700,51-4374,21]).

Conclusion

The booster dose recovered the IgG (anti-S) antibody titers acquired after the primary vaccination scheme. For participants who had no previous infection, the vaccine not only recovered antibody titers from the full vaccination but also increased them. Higher antibody titers corroborate with the higher vaccine effectiveness reported in literature for several population after booster vaccine dose.

Poster Reception II

Cathy Srokowski - AOXI0405

Duration of protection against SARS-CoV2: implications for development of new candidate vaccines and booster vaccination recommendations

Cathy Srokowski[1], Maciej Zatonski[1], Leonard R. Friedland[1], Tomas Mrkvan[1], Rafik Bekkat-Berkani[1], Selim Badur[1]

[1]GSK

Background

While vaccination offers an effective counter-measure to help mitigate the COVID-19 pandemic, several factors continue to determine its benefits: the challenges of a waning immune response and emergence of new variants erode protection against SARS-CoV2 infection and disease. The goals of vaccination and the duration of the level of protection afforded by vaccination have implications for the implementation of booster vaccination programs, their frequency, and/or need for novel vaccines.

Method

We reviewed the literature published on SARS-CoV2 with respect to the duration of humoral and cellular immune response and protection against non-symptomatic infections, mild or severe disease, hospitalizations, and death caused by different variants of concern in individuals who have been vaccinated against and/or infected by SARS-CoV2 with specific focus on evidence informing the future COVID-19 booster vaccination recommendations and development of novel vaccines.

Result

Clinical trials and real-world evidence indicate waning of antibody response with time since initial vaccination or after natural infection, suggesting a correlation between the efficacy/effectiveness of different vaccines against symptomatic disease and neutralizing antibody titers; however, protection against severe disease appears more durable, probably due to anamnestic humoral and cellular immunity. Emerging data demonstrate that heterologous vaccination and hybrid immunity expand the breadth of both humoral and cellular immunity. Other factors, such as age and underlying medical conditions, also impact the immune response. Concerns about the waning of vaccine-induced immunity and reduced vaccine effectiveness help inform recommendations for the need and timing of boosters for eligible populations. The accelerated emergence of new, highly transmissible variants that escape immunity, raises further challenges regarding the need for additional, variant-appropriate boosters and their frequency to sustain protection against severe disease.

Conclusion

The primary goal of immunization in the COVID-19 pandemic remains to protect against severe disease, hospitalization, and death by ensuring all eligible individuals receive up to date COVID-19 primary series and all currently recommended booster doses. The degree of protection and need for additional booster doses may differ between eligible populations and circulating SARS-CoV2 virus variants. New candidate vaccines are being developed to broaden variant coverage, improve the immune response, and impact transmission which may ultimately help improve control the COVID-19 burden of disease worldwide.

Poster Reception II

JIEUN PARK - AOXI0445

Evaluation of the attenuation degree of cold-adapted live attenuated SARS-CoV-2 vaccine candidate in K18-hACE2 transgenic mice

Ji-Eun Park[1], Ha-na Youn[1], Hyo-seon Joo[1], Da-ye Lee[1], Su-bin Park[1], Je-hyeon Jeong[1], Jun-beom Kim[1], Deok-hwan Kim[1], Chang-seon Song[1]

[1]KHAV

Background

Severe Acute Respiratory Syndrome Coronavirus 2 is a causative agent of infectious diseases that have been prevalent worldwide in 2019. It was first reported in China, and among the existing viral infections, it is highly contagious and has a high mortality rate. Many vaccine candidates are currently being developed including viral vector, recombinant protein-based vaccines, and mRNA vaccines. But the safety and efficacy of developed vaccines are still a concern as new variants are rapidly emerging. they deliver a robust immune response and are associated with the long-lasting cellular immunity. In this study, we developed a live attenuated SARS-CoV-2 vaccine candidates using cold-adaptation and the attenuation was confirmed using hACE2 transgenic mouse.

Method

Subculture of the SARS-CoV-2 Wuhan strain, an ancestral strain, was performed using Vero e6 cells by a low-temperature adaptation method. Growth of SARS-CoV-2 in Vero e6 cells was gradually adapted from 37°C to 31°C. The initial strain started culturing at 37°C, and then proceeded every 10 passages by lowering the temperature by 1°C. To confirm the attenuation of SARS-CoV-2 vaccine candidates in vivo, Transgenic mice were intranasally challenged with 104.7 Tissue Culture Infectious Dose (TCID) of cold-adapted vaccine candidates passage no. 30, 40, 50, 60 or wild type SARS-CoV-2 WUHAN strain. This experiment included for wild type and negative control(PBS). The infected mice were monitored for 2weeks. (Clinical symptoms, weight loss and mortality rates)

Result

In the p30, 40, and 60 groups, 2~40% of deaths occurred between 8 and 14 days after inoculation, but all p50 survived without weight loss. Clinical symptoms appeared from day 4. Clinical symptom test details include Anorexia, weight change, hair roughness, and movement. The Wild type of group all died on the 9th day after administration. The negative control group administered PBS did not lose weight. Through this experiment, we found the P50 vaccine candidate was successfully adapted without showing pathogenesis.

Conclusion

We evaluated pathogenicity of cold-adapted live attenuated SARS-CoV-2 vaccine candidate by its passage number. Through animal experiment using K18-hACE2 transgenic mice, we proved that the SARS-CoV-2 P50 candidate was sufficiently attenuated by the cold-adaptation method. This experiment will be an important basis for the mutation study for attenuation, and following efficacy tests leading to development of live SARS-CoV-2 vaccine.

Poster Reception II

Iuliia Desheva - AOXI0447

Surface expression of SARS-Cov-2 epitopes in Enterococcus L3 to develop live peroral vaccine

***Iuliia Desheva*[1], *Galina Leontieva*[1], *Olga Kopteva*[1], *Tatiana Gupalova*[1], *Tatiana Kramskaya*[1], *Elena Bormotova*[1], *Alexander Dmitriev*[1], *Alexander Suvorov*[1]**

[1]Federal State Budgetary Scientific Institution Institute of Experimental Medicine

Background

Probiotic microorganisms are currently considered as a promising platform for the development of recombinant vaccines expressing viral or bacterial antigens. In the current study, we assessed SARS Cov-2 S1 protein expression after the insertion of appropriate genetic element into the genome of a probiotic strain Enterococcus faecium L3 (L3). We studied the expression of the inserted viral gene fragment at the stage of mRNA synthesis and its localization in a bacterial cell.

Method

S1 SARS-Cov-2 gene fragment of 512 bp was inserted into major pili protein gene with d2 domain of enterococcal operon using integrative plasmid pentF-sarsS. Location of the insertion was confirmed by PCR and DNA sequencing. The expression of mRNA was studied using real-time PCR (rRT-PCR) using specific primers. For immunoelectron microscopy the L3-SARS bacteria were grown in Luria Broth (VWR Life Science Products, Amresco, Solon, United States) medium at 37°C for 18 h., washed three times in PBS by centrifugation and resuspended in 0.1 M NaCl to obtain 10x concentrate. The source of primary antibodies was human polyclonal serum containing IgG specific for S1 of SARS-Cov-2 which were previously adsorbed twice on pure non-modified L3 culture in a ratio of 1:10 in order to avoid nonspecific binding. Immunogold labeling was performed using goat IgG conjugated to 18 nm gold particles (1 mg/ml; Jackson ImmunoResearch Laboratories, West Grove, United States). Electron microscopy was performed on a JEM-2100 transmission electron microscope (JEOL, Tokyo, Japan) through the Resource Center of St. Petersburg State University.

Result

The expression of mRNA isolated from the recombinant enterococcal strain L3 with the insert of the SARS-Cov-2 gene S1 fragment employing RT-PCR revealed a significant degree of PCR product. At the same time, amplification did not occur when total RNA was isolated from a pure L3 culture. Electron microscopy of the strain L3-SARS demonstrated that gold-conjugated antibodies are distributed along the entire length of the piles. Unmodified E. faecium L3 not interacted with SARS-Cov-2-specific IgG.

Conclusion

Immune electron microscopy data shows that a fragment of spike protein from SARS-Cov-2 capable of being part of a properly assembled enterococcal pili. This finding makes the strain L3-SARS an interesting vaccine candidate due to the easy access of pili to the host immune system.

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Poster Reception II

Han Di - AOXI0449

Neutralization of SARS-CoV-2 by antibodies elicited after COVID-19 mRNA vaccination varies depending on immunization schedule and variants of concern/interest

Han Di[1], Li Wang[1], Markus Kainulainen[1], Nannan Jiang[1], Gaston Bonenfant[1], Lisa Mills[1], Michael Currier[1], Punya Shrivastava-Ranjan[1], Brenda Calderon[1], Mili Sheth[1], Brian Mann[1], Jaber Hossain[1], Xudong Lin[1], Sandra Lester[1], Elizabeth (Liz) Pusch[1], Joyce Jones[1], Dan Cui[1], Payel Chatterjee[1], Harley Jenks[1], Esther Morantz[1], Gloria Larson[1], Masato Hatta[1], Jennifer Harcourt[1], Azaibi Tamin[1], Yan Li[1], Ying Tao[1], Kun Zhao[1], Kristine Lacek[1], Ashley Burroughs[1], Suxiang (Sue) Tong[1], John Barnes[1], Mark Tenforde[1], Wesley Self[6], Nathan Shapiro[2], Matthew Exline[4], D. Clark Files[7], Kevin Gibbs[7], David Hager[3], Manish Patel[1], Alison Laufer Halpin[1], Laura McMullan[1], Justin Lee[1], Xuping Xie[5], Pei-Yong Shi[5], Christina Spiropoulou[1], Natalie Thornburg[1], Steve Oberste[1], Vivien Dugan[1], C. Todd Davis[1], David Wentworth[1], Bin Zhou[1], Terianne Wong[1]

[1]COVID-19 Emergency Response, Centers for Disease Control and Prevention, [2]Harvard University, [3]Johns Hopkins University, [4]Ohio State University, [5]University of Texas Medical Branch, [6]Vanderbilt University, [7]Wake Forest Baptist Medical Center

Background

The evolution of SARS-CoV-2 has resulted in the emergence of variant lineages that exacerbated the COVID-19 pandemic. The divergence into variants of concern/interest (VOC/VOI) necessitates analysis of the impact on virus neutralization by antibodies elicited post-vaccination.

Method

Because mRNA vaccines were the earliest and primary form of COVID-19 vaccines administered in the United States of America, we systematically evaluated the ability of VOC/VOIs containing various combinations of spike (S) protein mutations to escape neutralization by at least 20 individual post-vaccination sera using a focus reduction neutralization test (FRNT). To rapidly characterize emerging variants, we also generated SARS-CoV-2 fluorescent reporter viruses with VOC/VOI S protein substitutions and deletions compared to the index virus, hCoV-19/Wuhan/WIV04/2019 (S-614D), by reverse genetics.

Result

Significant differences in neutralization escape from post-vaccination sera were observed among the variants and varied depending on whether individuals received a second or third mRNA vaccine dose. The S-D614G substitution had minimal impact on the neutralizing activity of the vaccinee sera, compared to the progenitor 614D reference virus, in which the spike sequence is most closely related to that used in vaccine production. The Alpha variant (B.1.1.7) showed little escape from neutralization, while the Gamma (P.1), Delta (B.1.617.2 and AY.4.2), Epsilon (B.1.427/B.1.429), Zeta (P.2), Eta (B.1.525), Iota (B.1.526/B.1.526.1), Kappa (B.1.617.1), Lambda (C.37), and B.1.617.3 variants showed modest antigenic distinction/drift, with 4-fold reduction in neutralization titers against these viruses compared to the index virus. Theta (P.3), Mu (B.1.621), and Beta (B.1.351) variants showed moderate antigenic drift (i.e., ≥4-7-fold reductions in serum neutralization titers). Of note, the Omicron variant lineages (BA.1, BA.1.1, BA.2, BA.2.12.1) had the greatest escape from serum neutralization observed to date when tested with post-second dose vaccine sera (35-fold or higher reductions in serum neutralization titers). Neutralization titers to Omicron variant lineages increased after a third vaccine dose (>10-fold compared to post-second dose sera) but remained reduced (>8-fold) compared to those of the index virus.

Conclusion

These findings demonstrate that neutralizing antibodies elicited by mRNA vaccines neutralized most VOC/VOIs well. Omicron variant lineages, however, have significant antigenic drift away from the index viruses and escape neutralizing antibodies even after a third vaccine dose. Therefore, antigenic characterization of emerging SARS-CoV-2 variants will remain a critical component to assess suitability of mRNA vaccine antigens.

Poster Reception II

Thomas Luke - AOXI0451

SAB-185 protects human ACE2 transgenic Syrian hamsters against multiple SARS CoV-2 variants including Omicron

Thomas Luke[3], Hua Wu[3], Kristi Egland[3], Christoph Bausch[3], Eddie Sullivan[3], Zhongde Wang[2], William Klimstra[1], Theron Gilliland[1]

[1]Center for Vaccine Research and Department of Immunology, University of Pittsburgh, USA, [2]Department of Animal Dairy, and Veterinary Sciences, Utah State University, USA, [3]SAB Biotherapeutics, Inc. Sioux Falls, SD, USA

Background

Pandemic SARS CoV-2 has undergone rapid evolution resulting in the successive emergence of many variants with novel mutations in the Spike (S) protein, some of which appear to evade antibody neutralization, transmit more efficiently, and/or potentially increase virulence. These variants raise significant concerns regarding the long-term efficacy of protection elicited after primary infection, or from vaccines derived from single virus Spike genotypes, as well as the efficacy of anti-Spike monoclonal antibody-based therapeutics. To potentially address these concerns, SAB-185, a human anti-SARS-CoV-2 polyclonal antibody (pAb), was generated in the DiversitAbTM platform and evaluated in vitro and in vivo.

Method

The in vitro neutralizing capacity of SAB-185 was tested against seven variant SARS-CoV-2 strains: Munich (Spike D614G), alpha (B.1.1.7), beta (B.1.3.5), gamma (P.1), delta (AY.1) and omicron (BA.1-B.1.1.529) variants, and a variant isolated from a chronically infected immunocompromised patient (Spike ï„144-146). For in vivo protection studies, we used a new human ACE2 (hACE2) transgenic Syrian hamster model that results in death and/or severe disease after intratracheal administration of SARS-CoV-2 variants. SAB-185 was delivered prophylactically prior to challenge with the Munich, alpha, beta, delta, Spike ï„144-146, and Omicron variants.

Result

SAB-185 exhibited similar neutralization titers of the Munich, alpha, beta, gamma and ï„144-146 variants on Vero E6 cells and retained neutralization titers for the delta variant AY.1 and omicron BA.1 variants. In the in vivo protection studies with a human ACE2 (hACE2) transgenic Syrian hamster model, we show rapid lethality after intratracheal SARS-CoV-2 challenge with the Munich, alpha, beta, delta, and ï„144-146 variants. Interestingly, challenge with the omicron BA.1 variant resulted in a delayed, less severe, and non-lethal disease. Importantly, in this hamster model, prophylactic SAB-185 treatment protected the hamsters from death and minimized clinical signs of infection when challenged with the variant SARS-CoV-2 viruses, including omicron.

Conclusion

We show that SAB-185, comprised of human anti-SARS-CoV-2 pAbs, maintains in vitro neutralization and in vivo protection in hACE2 hamsters despite multiple Spike protein mutations in successive SARS CoV-2 variants, including omicron. This suggests that SAB-185 may be an effective immunotherapy even in the presence of ongoing viral mutation.

Poster Reception II

Deborah Fuller - AOXI0467

Self-amplifying Replicon RNA vaccine induces broad antibody responses in pre-immune nonhuman primates and durable protection from SARS-CoV-2 even after neutralizing antibodies wane to undetectable levels

Deborah Fuller[3], Amit Khandhar[1], Jesse Erasmus[2]

[1]HDT Bio, [2]HDT bio and Dept of Microbiology, University of Washington, [3]University of Washington

Background

The global SARS-CoV-2 pandemic prompted rapid development of COVID-19 vaccines and several vaccines have been licensed for human use. However, the SARS-CoV-2 pandemic continues. Emergent variants of concern, waning immunity in the vaccinated, evidence that vaccines may not prevent transmission and inequity in vaccine distribution have driven continued development of vaccines against SARS-CoV-2 to address these gaps in public health needs.

Method

We evaluated binding and neutralizing antibody, T cell responses and protective efficacy of a novel self-amplifying replicon RNA vaccine against SARS-CoV-2 in a pigtail macaques. We found that this vaccine elicited strong neutralizing antibody after one or two doses. However, neutralizing antibody waned to low to undetectable levels after six months. Prior to challenge, neutralizing antibody responses were boosted in a subset of animals to high levels prior to challenge and protection in these animals was compared to the remaining animals that had low to undetectable neutralizing antibody.

Result

All macaques, regardless of level of neutralizing antibody at the time of challenge, were protected from disease when challenged as evident by reduced viral replication, proinflammatory responses and gross pathology in the lung as well as reduced viral shedding in the nasal cavity. Furthermore, a separate set of macaques primed with a repRNA vaccines matching the original WA-1 strain and then boosted with updated repRNA vaccines matching the Delta and Omicron variants developed broad antibody responses against all VOCs.

Conclusion

Cumulatively, our data demonstrate a self-amplifying repRNA vaccine can prime for robust and broad neutralizing antibody responses and provide durable protective efficacy even after neutralizing antibody responses have waned to undetectable levels.

Poster Reception II

Seung-Gyu Jang - AOXI0483

Differences in seroprevalence between epicenter and non-epicenter areas of the COVID-19 outbreak in South Korea

Seung-Gyu Jang[1], Eun-Ha Kim[1], Mark Anthony Casel[1], Rare Rollon[1], Ju-ryeon Gil[1], Jeong-Ho Choi[3], Young Ki Choi[2]

[1]College of Medicine and Medical Research Institute, Chungbuk National University, Cheongju 28644, Republic of Korea, [2]College of Medicine and Medical Research Institute, Chungbuk National University, Cheongju 28644, Republic of Korea; ID Bio Corporation, 157, Suui-ro, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, 28370, Republic of Korea, [3]ID Bio Corporation, 157, Suui-ro, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, 28370, Republic of Korea

Background

During the first outbreak of COVID-19 in Korea, Daegu City constituted the highest confirmed cases. Herein, we aimed to investigate the seroprevalence between regions with high- and low-cumulative COVID-19 case rates.

Method

Outpatient sera were randomly selected daily at two tertiary referral hospitals, Daegu Gyeongbuk University Hospital (KNUH) and Chungbuk Chungbuk National University Hospital (CBNUH), from May 1, 2020 to July 17, 2020. To investigate the anti-SARS-CoV-2 seroprevalence, IgG and neutralizing antibody (NAb) was assayed using Vero cells.

Result

A total of 7,248 outpatients' serum samples, which were not diagnosed as COVID-19 positive at the time of this study, were collected from the two hospitals, 3,268 from KNUH and 3,981 from CBNUH. The IFA IgG results revealed that the samples from KNUH (Daegu City) showed 1.25% seropositivity while a 0.83% seropositivity from CBNUH against SARS-CoV-2. Interestingly, the 70-79-year-old age group showed the highest seroprevalence in Daegu City, while patients 20-29 years of age showed the highest seroprevalence in Chungbuk Province. Twenty-four of 41 (58.5%) seropositive samples from KNUH were ≥ 60 years old, while 10 of 33 (30.3%) seropositive samples were from ≥ 60-year-old age group of CBNUH. NAb titers were found in three samples from KNUH (3/3, 268, 0.09%) while none among the CBNUH samples. Further, we compared seroprevalence within the general population at the epicenter of the COVID-19 outbreak in South Korea with that of a non-epicenter area. Interestingly, the seroprevalence of SARS-CoV-2 in Daegu City was only 1.5 times higher than the Chungbuk Province while the incidence of COVID-19 (number of cumulative cases per 100,000 people in each area) in Daegu City was 64 times higher than that of Chungbuk Province. Further, the highest seroprevalence in Daegu City was found in elderly patients compared to the young adult patients in Chungbuk Province.

Conclusion

In summary, we compared the SARS-CoV-2 seroprevalence rates between the geographic area with the highest and lowest COVID-19 case rate in South Korea. The results revealed that Daegu City (epicenter) showed higher seroprevalence rate than that of the region with the lowest cumulative number of infections, Chungbuk Province. Although following the large outbreak during the first wave of SARS-CoV-2 infection, seropositivity against SARS-CoV-2 in the general population remained low in South Korea. Therefore, the attainment of herd immunity through natural infection would be very difficult in South Korea due to this low seroprevalence.

Poster Reception II

James Ferguson - AOXI0476

Dissecting heterogenous polyclonal antibody responses to Influenza vaccination using cryoEMPEM

James Ferguson[1], Rachael Wolters[2], Svearike Oeverdieck[1], Julianne Han[1], Seth Zost[2], Ivette Nuñez[2], James Crowe Jr.[2], Andrew Ward[1]

[1]Scripps Research, [2]Vanderbilt University

Background

Influenza virus neuraminidase (NA) is a key target for antibody-mediated protective immunity as it has been shown to be an independent correlate of protection against infection and has limited antigenic drift. However, we lack high resolution structural details as well as immunogenetic information to understand the breadth of the antibody response to NA.

Method

Here, we use cryoEM to investigate human polyclonal antibody (pAb) responses to novel epitopes on influenza B NA (NAB) and determine atomic-level interactions of NAB-reactive monoclonal antibodies (mAbs) after seasonal influenza vaccination. To determine whether mAbs were representative of the serum response to NAB we used Electron Microscopy Polyclonal Epitope Mapping (EMPEM) to characterize the diversity of NAB epitopes targeted by pAbs from the same donor.

Result

EMPEM revealed a minimum of five distinct epitopes targeted by pAbs, two of which correspond to mAbs isolated from the same donor that bind the active site and loop A. High resolution structures revealed that the active site-binding mAb-400 has a long CDRH3 loop, characteristic of NA active site binders, with a key glutamate that H-bonds to three conserved Arginines and a Tyrosine in the NA active site. These NA residues also coordinate the binding of sialic acid or oseltamivir. mAb-393 interacts with the loop A region, similarly to a recently published N9-reactive mAb (PDBID:6PZF). Both mAbs utilized previously unseen genes IGHV5-51 and IGKV3-20 (mAb-400) and IGHV4-39 and IGKV1-5 (mAb-393). Using cryo-EMPEM we determined high resolution structures of pAbs to reveal epitope paratope interactions and infer amino acid sequences of pAbs to determine antibody sequences targeting novel epitopes.

Conclusion

Using EMPEM we characterized the comprehensive landscape of NAB epitopes targeted by pAbs from a human donor after season seasonal vaccination, revealing both known and unknown epitopes. High resolution cryoEM structures of pAb and mAb from this donor provide insightful details of epitope paratope interactions that will aid future rational influenza vaccine design.

Poster Reception II

Monica Fernandez-Quintero - AOXI0526

Structural and dynamic characterization of broadly neutralizing anchor epitope binding antibodies

Monica Fernandez-Quintero[2], Julianna Han[1], James Ferguson[1], Klaus Liedl[2], Andrew Ward[1]

[1]Scripps Research Institute, [2]University of Innsbruck

Background

The antibody binding site, the paratope, exists as multiple interconverting conformational states in solution. Antibody antigen recognition as well as various biophysical properties are governed by the dynamic character/nature of the paratope. Recently, a distinct class of broadly neutralizing antibodies has been reported that target a discrete membrane-proximal anchor epitope of the haemagglutinin (HA) stalk domain.

Method

The structures of the germline and the matured 3G01 antibody were determined with cryo-EM following a previously published protocol.

We use state-of-the-art molecular dynamics simulations in combination with enhanced sampling techniques to capture a broad conformational space and to overcome the limitations of classical molecular dynamics simulations.

Result

Antibodies targeting the anchor epitope, have a highly restricted repertoire, containing two germline-encoded binding motifs, that are critical for antigen-recognition and for stabilizing the paratope. Here, we structurally and dynamically investigate an affinity matured and a germline reverted anchor epitope binding antibody 3G01 utilizing the variable genes, VH3-30 and VK3-11. We provide cryo-EM structures of both the affinity matured and the germline reverted anchor epitope binding antibodies in complex with hemagglutinin.

Conclusion

The structures allow us to further understand and characterize the anchor epitope and identify key interactions that govern antibody-antigen recognition. Additionally, we find a restricted conformational space for the affinity matured antibody compared to the germline, which does not only reveal a higher flexibility but also shows a different dominant minimum in solution.

Poster Reception II

Annette Regan - AOXI0459

Seasonal influenza vaccination associated with attenuated illness among hospitalized patients in four South American countries

Annette Regan[15], Carmen Sofia Arriola[12], Paula Couto[13], Lindsey Duca[12], Sergio Loayza[5], Francisco Nogareda[5], Walquiria Aparecida Ferreira De Almeida[14], Julian Antman[1], Soraya Araya[10], Marcela Alejandra Avendaño Vigueras[6], Silvia Carolina Battaglia[8], Ivan Fedor Brstilo[6], Patricia Bustos[2], Maria Eugenia Fandiño[1], Rodrigo Fasce[3], Carlos Maria Giovacchini[1], Cecilia Isaura González Caro[6], Marta Von Horoch[9], Maria del Valle Juarez[7], Nathalia Katz[7], María Fernanda Olivares[4], Daiana Araújo Da Silva[14], Érica Tatiane Da Silva[11], Viviana Sotomayor[4], Natalia Vergara[4], Eduardo Azziz-Baumgartner[12], Alba Maria Ropero[5]

[1]Área de Vigilancia, Dirección de Epidemiología, Ministerio de Salud de la Nación, [2]Departamento de Laboratorio Biomédico Instituto de Salud Pública de Chile, Ministerio de Salud de Chile, [3]Departamento de Laboratorio Biomédico Instituto de Salud Pública de Chile. Ministerio de Salud de Chile, [4]Department of Epidemiology, Ministry of Health of Chile, [5]Department of Family, Health Promotion and Life Course, Pan American Health Organization, [6]Department of Immunizations, Ministry of Health of Chile, [7]Dirección de Control de Enfermedades Inmunoprevenibles, Ministerio de Salud de la Nación, [8]Dirección General de Vigilancia de la Salud, Ministry of Public Health and Social Welfare, [9]Dirección General de Vigilancia de la Salud. Ministry of Public Health and Social Welfare, [10]Expanded Program on Immunizations, Ministry of Public Health and Social Welfare, [11]Fiocruz Brasília, [12]Influenza Division, Centers for Disease Control and Prevention, [13]Influenza Surveillance Unit, Pan American Health Organization, [14]Ministry of Health Brazil, [15]School of Nursing and Health Professions, University of San Francisco

Background

Few studies have evaluated whether influenza vaccination could attenuate influenza illness. We aimed to assess vaccine-attenuated influenza among hospitalized individuals in a broad range of vaccine target groups from multiple South American countries.

Method

Data were analysed from four countries (Argentina, Brazil, Chile, and Paraguay) participating in REVELAC-i, a multicenter test-negative design vaccine effectiveness network including 41 sentinel hospitals. Among individuals hospitalized with severe acute respiratory infection, influenza was confirmed by rRT-PCR. Using multivariable logistic regression weighted by inverse probability of vaccination and adjusted for antiviral use, duration of illness prior to admission and calendar week, we compared the adjusted odds (aOR) of intensive care unit (ICU) admission and/or in-hospital death among influenza-positive cases by vaccination status for three target groups: children aged 6-24 months, adults aged 18-64 years with health conditions, and adults aged ≥65 years.

Result

Between 2013-2019, 2,747 laboratory-confirmed influenza hospitalizations were identified. We observed 24% earlier discharge among fully vaccinated children and 78% earlier discharge among vaccinated adults with medical conditions compared to their unvaccinated counterparts. Compared to unvaccinated individuals, partially and fully vaccinated children had lower odds of ICU admission (aOR 0·64; 95% CI 0·44, 0·92 and aOR 0·52; 95% CI 0·28, 0·98), and vaccinated older adults had lower odds of ICU admission and in-hospital death (aHR 0·46; 95% CI 0·33, 0·64).

Conclusion

Influenza vaccination was associated with illness attenuation among those hospitalized with influenza. These results can be used for risk communication and to inform global health benefits of vaccination.

Poster Reception II

Wey Wen Lim - AOXI0537

Repeated influenza vaccination effects on vaccine effectiveness in vaccinated individuals in the United Kingdom

Wey Wen Lim[5], Benjamin J Cowling[6], Georgina Nakafero[1], Shuo Feng[3], Jonathan S Nguyen-Van-Tam[2], Hikaru Bolt[4]

[1]Academic Rheumatology, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, [2]Division of Epidemiology and Public Health, School of Clinical Sciences, University of Nottingham, Nottingham, United Kingdom, [3]Oxford Vaccine Group, University of Oxford, Oxford, [4]South East and London Field Services, National Infection Service, Public Health England, London, United Kingdom; Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, United Kingdom, [5]The University of Hong Kong, [6]WHO 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 Special Administrative Region, China; Laboratory of Data Discovery for Health Limited, Hong Kong Science Park, New Territories, Hong Kong

Background

Annual seasonal influenza vaccination is recommended in many locations, especially for individuals at high risk of developing post-infection complications. However, potential drawbacks of repeated influenza vaccination, including the attenuation of vaccine immunogenicity and effectiveness have been observed in some influenza seasons. We aim to investigate this phenomenon using routinely collected primary healthcare data from the Clinical Practice Research Datalink (CPRD) database in the UK in this retrospective cohort study.

Method

We extracted medical records and demographic information of individuals above 12 years old who received influenza vaccines at least once between September 1, 2011, and August 31, 2016, and compared the incidence of general practitioner-diagnosed influenza-like illness (GP-ILI) and medically-attended acute respiratory illnesses (MAARI) in individuals who have received influenza vaccines in past influenza seasons with first-time vaccinees over five influenza seasons from the 2011/12 to 2015/16 influenza seasons. Influenza vaccine effectiveness (VE) against GP-ILI, MAARI, and two negative outcomes (hip fractures and urinary tract infections) in individuals vaccinated for the first time in each influenza season were compared with individuals who had also been vaccinated in the previous five influenza seasons using proportional hazard models. Stratified analyses were performed on individuals between 12 and 24 years old in clinical risk groups and individuals above 65 years old.

Result

Prior vaccination history and vaccination in the prior and current influenza seasons could be associated with some reduction in relative VE for some influenza seasons. There were no statistically significant attenuations of relative VE against GP-ILI for individuals who received influenza vaccination for both the current and prior influenza seasons compared with first-time vaccinees for all five influenza seasons in this study (2011/12 to 2015/16). Relative VE against MAARI for individuals above 65 years old who were vaccinated in the current and previous influenza season were lower compared with first-time vaccinees in the 2011/12 (-8%, 95% confidence interval = -15%, to -2%, hazard ratio (HR) = 1.08, 1.02 to 1.15), 2012/13 (-8%, 95% CI = -16%, to -2%, HR = 1.08, 1.02 to 1.16) and 2014/15 (-15%, -25% to -67%, HR = 1.15, 1.067 to 1.25) seasons.

Conclusion

Evidence of any attenuation in influenza VE in this study is not strong enough to recommend against annual influenza vaccination in favor of an alternative interval-based strategy, particularly in high-risk populations.

Poster Reception II

Takeshi Arashiro - AOXI0492

COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection during Delta-dominant and Omicron-dominant periods in Japan (FASCINATE study): implications for studies of influenza and other respiratory viruses

Takeshi Arashiro[13], Yuzo Arima[12], Hirokazu Muraoka[2], Akihiro Sato[7], Kunihiro Oba[17], Yuki Uehara[18], Hiroko Arioka[18], Hideki Yanai[3], Jin Kuramochi[8], Genei Ihara[10], Kumi Chubachi[1], Naoki Yanagisawa[19], Yoshito Nagura[16], Yasuyuki Kato[5], Akihiro Ueda[6], Akira Numata[4], Hideaki Kato[20], Koji Ishii[15], Takao Ooki[15], Yusuke Nishida[14], Hideaki Oka[14], Ashley Stucky[12], Chris Smith[11], Martin Hibberd[9], Koya Ariyoshi[11], Motoi Suzuki[12]

[1]Chubachi Internal Respiratory Medicine Clinic, [2]CLINIC FOR Tamachi, [3]Fukujuji Hospital, [4]Ikebukuro Metropolitan Clinic, [5]International University of Health and Welfare, [6]Japanese Red Cross Medical Center, [7]KARADA Internal Medicine Clinic, [8]Kuramochi Clinic Interpark, [9]London School of Hygiene and Tropical Medicine, [10]Machida Ekimae Naika Clinic, [11]Nagasaki University, [12]National Institute of Infectious Diseases, [13]National Institute of Infectious Diseases; London School of Hygiene and Tropical Medicine; Nagasaki University, [14]Saitama Medical Center, [15]Saitama Sekishinkai Hospital, [16]Shinjuku Home Clinic, [17]Showa General Hospital, [18]St. Luke's International Hospital, [19]Yanagisawa Clinic, [20]Yokohama City University Hospital

Background

Similar to influenza, SARS-CoV-2 transmission occurs through a complex interplay of public health and social measures (non-pharmaceutical interventions), high-risk behaviors, past infection, and vaccination. Although several COVID-19 vaccines initially showed high efficacy, concerns have arisen due to waning immunity and the emergence of variants with immune escape capacity.

Method

To evaluate the effectiveness of COVID-19 vaccines in the context of waning immunity, variants, and varying public health and social measures, a prospective test-negative case-control study was conducted in 16 healthcare facilities in Japan during the Delta-dominant period (August-September 2021) and the Omicron-dominant period (January-March 2022). Vaccine effectiveness (VE) against symptomatic SARS-CoV-2 infection was calculated for 2 doses for the Delta-dominant period and 2 or 3 doses for the Omicron-dominant period, compared to unvaccinated individuals.

Result

The analysis included 5795 individuals with 2595 (44.8%) cases. The median age (interquartile range) was 35 (27-46) years and 1491 (25.7%) had comorbidities. Among vaccinees, 2242 (55.8%) received BNT162b2 and 1624 (40.4%) received mRNA-1273 at manufacturer-recommended intervals. During the Delta-dominant period, VE was 88% (95% CI: 81-93) 14 days-3 months after dose 2 and 86% (95% CI: 37-97) 3-6 months after dose 2. During the Omicron-dominant period, VE was 56% (95% CI: 37-70) 14 days-3 months since dose 2, 52% (95% CI: 41-62) 3-6 months after dose 2, 49% (95% CI: 34-60) 6+ months after dose 2, and 74% (95% CI: 61-83) 14+ days after dose 3. Analysis with additional adjustments for preventive measures, including mask-wearing and high-risk behaviors (dining at a restaurant/bar at night with alcohol consumption in a group was used as a proxy), yielded similar estimates: 85-87% vs. 86-88% after 2 doses during the Delta-dominant period, and 51-55% vs. 49-56% after 2 doses and 77% vs. 74% after 3 doses during the Omicron-dominant period.

Conclusion

In Japan, where most are infection-naïve and strict prevention measures are maintained regardless of vaccination status, two-dose mRNA vaccines provided high protection against symptomatic infection during the Delta-dominant period and moderate protection during the Omicron-dominant period. Among individuals who received an mRNA booster dose, VE recovered to a high level. As society and individuals continue to adopt various degrees of public health and social measures against COVID-19, it would be important to account for these factors in evaluating the effectiveness of COVID-19 vaccines as well as influenza vaccines.

Poster Reception II

Joshua Nealon - AOXI0505

Reported effectiveness of COVID-19 booster vaccines: a systematic review of early literature and implications for emerging vaccination policy

Joshua Nealon[2], Yonatan Mefsin[2], Martina McMenamin[2], Kylie Ainslie[1], Benjamin Cowling[2]

[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands, [2]World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health

Background

Third "booster" doses of COVID-19 vaccines have been shown in vaccine effectiveness (VE) studies to protect against mild, hospitalized and severe disease. These published/pre-print studies are numerous, heterogeneous and have been conducted rapidly in populations with varying levels of SARS-CoV-2 immunity. Policy interpretation of resulting VE estimates is complicated by study choices and uncertain applicability for public health.

Method

We conducted a rapid, systematic literature review to describe reported VE of booster COVID-19 vaccine doses stratified by vaccine type, comparator population, SARS-CoV-2 variant and outcome, and discussed implications for COVID-19 vaccination policy. We searched PubMed, medRxiv and other sources for peer-reviewed and preprint studies on 31 March 2022. Pre-specified data including a subset of non-duplicate VE estimates were extracted. Data were summarized descriptively including in a forest plot of VE estimates.

Result

A total of 48 eligible studies were captured, many from the United States and Israel. Following exclusions, we identified 160 VE estimates; 139/160 (87%) described mRNA vaccines, mostly enrolling broad age groups. Half of estimates described VE against the Delta variant (80 estimates; 50%), around a third (56; 35%) against Omicron with the remainder including multiple variants. Just over half of studies compared outcomes in boosted populations vs unvaccinated individuals; the others vs fully vaccinated comparators. Overall, 151/160 (94%) estimates reported VE point estimates ≥50% and 111/160 (69%) reported VE ≥80%. VE appeared higher 1) when the unvaccinated rather than a fully vaccinated population was used as the comparator; 2) against the Delta variant compared with Omicron; 3) against hospitalized and fatal endpoints compared with milder endpoints; and 4) for mRNA booster vaccines compared with other booster vaccine types.

Conclusion

Existing observational data provide evidence that recent booster COVID-19 vaccines offer robust protection against SARS-CoV-2 infection, hospitalization and severe disease. Study design features including vaccination/infection history of comparator populations, follow-up time and clinical outcomes enrolled in studies appear deterministic of VE and should be carefully considered when using these data to develop COVID-19 booster policy.

Poster Reception II

Julia Bennett - AOXI0542

COVID-19 Vaccine Effectiveness During Delta and Omicron Waves in a University Population

Julia Bennett[3], Ana Weil[3], Kyle Luiten[3], Jessica O'Hanlon[3], Peter Han[1], Devon McDonald[3], Tessa Wright[3], Caitlin Wolf[3], Geoffrey Gottlieb[4], Katia Harb[5], James Hughes[2], Lea Starita[1], Helen Chu[3]

[1]Brotman Baty Institute, Seattle, WA; Department of Genome Sciences, University of Washington, Seattle, WA, [2]Department of Biostatistics, University of Washington, Seattle, WA, [3]Department of Medicine, University of Washington, Seattle, WA, USA, [4]Department of Medicine, University of Washington, Seattle, WA, USA; Environmental Health & Safety Department, University of Washington, Seattle, WA, [5]Environmental Health & Safety Department, University of Washington, Seattle, WA

Background

SARS-CoV-2 testing programs are recommended for universities and offer the opportunity to monitor COVID-19 vaccine effectiveness (VE) over time and against new variants of concern in relatively young, healthy populations with near-universal COVID-19 vaccination.

Method

SARS-CoV-2 testing was provided to faculty, staff, and students at a large university in Seattle, Washington, USA. Symptoms and COVID-19 vaccination were self-reported. Samples were tested for SARS-CoV-2 by qRT-PCR. We used a test-negative design and logistic regression to estimate VE of primary series and booster vaccination compared to primary series only against any and symptomatic SARS-CoV-2 infection adjusted for age and week of testing during Delta (Sept 9-Nov 30, 2021) and Omicron (Jan 8-May 30, 2022) waves. Viral genome sequencing of a subset of samples was used to define campus Delta and Omicron periods. Within 90-day intervals, we included the first positive swab from each individual as cases and the first negative swab from each individual without any positive swabs as test-negative controls. We excluded swabs from individuals with unknown vaccine status at the time of testing and those who received their last dose within two weeks of testing.

Result

From Sept 9, 2021 to May 30, 2022, we collected 115,426 swabs, of which vaccination status at the time of testing was current for 86,423 (74.9%) and 5,413 (4.7%) were positive for SARS-CoV-2. Swabs from 19,279 unique individuals were included in this analysis, including 18,662 from individuals with primary series vaccination only and 13,562 with primary series and booster vaccination at the time of testing. Median age was 21 and 22 years for cases and controls, respectively. A greater proportion of cases reported symptoms within +/- 7 days of testing compared to controls (86% vs. 42%, P<0.001). We did not detect a difference in protection against any or symptomatic infection for booster and primary series compared to primary series only for Delta (adjusted odds ratio [OR]=0.59, 95% CI: 0.21-1.67, P=0.3 and 1.39, 0.49-3.95, P=0.5, respectively). During the Omicron wave, booster and primary series was 34% effective against any infection (adjusted OR=0.66, 0.59-0.72, P<0.001) and 30% effective against symptomatic infection (adjusted OR=0.70, 0.62, 0.80, P<0.001) compared to primary series.

Conclusion

In a highly vaccinated university population, COVID-19 booster vaccination provided additional protection compared to primary series vaccination against infection with Omicron, which was similar for any and symptomatic infection. We were unable to detect a difference against Delta. Campus based testing cohorts can be utilized for VE studies of influenza vaccines as we anticipate an annual influenza-COVID vaccine.

Poster Reception II

Hau Chi So - AOXI0544

Association of Previous Influenza Vaccination Practice and COVID-19 Vaccine Acceptance

Nicole Ngai Yung Tsang[1], Siu Kan Kwok[1], Chun Wai Leung[1], Ka Yan Ng[1], Hau Chi So[1], Gabriel M Leung[1], Dennis Kai Ming Ip[1]

[1]WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, [2]WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Background

Reaching high vaccination coverage is widely regarded as the key for successful control of COVID-19 pandemic in different countries. Relationship between the acceptance of the novel COVID-19 vaccine and the usual practice for influenza vaccine remained poorly elucidated; a proper understanding of which will give a better insight regarding the phenomenon of vaccine hesitancy across different vaccine candidates, and may potentially help to inform a targeted health promotion approach to facilitate an efficient scalable national-wide COVID-19 vaccination programme.

Method

A prospective longitudinal cohort of 978 individuals aged ≥18 was followed-up for a consecutive period of three years, from 2018 to 2021. Demographics characteristics and medical history were recorded on baseline; influenza vaccination practice and occurrence of any influenza/ upper respiratory tract infection were ascertain annually. Their risk perception of COVID-19, intention to receive COVID-19 vaccine and vaccine-related concerns were examined by a self-administered paper-based survey between 25 August and 9 November 2020, a relative quiescence period between epidemic waves in Hong Kong before the COVID-19 vaccine was available locally (26 February 2021).

Result

Of 978 individuals in our cohort, 757 participants (77.4%) completed the questionnaire on COVID-19 vaccination intention and concern. Individuals were classified, according to their influenza vaccination practice in the past two study years (received in 0/2, 1/2, and 2/2 years respectively), into non-vaccinees (NV) (76.35%), occasional vaccinees (OV) (13.34%), and habitual vaccinees (HV) (10.30%). Slightly more than half (53.8%) were willing to receive COVID-19 vaccination, 31.3% were undecided, and remaining 14.0% refused to vaccination. Non-vaccinees (OR: 0.43, 95% CI: 0.25-0.72), and occasional vaccinees (0.48,0.25-0.89) were associated with hesitancy to COVID-19 vaccines. Among the HV, higher level of perceived severity (4.90,1.06-24.35) was a determinant of greater acceptance of COVID-19 vaccines. For NV, perceived worry (1.78,1.07-2.95), perceived susceptibility (1.70,1.12-2.56), concern on vaccine supply of COVID-19 (3.24,2.04-5.18) were associated with the intention towards COVID-19 vaccines. Concern on vaccine effectiveness was a common determinant of refusing COVID-19 vaccine among both NV (0.24,0.10-0.52) and OV (0.21,0.03-0.83).

Conclusion

The practice of influenza vaccination is an independent indicator for COVID-19 vaccine intention, with particularly higher hesitancy among non-vaccinees and occasional vaccinees. Important determinants among non-vaccinees include concern on vaccine effectiveness and perceived susceptibility, that may help to inform a high-risk targeted approach to tackle hesitancy for COVID-19 vaccine.

Poster Reception II

Mai-Chi Trieu - AOXI0446

Durable seroprotective antibody responses after repeated trivalent seasonal influenza vaccination in healthcare workers

Mai-Chi Trieu[3], Anders Madsen[4], Amit Bansal[4], Marianne Sævik[2], Sonja Ljostveit[4], Jörg Assmus[1], Rebecca Jane Cox[5]

[1]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway, [2]Department of Medicine, Haukeland University Hospital, Bergen, Norway, [3]Inflenza Centre, University of Bergen, [4]Influenza Centre, Department of Clinical Science, University of Bergen, Bergen, Norway, [5]Influenza Centre, Department of Clinical Science, University of Bergen; Department of Research and Development, Haukeland University Hospital, Bergen, Norway

Background

Vaccination is the main preventive strategy against influenza. High-risk groups and healthcare workers (HCW) are often recommended for annual influenza vaccination. However, the impact of repeated annual vaccination on antibody responses is unclear, with conflicting results reported. The novel A/H1N1pdm09 virus emerged in 2009 and was subsequently included in seasonal vaccines until 2016/17, allowing us to investigate the effect on antibody responses after repeated vaccination against the same virus compared to the other vaccine components (A/H3N2 and B viruses), which were changed between seasons.

Method

HCW (n=250) were vaccinated with the AS03-adjuvanted pandemic A/H1N1pdm09 vaccine in 2009 and subsequently either vaccinated with the trivalent inactivated seasonal vaccines (TIV) including A/H1N1pdm09, A/H3N2 and B viruses or received no further vaccination between the seasons 2010/11 and 2013/14. We investigated the hemagglutination-inhibition (HI) antibody responses after each TIV in vaccinated HCW and yearly in unvaccinated HCW.

Result

High rates of influenza infection by seroconversion were found in HCW who were not vaccinated with seasonal vaccines between 2010/11 and 2013/14. In vaccinated HCW, the HI antibodies were significantly boosted to above the protective threshold HI titres ≥40 against all 3 vaccine viruses after each TIV. No significant difference in post-TIV antibody responses was found between HCW who were vaccinated in 2 consecutive seasons and those who were vaccinated in the current season only. Upon repeated vaccination, the pre-TIV HI titres increased, whereas the post-TIV antibody fold-induction declined. Updating vaccine viruses between seasons improved the antibody fold-induction. The duration of antibody half-life increased with repeated vaccination against the same A/H1N1pdm09 and A/H3N2 viruses, but not against B viruses.

Conclusion

Regular seasonal vaccination increased the durability of seroprotective antibodies resulting in higher pre-existing antibodies throughout one season in HCW. Without the boost from seasonal vaccination, antibody titres remained low and unvaccinated HCW were more likely to be infected with circulating influenza viruses.

Poster Reception II

Claudia Maria Trombetta - AOXI0466

FLUCOP collaborative study: assay harmonization for improving the reproducibility of the virus neutralization assay

Emanuele Montomoli[11], Lingyi Zheng[9], Edmond J Remarque[2], Alexandre Civet[8], Nedzad Music[10], Hanna Sediri-Schoen[6], Marie-Clotilde Bernard[9], Claudia Maria Trombetta[11], Serena Marchi[11], Serge Van de Witte[1], Peter Van Amsterdam[1], Sophie Germain[3], Thierry Ollinger[3], Britta Neumann[6], Katia Hoschler[7], Sammy Ho[7], Maria Rita Castrucci[4], Marzia Facchini[4], Joanna Waldock[5], Othmar G Engelhardt[5], Giuseppe Palladino[10]

[1]Abbott Healthcare Products B.V., The Netherlands, [2]Biomedical Primate Research Centre, Rijswijk, The Netherlands, [3]GSK, Belgium, [4]Istituto Superiore di Sanità, Italy, [5]National Institute for Biological Standards and Control, Potters Bar, United Kingdom, [6]Paul-Ehrlich-Institut, Germany, [7]Public Health England, United Kingdom, [8]Quinten, Paris, France, [9]Sanofi Pasteur, USA, [10]Seqirus, Cambridge, MA, USA, [11]University of Siena

Background

The virus neutralization (VN) assay is a serological technique designed to directly measure functional antibodies able to neutralize the ability of the virus to enter or replicate in mammalian cells, thus measuring all antibodies involved in protection. The assay is also recommended for highly pathogenic avian viruses and officially included in the European Medicine Agency guidelines on influenza vaccines. Moreover, the VN assay becomes a first choice for some recent H3 strains. Based on the incubation time, there are two main VN forms: the 2-day ELISA based (short incubation time); and the 3-7 days (long incubation time), in which several read-out methods are published. The assay is characterized by poor reproducibility, being highly susceptible to high inter and intra-laboratory variability.

This study aimed at evaluating the inter-laboratory variability using standards and the impact of harmonising the VN protocol.

Method

Human pre- and post-vaccination sera from individuals (n=30) vaccinated against influenza were tested across seven laboratories for the short form (SF) assay and 4 laboratories for the long form (LF) assay. We used a design of experiment method to evaluate the impact of assay parameters on inter-laboratory variability. Statistical and mathematical approaches were used for data analysis. A consensus protocol has been developed for the LF and SF assays. Additionally, we tested the performance of a calibrator (standard).

Result

A quantitative comparison between SF and LF assays showed a good correlation for every influenza strain (R 0.8718-0.9419). Comparing to the haemagglutination inhibition (HAI) assay, the SF and LF generated higher titers for A strains (GMR 5.41-8.95 for SF and GMR 2.44-4.17 for LF). For the B strains, titers are comparable (GMR 0.47-1.43 for SF and GMR 0.42-0.80 for LF), likely due to the use of ether treatment in HAI assay. The SF and HAI correlate well, unlike the LF and HAI. The calibrator almost always significantly reduced lab-to-lab variability. The reduction in between-laboratory variation was most pronounced for the H3N2 egg and cell viruses for both SF and LF. Of note is that the GMTs for the Yamagata strain were lower than for the other strains.

Conclusion

Overall, the SF and LF of the VN assay are quantitatively different, and direct comparison between titers generated by the two formats is not feasible. This study demonstrates that normalisation significantly reduces between laboratory variation, especially for the H3N2 egg and cell strains. In addition, the use of a calibrator has a significant effect in reducing inter-laboratory variability.

Poster Reception II

Raul Gomila - AOXI0481

Machine learning modeling of hemagglutinin antigenic relationships towards selection of broadly protective H3 antigens

Philip Davidson[3], Lauren Intravaia[8], Katherine Roebke[3], Bianca Baum[7], Paul Stirba[7], John Hamberger[3], Svetlana Pougatcheva[3], Timothy Farrell[3], Irina Ustyugova[3], Ana Goncalvez[3], Guadalupe Cortes-Garcia[3], Dustin Holloway[5], Tod Strugnell[3], Philippe-Alexandre Gilbert[4], Tim Alefantis[6], Mario Barro[1], William Warren[3], Maryann Giel-Moloney[3], Armaghan Naik[2], Konstantin Zeldovich[3]

[1]Sanofi, R&D, Cambridge, MA; RA Ventures, [2]Sanofi, R&D, Cambridge, MA; Sentiome LLC, [3]Sanofi, R&D, Cambridge, MA, [4]Sanofi, R&D, Cambridge, MA; Bill & Melinda Gates Foundation, [5]Sanofi, R&D, Cambridge, MA; Takeda Pharmaceuticals, Cambridge, MA, [6]Sanofi, R&D, Swiftwater, PA, [7]Yoh Services LLC, Philadelphia PA, [8]Yoh Services LLC, Philadelphia PA; University of Massachusetts Medical School

Background

Influenza is a respiratory disease of high importance for public health, with broader health impacts including cardiovascular events and the exacerbation of chronic underlying conditions. Each season, extensive epidemiological surveillance, strain sequencing, and antigenic evaluation in animal models and humans are conducted to best inform vaccine strain recommendations. These recommendations are included in licensed seasonal standard of care (SoC) influenza vaccines. Despite these tremendous efforts, vaccine mismatches do occur, especially for the A/H3N2 subtype. Sanofi is developing a potential broadly protective influenza vaccine, based on wildtype influenza hemagglutinin (HA) antigens with improved breadth of coverage compared to the SoC, either in a licensed influenza vaccine platform or in an mRNA-based vaccine. Such a vaccine could also provide protection beyond flu, that is improved protection against flu complications.

Method

We developed a sequence-based machine learning (ML) model of influenza H3 antigenicity, aimed at predicting antibody titer in the naïve ferret model, hemagglutination inhibition (HAI) and microneutralization assays (mNT) for a given pair of HA sequences of the antigen and test virus. The model has been trained on the data collected from the Francis Crick Institute reports since 2003, as well as internal data. The model has successfully reproduced the major features of H3 antigenicity, including clade-specific responses and antigen versus test strain asymmetry of immune response in ferrets.

Result

Model predictions have been used to perform several iterations of selections of broadly protective H3 candidate antigens, followed by recovery of H3N2 viruses in 6:2 PR8 background, and testing the viruses in the naïve ferret infection model. Ferret antisera was then tested against a diverse readout panel of influenza strains in HAI and mNT assays, comparing the breadth of coverage to the standard of care strains recommended for licensed influenza vaccines. These experiments demonstrate that, in the ferret model, there exist wildtype influenza strains contemporaneous with the SoC yet offering higher antibody titers against a larger set of strains compared to the SoC.

Conclusion

Influenza H3N2 strains with improved breadth can be identified through a combination of predictive ML modeling with screening in an animal model. Modeling of immune response of selected antigen candidates against large sets of historically observed circulating strains suggests improved antigenic coverage compared to the SoC strains and a potentially improved method of vaccine strain selection using ML, which could contribute to improvement in vaccine effectiveness.

(Study funded by Sanofi)

Poster Reception II

Mariia Sergeeva - AOXI0521

Human antibody response to trivalent split and polymer adjuvanted subunit influenza vaccines during one year after immunization

Mariia Sergeeva[1], Ekaterina Romanovskaya-Romanko[1], Vera Krivitskaya[1], Irina Amosova[1], Tatyana Zubkova[1], Janna Buzitskaya[1], Marina Stukova[1]

[1]Smorodintsev Research Institute of Influenza MoH Russian Federation

Background

Serum antibody response is considered to be a correlate of vaccine-induced protection for inactivated influenza vaccines (IIV).

The level of antibody response is often measured three to four weeks post vaccine administration. However, the mass vaccination campaign may take place 3 to 6 months before the peak of the seasonal epidemic. Thus, the duration of antibody response is of concern to ensure protection of population against influenza.

Method

We performed the single-center open-label observational study of the antibody response during one year after immunization with seasonal IIV. Study included 99 healthy individuals ≥ 18 years old (51 years median age). Participants were vaccinated with trivalent split influenza vaccine, or subunit influenza vaccine with synthetic polymer adjuvant.

Antibody titers to individual vaccine viral strains were assessed in serum samples obtained before vaccination, 7- and 21-days after, and 3-, 6- and 12-months post vaccination using hemagglutination inhibition (HI), microneutralization (MNA) and avidity test (AV).

Result

Seroconversion of virus-specific antibodies has already been observed from Day 7 post vaccination for the majority of responders. The decline of HI and MNA antibody geometric mean titer (GMT) started 3 months post vaccination, and near 2-fold decrease was observed 6 months post vaccination. The proportion of individuals with antibody titers ≥ 40 peaked on Day 21 and was still higher a year after than before vaccination.

The strong negative correlation was observed between pre-vaccination antibody titer and post-vaccination antibody response. However, the response to the vaccine component B/Victoria was weaker than to H1N1pdm09, despite that before vaccination there were fewer volunteers seropositive to B/Victoria.

The antibody avidity index substantially decreased on Day 7 and restored by Day 21 post vaccination for the majority of participants probably reflecting the early recall of memory B-cells followed by de-novo antibody generation.

Conclusion

The peculiarities and duration of antibody immune response to influenza vaccine strains should be considered when planning vaccination campaign.

Poster Reception II

Wey Wen Lim - AOXI0539

Hemagglutination inhibition antibody titer is a partial mediator of seasonal and pandemic influenza vaccines

Wey Wen Lim[1], Benjamin J Cowling[2]

[1]The University of Hong Kong, [2]WHO 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 Special Administrative Region, China; Laboratory of Data Discovery for Health Limited, Hong Kong Science Park, New Territories, Hong Kong

Background

The hemagglutination inhibition antibody titer (HAI titer) is an established correlate of protection for inactivated seasonal and pandemic influenza vaccines. Increased levels of post-vaccination HAI titer have long been associated with increased protection against influenza infection and severe disease but the causal contribution of HAI titers to the protective effect of influenza vaccination had not been quantified. We estimated the proportion of influenza VE mediated by HAI titer against laboratory-confirmed influenza A(H1N1), A(H3N2), and B/Victoria infections using data collected in an international randomized-controlled clinical trial of a quadrivalent inactivated influenza vaccine in children.

Method

We analyzed data collected for a phase 3 randomised controlled trial conducted in 8 countries in Asia, the South Americas, and the Caribbean between the years 2010 and 2011. In the trial, children between 3 and 8 years old were randomized to receive either an inactivated seasonal quadrivalent influenza vaccine candidate or an active-comparator hepatitis A vaccine and followed up for at least 6 months to identify laboratory-confirmed influenza infections. Causal mediation analysis was performed to identify the causal contribution of post-vaccination HAI titers to vaccine-conferred protection against symptomatic, laboratory-confirmed influenza A(H1N1), A(H3N2), and B/Victoria infections.

Result

We included 5,067 children from the randomized trial in this analysis. Vaccine effectiveness against laboratory-confirmed A(H1N1), A(H3N2), and B/Victoria infections were 58% (95% CI = 26%, 76%), 60% (95% CI = 33%, 76%), and 45% (95% CI: 13%, 66%) respectively. B/Yamagata cases were excluded from further analyses due to low case numbers in this cohort. The proportion of vaccine efficacy mediated by post-vaccination HAI titers against influenza A(H1N1), influenza A(H3N2), and influenza B/Victoria are 30% (95% CI = 33%, 48%), 20% (95% CI = 16%, 39%), and 37% (95%CI = 26%, 85%) respectively.

Conclusion

Post-vaccination HAI titers following vaccination with inactivated influenza vaccines only partially mediate vaccine-induced protection against symptomatic laboratory-confirmed influenza infections. This suggests that other correlates of protection such as the neuraminidase-inhibition antibody titer and markers of cellular immunity might also contribute to vaccine-induced protection. Seasonal influenza vaccines can be improved by including antigens or components that can target these components.

Poster Reception II

Alexandra Mellis - AOXI0545

Household transmission of SARS-CoV-2: Effect of vaccination

Alexandra Mellis[1], Melissa Rolfes[1], Carrie Reed[1], Constance Ogokeh[1], Jessica Deyoe[1], Edwin Asturias[2], Rasika Behl[6], Edward Belongia[5], Natalie Bowman[9], Samuel Dominguez[2], Katherine Ellingson[7], Hector Izurieta[4], Jessica Lin[8], Karen Lutrick[7], Yvonne Maldonado[6], Son Mclaren[3], Huong Mclean[5], Daniel Olson[2], Suchitra Rao[2], Lisa Saiman[3], Ellen Sano[3], Clea Sarnquist[6], Melissa Stockwell[3], Rosita Thiessen[6], Jonathan Schmitz[10], Christopher Lindsell[10], H. Keipp Talbot[10], Carlos Grijalva[10]

[1]Centers for Disease Control and Prevention, [2]Children's Hospital Colorado, [3]Columbia, [4]Food and Drug Administration, [5]Marshfield Clinic, [6]Stanford, [7]University of Arizona, [8]University of North Carolina at Chapel Hill, [9]University of North Carolina Chapel Hill, [10]Vanderbilt University Medical Center

Background

Household transmission of SARS-CoV-2 is a significant concern. We followed US individuals with known household exposure and assessed infection by SARS-CoV-2 variant and vaccination status.

Method

Households with an individual who tested positive for SARS-CoV-2 at 7 US academic medical centers between Sep. 2021 and May 2022 were screened and enrolled if symptom onset in the index case (or test date, if asymptomatic) was within the prior 6 days. Household contacts and the index case were prospectively followed for 10 days, and daily self-collected nasal swabs were tested by transcription mediated amplification for SARS-CoV-2. Vaccination status was based on number of doses (any manufacturer) recorded via plausible self-report, vaccine cards, registries, or medical records. Vaccination effects were reported as adjusted incidence rate ratios (aIRR) and 95% confidence intervals (CI) from Poisson regression accounting for household size and clustering. This study is ongoing, and results will be stratified by vaccination of the household's primary case as sample size increases.

Result

Among 197 contacts (98 households), the median age was 33 years (IQR: 12, 46 years; 5% <5 years), 51% were female, 72% non-Hispanic White, and 72% had ≥2 doses of a COVID-19 vaccine by enrollment (median time since last dose: 114; IQR: 64, 189] days). 128 contacts were exposed to an index case who had received ≥2 doses of a vaccine, and 69 to an index case who had received 0-1 dose. Sixty-six percent of contacts were infected (with onset a median of 4, IQR: 2, 5 days after index onset); fewer in households enrolled while Delta was the dominant variant (before Dec. 21 2021, 51% infected) compared with households enrolled after Omicron became dominant (70% infected). Among contacts 12 years or older enrolled during the Omicron period with no prior COVID-19 infection, 12 of 17 contacts with 0-1 vaccine doses were infected, compared to 23 of 35 contacts who had received 2 doses (aIRR 0.92, CI 0.6-1.4) and 35 of 64 contacts who had received 3+ doses (aIRR 0.74, CI 0.5-1.1).

Conclusion

Household transmission of SARS-CoV-2 was high, particularly when the Omicron variant predominated. Three or more doses of a COVID-19 vaccine may reduce the risk of infection in household contacts.

Poster Reception II

Eun Ha Kim - AOXI0565

Evaluation of Major Components of Green Plants, as Potential Therapeutics for SARS-CoV-2 variants

Eun Ha Kim[1], Se-Mi Kim[3], Seung-Gyu Jang[1], Mark Anthony B. Casel[1], Rollon Rare[1], Young Ki Choi[2]

[1]Chungbuk National University, [2]Chungbuk National University, Korea Virus Research Institute, [3]Korea Virus Research Institute

Background

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several variants have been a serious global health crisis of the 21st century resulting in high numbers of morbidity and mortality. Despite the development and deployment of highly effective antibody and vaccine countermeasures, still, SARS-CoV-2 continuously evolves generating new variants that spread rapidly. During the series of recent outbreaks, the need for therapeutics has become apparent. To overcome these hurdles, multi-targeted and broader spectrum antiviral agents are needed. Herein, we conducted a multi-step screening strategy to identify potential edible plant candidates with anti-SARS-CoV-2 properties and to evaluate synergistic antiviral effects between specific combinations of active constituents.

Method

First, chromatography-based screening analysis identified four bioactive compounds. We have measured the antiviral properties of identified compounds by in vitro and in vivo systems using Vero cell lines or animal models with adapted golden Syrian hamsters and hACE2 transgenic (TG) mice. Additionally, we monitored the induction level of proinflammatory cytokines and chemokine using BALF of SARS-CoV-2-infected hACE2 TG mice.

Result

s showed that phytochemicals extracted from Chlorella spp. and Psidium guajava possess broad-spectrum antiviral activity against a range of SARS-CoV-2 variants. Further, oral treatment of these compounds attenuates virus replication in Syrian hamsters and protects hACE2 TG mice from lethal challenges with Alpha, Beta and Omicron variants along with the parental strain. Moreover, treatment with these compounds significantly attenuates SARS-CoV-2-induced proinflammatory responses

Conclusion

Taken together, we identified plant-derived bioactive compounds possessing antiviral properties against a broad range of SARS-CoV-2 strains and variants. Thus, our data provide evidence that phytochemicals from edible plants can be an ideal candidate in tackling the broad spectrum of SARS-CoV-2 strains and variants for both therapeutic and prophylactics purposes.

Poster Reception II

Michael Schotsaert - AOXI0625

SARS-CoV-2 Ancestral and Variant of Concern Breakthrough infections boost both cross-reactive cellular and humoral immune responses in mRNA-vaccinated Hamsters.

Juan Garcia-Bernalt Diego[1], Gagandeep Singh[1], Sonia Jangra[1], Manon Laporte[1], Lauren A. Chang[1], Kim Handrejk[1], Raveen Rathnasinghe[1], Sara El Zahed[1], Max W. Chang[2], Prajakta Warang[1], Sadaf Aslam[1], Ignacio Mena[1], Christopher Benner[2], Florian Krammer[1], Adolfo García-Sastre[1], Michael SCHOTSAERT[1]

[1]Icahn School of Medicine at Mount Sinai, [2]University of California San Diego

Background

SARS-CoV-2 infections and COVID-19 prevalence dropped drastically in humans after the first mRNA vaccine shot, even before strong neutralizing antibody responses were induced. We wanted to address the question of what drives protection in the absence of detectable neutralizing antibodies at the moment of infection.

Method

Syrian Golden Hamsters were vaccinated once with a suboptimal dose of Pfizer/BioNTech COVID-19 mRNA vaccine (5ug/animal). Four weeks post vaccination, animals were challenged with different variants of SARS-CoV-2.

Result

Although vaccination resulted in detectable antibody ELISA titers against the ancestral SARS-CoV-2 spike protein, antibody titers were too low for efficient neutralization of the antigenically matching USA-WA1/2020 or variants of concern (Alpha, Beta, Delta and Mu). Despite absence of virus-neutralizing antibodies, vaccination resulted in reduced morbidity for USA-WA1/2020 and Alpha-challenged animals and complete control of lung virus titers for USA-WA1/2020, Alpha and Delta but with breakthrough infection for Beta and Mu. T cell responses measured in the spleen were higher in vaccinated animals compared to unvaccinated animals at 5 days post infection, suggesting vaccination was able to efficiently prime T cell responses that were recalled during infection. Infection with different SARS-CoV-2 variants also back-boosted neutralizing antibody responses against challenge virus and in the case of the variants of concern, against antigenically distant but vaccine-matched ancestral USA-WA1/2020. Transcriptomic analysis of host immune responses to infection reflects both vaccination status and disease course, is further compared with lung pathology data and suggests a role for interstitial lung macrophages in vaccine-mediated protection.

Conclusion

We show that suboptimal vaccination protects against SARS-CoV-2 challenge with different variants of concern, using the hamster SARS-CoV-2 vaccination and challenge model. This protection correlates with recall of vaccine-induced B and T cell responses during virus infection in the absence of neutralizing antibody titers.

Poster Reception II

Marilda Siqueira - AOXI0632

SARS-CoV-2 VOCs monitoring using RT-PCR protocols by inference in Brazil

Leonardo Saboia-Vahia[3], Paola Resende[3], Marilda Siqueira[3], Tiago Gräf[1], Vanessa Oikawa-Cardoso[2], Eduardo Volotão[3], Fernando Motta[3]

[1]Institute Carlos Chagas; FIOCRUZ-Paraná - Brazil, [2]Institute Gonçalo Muniz; FIOCRUZ-BAHIA - Brazil, [3]Laboratory of Respiratory Viruses and Measles (LVRS), Institute Oswaldo Cruz, FIOCRUZ-Rio de Janeiro - Brazil.

Background

The constant evolution of these viruses still put pressure on health services and harm the world economy. However, protocols faster than sequencing can help surveillance systems recognize these new variants in a shorter time and more cost-effectively. In Brazil, the variants circulating over 2020-2022 were Gama (P.1), Delta (AY.99.2, AY.101 and AY.*+B.1.617.2) and Omicron (BA.1, BA.2, BA.4, BA.5) (FIOCRUZ, 2022). Although sequencing the SARS-CoV2 genome is the best way to identify the different variants of the virus, it is a high cost methodology and requires qualified personnel, which makes implementation difficult.

Method

Therefore, as an alternative form of surveillance, our group, in collaboration with the Institute of Technology in Immunobiologicals/Bio-Manguinhos and the Brazilian Health Ministry developed a multiplex assay for detection of Variants of Concern (VOC). The 4Plex SARS-CoV2 RT-PCR kit allows screening samples for detection of different VOCs: Alfa, Beta, Gama, Delta and Omicron. All data is available in the GISAID database and uploaded to http://www.genomahcov.fiocruz.br/dashboard-en/. This inference was possible because Delta VOC has no mutation in the considered regions whereas BA.1 has in both regions and BA.2 has only in one region.

Result

23230 tests were carried out in 21 federative units between December 2021 and April 2022, AC (n = 534), AM (n = 730), AP (n = 1,192), BA (n = 1,121), CE (n = 6,985 data from HEMOCE and FIOCRUZ-CE), DF (n = 744), MA (n = 3,392), MG (n = 999), MS (n = 474), PA (n = 426), PB (n = 408), PI (n = 220), RJ (n = 923), RN (n = 231), RO (n = 508), RR (n = 522), RS (n = 2,046), SC (n = 492), SE (n = 29), SP (n = 467) and TO (n = 654). The application of these tests has demonstrated its relevance, as it increases the agility and reduced cost for monitoring the advancement of Ômicron sublines such as BA.2, which currently dominates the epidemiological scenario in Brazilian territory. The use of these protocols reinforces their importance with an increase in the frequency of sublines BA.4 and BA.5, since they allow surveillance of the processes of competition and substitution between these different variants.

Conclusion

We demonstrated that the inference strategy based on the kit's ability to screen samples and detect variants and intravariants, allow the characterization of VOCs circulating in regions with limited resources. The implementation of this strategy in Brazilian health centers will give more efficiency in the detection and characterization of VOCs, in addition to supporting faster decision-making, contributing to the mitigation and reduction of the impact of the COVID-19 Pandemic.

Poster Reception II

JEIHYUN JEONG - AOXI0661

Intranasal delivery of recombinant subunit vaccine formulated with novel mucosal adjuvant protects mice and ferrets against SARS-CoV-2 challenge

JEIHYUN JEONG[1]

[1]KHAV, Inc.

Background

Despite the remarkable success of currently commercialized COVID-19 Vaccines, there are several opportunities for continued vaccine development against COVID-19. The respiratory organ serves as a primary target site for SARS-CoV-2. Thus, the Immune responses of the respiratory tract is significant in controlling SARS-CoV-2 infection. Notably, currently approved vaccines are administered by intramuscular injection, resulting in robust systemic yet uncertain mucosal immunity. In contrast, intranasal administration has a great potential to elicit both systemic and local responses with the ease of vaccination, including the production of IgA in the respiratory tract. In this Study, we show that recombinant RBD-S1 chimeric antigen admixing with novel mucosal adjuvant ECLS, enhances the humoral and cellular immune responses and protects against SARS-CoV-2 challenge in mice and ferrets models.

Method

His-tagged RBD-S1 chimeric antigen expressed in the human embryonic kidney 293 cells was provided from BIONOTE, Inc. ECLS mucosal adjuvant, which is known to enhance the immune response by activating various immune cells, was purchased from Eubiologics, Inc., employed as an adjuvant. K18-hACE2 transgenic mice and ferrets were vaccinated twice with ECLS subunit vaccine via various routes. The systemic humoral and cellular responses and the anti-SARS-CoV-2 responses were monitored. Furthermore, we challenged the vaccinated mice and ferrets with SARS-CoV-2 variants, and observed protective immunity against COVID-19 infection.

Result

All mice and ferrets vaccinated with ECLS subunit vaccine produced strong humoral and cellular immune responses after the second immunization. Neutralization titers did not show statistically significant differences between the routes of immunization. Both immunization evoked significantly greater antigen-specific T-cell responses compared to unimmunized control groups. After a challenge with SARS-CoV-2 in mice and ferrets, the ECLS subunit vaccination resulted in a drastic reduction in viral load in the lungs and nasal washes and improved survival rates compared to the control in mice experiments.

Conclusion

ECLS adjuvants demonstrated an enhanced response in the intranasal vaccine route. Moreover, the findings of the study proved the efficiency of an intranasally mucosal immunization strategy, which can be less painful and more effective in enhancing the respiratory tract immunity against respiratory infectious diseases. This study demonstrates that ECLS subunit mucosal vaccines are an effective recombinant protein vaccine candidate against SARS-CoV-2.

Poster Reception II

Yuanyuan He - AOXI0638

Antibody Inhibition of Influenza A Virus Assembly

***Yuanyuan He*[1], *Sofie Subiaur*[1], *Michael Vahey*[1]**

[1]Biomedical Engineering/ Washington University in St. Louis/United States

Background

The antibodies induced by vaccination and natural infection interfere with influenza virus replication through multiple mechanisms. These include directly blocking virus entry, inhibiting virus release, and eliciting Fc-mediated effector functions. However, our understanding of how these specific mechanisms separately contribute to the overall potency of an antibody remains incomplete. In particular, methods to quantify antibody inhibition of virus assembly and release are lacking. Motivated by this need, we investigated how antibodies specific to a range of antigenic sites on the IAV surface proteins contribute to protection by specifically inhibiting virus assembly and release.

Method

We infect MDCK cells with IAV at MOI ~1 and treat them with monoclonal antibodies (mAbs) at varying concentrations, starting at two hours post infection. At 8 hours post-infection, we collect, label, and immobilize viruses onto coverslips for imaging and quantification [Fig 1A].

Result

We find that both HA- and NA- specific mAbs targeting a range of antigenic sites significantly decrease the number of viruses released during a single replication cycle [Fig 1B&C]. The extent of inhibition is not significantly affected by virus morphology and persists in the presence in exogeneous sialidase, suggesting that it is not due to inhibition of NA activity [Fig 1C]. All mAbs tested show an ability to inhibit virus release, and for a subset of mAbs this potency is similar to their potency in inhibiting virus entry. Using fluorescence recovery after photobleaching, we find that the stem-binding IgG mAb CR9114 crosslinks cell surface HAs while its Fab fragment does not, suggesting a possible mechanism for inhibition of virus release. Consistent with this model, a monovalent CR9114 IgG shows reduced inhibition but retains some potency at higher concentrations. Additional inhibition mechanisms likely exist.

Conclusion

These results demonstrate that antibody inhibition of virus release is a general feature of antibodies targeting a range of antigenic sites on the IAV surface proteins. Dissecting specific mechanisms through which antibodies inhibit virus release could enhance the development of improved antibody therapeutics.

Poster Reception II

André León - AOXI0650

Mapping the Polyclonal IgG Response To Hemagglutinin After Acute H1N1 or H3N2 Influenza Virus Infections

André León[1], Julianne Han[2], Alba Torrents de la Peña[2], Philip Mudd[5], Rachel Wolters[3], Abigail Jackson[2], Sara Richey[2], Alesandra Rodriguez[2], James Crowe Jr.[4], Ali Ellebedy[6], Andrew Ward[2]

[1]The Scripps Research Institute, [2]The Scripps Research Institute, Department of Integrative Structural and Computational Biology, [3]Vanderbilt University Department of Pathology, Microbiology, and Immunology, [4]Vanderbilt Vaccine Center; Vanderbilt Department of Pediatrics and Pathology; Vanderbilt Department of Microbiology and Immunology, [5]Washington University in St. Louis, Department of Emergency Medicine, [6]Washington University in St. Louis, Department of Pathology and Immunology

Background

Influenza virus infection can induce broad and long-lasting immunity. Current seasonal influenza vaccines fail to elicit similar responses. As influenza virus hemagglutinin (HA) is the prime target of neutralizing antibodies, understanding how antibody response against HA differs in infection and vaccination may inform how to design better vaccines that can replicate certain aspects of the immunity elicited by infection. Using negative stain (ns) electron microscopy polyclonal epitope mapping (EMPEM) we mapped the IgG antibody response against H1 or H3 HAs from vaccinated or infected human patient cohorts.

Method

In the 2018-2019 influenza season, sera were collected from seven patients with confirmed influenza virus infections. Sequencing confirmed that four were infected with H1N1 and the remaining 3 with H3N2. For each patient, IgG was isolated from 1 mL serum and digested to Fab. Fab was complexed with H1 HA (A/Michigan/45/2015) or H3 HA (A/Singapore/INFIMH-16-0019/2016), purified, and imaged with nsEM. Data was processed using Relion 3.0. Ten week 0 and week 2 serum samples from individuals who received the 2018-2019 Flucelvax quadrivalent vaccine were processed and similarly analyzed.

Result

Unvaccinated H1N1-infected patients presented robust responses against the H1 HA stem epitope as well as less ubiquitous head, esterase, anchor, and trimer interface responses. A vaccinated 73-year-old H1N1 patient presented a particularly diverse stem response and a 39-year-old active cancer patient presented only a stem response. All H1N1-infected patients also presented stem responses and 3 of 4 presented head responses against H3 HA. In contrast, H3N2-infected patients' antibodies targeted a much lower diversity of epitopes in both H3 and H1 HA: head, stem, and in some cases trimer interface. Epitope mapping of the vaccine cohort at week 0 found that all participants had pre-existing IgG antibodies against the head and stem epitopes of H1 HA and H3 HA (A/North Carolina/36/2016) and that by week 2 vaccination had not induced IgG responses against additional epitopes in most participants.

Conclusion

Both the vaccine cohort and infection cohorts had pre-existing IgG antibodies that targeted highly conserved regions in both H1 and H3 HA, including the HA stem, membrane anchor, and trimer interface, which are key targets in universal influenza vaccine design. As vaccination did not appear to elicit responses against new epitopes, serological analysis and high-resolution cryo-electron microscopy will be used to investigate if and how vaccination elicits new antibodies against shared epitopes and how this progression compares to responses elicited by infection.

Poster Reception II

Yawei Wang - AOXI0563

Consistency of Comparative Side Effect Profiles of Inactivated Influenza Vaccine (IIV) and Live-Attenuated Influenza Vaccine (LAIV) among School Children in Hong Kong: A three-year longitudinal study

Yawei Wang[1], Chun Wai Leung[1], Jiajie Chen[1], Hau Chi So[1], Nicole Ngai Yung Tsang[1], Benjamin John Cowling[1], Gabriel Matthew Leung[1], Dennis Kai Ming Ip[1]

[1]School of Public Health; The University of Hong Kong

Background

The Hong Kong (HK) government has launched a school-based vaccination (SBIV) program since 2018/19 influenza season, offering two vaccine candidates, IIV and LAIV, to eligible students. Both vaccine candidates generally have comparable effectiveness, so their respective side effects (S/E) become an essential factor for parental consideration. However, a detailed understanding of the comparative S/E of IIV and LAIV and the potential variability of S/E over different influenza seasons remains poorly investigated. We reported a comparison of the S/E of LAIV and IIV and consistency over consecutive three years among vaccinated school children.

Method

From 2019/20 to 2021/22, 15335 children from 49 schools were consented and vaccinated by the SBIV program provided by our outreach vaccination team as a service provider under the Vaccine Subsidy Scheme of the (HK) government. 38% and 62% had received IIV and LAIV, respectively. A questionnaire on S/E was completed daily by parents for four consecutive days since the day of vaccination (Day 0 to Day 3). 15 common S/E symptoms were covered, each with a severity scale ranging from 0 (no symptom) to 3 (severe symptom disturbing the activity of daily living). The difference in the proportion of children with S/E, severity of S/E, and temporal pattern of S/E between the two vaccines was examined using Fisher's exact test. A $p < 0.05$ was considered statistically significant.

Result

The proportion of children reporting any S/E over the four days was comparable and statistically non-significant between the LAIV and IIV groups over the three years. Children receiving LAIV were more likely to report severe or moderate S/E (severity score 2 or 3) than those receiving IIV. A trend persisted over three years but only attained statistical significance in 2021/22 (OR 1.56, 95% CI 1.20-2.02). There was a different temporal pattern of S/E occurrence and severity of the two vaccines, consistent over the three years. Compared with the IIV group, the proportion of children reporting any S/E was significantly lower in the LAIV group on day 0 (OR 0.3-0.45, $p <0.001$ for all 3 years) but significantly lower on Day 2 and 3 (OR 2.24-4.85, $p <0.001$ for all 3 years). The severity of S/E was reflected by either the proportion of children having S/E with score ≥2 or the mean total daily symptom score. Both followed a broadly similar pattern.

Conclusion

The S/E profiles are generally comparable between IIV and LAIV, and the trends are similar over three years. LAIV was noted to have more severe S/E than IIV and symptoms were generally delayed, concentrated mainly on the second-and third-day post-vaccination. In contrast, side effects of IIV appeared mainly on the day of vaccination.

Poster Reception II

Annette Fox - AOXI0571

Impact of prior vaccination on breadth of antibody response among healthcare workers after influenza vaccination

Annette Fox[5], Arseniy Khvorov[1], Yeu-Yang Tseng[1], Louise Carolan[4], Maria Auladell[1], Ian Barr[4], David Price[2], Min Levine[3], Yoo Young[3], Mark Thompson[3], Sheena Sullivan[5]

[1]Department of Infectious Diseases, University of Melbourne, Australia, [2]Department of Infectious Diseases, University of Melbourne, Australia; School of Population and Global Health, University of Melbourne, Australia, [3]Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA, [4]WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia, [5]WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia; Department of Infectious Diseases, University of Melbourne, Australia

Background

Studies suggest that influenza vaccine immunogenicity decreases with repeated annual administration, especially against influenza A(H3N2) virus. We examined the breadth of serum antibody responses to influenza vaccination among healthcare workers (HCWs) by prior vaccination history.

Method

Samples were from two cohorts of HCWs followed for three influenza seasons in Israel (2016-2017 to 2018-2019) and Peru (2016 to 2018). These were selected to obtain similar numbers, and age and sex distribution, of HCWs who had been vaccinated during two or less of the past 5 years (infrequently vaccinated) or all of the past 5 years (frequently vaccinated). Pre-vaccination, 21-28 days and 7 months post-vaccination sera were assessed by haemagglutination inhibition (HI) assay against a panel of 35 influenza A(H3N2) viruses that circulated from 1968 to 2019. Responses to the vaccine viruses were assessed, as well as the breadth of the responses across all 35 viruses. Breadth was quantified as the average fold-rise against the viruses that circulated each year after that individual was born (landscape fold-rise). Landscapes were compared between frequently and infrequently vaccinated HCW.

Result

A total of 357 HCWs were assessed. Among them, 157 were infrequently vaccinated and 180 were frequently vaccinated. Across the three seasons and two countries, post-vaccination vaccine strain titres were higher for infrequently (GMT=222; 95% CI 184-269) compared to frequently vaccinated HCWs (GMT=135; 95% CI 116-158). The corresponding post-to-pre-vaccination fold-rise was 5.83-fold (95% CI 5.76, 7.13) for infrequently vaccinated HCWs versus 2.10-fold (95% CI 1.87, 2.37) for frequently vaccinated HCWs. Similar trends were seen for titres against cell-grown equivalents of vaccine viruses, with GMTs exceeding 80 for the infrequently vaccinated group only. Vaccination induced mean fold titre rise exceeded two against strains dating back to 2007 among the infrequently vaccinated. Accordingly, the mean fold rise across the landscape of viruses spanning 2007-2019 was 3.69 (95% CI 3.18, 4.29) for the infrequently vaccinated compared with 1.69 (95% CI 1.55, 1.83) for the frequently vaccinated. Similar findings were observed when data were separated by location and season.

Conclusion

This study of influenza vaccination across three different years and two geographical locations found that vaccine immunogenicity was consistently and substantially compromised among the frequently vaccinated HCWs, not only for the vaccine viruses, but also for previously-circulating viruses. Better vaccines and vaccination strategies may be needed to optimize immunogenicity for populations that are annually or regularly vaccinated.

Poster Reception II

Xiu-Feng Wan - AOXI0588

Selecting high-yield vaccine candidates directly from epidemic influenza viruses using machine learning

Xiu-Feng Wan[5], Cheng Gao[5], Feng Wen[3], Minhui Guan[5], Lei Li[2], Feng Luo[1], Hang Xie[6], Richard Webby[4]

[1]Clemson University, [2]Georgia State University, [3]Mississippi State University, [4]St. Jude Children's Research Hospital, [5]University of Missouri - Columbia, [6]US Food and Drug Administration

Background

Despite substantial effort, the effectiveness of influenza vaccines remains suboptimal. Engineering an antigenic matched, high-yield vaccine seed strain in a timely manner is critical to the success of influenza vaccination.

Method

Here, by targeting the hemagglutinin receptor-binding site of the poor growth A/California/04/09(H1N1), we generated a pool of 189 mutants with diverse growth and glycan receptor binding properties. Through machine learning, we are reporting a set of high-yield signatures to improve virus growth in both embryonated chicken eggs and MDCK cells without changing their antigenicity, and changes at these residues diversify virus binding to different sialylated glycan receptors. Based on these features, a genomic sequence-based machine learning model was developed and applied in selecting influenza vaccine strain from 2009 H1N1 viruses with unique HA sequences (n = 11,424) for the 2009-2020 influenza seasons.

Result

Compared to sporadic viruses in earlier influenza seasons, the proportion of high-yield 2009 H1N1 viruses significantly increased in the years of 2019 (11.65%) and 2020 (43.13%), and such a phenotypic trait appears to emerge randomly and are distributed across multiple genetic lineages and geographic orders. Four vaccine candidates (2016-2020) selected by the model were synthesized and validated to antigenically match vaccine strains and with high growth properties in both cells and eggs.

Conclusion

The computational model from this study can be used to select high-yield influenza antigenic variants based on genomic sequences.

Poster Reception II

Annette Fox - AOXI0656

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

Annette Fox[9], Arseniy Khvorov[2], Yeu-Yang Tseng[2], Louise Carolan[8], Stephany Sanchez[2], A. Jessica Hadiprodjo[2], Chris Blyth[6], Allen Cheng[1], Julia Clark[5], Kristine Macartney[7], Helen Marshall[10], Peter Wark[3], Kanta Subbarao[8], Adam Kucharski[4], Sheena Sullivan[9]

[1]Alfred Health and Monash University, Melbourne, Australia, [2]Department of Infectious Diseases, University of Melbourne, Australia, [3]John Hunter Hospital and University of Newcastle, Newcastle, Australia, [4]London School of Hygiene and Tropical Medicine, [5]Queensland Children's Hospital and University of Queensland, Brisbane, Australia, [6]Telethon Kids Institute, Perth, Australia, [7]The Children's Hospital at Westmead; Sydney Children's Hospital Network, Sydney, Australia, [8]WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia, [9]WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia; Department of Infectious Diseases, University of Melbourne, Australia, [10]Women and Children's Hospital and University of Adelaide, Adelaide, Australia

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 (≥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.

Discussion: 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. PBMC's 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.

Poster Reception II

Chakshusmathi Ghadiyaram - AOXI0573

Development of novel, recombinant seasonal Influenza vaccine

Chakshusmathi Ghadiyaram[1], Suman Pandey[1], Madhuraj Bhat[1], Aswani Kumar Kancherla[1], Gautham Nadig[1], Raghavan Varadarajan[2]

[1]Mynvax Private Limited, [2]Mynvax Private Limited, Indian Institute of Science

Background

Influenza results in high morbidity, disability, and mortality burdens worldwide. Influenza vaccination is the preferred and most cost-effective intervention tool currently available to prevent influenza virus infection and disease. Licensed influenza vaccines include inactivated whole or split viruses, live attenuated vaccines, and recombinant viral subunit vaccines. These vaccines can reduce influenza incidence, and associated disease severity and mortality, yet their effectiveness remains moderate, especially for the elderly and individuals with co-morbidities. Thus, there is a clear need for more efficacious, rapidly producible Influenza vaccine with high surge capacity to combat the seasonal changes of the virus and facilitate pandemic preparedness. To address this unmet need, Mynvax Private Limited has developed Mynflu001, a novel, recombinant, HA based tetravalent vaccine which is now ready for human clinical trials.

Method

Four novel, recombinant HA constructs engineered for enhanced expression, based on 2021-22 NH recommendations by WHO were expressed, purified from insect (SF9) cells and characterized. Purified antigens were mixed with equal volumes of Sepivac® adjuvant and immunogenicity and protection studies were carried out in mice and ferrets. Influvac (IVV) from Abbott laboratories was used as a comparator. Mynflu001 was also tested for immunogenicity in hamsters and guinea pigs and for repeat-dose safety-toxicity assessment rats.

Result

SF9 expression and purification was optimized with yields of around 20mg/L at the 10L bioreactor scale. Individual antigens were purified to >90% purity. Far UV CD and Fluorescence spectroscopy showed a native folded conformation for all antigens, which exist as oligomers as found by SEC/ Western Blot. Purified antigens bind to conformation specific monoclonal antibodies. Challenge studies confirmed protection with Mynflu001 to be superior to Influvac for H3 and B heterologous challenge in mice with lower mortality and morbidity. Sera from mice, hamsters and guinea pigs immunized with Mynflu001 also showed significantly higher HI titers than corresponding sera elicited with Influvac at equivalent doses. Mynflu001 immunized groups showed no weight loss upon H3N2 virus challenge in Ferrets. The 28-day repeat dose safety-toxicity in rats showed no difference between adjuvant and test groups in body weight or biochemical/ clinical observations.

Conclusion

Mynflu001, a novel recombinant HA based tetravalent vaccine candidate conferred protection upon heterologous virus challenge in multiple animal species and was found to be safe in GLP safety toxicity studies in rodents. Clinical development of Mynflu001 is underway.

Poster Reception II

Saranya Sridhar - AOXI0630

Machine-Learning based selections of Different H3 Hemagglutinin Antigens show diverse breadth of immune response: A Randomized Controlled Trial of Recombinant Influenza Vaccine Formulations in Healthy Adult Subjects 18 to 30 Years of Age

Saranya Sridhar[4], Rumi Naik[1], Ya Meng[3], Tim Alefantis[3], Philip Davidson[3], Guadalupe Cortes-Garcia[3], Maryann Giel-Moloney[3], Ana Goncalvez, Aseem Pandey, Tod Strugnell[3], Camille Salamand[3], Charleene Tournier, Irina Ustyugova, Konstantin Zeldovich, Mario Barro[2], William Warren

[1]Independent, [2]RA ventures, [3]Sanofi, [4]Sanofi Vaccines

Background

The unpredictable variability in Influenza vaccine effectiveness every year is a key driver for efforts to develop more broadly protective influenza vaccines. We developed machine-learning (ML) based models to select wild-type influenza vaccine strains with potential for broader cross-reactivity to circulating strains. In this proof-of-concept randomized controlled trial, we assessed different H3 recombinant antigens which were selected from circulating strains using different ML algorithms which predicted greater antigenic coverage

Method

We conducted a Phase I, randomized, open label, controlled, multi-center study conducted in 150 healthy adult subjects 18 to 30 years of age in the US to assess the safety and immunogenicity of 4 different formulations of quadrivalent recombinant influenza vaccine. Each of the four formulations contained different H3 antigens, selected by ML-algorithms, compared to the quadrivalent RIV containing WHO recommended H3 antigen for the 2018-2019 NH region (A/Singapore from 3C.2a clade). All 4 quadrivalent RIV formulations and the control vaccine contained the same influenza A/H1N1, B/Yamagata, and B/Victoria antigens, per WHO recommendation for the 2019-2020 NH influenza season. Only the H3 antigens were different in each group. Serum samples collected at Day 0 and 28 days after vaccination were assessed against a broad panel of H3 strains from both the 3C.3a and 3C.2a clade by Haemagglutination-inhibition assay, neutralization assay and a multiplex ELISA assay.

Result

We observed higher HAI titers in Group 1 containing A/Osorno and Group 2 containing A/Kenya compared to the control group against H3 strains from both the 3C.2a and 3C.3a clades. In the NT assay, Group 2 showed this increase across all 10 strains in the readout panel including the WHO-recommended H3 strain (A/Singapore) while Group 1 showed this increase in 7/10 strains including 3C2a and 3C.3a clades. Seroconversion rates to 6/6 strains in the HAI assay were higher in Group 1 and Group 2 compared to WHO-recommended H3 strain containing vaccine. Cross-clade cross-reactivity higher than the control was observed for 2 of the 4 Machine-Learning selected H3 antigens. No safety concerns were observed in the trial.

Conclusion

Alternative H3 selection strategy identified wild-type circulating H3 strains which can induce broader immune responses, cross-clade antibody responses and higher immunogenicity. This trial provides clinical proof-of-concept for the ability to induce cross-clade immunity using machine-learning selections and provides proof-of-concept for an alternative strategy for influenza strain selection to develop improved seasonal influenza vaccines.

Poster Reception II

Annette Fox - AOXI0642

Egg adaptations and vaccine immunogencity: beneficial effect of maintaining glycosylation while allowing other egg-adaptive changes

A. Jessica Hadiprodjo[1], Yeu-Yang Tseng[1], Louise Carolan[2], Harry Stannard[2], Paul Whitney[2], James Barnes[2], Ian Barr[2], Kanta Subbarao[2], Edin Mifsud[2], Annette Fox[3]

[1]Department of Infectious Diseases, University of Melbourne, Australia, [2]WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia, [3]WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia; Department of Infectious Diseases, University of Melbourne, Australia

Background

A(H3N2) viruses that emerged during 2014 have a T160K substitution within hemagglutinin (HA), which results in N158 glycosylation, shielding immuno-dominant site B from antibodies. This substitution reverts to K160T when viruses are grown in eggs. A(H3N2) viruses also adapt to grow in eggs by substituting G186V or L194P. Studies with older viruses show that G186V has less antigenic effect than L194P, so is preferred for vaccine strains. In this study, we investigate how these substitutions affect the antigenicity of A/Hong Kong/4801/2014 (HK14).

Method

Four ferrets each were inoculated with reverse genetics (RG) viruses containing egg-grown HK14 HA with either G186V or L194P substitution, with and without substitution of T160K. The inoculation dose was standardized to 10^4 TCID50. Viral titres in daily nasal washes were determined by TCID50 and qRTPCR. Sera were collected on day 14 and titrated by HI assay against inoculating strains and against RG virus containing cell-grown HK14 HA.

Result

Virus shedding dynamics were similar across the four RG virus variants. Sera raised against G186V and L194P adapted viruses had high geometric mean titres (GMTs) against homologous strains (7512 and 3044, respectively), but low GMTs against cell-grown HA virus (360 and 469, respectively). Sera raised against G186V and L194P adapted viruses engineered to retain 160T had relatively high GMTs against both homologous virus (1586, 1613, respectively) and cell-grown HA virus (1811, 3352, respectively). To investigate how much HI antibody reacted with site B, sera were titrated against a site B mutant HK14 virus generated by substituting Y159Q, D188N, and K189Q. Sera raised against 160K viruses had 2.5-fold lower titres against site B mutant virus, indicating the presence of site B reactive antibodies, whereas sera raised against 160T viruses recognized homologous strain, site B mutant strain and 160K strains equally.

Conclusion

These results suggest that the T160K substitution accounts for the bulk of antigenic difference between egg- and cell-grown HK14, and that viruses that are egg-adapted via G186V or L194P, but engineered to maintain glycosylation could be promising vaccine candidates.

Poster Reception II

Linsey Marr - AOXI0596

Multidisciplinary INvesTIGAtion of Transmission to Ease influenza (MITIGATE FLU)

Linsey Marr[4], Aaron Prussin II[4], Krista Wigginton[2], Seema Lakdawala[3], Anice Lowen[1], Emily Martin[2], Andrew Hashikawa[2], Herek Clack[2], Adam Lauring[2], Peter Vikesland[4]

[1]Emory University, [2]University of Michigan, [3]University of Pittsburgh, [4]Virginia Tech

Background

The Covid-19 pandemic has raised awareness about the potential for all respiratory viruses to spread via aerosols. There is plentiful evidence that aerosol transmission of influenza, both in close proximity and at a distance, can occur, but we do not yet know the relative importance of this route. Non-pharmaceutical interventions for influenza such as handwashing, respiratory etiquette, surface cleaning, and social distancing are well established, but much less is known about the effectiveness of interventions that target cleaning the air.

Method

The overall goals of this research are to determine how behavioral and environmental factors affect transmission of influenza and to identify the most effective air-cleaning interventions for reducing transmission in child care and school settings. The research program aims to transform our understanding of influenza transmission through a multidisciplinary approach that integrates data from three projects: (1) development of innovative sensors and assays to detect viruses in the air and on surfaces, (2) reimagined studies of transmission in animals, and (3) modeling of transmission in child care centers. We will evaluate the impact of ventilation, air filtration, and humidification on exposure to the virus and the dynamics of transmission.

Result

We have completed pilot studies of transmission with ferrets in an enclosure containing one donor and multiple recipients, with realistic ventilation rates and thorough characterization of virus in the air and on surfaces. We have also completed pilot studies to map the presence and quantity of influenza virus in the air and on surfaces in child care centers. These studies are tightly integrated and closely coordinated with efforts to develop improved sampling and analysis methods. In future experiments, we will vary ventilation rates, deploy portable air filtration units, and adjust humidity levels to determine their impact on exposure and transmission.

Conclusion

Our comprehensive research program will advance understanding of the mechanisms of influenza transmission and will illuminate the dynamics and drivers of transmission. Our improved detection methods will empower both this effort and future studies of virus transmission and fate in the environment. We will identify environmental interventions to slow transmission and reduce influenza's impact on human health, and associated economic costs. Furthermore, the approach, methods, and results of this research will provide a rigorous framework for the study of other respiratory viruses, such as SARS-CoV-2.

Poster Reception II

Nadia Rimi - AOXI0598

Experiments to Evaluate Respirable Aerosols Produced during Different Poultry Defeathering Methods

Nadia Rimi[3], Md. Fahad[4], Andrew Clark[6], Joshua Mott[2], Rebeca Sultana[4], David Swayne[7], Kamal Hossain[4], Syed Mortaza[4], Md. Saifullah[4], Ireen Shanta[4], Md. Giasuddin[1], Md. Hassan[1], James Kile[2], William Lindsley[5]

[1]Bangladesh Livestock Research Institute, Savar, Dhaka, Bangladesh, [2]Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA, [3]icddr,b, [4]icddr,b, Dhaka, Bangladesh, [5]National Institute for Occupational Safety and Health (NIOSH), Morgantown, West Virginia, USA, [6]Private Veterinary Consultant, [7]U.S. Department of Agriculture, Athens, Georgia, USA

Background

Influenza viruses can be aerosolized during slaughtering and defeathering of infected chickens, increasing the risk of zoonotic transmission. We evaluated aerosol generation during different poultry defeathering methods used in Bangladeshi live bird markets.

Method

The experiments were performed in an air-movement controlled booth within a temperature-controlled room in Bangladesh Livestock Research Institute following the stun, bleed and slaughtering steps. Nine chickens were defeathered using each of five machine lid designs, for a total of 45 chickens: 1) no lid; 2) half-closed by a hinged lid; 3) partially covered by a lid with a hole; 4) fully closed by a lid with a hole and pivot door; and 5) fully closed by a slidable solid dish. The slaughterers poured 2.5 litres of normal room temperature water (~25-26ºC) inside the machine during the process. Three PATS+ aerosol monitors were placed 148 cm above the floor, corresponding to a worker's breathing level, to measure concentrations of <2.5 µm airborne particles at baseline and during defeathering. We interviewed the slaughterers to collect feedback on the acceptability of the different methods.

Result

The average particle concentrations were: 1) defeathering machine without a lid, 10 µg/m3 (SD 6.5); 2) machine half-closed by a hinged lid, 7.5 µg/m3 (SD 6.7); 3) machine partially closed by a lid with a hole, 3.3 µg/m3 (SD 3.4); 4) machine fully closed by a lid with a hole and pivot door, 0.0 µg/m3 (SD 0.0); and, 5) machine fully closed by a solid dish, 0.0 µg/m3 (SD 0.1). Covering defeathering machines fully with a solid dish or a lid with a hole and pivot door reduced particle concentrations below detectable levels ($P < 0.001$). Defeathering with machines covered partially by a hinged lid reduced concentrations by 25% ($P = 0.221$), while a lid with a hole led to a 67% reduction ($P = 0.009$). The slaughterers preferred the fully closed by a dish method, since they commonly practiced it in the live bird markets, followed by the half-closed by hinged lid method which allows pouring water during the process. They did not prefer the lid with a hole and pivot door method, as they had never practiced or observed it before, and it was more difficult to use.

Conclusion

Covering defeathering machines fully with a solid dish reduced particle concentrations and was preferred by the slaughterers. However, the lid with a hole and pivot door and the solid dish methods produced the lowest particle concentrations, potentially making them the safest methods to use. The findings can be used to educate slaughterers and promote methods that can minimize human exposure to potentially hazardous aerosol particles during poultry defeathering in the live bird markets.

Poster Reception II

Yiyang Guo - AOXI0559

Comparative antibody persistence after natural COVID-19 infection or a primary course of 2 doses of either mRNA or inactivated COVID-19 vaccines

Wing Kwan Ng[1], Yiyang Guo[1], Siu Kan Kwok[1], Kin Keung Mok[1], Hau Chi So[1], Joseph Sriyal Malik Peiris[1], Kai Ming Dennis Ip[1]

[1]School of Public Health, The University of Hong Kong

Background

Although existing studies have contributed some understanding on the antibody response and waning after natural infection or mRNA vaccine of COVID-19, the comparative persistence pattern of antibody developed by these two mechanisms, however, remained unclear. In particular, understanding on the antibody persistence pattern after a primary course (2 doses) of inactivated COVID-19 vaccines is lacking. We reported an observational study to compare the antibody persistence pattern following natural infection/ different vaccines in Hong Kong.

Method

This study was performed from Jun 2020 to Aug 2021. Convenience sample of unvaccinated COVID-19 infectees, and never infected and 2 doses vaccinees of either BNT162b2 or CoronaVac were recruited. After completing a baseline survey, a serum sample was collected to test for IgG antibody. A subset of infected cases had also contributed a second sample after >1 month. The samples were firstly tested ELISAs. Samples with ELISA positive (optical density > 0.5) or controversial result were further confirmed using sVNT. ELISA & sVNT results were examined by descriptive statistics and boxplot stratified by months according to the duration between sampling and the date of diagnosis/ 2nd dose vaccinations, and compared over the initial 4 months between the 3 groups (BNT162b2/ CoronaVac/ Infection). 95% CI of antibody level were obtained by bootstrap.

Result

A total of 844 participants have been recruited, including 251 unvaccinated infectees, sampled from 22 days to 13 months after the diagnosis date; and 593 vaccinees completed 2 doses COVID-19 vaccinations (BNT162b2:314, CoronaVac:279), sampled from 0 days to 3 months after their 2nd dose. In the initial 4 months, the antibody result of both tests of all 3 groups were maintained well above the corresponding threshold values, with the levels being highest among the BNT162b2 group, followed by the infection group, and lowest in the CoronaVac group. (Table 1) For the infection group, the data availability of longer duration between infection confirmation and sampling had indicated antibody developed after natural infection lasted over the threshold for at least up to 12 months.

Conclusion

Within the initial 4 months after 2 dose vaccination/ diagnosis, natural infection-induced antibody level was lower than mRNA vaccine-induced but higher than inactivated vaccine-induced antibody level. Infection-induced antibody level could last for at least up to 12 months.

Poster Reception II

Yiyang Guo - AOXI0562

Differential antibody response of 1 dose of either mRNA or inactivated COVID-19 vaccines after natural COVID-19 infection compared to 2 doses of vaccination in healthy population

Yiyang Guo[1], Wing Kwan Ng[1], Siu Kan Kwok[1], Kin Keung Mok[1], Hau Chi So[1], Joseph Sriyal Malik Peiris[1], Dennis Kai Ming Ip[1]

[1]School of Public Health, The University of Hong Kong

Background

Previous studies indicated antibody responses to 1 dose mRNA vaccine after COVID-19 infection were similar to completing a primary course (two doses) mRNA vaccine in never infected individuals. However, whether this finding can also be generalized to inactivated vaccine is unclear. Our study compared the antibody persistence pattern following one dose of vaccine in COVID-19 infectee, and people without prior infection and completed 2 doses either mRNA or inactivated COVID-19 vaccines.

Method

This study was performed from Jun 2020 to Aug 2021 in Hong Kong. Participants who had 2 doses vaccination or just 1 dose after infection were recruited by convenience sampling. A serum sample was collected to test for IgG antibody ELISAs, positive (optical density > 0.5) or controvertible samples were further confirmed using sVNT). A subset of infectees with controversial antibody test had also contributed a second sample after >1 month. ELISA & sVNT results were examined by descriptive statistics and boxplot with stratification by months between sampling and the date of last dose of vaccinations, and compared over the initial 4 months between groups. 95% CI of antibody level were obtained by bootstrap. $p < 0.05$ was considered statistically significant.

Result

A total 705 participants with their last dose of vaccination within 4 months have been recruited, including 593 2 doses vaccinee (BNT162b2:314; CoronaVac:279) and 112 previously infected and 1 dose vaccines (BNT162b2:81; CoronaVac:31). Eight with prior infection had contributed an additional sample. For BNT162b2, high antibody levels were maintained over the 4 months both for 2 doses and 1 dose after infection, with all above the corresponding threshold of ELISA and SVNT. For CoronaVac, mean OD450 of ELISA level were similar, but mean % signal inhibition of SVNT were substantially higher in 1 dose after infection then those with 2 doses and no prior infection. (Table 1) In either group, a higher antibody level was seen in the BNT162b2 than the CoronaVac group.

Conclusion

Within 4 months after the last dose of vaccination, BNT162b2-induced antibody response was similar in people with 1 dose after infection and those with no prior infection and received 2 doses. For CoronaVac, antibody level was substantially higher in 1 dose after infection then those with 2 doses and no prior infection. For either 1 dose plus infection or 2 doses, BNT162b2 gave a higher antibody level than the CoronaVac group.

Poster Reception II

Lora alsawalha - AOXI0671

Effective use of influenza surveillance and response capacities for Covid-19 utilizing Pandemic Influenza Preparedness Program: an experience from Jordan

Lora Alsawalha[1]

[1]WHO / EMRO

Background

Jordan has established systems and capacities to detect and diagnose influenza and respiratory viruses of epidemic and pandemic potential. The Covid-19 pandemic has highlighted the need of timely data sharing . International community has realized the importance and relevance of of solid national surveillance systems. There is a continuous need to support sustaining the capacities and performance of these systems.

The aim of Pandemic Influenza Preparedness , which started in 2015, is to maintain and expand on national diagnostic and detection capacities to support the Global Influenza Surveillance and Response System (GISRS) and build epidemic and pandemic preparedness. GISRS is a system fostering global confidence and trust through effective collaboration and sharing of viruses, data and benefits from Member States' commitment to a global public health model. PIP is jointly implemented by WHO and Ministry of Health

Method

Rapid review of the available documentation on existing infrastructure on surveillance and response systems for influenza and other respiratory viruses with epidemic or pandemic potential was carried out. Such as PIP activity plan, surveillance reports etc. Analysis was carried out to assess activities, identify successes and challenges expected to support the maintenance and expansion of national preparedness and response capacities.

Result

Activities that were identified and implemented to enable the health system to better respond to influenza and other pandemics included integration of the influenza like illness and severe acute respiratory diseases sentinel surveillance, with geographic representations across the country and implementation of the standards in clinical and public health laboratories including biosafety measures. Furthermore, strengthening capacity for genomic surveillance, development of a detailed risk communications and community engagement plan, and establishment of a national network of laboratories , also implemented. Other activities included institutionalization of "One Health", and establishment of a pool of multi-sectoral experts to conduct risk assessments for priority zoonotic diseases.

Challenges faced in implementation of activities included standardizing the collection and rapid sharing of epidemiological data from sentinel surveillance systems, staff turnover , and the deployment of experienced staff to support the Covid-19 response thereby diverting their focus to COVID-19.

Conclusion

PIP activities have proven useful in providing the foundation for COVID-19 response. Building upon existing national capacities and infrastructure to achieve integrated surveillance and response systems is the key to better preparedness and future response to epidemics and pandemics .