United States — Japan Cooperative Medical Sciences Program

2024 International Conference on Emerging Infectious Diseases (EID) in the Pacific Rim

And meetings of the Acute Respiratory Panel, Cancer Panel, AIDS Panel, Hepatitis Panel, Viral Diseases Panel, Immunology Board, and the 2nd International Symposium for Infectious Diseases Research Institutes Cooperation (IDRIC)

March 5-8, 2024
Hybrid and Grand Hyatt Hotel
Incheon, South Korea

Japan Agency for Medical Research and Development

Ministry of Health, Labour, and Welfare (MHLW) of Japan

Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan

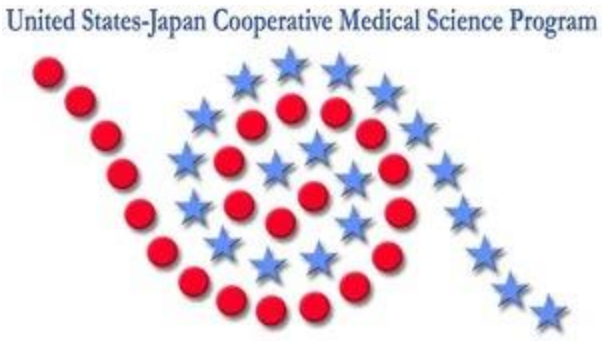
Ministry of Foreign Affairs (MOFA) of Japan

Korea Disease Control and Prevention Agency
National Institute of Health
National Institute of Infectious Diseases

International Vaccine Institute

National Institute of Allergy and Infectious Diseases

National Cancer Institute (NCI)



The Joint 24th International Conference on Emerging Infectious Diseases in the Pacific Rim of the U.S.-Japan Cooperative Medical Sciences Program (USJCMSP)

ABSTRACT E-BOOK

March 7 and 8: Acute Respiratory Infections Panel

[in order of presentation]

SESSION ONE: SARS-CoV 2: Current Advances and Tracking Viral Evolution

Masahiro Ishikane – National Center for Global Health and Medicine, Japan

The infectivity of SARS-CoV-2 in immunocompromised patients and their de-isolation

More than 4 years have passed since the beginning of the COVID-19 pandemic, and although there have been rapid developments in treatments and vaccines, and many problems have been solved, some of the clinical problems of COVID-19 in immunocompromised patients remain unresolved.

I will present the results of two studies. In the first study, the infectivity of SARS-CoV-2 was assessed in immunocompromised patients (Open Forum Infectious Diseases, Volume 10, Supplement 2, December 2023). We conducted a prospective cohort study at two tertiary care centers in Japan. One hundred and sixty-three nasopharyngeal specimens were collected from 41 patients, with 47 specimens from nine severely immunocompromised patients and 116 specimens from 32 moderately immunocompromised patients. In the severely immunocompromised group, 87.2% (41/47) of the specimens were polymerase chain reaction (PCR)-positive, with a median Cq value of 26.1 (interquartile range [IQR]: 20.5–30.2) and 36.2% (17/47) were culture-positive. In the moderately immunocompromised group, 75.0% were PCR-positive, with a median Cq value of 21.9 (IQR: 18.4–28.6), and 38.8% (45/116) were culture-positive. Of the 62 culture-positive samples, five (8.1%) were culture-positive after day 20, all from severely immunocompromised patients (P = 0.001). None of the moderately immunocompromised patients were culture-positive after day 12. The results of this study suggest that the duration of viral shedding should be carefully monitored in immunocompromised patients, particularly in severely immunocompromised patients. The second study evaluated the criteria for nosocomial de-isolation of immunocompromised patients with COVID-19 (PMID: 38162429). We conducted a comprehensive search of articles using real-world data from the National Center for Global Health and Medicine, the national center specializing in infectious diseases in Japan, and reviewed them with several experts at the hospital. A protocol for the de-isolation of patients with COVID-19 was developed in February 2023.

Based on the results of these two studies, I would like to discuss the infectivity of SARS-CoV-2 in immunocompromised patients and the criteria for de-isolation in hospital settings to help solve the clinical problem of COVID-19 in immunocompromised patients.

Suk Kyeong Lee – The Catholic University of Korea

Epstein-Barr Virus Disrupts Sphingolipid Metabolism to Maintain Viral Latency in Gastric Carcinoma

Tadaki Suzuki – National Institute of Infectious Diseases, Japan

Pathological Analysis of COVID-19 Cases and Animal Model Development

In the case of infectious diseases such as COVID-19, which present a variety of pathological conditions ranging from asymptomatic to severe, fatal, and sequelae, precise evaluation of each pathological change induced in the organs and tissues by the infection is important for understanding of the pathogenic mechanism of viral infection is crucial. However, conventional virological tests and diagnostic imaging are inadequate for determining the precise location of pathogens within the lesions; therefore, pathological investigations employing tissue samples from patients and infected animal models are critical for comprehending the pathogenesis and pathology of infectious diseases.

In addition, various approaches have been utilized to evaluate the potential for pathogenicity, infectivity, and immune evasion of SARS-CoV-2 variants. Methods which integrate pathological analysis of COVID-19 autopsy cases with the development of animal models prove to be advantageous in assessing the pathogenicity of SARS-CoV-2 variants. A continuous evolutionary process is currently being observed in the SARS-CoV-2 variants. Consistent monitoring of changes in the pathogenicity of newly identified variants using COVID-19 animal models and human autopsy case samples is thus beneficial for assessing the risk of pathogens to public health.

Sue Huang, Ph.D – Institute for Environmental and Science Research

The impact of COVID-19 on community and household cohorts in New Zealand

Longitudinal community and household cohort provides opportunity to understand non-medically attended respiratory illness and associated viral infections and risk factors at the community level, which is essential for building full spectrums of disease burden and informing future plan/prediction on viral transmission and public health interventions. The community cohort combined with a nested household transmission study allows to assess the dynamics of the spread of the virus from primary case to secondary cases and associated risk/protective factors, which is valuable for pandemic preparedness and response. In this presentation, I will provide background of SHIVERS-II (adult), III (infant), IV (household) cohorts and their responses to COVID-19 pandemic. These cohorts helped to understand community respiratory disease burden, transmission dynamics, impact of public health and social measures on SARS-CoV-2, influenza and other common respiratory viruses, and impact of COVID-19 vaccine effectiveness, vaccination and vaccine roll out on COVID-19 associated acute respiratory infections.

Kaori Sano – National Institute of Infectious Diseases, Tokyo, Japan

Induction of mucosal antibody responses by SARS-CoV-2 mRNA vaccination in previously infected individuals

SESSION TWO: RSV and Other Viral Respiratory Infections

Yuto Yasui – Kawasaki Medical University

Evaluation of Virus Detection using Quantitative Multiplex PCR in Pediatric Patients Hospitalized with Respiratory Tract Infections

(Purpose) In recent years, with the development of Multiplex PCR, it has become possible to rapidly and simultaneously detect various viruses. Although Multiplex PCR is highly sensitive, simultaneous detection of multiple viruses can lead to challenges in interpretation. Therefore, our study aimed to use quantitative Multiplex PCR in pediatric cases hospitalized with respiratory tract infections to not only identify the types of viruses but also compare the quantities of each virus in cases with multiple detections.

(Methods) From April 2022 to March 2023, we surveyed all pediatric cases admitted to our pediatric department with respiratory tract infections. Nasopharyngeal samples were collected, and real-time PCR using FTD Respiratory pathogens 21 (manufactured by RIKEN Genesis) was performed to detect the presence or absence of 20 respiratory viruses. The Ct values at the time of detection were investigated, and in cases with multiple detections, the virus with the lower Ct value was considered as the main virus infected.

(Results) Among the 149 cases under study, 97 cases (65.1%) tested positive for virus detection, and among these, 26 cases (26.8%) showed detection of multiple viruses. The total virus-detected patients detection numbers (number of multiple-virus detections/number of main detected virus) for the main viruses were, in descending order: Rhinovirus 40 (16/10), RS Virus A/B 27 (11/5), Parainfluenza 3 15 (7/3), Human Metapneumovirus A/B 13 (3/3), and Bocavirus 7 (6/0).

(Discussion) In nearly 30% of the cases studied, multiple viruses were detected, including viruses that were not the main virus. Therefore, careful interpretation, considering clinical symptoms, is necessary when viruses are detected in respiratory samples. Accumulating similar data in the future will allow us to evaluate methods for identifying causative viruses in respiratory tract infections.

Toru Sakamoto – Kurume University

The impact of influenza A H3N2 evolution from 1968 to 2023 on polymerase activity

Background: It is well known that influenza A H3N2,which appeared in 1968,has continued to mutate and spread among humans every year. However, it is not known how those mutations, acquired over the years, have affected the formation of the hybrid species with other subtypes. Previous study reported that Co-incorporation of PB2 and PA from the same virus of origin appears to be significant for efficient virus replication. In this study, we evaluated how the affinity of H3N2 PB1 with other subtypes of PA-PB2 has changed over 50 years.

Method: cDNA clones isolated from the following influenza strains were used: A/WSN/1933(H1N1),A/Vietnam/2004(H5N1),A/1968(H3N2:NT),A/Japan/2023(H3N2:KU), A/China/2015(H7N9).Luciferase reporter assay: HEK 293T cells were transfected with PA, PB1, PB2, NP and vLuc expression vectors, and cells were lysed at 30h. Luciferase activity was measured using a Luminometer and was calculated as a relative light unit.

Primer extension: HEK 293T cells were transfected with the above and vNA expression vectors and RNA was isolated 30h post-transfection. Primer extension was performed using three primers labelled with 32P: vRNA, mRNA, cRNA.

Result: Luciferase reporter assay and primer extension had similar results. When PB1 was replaced from NT to KU for each subtype of PA-PB2 combination (WSN, H5N1, H7N9), RNP activity was reduced in all. Comparing PB1 from NT and KU, we found 17 amino acid mutations that may change the properties.

Conclusion: Combined PB1 from H3N2 and other subtypes of PA-PB2, polymerase activity was greatly reduced in KU compared to NT.

Koo Nagasawa – Chiba University

Disease burden of respiratory syncytial virus (RSV) infection in the pediatric population in Japan

Respiratory syncytial virus (RSV) is the most common viral pathogen causing acute lower respiratory infection (ALRI) in children. At least 50% of infants become infected during their first year of life and nearly 100% by their second year. In 2019, globally there were 33.0 million episodes of RSV-ALRI, which resulted in around 3.6 million hospitalizations, and 26,300 in-hospital deaths in children aged <5 years (Li Y, et al. Lancet. 2022). Therefore, vaccines and long-acting antibody drugs against RSV have been developed in recent years, and it is expected that they will be available in Japan in the near future. Upon the future approval of these medications, the effectiveness can only be adequately assessed by comparison of epidemiological data before and after approval of them. However, in Japan, such data are mainly derived in single-center setting and there is no population based epidemiological data. We are conducting research to clarify the RSV disease burden before the introduction of these drugs in Japan.

First, we conducted a literature review on the disease burden of RSV in Japan (Nagasawa K and Ishiwada N. J Infect Chemother. 2022). We comprehensively searched domestic RSV-related documents published in PubMed and Ichushi from 2010 to 2020, and finally analyzed 143 documents. Although almost all reports suggested that RSV accounts for a large proportion of children hospitalized due to respiratory infections, it was shown that the specific numbers vary widely, ranging from 8.9% to 66.7% depending on the disease definition and population.

In addition, we have been conducting epidemiological research to clarify the RSV hospitalization rate per population in Chiba and Ichihara cities in Japan since 2020. At the stage of interim analysis up to 2022, the rate of hospitalizations per 1,000 infants in Chiba City in 2021 and 2022 were 19.8 and 5.7, respectively. These results suggest that multiple years of epidemiological analysis data are necessary because the hospitalization rate changes depending on the scale of the RSV epidemic. Continued epidemiological analysis is necessary to accurately clarify the disease burden of RSV.

SESSION THREE: Influenza: an Emerging and Re-Emerging Pathogen

Irina Chon, Niigata University

Detection of A(H3N2) influenza viruses with PA/I38T drug resistance substitution after and prior to baloxavir marboxil treatment during the 2022-2023 influenza season in Japan

Baloxavir marboxil (baloxavir) was approved as an anti-influenza drug in Japan in March 2018. Emergence of substitutions in the polymerase acidic (PA) protein that confer reduced susceptibility to baloxavir in influenza viruses can reduce therapeutic efficacy. Here, we assessed the presence of PA substitutions in clinical samples obtained from influenza-infected children and adults prior to and following baloxavir treatment. Additionally, we evaluated the impact of PA substitution on the duration of fever and symptoms in patients. During the 2022-2023 influenza season, the predominant circulating influenza subtype detected by cycling-probe RT-PCR was A(H3N2) (n=231), with minor circulation of A(H1N1)pdm09 (n=7). Of the 53 paired influenza A(H3N2) viruses collected prior to and following baloxavir treatment, 3 (5.7%) viruses carry PA/I38T substitution. All three PA/I38T viruses were isolated from children 7-14 years of age after baloxavir treatment. Their fever dropped below 37.5 °C within two days and duration of all symptoms was similar with wild type. Of the 231 influenza A(H3N2) viruses collected prior to baloxavir treatment, 2 (0.8%) viruses carry the PA/I38T substitution. One virus with PA/I38T was isolated from a toddler and one from an adult, indicating the presence of viruses with reduced susceptibility to baloxavir without any prior exposure to the drug. No other substitutions in PA conferring reduced susceptibility to baloxavir and those in neuraminidase that cause resistant to neuraminidase inhibitors were detected by next generation sequencing. These findings highlight the importance of continued surveillance for the emergence of baloxavir-resistant viruses, for public health purposes and specific clinical recommendations on antiviral drug use for seasonal influenza.

Manon Ragonnet-Cronin, Ph.D.

Influenza: an Emerging and Re-Emerging Pathogen

Seasonal flu epidemics stem from the circulation of influenzas A (H1N1 and H3N2, distinguished by their hemagglutinin and neuraminidase proteins) and B. Influenza has a high mutation rate, and within each influenza type, evolution enables viral evasion from prior immune responses, allowing for reinfection. The immune landscape is further complicated by the phenomenon of imprinting, or “original antigenic sin”, whereby life-long influenza immune responses are shaped by initial exposure. While influenza vaccines can offer effective protection when well-matched to circulating viruses, predicting dominant strains remains challenging.

In addition to evolving through drift, influenza genome segments can reassort with those from other viruses through "shift," further increasing viral genetic diversity. The highest risk occurs with cross-species genetic reassortment, for instance the 2009 H1N1 pandemic resulted from a triple reassortment between human, swine, and avian viruses. Zoonotic infection of humans with influenza A viruses from animal reservoirs continues to pose a pandemic risk.

In conclusion, the dynamic nature of influenza underscores its significance as an emergent and reemergent pathogenic threat.

Louise Rowntree, Ph.D.

CD8+ T cell immunity directed at Influenza A and Influenza B viruses in First Nations peoples

Influenza-specific T cells act to limit disease severity and drive rapid recovery during influenza virus infections. One of the hallmarks of antigen-specific CD8+ T cells is their antigen-specificity and establishment of long-term, broadly cross-reactive memory pools capable of recall responses against distinct influenza strains and subtypes, including newly-emerging influenza strains. When the new avianH7N9 virus emerged in China in 2013, causing >35% mortality, patients with early prominent influenzaspecific CD8+ T cell responses had most rapid recovery, while individuals who succumbed had minimal influenza-specific immunity and little evidence of T cell activation. While over 261 IAV and 37 IBV CD8+T cell epitopes have been described, there are large variances in the HLA allele coverage across ethnicities. While Indigenous populations globally are highly susceptible to severe influenza disease, apart from HLA-A*02:01, the HLA allotypes commonly expressed in Australian First Nations peoples are rarely identified in the general population and there are only a few known influenza epitopes for the majority of these allotypes. To identify novel immunodominant CD8+ T cell epitopes key for First Nations peoples, we used immunopeptidomics to define influenza A and B-derived peptides naturally processed and presented by prominent HLA alleles in First Nation Australians (HLA-A*11:01, 24:02, 34:01 and B*13:01). Candidate peptides were identified by mass spectrometry and screened against HLA-typed First Nations and non-Indigenous donors. Confirmation of T cell epitope specificity and HLA-restriction allowed analysis of T-cell receptor (TCR) clonal expansion and diversity within epitope-specific CD8+ T cell responses. An average of 62 virus-derived candidate peptides were yielded per allotype, with between six and eleven immunogenic influenza epitopes per allotype. This provides >95% population coverage for prominent CD8+ T-cell responses in Australian First Nations peoples. Analysis of TCRs from CD8+ T cells specific for a subset of HLA-A*34:01-restricted influenza epitopes revealed a range of repertoire diversity, providing compelling evidence of breadth across the CD8+ T cell immune landscape against influenza A and B viruses. The discovery of peptides presented by high frequency HLA alleles in Australian First Nations peoples potentiates their use in universal CD8+ T cell-based vaccines to generate broadly cross-reactive immunity against distinct strains and subtypes of influenza viruses.

SESSION FOUR: Other Acute Respiratory Infections

Hyukmin Lee, MD, PhD

Recent trend of respiratory infections in Korea

Dr. Jason Rosch – St. Jude Children's Research Hospital

Pathogens Sticking Together: New Synergies Operative in Polymicrobial Infections

It is firmly established, based on both clinical observations and experimental modeling, that co-infections within the upper respiratory tract exacerbate disease severity and contribute to poorer outcomes. Among the most thoroughly studied co-infections is the enhancement of secondary bacterial infections by viral agents. Our findings suggest that this synergistic effect extends to early disease events through direct interactions between influenza virus and bacterial surfaces. These intricate pathogen interactions markedly augment bacterial adherence to human respiratory cells and escalate disease severity within the upper respiratory tract. Notably, viral-bacterial complexes seem to be a common feature among various respiratory pathogens, including RSV and influenza, along with several other bacterial species. While the mechanisms and consequences of respiratory tract co-infections are complex, high-throughput genetic approaches have illuminated key pathways at play in such scenarios. In response, we have developed innovative strategies for live attenuated vaccines targeting multiple pathogens to counteract polymicrobial infections and diseases stemming from diverse etiologies.