Abstracts for Poster Presentation: Infectious Diseases

ID-1-57

Preemptive Homology-Directed DNA Repair Fosters Complex Genomic Rearrangements in Hepatocellular Carcinoma

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Introduction and Project Objectives: Degree of genomic instability closely correlates with poor prognosis, drug resistance as well as poor survival across human cancer of different origins. We aim to identify the pathogenic molecular events in DNA damage response (DDR) and their functional significance towards genomic instability in hepatocarcinogensis.

Methods: This study assessed the relationship between DDR and chromosome instability in hepatocellular carcinoma (HCC). We investigated DDR signalling in HCC cells by analysing DNA damage-dependent redistribution of major DDR proteins to damaged chromatin using immunofluorescence microscopy and Western blotting experimentations. We also performed gene conversion and metaphase analyses to address whether dysregulated DDR may bear any biological significance during hepatocarcinogenesis.

Results: We demonstrated that HCC cell lines suffered from elevated spontaneous DNA double-strand breaks (DSBs). In addition, analyses of HCC metaphases revealed marked aneuploidy and more frequent sister chromatid exchanges when compared to immortalized hepatocytes, the latter of which were further induced following camptothecin-induced DSBs.

Conclusion: Our study showed that homology directed DNA repair is functional and augmented for DSB repair in HCC. The observed upregulated phosphorylation of ATM in HCC suggests that ATM activation and the downstream ATM-licensed molecular pathways might be essential in the initiation and/or progression of hepatocarcinogenesis. We propose that genomic instability in HCC may be caused by erroneous DNA repair in attempt to mend DSBs for cell survival. Such preemptive measures inadvertently foster chromosome instability and thus complex genomic rearrangements in HCC.

Project No.: 14131132

ID-2-30

Heterosubtypic Protection Induced by a Live Attenuated Influenza Virus Vaccine Expressing Galactose-α-1,3-Galactose Epitopes in Infected Cells

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Introduction and Project Objectives: Influenza A viruses have multiple HA subtypes that are antigenically diverse. Classical influenza virus vaccines are subtype specific, and they cannot induce satisfactory heterosubtypic immunity against multiple influenza virus subtypes. There is a need of novel strategies for developing broadly reactive influenza vaccines to induce heterosubtypic protection.

Methods: Anti-galactose-α-1,3-galactose (anti-α-Gal) antibody is naturally expressed at a high level in humans. It constitutes about 1% of immunoglobulins found in human blood. Here, we designed a live attenuated influenza virus vaccine that can generate α-Gal epitopes in infected cells in order to facilitate opsonization of infected cells, thereby enhancing vaccine-induced protection.

Results: We generated a live attenuated influenza virus vaccine that can generate α-Gal epitopes in infected cells. In the presence of normal human sera, cells infected with this mutant can enhance phagocytosis of human macrophages and cytotoxicity of NK cells in vitro. Using a knockout mouse strain that allows expression of anti-α-Gal antibody in vivo, we showed that this strategy can increase vaccine immunogenicity and the breadth of protection. This vaccine can induce 100% protection against a lethal heterosubtypic group 1 (H5) or group 2 (mouse-adapted H3) influenza virus challenge in the mouse model. In contrast, its heterosubtypic protective effect in wild-type or knockout mice that do not have anti-α-Gal antibody expression is only partial, demonstrating that the enhanced vaccine-induced protection requires anti-α-Gal antibody upon vaccination. Anti-α-Gal-expressing knockout mice immunized with this vaccine produce robust humoral and cell-mediated responses upon a lethal virus challenge. This vaccine can stimulate CD11blo/- pulmonary dendritic cells, which are known to be crucial for clearance of influenza virus.

Conclusion: Our approach provides a novel strategy for developing next-generation influenza virus vaccines.

Project No.: 14131092

ID-3-31

Detection and Characterization of Antibody-dependent Cell-mediated Cytotoxicity (ADCC) Responses against Human Influenza Virus in Humans and Mice

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Introduction and Project Objectives: Cross-reactive influenza virus-specific antibody-dependent cellular cytotoxicity (ADCC)-activating antibodies are readily detected in healthy adults. However, little is known about the kinetics of these ADCC

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responses. Here, we studied the role ADCC response against influenza virus infections.

Methods: We used human blood samples from health donors during 2009-2010 to study ADCC responses against hemagglutinin (HA) of human (pandemic H1N1/2009) or avian (H7N9) influenza virus. We used peptide libraries of influenza HA proteins to screen for ADCC-inducing epitopes in ELISA. Representative ADCC-inducing epitopes were tested in mice to determine its protective role against virus infection.

Results: All healthy donors had ADCC responses against 2009 pandemic H1 influenza virus and H7 avian influenza virus despite being seronegative for these viruses in standard hemagglutination inhibition and microneutralization serological assays. No correlation between ADCC responses to influenza virus-specific immunoglobulin G1 concentration or age. A(H1N1)pdm09 exposure did not boost ADCC responses specific for H7 HA antigens. Peptide-mapping for ADCC reactivity of H1-HA and H7-HA proteins from human serum samples identified high ADCC-inducing peptides in both the HA1 and HA2 regions. Vaccination of mice with single ADCC-peptides induced ADCC activity leading to partial protection from lethal influenza challenge, with increased survival, reduced viral loads, and reduced activation of NK cells in the lungs.

Conclusion: Cross-reactivity ADCC responses against different influenza viruses can be readily found in health human individuals. ADCC-epitopes are present in both the HA1 and HA2 regions, and single ADCC-activating peptides provided partial protection from lethal influenza challenge, therefore representing a possible target in future combination vaccination strategies.

Project No.: 15141052

ID-4-103

Comparative Analysis of Plasma Cytokine/Chemokine and In Vitro Transcriptomic/Lipidomic Profile Induced by Influenza B Virus and Human Rhinovirus Infection

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Introduction and Project Objectives: Influenza A virus (IAV), influenza B virus (IBV) and rhinovirus (RV) are common causes of respiratory tract infection. Few studies have directly compared these infections. Here, we used a multi-pronged approach to systemically compared IAV, IBV and RV infection.

Methods: Part I analyzed the clinical characteristics of critically-ill patients with RV. Part II compared the clinical characteristics of adult hospitalized RV patients with age-matched IAV/IBV patients. Parts III and IV used RNAseq and LC-MS to analyze the transcriptomic profile and lipidomic profile of RV/IAV/IBV infection in a bronchial epithelial cell line, respectively.

Results: Part I: Exacerbation of underlying pulmonary or non-pulmonary disease occurred in 54.5% of critically-ill RV patients. Among RV patients with pneumonia, the most common chest radiographic finding was consolidation (46.2%). The rate of seizure was higher among patients with RV (22.7%) than those with other respiratory virus infection. Part II: Severe disease was more common among RV patients than IAV/IBV patients (34% vs 11%). RV infection was characterized by a prominent TH2 response, including higher levels of eosinophil and interleukin-5 when compared with IAV/IBV infection, even among patients without asthma. CXCL-10 was found to be a potential biomarker differentiating IAV/IBV and RV infection (AUC, 0.918).
Part III: RV-infected cells exhibited a more blunted host response with fewer differentially expressed genes (DEGs) than IAV/IBV infection. DEGs that were highly expressed for all 3 viruses were mainly genes related to type I or type III interferons and chemokines. Notably, ICAM5, a known receptor for enterovirus D68, was highly expressed during RV infection only. Pathway analysis showed that pathways related to interferon response, innate immunity, or regulation of inflammatory response were most perturbed for all three viruses.
Part IV: Most lipid features were found to be downregulated for IAV, IBV or RV. Sphingomyelin metabolism was the most affected pathway. Bacterial sphingomyelinase suppressed the replication of IAV, IBV and SARS-CoV-2, but promoted the replication of RV.

Conclusion: RV is more likely to be associated with exacerbation of underlying lung disease and extrapulmonary complications. RV was associated with a TH2 type response. Transcriptomic study revealed a distinctive role of ICAM5 for RV infection. Lipidomic study showed that the sphingolipid pathway is downregulated for RV/IAV/IBV, although sphingomyelinase treatment has an opposite effect on the replication of RV and IAV/IBV/SARS-CoV-2. These studies have enhanced the understanding or RV/IAV/IBV infections, and have revealed potential therapeutic targets.

Project No.: HKM-15-M03

ID-5-162

A Randomized Controlled Trial on the Effect of Fever Suppression by Antipyretics on Influenza

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Introduction and Project Objectives: While fever is commonly

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regarded as an illness to be treated, preliminary evidence from animal and observational human studies are suggesting that antipyretic use for fever suppression in URTIs might prolong the duration of illness and increase the amount and duration of viral shedding, signifying that routine suppression of fever may potentially increase the risk of further transmission and propagation of epidemics, and carrying potential downstream public health implications. A robust examination of the effect of fever suppression by antipyretics on viral shedding and clinical symptomology in naturally-occurring influenza infections is currently lacking.

Methods: With a double-blind randomized placebo-controlled trial, a total of 1861 young adults aged 18-30 presenting with ≥2 URI symptoms within 48 hours of illness onset were screened in a university health clinic in Hong Kong from March 2016 to August 2018. Among whom 319 having a positive QuickVue Influenza A & B rapid testing result were randomized to receive either paracetamol 500mg or matching placebo four times daily for 5 days. Viral identification and subtyping by quantitative RT-PCR was performed on nasal and throat swabs on days 1 (baseline)/4/7/10. Self-recording of body temperature and common symptoms of influenza were monitored twice daily for ten days.

Results: A total of 206 patients with PCR-confirmed influenza infection were included in the analysis. No difference in clinical illness duration and symptoms severity was detected between the paracetamol (n=108) and placebo groups (n=98). Total symptom scores by AUC analysis were also comparable. In terms of transmissibility, no significant prolongation in viral shedding was observed in paracetamol group on the mean durations of viral shedding estimated, and the time to resolution of viral shedding. Total amount of virus shedding as reflected by the AUC for quantitative influenza viral load was also comparable.

Conclusion: Our findings suggested there is no observable evidence to substantiate that the use of paracetamol might significantly increase the amount of viral shedding, nor the clinical illness in naturally-occurring PCR-confirmed influenza infection in human. Current evidence is not sufficient for a conclusive argument on the impact of widespread usage of antipyretics on URI transmission and epidemic propagation in the community. Further study on the mechanisms between fever, viral shedding, infectivity, and disease transmission would be important for better informing the proper use of antipyretics in influenza virus infection.

Project No.: 15141162

ID-6-170

Using a Smartphone Application-Based School Absenteeism Monitoring to Improve the Surveillance Performance for Influenza Activity in Hong Kong

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Introduction and Project Objectives: Schools are high risk settings of influenza transmission and outbreaks, especially during influenza seasons. School absenteeism is becoming a major component of influenza surveillance systems in many parts of the world, and is reported to be useful for reflecting influenza activities in the community. Major drawbacks of school absenteeism data, however, included poor timeliness, heavy workload for manual collection, and suboptimal specificity. Currently, local surveillance of influenza-like-illness (ILI) is lacking a component for prospective, routine and continuous monitoring in local schools. We explored the feasibility of adopting a smartphone application (App)-based school absenteeism reporting platform for ILI surveillance in Hong Kong.

Methods: An App was developed for parents to submit applications for student absenteeism, with the simple reporting of also the nature (sickness/ non-sickness absence), cause, and symptom details if any. Product of the weekly proportion of ILI reported by the sentinel General Practitioner (GP) network and the weekly percentage of positive influenza isolates from the Public Health Laboratory Services Branch (PHLSB) were used as the gold-standard for assessing the performance of our App-based absenteeism data according to the US CDC evaluation framework. Each study weeks was classified as either having high or low influenza activity (epidemic/ non-epidemic) using specific thresholds. Surveys were completed by teachers and parents for assessing acceptability.

Results: Our App covered a total of 7,711 students in 13 participating schools, and captured 95,412 person-days of absence over the study period (11/2016-06/2018). The temporal pattern of ILI activity was much better delineated by the school absenteeism than the GP ILI data. Epidemic peaks shown by the student absenteeism data preceded those shown by GP ILI surveillance data by 2-3 weeks. Rescaling of all-cause absence rate by the percentage of sick leave due to upper respiratory tract infection (URTI/SL) improved the performance of the surveillance, in terms of sensitivity (from 68.4% to 73.7%), specificity (from 55.8% to 57.7%) and PPV (from 36.1% to 38.9%). Most teachers and parents found the App stable, simple, easy to use, and helpful to reduce their workload.

Conclusion: Smartphone App-based student absenteeism monitoring represents a feasible approach for prospective ILI

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surveillance. The system is stable and acceptable, and achieved an improvement of both data specificity and timeliness. The workload reduction may also help to avoid surveillance fatigue and contribute to better data accuracy and system sustainability.

Project No.: 15141522

ID-7-182

Harnessing the Potential of Blood Donation Archives for Influenza Surveillance and Control

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Introduction and Project Objectives: Many blood donation services around the globe maintain large archives of serum and/or plasma specimens of blood donations which could potentially be used for serologic surveillance and risk assessment of influenza. Harnessing this potential requires robust evidence that the outcomes of influenza serology in serum, which is the conventional choice of specimens, is consistent with that in plasma, which is rarely used for influenza serology.

Methods: We harvested EDTA-plasma specimens from the blood donation archive of Hong Kong Red Cross Blood Transfusion Services and compared their antibody titres and responses to that in serum. Influenza A/H1N1/California/7/2009 and A/H3N2/Victoria/208/2009 were the test strains.

Results: Our results showed that antibody titres in 609 matched serum/EDTA-plasma specimens (i.e. obtained from the same donor at the same time) had good agreement inferred by Intraclass Correlation Coefficient, the value of which was 0.82 (95% CI: 0.77–0.86) for hemagglutination inhibition assay and 0.95 (95% CI: 0.93–0.96) for microneutralization assay; seroconversion rates (based on hemagglutination inhibition titres) during the 2010 and 2011 influenza seasons in Hong Kong inferred from paired EDTA-plasma were similar to that inferred from paired sera.

Conclusion: Our study provides the proof-of-concept that blood donation archives around the globe could be leveraged as a valuable source of longitudinal blood specimens for the surveillance, control, and risk assessment of both pandemic and seasonal influenza.

Project No.: HKS-17-E14

ID-8-191

Interactions between Lung Microvascular Endothelial Cells and Alveolar Epithelial Cells in Severe Influenza Virus Infection Associated Acute Lung Injury

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Introduction and Project Objectives: Highly pathogenic avian influenza (HPAI) virus infections cause significant mortality in humans. In normal lungs, the integrity of the epithelial-capillary barrier is key to maintaining lung fluid clearance. However, the role of the respiratory epithelial-endothelial barrier in the pathogenesis of human influenza diseases remains unclear. The aim of this study is to establish an in vitro alveolocapillary lung injury model for investigating how influenza virus infection affects alveolar fluid clearance (AFC) and alveolar protein permeability (APP), which are important mechanisms involved in the exacerbation of lung injury. The regulation of sodium/chloride transporter proteins, cellular and tight junction integrity during infection will be examined along with the potential therapeutic effect of VEGF-A and ANG1 in resolving impaired lung function.

Methods: The HPAI viruses A/Shanghai/2/2013 (H7N9) and A/Hong Kong/483/97 (H5N1), a 2009 pandemic influenza virus A/Hong Kong/415742/2009 (H1N1pdm) and a seasonal influenza virus A/Hong Kong/54/1998 (H1N1) were used in this study. Alveolar epithelial cells (AEC) isolated from human non-tumour lung tissues and human lung microvascular endothelial cells (HMVEC) were used to develop the human alveolocapillary lung injury model. Virus infection of the lung injury model was carried out to observe the differential induction of AFC and APP, and to examine the therapeutic potential of VEGF-A and ANG1 upon HPAI or low pathogenic influenza virus infections.

Results: A highly physiologically relevant human alveolocapillary lung injury model was established with the co-culture of AEC and HMVEC. H5N1 significantly reduced AFC and increased APP compared to H7N9, H1N1pdm and H1N1 viruses. Significantly downregulated mRNA expressions of alpha1-Na+K+ATPase, alpha3-Na+K+ATPase and CFTR were observed in H5N1-infected AEC compared to H1N1-infected cells, with the effect being recapitulated in the virus-free conditioned medium-treated cells, which suggest that the soluble factors secreted by AEC upon H5N1 infection were responsible for the downregulation of ion channels. The mRNA expressions of major pro-inflammatory cytokines and chemokines were significantly greater in H5N1-infected AEC and HMVEC than in H1N1- or mock-infected cells. When administered simultaneously, VEGF-A and ANG1 restored the endothelial permeability and cellular integrity in both AEC and HMVEC cells upon H5N1 virus infection.

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Conclusion: The results offered an innovative insight into the mechanistic role of epithelial-endothelial cell interactions in the pathogenesis of influenza virus-induced lung injury. The ability of VEGF-A and ANG1 to enhance endothelial permeability and tight junction integrity indicate a novel potential therapeutic strategy for the treatment of severe human influenza virus-induced diseases.

Project No.: 15141022

ID-9-197

Limited Onward Transmission Potential of Reassortment Genotypes from Chickens Co-Infected with H9N2 and H7N9 Avian Influenza Viruses

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Introduction and Project Objectives: Live poultry markets where birds infected with genetically diverse avian influenza viruses congregate may have the potential to generate genetically diverse avian influenza viruses with increased zoonotic potential through genetic reassortment. We aimed to characterize the novel reassortant viruses after co-infection of A(H7N9) and A(H9N2) viruses in ovo and in chickens. We also investigated the sequential transmission potential of novel reassortant genotypes in chickens.

Methods: A Pearl River Delta lineage A(H7N9) viruses A/silkie Chicken/Hong Kong/1772/2014 (designated as HK1772) was selected to co-infect with four A(H9N2) viruses of different lineages, including A/chicken/Beijing/16/2013 (designated as BJ16) that belonged to the G57-lineage and co-circulated with the A(H7N9) viruses, A/chicken/Zhejiang/HJ/2007 (designated as HJ) that represents an early G57-lineage isolate, A/silkie chicken/Hong Kong/YU335/2007 (designated as YU335) that circulated prior to the G57 viruses, and A/quail/Hong Kong/G1/1997 that has been established in the Middle East countries. Novel reassortant genotypes generated in co-infected eggs or chickens were characterized by picking and testing individual plaques using high-resolution melting analysis. Sequential transmission experiments were performed by co-infecting donor chickens with A(H7N9) and A(H9N2) and exposing the 1st contact chickens with the donors (from day 1 to 3 post-inoculation) and followed by exposing the 2nd contact chickens with the 1st contacts (from day 3 to 5 post-inoculation).

Results: Co-infection with A(H7N9) and A(H9N2) viruses may lead to the emergence of novel reassortant viruses in ovo and in chickens, albeit with different reassortment patterns. We observed the dominance of A(H7N9) virus in ovo and the dominance of A(H9N2) viruses in co-infected chickens. Despite of detecting multiple novel reassortant viruses in donors after co-infection of A(H7N9) and A(H9N2) viruses, most of the novel reassortant viruses were not detected in contact chickens after exposure. Onward transmission of novel reassortant viruses from co-infected donors to the 1st and the 2nd contacts was only observed in the HK1772+YU335 group. Furthermore, among multiple novel reassortant viruses detected in donors co-infected with HK1772+BJ16, only the parental BJ16 virus was transmitted to the 1st and 2nd contacts. Taken together, these findings suggest limited onward transmission potential of novel reassortants generated in chickens co-infected with A(H7N9) and A(H9N2) viruses.

Conclusion: Our results demonstrated different patterns by which influenza viruses may acquire genetic diversity through co-infection in ovo, in vivo, and under sequential transmission conditions.

Project No.: 17160882

ID-10-209

Inference on Influenza Transmission in Swine Farms and During Transport in the Swine Supply Chain

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Introduction and Project Objectives: Newly emerging diseases, in particular those having a zoonotic origin, continue to be a threat to human health. Understanding the dynamics of viral transmission in animals is of importance in assessing feasibility of critical control points that may be amenable to disease control interventions. Swine have been considered as a possible intermediate host of influenza viruses and a source of pandemic emergence.

In Hong Kong, over 90% of the pigs are imported from mainland China, with an annual volume of about 1.5 million. Live pigs for consumption are transported in trucks from the source farm to a quarantine site at the Shenzhen-Hong Kong border. During this transport chain, there is opportunity for virus transmission between different consignments of pigs originating in different farms and stress association with transport may increase infection risk.

Methods: We utilized 6,675 paired serum samples and nasal swabs samples collected from a prospective longitudinal active influenza surveillance at the abattoir in Hong Kong, 2012-2016. We performed virological testing to identify influenza viruses in

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the swabs and serological testing on the serum samples against the A/Swine/Binh Duong/03_06/10-like H3N2 lineage. Antibody titers ≥1:40 were regarded as seropositive. Haemagglutination inhibition (HI) assays were used to identify and subtype virus isolates. Based on the test results from the paired samples, we identified recent primary infections of H3N2 and swine naïve to H3N2, which allows the estimation of the weekly force of infection in farms and during transportation.

Results: We detected low isolation rate (1%) of influenza H3N2 virus from swine originated from different places in mainland China. There was no strong seasonal pattern of H3N2 prevalence in the farms and also infections during transport. Based on different assumptions on the exposure durations in farms, the relative force of infection during transport versus in farms was about 40-119% and 17-50% in Guangdong and Hunan respectively, indicating a noticeable transmission risk during transportation for swine originated in Guangdong.

Conclusion: There is no evidence that longer distance of transportation increases the risk of transmission substantially. Transportation is an important component of biosecurity for the swine supply chain. The continued assessment of relative contribution of influenza transmission during transportation will inform the allocation of resources in improving disease control.

Project No.: HKS-15-E02

ID-11-215
PB1-F2 Protein of Influenza A (H7N9) Virus Specifically Suppresses MAVS Aggregation and Activation to Inhibit Type I Interferon Production and Inflammasome Activation

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Introduction and Project Objectives: Why human infection with avian influenza A (H7N9) virus results in high pathogenicity remains elusive. As a critical pathogenicity factor, PB1-F2 protein is known to suppress early type I interferon response and inflammasome activation, but its mechanism of action is incompletely understood.

Methods: Gain-of-function and loss-of-function experiments have been performed to characterize the MAVS suppressing activity of H7N9 PB1-F2 protein in transfected and infected cells including macrophages. Importantly, a recombinant influenza A virus which does not express H7N9 PB1-F2 has been constructed and analyzed in detail. The molecular mechanism by which H7N9 suppresses the function of MAVS has been investigated.

Results: In this study we demonstrate potent suppression of antiviral signaling by PB1-F2 protein of H7N9 virus. PB1-F2 forms protein aggregates on mitochondria and prevents MAVS from K63-linked polyubiquitination and aggregation. Unaggregated MAVS that accumulates on fragmented mitochondria is less stable and more susceptible to proteasomal and lysosomal degradation. This results in inhibition of TRIM31-MAVS and MAVS-NLRP3 interaction in infected cells including human monocyte-derived macrophages. These properties are subtype-specific and not seen in PB1-F2 of WSN virus. A recombinant virus deficient of PB1-F2 of H7N9 induces more interferon β and interleukin 1β in infected cells.

Conclusion: Our study documents an H7N9-specific mechanism for degradation of MAVS, suppression of interferon response and suppression of NLRP3 inflammasome activation by PB1-F2 of H7N9 virus. Our findings have implications in prevention and intervention of H7N9 infection.

Project No.: 15140662

ID-12-28
Unveiling the Characteristics of Emerging Staphylococcus Lugdunensis Sequence Type 3 Clone by Genomic Analysis

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Introduction: Antimicrobial resistance is emerging in Staphylococcus lugdunensis and linked to a clonal cluster (CC) 3 lineage.

Project Objectives: To resolve and characterize antimicrobial-resistant subclone(s) in S. lugdunensis by whole genome sequencing and to identify the mobile genetic elements profiles and repertoire of resistance and virulence determinants in the antimicrobial-resistant subclones.

Methods: Sixty CC3 and 65 non-CC3 isolates were sequenced. The isolates were sampled from previously published collections and clinical isolate archives, including isolates from six different hospitals, clinical and carriage isolate sources, community-associated and healthcare-associated sources and different time periods (1998-2002, 2008-2012, 2013-2017). The genomic data were analyzed by previously published bioinformatics methods and analyzed against available epidemiological data.

Results: In the 125 isolates, CRISPR (including 33 type II and 24 type IIIA) was detected in 57 isolates. CRISPR was deleted in 100% and 12% of the CC3 and non-CC3 isolates. Univariate analysis revealed that CRISPR deletion was positively associated with CC3 lineage, number of virulence factors and resistance genes (blaZ, mecA, tetK, aacA-aphD and ermC). However, only

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CC3 lineage was significantly associated with CRISPR deletion in the multivariate analysis. Mosaic plasmids, mainly in CC3 isolates were found to harbor multiple resistance genes. Novel SCCmec V subtypes with mosaic modules in J1 region were harbored by the methicillin-resistant strains which were mostly of CC3 lineage. In the non-CC3 isolates, novel putative anti-plasmid spacers were identified with BLAST hits to over 400 staphylococcal plasmids.

Conclusion: This study documented the genomic profiles of a multidrug-resistant CC3 lineage by whole genome sequencing.

Project No.: 15140862

ID-13-53

Augmented Surveillance and Infection Control Measures for Multiple Drug Resistant Bacteria in Hospitals and Elderly Homes

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Introduction and Project Objectives: Multiple drug resistant organisms (MDROs) pose an increasingly threat to our hospitals and elderly homes. We implemented active surveillance and promoted innovative infection control measure of directly-observed hand hygiene (DOHH) to tackle the emerging MDROs.

Methods: In Queen Mary Hospital, patients were prospectively screened for MDROs, including carbapenemase-producing Enterobacteriaceae (CPE), carbapenem-resistant or multiple-drug-resistant Acinetobacter baumannii (CRAB or MRAB), and vancomycin-resistant enterococci (VRE) in the active surveillance program (admission screening, opportunistic screening, safety net screening, and contact tracing screening during hospitalization). In the elderly homes, research nurses were recruited for collection of clinical and environmental samples. DOHH, delivery of alcohol-based hand rub to all conscious persons before meal and medication, was promoted in both hospitals and elderly homes.

Results: From 1 July 2011 to 30 June 2019, 199,192 fecal specimens from 77,194 patients were screened for CPE in Queen Mary Hospital. Although the incidence of CPE per 1000 patient admission significantly increased from 0.01 (2012) to 1.9 (2018) ($p<0.01$), the incidence of nosocomial CPE per 1000 CPE colonization day paradoxically decreased from 22.34 (2014) to 10.65 (2018) ($p=0.0094$) due to the implementation of DOHH-based infection control measure. With the practice of DOHH, the incidence of MRAB bacteremia reduced from its peak, 1.86 (14 cases) per 100,000 patient-days in 2013 to 0.77 (one case) in the first 6 months of 2014 ($p < 0.001$). Territory-wide implementation of DOHH reverted the rising VRE incidence of +16.5% per month ($p<0.001$) to a reduction of -9.8% per month ($p<0.001$), while the outbreak rate reverted from an increasing trend of +10.5% per month ($p<0.001$) to a decreasing trend of -13.3% per month ($p<0.001$) between January 2011 and October 2015. In the audit of DOHH, the compliance was 97.2% (428/440 episodes), which was significantly higher than patients' self-initiated hand hygiene (37.5%, 218/582 episodes, $p<0.001$).

Of 28 elderly homes, 1408 residents were screened between 1 July and 31 August 2015. CRAB, MRSA, CPE, VRE colonization was identified in 92 (6.5%), 454 (32.2%), 1 (0.07%), and 0 respectively. With the implementation of DOHH in elderly homes, environmental specimens revealed a significant reduction in MRSA (79/600, 13.2% vs 197/600, 32.8%, $p<0.001$) and CRAB (56/600, 9.3% vs 94/600, 15.7%, $p=0.001$) collected from July to August 2017.

Conclusion: An innovative DOHH-based infection control measure should be further promoted to tackle the emerging MDROs in both hospitals and elderly homes in Hong Kong.

Project No.: HKM-15-M12

ID-14-61

A Novel Anti-microbial Crystal for the Treatment of Helicobacter Pylori Infection

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Introduction and Project Objectives: Helicobacter pylori (H.pylori) is a gram-negative bacterium which colonizes the gastric mucosa of almost half of the world's population. Current treatments for H.pylori infection are based on a combination therapy consisting of a proton-pump inhibitor (PPI), H_2 antihistamine, bismuth, and several antibiotics. However, drug resistance poses a major threat to the continued efficacy of these antimicrobials, resulting in increasingly poor clinical outcomes. One avenue to overcome this challenge is the use of antimicrobial peptides (AMPs), which have shown to possess broad antimicrobial spectrum, including bacteria, fungi, parasite and enveloped viruses. However, one major obstacle in the application and delivery of AMPs is their sensitivity to proteolytic degradation, especially when targeting H.pylori due to the acidic and proteolytic environment in the stomach. Our laboratory has developed a novel delivery system that can potentially overcome this limitation. The delivery platform is based on sub-micrometer-sized Cry protein crystals that naturally form within the bacterium Bacillus thuringiensis (Bt). Previous studies have shown that Cry could be fused to different proteins and the resultant Cry-fusion proteins still

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formed crystals in the Bt cells without apparent loss of function. Notably, the Cry crystal framework appeared to protect the encapsulated protein cargo from proteases, thereby prolonging its lifetime in vitro and in vivo. We thus hypothesized that the Cry delivery platform could be utilized to enhance the anti-H.pylori activity of AMPs.

Methods: Different AMPs and three 7-mer peptides reported to specifically bind to H.pylori were screened. A metal ion-inducible autocleavage (MIIA) domain was mutated for controlled release of the AMP from the fusion crystal. The aforementioned elements were incorporated into the final expression construct for the production of Cry fusion crystals in Bt. The antimicrobial efficacy of the resultant fusion crystals was investigated both in vitro and in vivo.

Results: A synergistic combination of AMPs and a 7-mer peptide (P17) exhibiting the highest specific binding towards H.pylori were identified. The Cry-MIIA-AMP-P17 fusion crystals were successfully produced. In vitro antimicrobial assays indicated that these fusion crystals exhibited enhanced antimicrobial activity compared to the free AMP. H.pylori-infected mice orally treated with the fusion crystals have a significantly reduced H.pylori burden in their stomach compared to no treatment control.

Conclusion: Cry-MIIA-AMP-P17 fusion crystals were effective in inhibiting H.pylori growth in vivo. The Cry platform could potentially be used in the delivery of other AMPs for the treatment of other gastric diseases.

Project No.: 15140252

ID-15-113
Outcomes of Carbapenem-Resistant Enterobacteriaceae Infections in Hong Kong

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Introduction and Project Objectives: There is a paucity of data evaluating whether carbapenemase production is associated with worse clinical outcomes among patients with carbapenem-resistant Enterobacterales (CRE) infections. This study aimed to determine the outcomes of patients hospitalized with clinical infections caused by CRE

Methods: We performed a multi-centre retrospective observational study. Patients with carbapenemase producers were matched (by age, sex, pathogen and type of infection) for up to three controls with non-carbapenemase-producing CRE infections. We determined independent predictors of 30-days mortality in a multivariable logistic regression model.

Results: Forty-four patients with carbapenemase-producing CRE infections and 113 matched controls were included. Median age was 77 (IQR 63-86) years, 57% were male, 24% were nursing home residents, and most patients had urinary tract (48%) or respiratory tract infections (29%). Among carbapenemase producers, 26 (59%) were NDM, while 14 (35%) were KPC. Carbapenemase producers had a higher risk of being hospitalized outside Hong Kong
Thirty-day mortality did not differ between carbapenemase and non-carbapenemase producers (36% vs. 29%, p=0.385). On multivariable analysis, age, respiratory tract infection, primary bloodstream infection, and use of colistin as definitive treatment were independently associated with higher risk of 30-day mortality.

Conclusion: Carbapenemase and non-carbapenemase-producing CRE infections had similarly high 30-day mortality risk.

Project No.: CU-18-C23

ID-16-217
Investigation of the Transmission Risk of Methicillin-Resistant Staphylococcus Aureus (MRSA) in Residential Care Home for Elderly (RCHE) in Hong Kong

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Introduction and Project Objectives: Residential Care Homes for Elderly (RCHEs) are important reservoirs for Methicillin-Resistant Staphylococcus aureus (MRSA). Compared to hospitals, little is known about the MRSA epidemiology in RCHEs. Therefore, this project aims to identify the RCHE facility, characteristics of RCHE residents and infection control practice associated with MRSA infection/colonization and persistent colonization.

Methods: We applied a multi-level random-effects model, accounting for clustering of residents in RCHEs, to a previous

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dataset. It was about a longitudinal study of two rounds, which were 2.7-13.7 months apart, screening residents from study RCHEs in Hong Kong for MRSA in 2011-2012. Using the status of nasal colonization as the response variable, we consider variables of RCHE facility, residents' characteristics and infection control practice as possible covariates of the proposed statistical models. A statistical significance of 0.05 was specified.

Results: Data of 2278 residents from 32 RCHEs (Round 1) were analyzed. The study residents was on average 82.5 years, and the average length of stay in RCHEs was 3.6 years. Majority of residents had Charlson Index>1 (83%), and Barthel score ≤80 (68.4%). Most RCHEs (84.4%) had medium facility size or above (≥64 beds). Proportion of residents with urinary catheter (range: 0-13.9%) and that with nasogastric tube (range: 0-21.7%) varied by RCHEs. The rate of nasal colonization was 17.8%, and differed by RCHEs (range:4.0-31.1%). On the resident-level, MRSA colonization was associated with being male (adjusted OR[aOR]:1.38; 95% CI:1.09,1.74), Charlson Index (aOR:1.21-2.36; p<0.05), Barthel score (aOR:0.99; 95% CI: 0.98,0.99), use of medical device (aOR:1.79; 95% CI:1.33,2.41), and presence of skin conditions (aOR:2.44; 95% CI:1.39,4.26). On the RCHE-level, MRSA level appeared to be associated with the proportion of residents using medical device (p<0.05).There were 1832 residents who joined Round 2, and 6% (110/1832) of them were colonized in both rounds (denoted as persistent colonization). Except for gender, other variables associated with MRSA colonization in Round 1 remained significantly associated with persistent colonization.

Conclusion: The health status predominantly determined the MRSA colonization status. On the RCHE-level, the prevalence of MRSA colonization in a RCHE was associated with the use of medical device. While the individual health status is expensive and time-consuming to assess, the RCHE-level figures and data are handy to retrieve. Therefore, it will be useful to have RCHEs to routinely report RCHE-level health-related figures in order to grasp a macro-picture of the MRSA endemicity in community RCHEs.

Project No.: CU-17-C18

ID-17-51
Biological Crystal Subunit Vaccines for Mycobacterial Diseases

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Introduction and Project Objectives: This project focused on developing a TB vaccine by genetically fusing TB antigens and various inflammatory factors to crystal forming Cry proteins, producing these crystals in Bacillus thuringiensis, and delivering these Cry3Aa-TB antigen fusion crystals to mice. The objectives were to: (1) confirm the TB mouse protection studies of previous generation Cry3A-TB antigen constructs; (2) explore strategies to improve the protective immunity of Cry-TB antigen formulations against M. tuberculosis infection by altering the T-cell helper peptide used, and incorporating various TLR receptor binding ligands, and(3) test the optimized Cry-TB antigen formulation both alone and in prime boost with BCG to protect against M. tuberculosis infection.

Methods: Formulations consisting of crystals of Cry3A fused to the antigens ESAT6 and Ag85, an immune activating T-cell helper peptide, and a series of Toll like receptor sequences were prepared and their efficacy against TB was determined using mouse TB challenge experiments based on the level of infection in mice in the presence and absence of the vaccine formulation.

Results: Our results are summarized below.
1. We have confirmed that particles of Cry3AD1-Ag85-VSV-ESAT6-VSV provide modest protection against TB, albeit lower than BCG.
2. We show that replacing either VSV T-cell helper peptide in the original construct with a TT T-cell helper peptide does not provide increased protection against TB. Indeed, it appeared to primarily increase the toxicity of the vaccine.
3. We successfully fused 3 different TLR receptor-binding proteins to the C-terminus of Cry3AD1-Ag85-VSV-ESAT6-VSV. The results from these TB protection experiments for each construct were: a. Cry3AD1-Ag85-VSV-ESAT6-VSV-PorB showed no benefit. b. Cry3AD1-Ag85-VSV-ESAT6-VSV-FliC was ambiguous.c. Cry3AD1-Ag85-VSV-ESAT6-VSV-IC31, gave comparable to slightly better protection against TB than BCG in the lung and spleen.
4. Particles of both Cry3AD1-Ag85-VSV-ESAT6-VSV-FliC and Cry3AD1-Ag85-VSVESAT6-VSV-IC31 have also been used in prime-boost with BCG for TB protection. a. BCG + Cry3AD1-Ag85-VSV-ESAT6-VSV-FliC prime boost vaccination yielded improved TB protection over BCG alone in the spleen. b. BCG + Cry3AD1-Ag85-VSV-ESAT6-VSV-IC31 prime boost vaccination resulted in improved TB protection of the lung and spleen against TB infection when compared to BCG alone.

Conclusion: Cry3AD1-Ag85-VSV-ESAT6-VSV-IC31 was the most promising recombinantvsubunit TB vaccine construct identified in our study.

Project No.: 14130052

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ID-18-64

Broad and Effective Protection against Staphylococcus Aureus is Elicited by a Multi-Valent Vaccine Formulated with Novel Antigens

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Introduction and Project Objectives: With the emergence of various Methicillin-resistant Staphylococcus aureus (MRSA) isolates, Staphylococcus aureus infection is causing increased morbidity and mortality in hospitals. The demand for a prophylactic vaccine against MRSA has motivated numerous dedicated research groups to design and develop such a vaccine.

Methods: In this study, we have developed a multi-valent vaccine Sta-V5 composed of five conserved antigens involved in three important virulence mechanisms. In particular, PmtA and PmtC have made their debut as novel vaccine components.

Results and Conclusion: This prototype vaccine conferred exceptional protection against multiple epidemiologically relevant S. aureus isolates in five different mouse models. The vaccine not only elicits functional antibodies that mediate opsonophagocytic killing of S. aureus but also mounts robust antigen-specific T-cell responses.

Project No.: HKM-15-M09

ID-19-65

Virus-like particle (VLP)-based Mucosal Vaccine for Inducing Cross-serotype Immunity against Streptococcus Pneumoniae Infection

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Introduction and Project Objectives: Streptococcus pneumoniae (S. pneumonia) is a common pathogen in hospitals and in the community. In recent years, due to the emergence of multiple drug-resistant strains, the development of immunotherapy against S. pneumonia, whether active or passive, has resurgence.

Methods: Based on the conservative nature and surface localization of antigens in different serotypes, 67 unique potential epitopes were identified from 15 cell wall proteins from the S. pneumonia Genome Database (SPGDB). To enhance the immune response, VLP was choose as carrier for the vaccine candidates. We then chose the flexible and efficient SpyCatcher-SpyTag System to connect the VLP with antigen proteins.

Results: We successfully constructed fusion expression vectors of 9 proteins and SpyTag respectively. Soluble expression of 8 proteins were obtained for subsequent vaccine testing. Meanwhile, hepatitis B core (HBc) VLP with SpyCatcher fusion was successfully expressed and purified and confirmed by SDS-PAGE, Western blot, and transmission electron microscope (TEM). In the animal experiments, ELISA results showed that these 8 soluble proteins could induce significant specific antibody production. In lethal challenge experiment, immunization with Spr1875-R4 resulted in increased survival rate compared with control mice. Unfortunately, the mice immunized with LysM-R, LysM, SCP, Lys-O-I, Lys-OX, CWRP, CWAP did not shown any protection compared with the control mice. We also evaluated the efficacy of three potential antigens with VLP-Spy (VLP-Spr1875-R4, VLP-CWAP and VLP-LysO-X) in the pneumonia model. The survival rate of mice immunized with VLP-Spr1875-R4 (50%), VLP-Lys-O-X (40%) or VLP-Lys-CWAP (25%) was always significantly superior to that observed in mock.

Conclusion: From this result, we conclude that VLP can enhance the protection efficacy of these potential antigens.

Project No.: 16150422

ID-20-83

Economic Evaluation of the Introduction of Rotavirus Vaccine in Hong Kong

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Introduction and Project Objectives: Rotavirus is a common cause of severe gastroenteritis in young children in Hong Kong (HK) with a high economic burden. This study aimed to evaluate the cost-effectiveness of introducing rotavirus vaccination into the HK Government's Childhood Immunisation Programme (CIP) and to include the potential protective effect of the vaccine against seizures.

Methods: A decision-support model was customised to estimate the potential impact, cost-effectiveness and benefit-risk of rotavirus vaccination in children below 5 years over the period 2020–2029 in HK. Two doses of Rotarix® and three doses of RotaTeq® were each compared to no vaccination. Rotavirus treatment costs were calculated from a governmental health sector perspective (i.e., costs of public sector treatment) and an overall health sector perspective (both governmental and patient, i.e., costs of public sector treatment, private sector

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treatment, transport and diapers). We ran probabilistic and deterministic uncertainty analyses.

Results: Introduction of rotavirus vaccination in HK could prevent 49,000 (95% uncertainty interval: ~44,000–54,000) hospitalisations of rotavirus gastroenteritis and seizures and result in ~50 (95% uncertainty interval: ~25–85) intussusception hospitalisations, over the period 2020–2029 (a benefit-risk ratio of ~1000:1), compared to a scenario with no public or private sector vaccine use. The discounted vaccination cost would be US$51–57 million over the period 2020–2029 based on per-course prices of US$72 (Rotarix®) or US$78 (RotaTeq®), but this would be offset by discounted treatment cost savings of US$70 million (government) and US$127 million (governmental and patient health sector). There was a greater than 94% probability that the vaccine could be cost-saving irrespective of the vaccine product or perspective considered. All deterministic 'what-if' scenarios were cost-saving from an overall health sector perspective (governmental and patient).

Conclusion: Rotavirus vaccination is likely to be cost-saving and have a favourable benefit-risk profile in HK. Based on the assumptions made, our analysis supports its introduction into CIP.

Citation: Yeung KHT, Lin SL, Clark A, McGhee SM, Janusz CB, Atherly D, Chan KC, Nelson EAS. Economic evaluation of the introduction of rotavirus vaccine in Hong Kong. Vaccine 2021;39:45–58. https://doi.org/10.1016/j.vaccine.2020.10.052

Project No.: 16151032

ID-21-84
Increasing Influenza Vaccine Uptake in Children: A Randomised Controlled Trial

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Introduction and Project Objectives: Influenza vaccine is not included in the Hong Kong Government's universal Childhood Immunisation Programme but eligible children can receive subsidised vaccine through the private sector using the Vaccination Subsidy Scheme (VSS). This study examined whether a simple intervention package can increase influenza vaccine uptake in Hong Kong children.

Methods: Two study samples were enrolled: families of children who had participated in a previous knowledge, attitudes and practices study; and mother-infant pairs recruited from postnatal wards. Control groups received publicly available leaflets about VSS. Intervention groups additionally received: (1) a concise information sheet about influenza and its vaccine; (2) semi-completed forms to utilise the subsidy; (3) contacts of VSS clinics that did not charge above the subsidy; and (4) text message reminders for vaccination. Enrolled mothers were contacted when children were approximately 1 and 2 years old to determine influenza vaccination status of the families and their plan to vaccinate their children. Mothers' attitudes towards influenza vaccine were assessed at enrolment and at the end of the study.

Results: A total of 833 eligible mother-infant pairs were enrolled from the two samples. The intervention package improved influenza vaccine uptake by 22% at one year and 25% at two years of age. Maternal influenza vaccine uptake in intervention group was higher during this two-year period in those who had never been previously vaccinated. Mothers' self-efficacy regarding the use of influenza vaccine in her child, i.e., belief and confidence in her own ability to make a good decision, was also improved with the intervention.

Conclusion: A four-component intervention package could improve influenza vaccine uptake in Hong Kong children and their mothers during the first two years of life and depending on vaccine effectiveness could potentially reduce influenza-associated hospital admissions in children below 2 years old by 13–24%.

Citation: Yeung KHT, Tarrant M, Chan KCC, Tam WH, Nelson EAS. Increasing influenza vaccine uptake in children: A randomised controlled trial. Vaccine 2018;36(37):5524-5535. https://doi.org/10.1016/j.vaccine.2018.07.066

Project No.: 14131452

ID-22-109
Determinants of Seasonal Influenza Vaccination and Preferences for Future Vaccination Programmes among Hospital-based Healthcare Workers in Hong Kong

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Introduction and Project Objectives: Although annual seasonal influenza vaccination is recommended for healthcare personnel

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(HCPs), their vaccination uptake has been suboptimal. This study examined the psychosocial determinants of influenza vaccination among HCPs in Hong Kong using a longitudinal study design based on behavioral change theories.

Methods: Participants were invited to complete a baseline survey before the 2017/18 influenza vaccination campaign to measure their baseline perceptions and vaccination intention, and followed up for 9 months to measure actual vaccination uptake. The survey used a theoretical framework combining the Health Belief Model and Theory of Planned Behaviour with extended psychosocial factors for predicting HCPs' vaccination uptake. Structural equation modelling was used to test the theoretical model and estimate path coefficients (β) to infer associations of psychosocial factors with HCPs' influenza vaccination uptake.

Results: Of the 845 participants who completed follow-up, 43.0% indicated intending to take vaccination and 30.8% reported actual receipt of the vaccination. The structural equation modeling analysis showed that positive attitude towards influenza vaccination (β = 0.69), greater perceived susceptibility to influenza virus infection (β = 0.34), greater anticipated regret for not vaccinating (β = 0.31), and more cues to action (β = 0.29) were significantly associated with higher vaccination intention which directly predicted greater vaccination uptake (β = 0.82). Norms were found to have an indirect association with vaccination intention through the mediation of attitude towards influenza vaccination (β = 0.63). Self-efficacy was significantly associated with actual receipt of influenza vaccination (β = 0.13) but not vaccination intention. The structural equation model explained 84.7% and 69.6% of the variance, respectively, in HCPs' intention to receive and actual receipt of influenza vaccination.

Conclusion: Attitude towards influenza vaccination was the strongest predictor of HCPs' intention and actual receipt of influenza vaccination. Social norm approach may be an intervention strategy to shape HCPs' attitude towards influenza vaccination and their subsequent decision-making for influenza vaccination.

Project No.: 16150852

ID-23-116
Intra-season Waning of Influenza Vaccination Effectiveness in Children

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Introduction and Project Objectives: The protection conferred by influenza vaccination is generally thought to last less than a year, necessitating annual revaccination. However, the speed with which influenza vaccine effectiveness might decline during a year is unknown. We assessed how influenza vaccine effectiveness (VE) changes by time intervals between vaccination and admission to hospital in Hong Kong.

Methods: We analysed VE in children (aged 6 months to 17 years) who were admitted to hospital in Hong Kong in 2012-17. We included those who were admitted to general wards in four public hospitals in Hong Kong with a fever (≥38°C) and any respiratory symptom. We used direct immunofluorescence assay and reverse transcription PCR to detect influenza virus infection, and recorded children's influenza immunisation history. We compared characteristics of positive cases and negative controls and examined how VE changed by time.

Results: Between Sept 1, 2012, and Aug 31, 2017, we enrolled 15, 695 children hospitalised for respiratory infections, including 2500 (15.9%) who tested positive for influenza A or B and 13 195 (84.1%) who tested negative. 159 (6.4%) influenza-positive cases and 1445 (11.0%) influenza-negative cases had been vaccinated. Influenza-related admissions to hospital occurred year-round, with peaks in January through March in most years and a large summer peak in 2016; pooled VE for children of all ages was 79% (95% CI 42-92) for September to December, 67% (57-74) for January to April, and 43% (25-57) for May to August. VE against influenza A or B was estimated as 79% (95% CI 64-88) within 0·5-2 months of vaccination, 60% (46-71) within >2-4 months, 57% (39-70) within >4-6 months, and 45% (22-61) within >6-9 months. In separate analyses by type and subtype, we estimated that VE declined by 2-5 percentage points per month.

Conclusion: Influenza VE decreased during the 9 months after vaccination in children in Hong Kong. Our findings confirmed the importance of annual vaccination in children. Influenza vaccines that provide broader and longer-lasting protection are needed to provide year-round protection in regions with irregular influenza seasonality or lengthy periods of influenza activity.

Project No.: HKS-18-E18

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ID-24-118

Influenza Vaccine Effectiveness against Hospitalization among Partially and Fully Vaccinated Children in Hong Kong, 2012/13 - 2019/20

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Introduction and Project Objectives: Influenza virus infections can cause hospitalizations in children, and annual vaccination of children can provide protection against influenza.

Methods: We analyzed a test-negative design study with data spanning from 2010/11 through 2019/20 to evaluate influenza vaccine effectiveness (VE) against influenza hospitalization in children by age group, influenza type/subtype and time period within each season. We enrolled children admitted to hospital with acute febrile respiratory illnesses. Nasopharyngeal aspirates were tested by culture and/or RT-PCR to determine influenza status, and vaccination status was obtained by interviewing parents or legal guardians and was verified where possible. VE was estimated by conditional logistic regression model adjusting for sex, age and age-squared, matching on week.

Results: Influenza seasons in Hong Kong are prolonged with influenza-associated hospitalizations occurring in almost every month of the year during the study period. Influenza vaccination was effective in preventing influenza-associated hospitalizations in children of all ages. Influenza VE was higher in younger children than in older children, and higher against hospitalization due to influenza A(H1N1)pdm09 than A(H3N2) and B.

Conclusion: The childhood influenza vaccination program in Hong Kong has prevented influenza-associated hospitalizations particularly in younger children. Our findings support the use of influenza vaccines in children as an effective approach to influenza control and prevention.

Project No.: HKS-19-E20

ID-25-126

Effectiveness and Parental Acceptability of Using Social-networking Intervention to Promote Childhood Seasonal Influenza Vaccination: a Randomized Control Trial

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Introduction and Project Objectives: The seasonal influenza vaccination (SIV) uptake rate among young children remained suboptimal despite with active government promotion effort. This study was to test the effectiveness of sending a vaccination reminder through WhatsApp discussion groups (social-networking intervention) for promoting parents to take their young child for SIV and whether including a time reminder about the remaining time of optimal vaccination timing (time constraint) into the vaccination reminder could modify the effect of the vaccination reminders.

Methods: Mothers who had at least one child aged between six months and six years were randomly allocated to the Control who received no vaccination reminders, or the social-networking intervention groups who received either vaccination reminders with or without a time constraint component (SNI/+TC and SNI/-TC, respectively). All participants first completed a baseline assessment and then the intervention groups received the respective reminders, each per week over eight weeks in Oct-Dec 2017. The social-networking intervention groups also participated in the discussion about influenza and SIV with the facilitation of a moderator during the intervention period. A follow-up assessment was conducted in April-May 2018.

Results: A total of 205, 80, and 80 of mothers were randomly allocated into the Control, SNI/+TC and SNI/-TC, respectively, based on a ratio of 5:2:2. The SIV uptake rates among the target children at the follow-up were 37.9%, 38.3% and 33.3% in the Control, SNI/+TC and SNI/-TC, respectively. There was no significant effect of the vaccination reminders and time constraint component on children's SIV uptake. The social-networking intervention significantly promoted mothers' perceived self-efficacy in taking children for SIV (OR=2.56, 95%CI: 1.33-4.93) compared with the control. Content analysis of the WhatsApp discussion revealed that of 434 relevant participants' posts, 52.1% were about sharing experience/views, 27.4% were about seeking information/opinions and 24.4% were about sharing knowledge/information. Around 44.7% of the experience/views shared by participants were negative including their concerns over vaccine safety/side effects and vaccine effectiveness, negative values of vaccination, and negative vaccination experience. Although participants mainly shared their negative experience/views at

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the beginning of group discussion, with the involvement of moderator throughout the discussion, the group discussion shifted to more positive experience/view sharing and more knowledge/information sharing.

Conclusion: Participants remained having various concerns over SIV. The active involvement of health professional in the online discussion is likely to shape a positive discussion about vaccination, which can be useful for combating vaccine hesitancy in the Information Age.

Project No.: 16150752

ID-26-181
Cost Effectiveness Analysis of a Hypothetical Bivalent Vaccine against Hand, Foot and Mouth Disease in China

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Introduction and Project Objectives: New monoclonal antibodies (mAbs) and vaccines against RSV with promising efficacy and protection duration are expected to be available in the near future. We evaluated the cost-effectiveness of the administration of maternal immunisation (MI), infant mAb (IA) and paediatric immunisation (PI) as well as their combinations in eight Chinese cities.

Methods: We used a static model to estimate the impact of these preventive interventions on reducing the burden of RSV-ALRI in twelve monthly birth cohorts from a societal perspective. In addition to year-round administration, we also considered seasonal administration of MI and IA (i.e., administered only to children born in selected months). The primary outcome was threshold strategy cost (TSC), defined as the maximum costs per child for a strategy to be cost-effective.

Results: With a willingness-to-pay threshold of one national GDP per capita per QALY gained for all the cities, TSC of year-round strategies was: (i) US$2.4 (95% CI: 1.9-3.4) to US$14.7 (11.6-21.4) for MI; (ii) US$19.9 (16.9-25.9) to US$144.2 (124.6-184.7) for IA; (iii) US$28.7 (22.0-42.0) to US$201.0 (156.5-298.6) for PI; (iv) US$31.1 (24.0-45.5) to US$220.7 (172.0-327.3) for maternal plus paediatric immunisation (MPI); and (v) US$41.3 (32.6-58.9) to US$306.2 (244.1-441.3) for infant mAb plus paediatric immunisation (AP). In all cities, the top ten seasonal strategies (ranked by TSC) protected infants from 5 or fewer monthly birth cohorts.

Conclusion: Administration of these interventions could be cost-effective if they are suitably priced. Suitably-timed seasonal administration could be more cost-effective than their year-round counterpart. Our results can inform the optimal strategy once these preventive interventions are commercially available.

Project No.: HKS-18-E19

ID-27-186
Cost-benefit and Cost-effectiveness of Routine Female Adolescent Nonavalent HPV Vaccination for Reducing Cervical Cancer Burden in Hong Kong

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Introduction and Project Objectives: Although routine vaccination of females before sexual debut against human papillomavirus (HPV) has been found to be cost-effective around the world, its cost-benefit has rarely been examined. One major obstacle is the lack of data on assortativity of sexual mixing. In this study, we evaluate both the cost-effectiveness and cost-benefit of routine female adolescent nonavalent HPV vaccination in Hong Kong to guide its policy on HPV vaccination. We also infer the sexual mixing parameters from HPV epidemiologic data.

Methods: We use an age-structured transmission model coupled with stochastic individual-based simulations to estimate the health and economic impact of routine nonavalent HPV vaccination for girls at age 12 on cervical cancer burden and consider vaccine uptake at 25%, 50%, and 75% with at least 20 years of vaccine protection. Bayesian inference was employed to parameterise the model using local data on HPV prevalence and cervical cancer incidence. We use the human capital approach in the cost-benefit analysis (CBA) and GDP per capita as the indicative willingness-to-pay threshold in the cost-effectiveness analysis (CEA). Finally, we estimate the threshold vaccine cost (TVC), which is the maximum cost for fully vaccinating one girl at which routine female adolescent nonavalent HPV vaccination is cost-beneficial or cost-effective.

Results: As vaccine uptake increased, TVC decreased (i.e., economically more stringent) in the CBA but increased in the CEA. When vaccine uptake was 75% and the vaccine provided only 20 years of protection, the TVC was US$444 ($373–506) and $689 ($646–734) in the CBA and CEA, respectively, increasing by approximately 2–4% if vaccine protection was assumed lifelong. TVC is likely to be far higher when non-cervical diseases are included. The inferred sexual mixing parameters suggest that sexual mixing in Hong Kong is highly assortative by both age and sexual activity level.

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Conclusion: Routine HPV vaccination of 12-year-old females is highly likely to be cost-beneficial and cost-effective in Hong Kong. Inference of sexual mixing parameters from epidemiologic data of prevalent sexually transmitted diseases (i.e., HPV, chlamydia, etc.) is a potentially fruitful but largely untapped methodology for understanding sexual behaviours in the population.

Project No.: HKS-17-E12

ID-28-232

Immunogenicity of Intradermal Quadrivalent Influenza and 13-valent Pneumococcal Conjugated Vaccination with Topical Imiquimod in at Risk Individuals

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Introduction and Project Objectives: Both influenza and Streptococcus pneumoniae infection can cause life-threatening pneumonia and complications. Application of topical TLR7 pretreatment before intradermal (ID) influenza vaccination has demonstrated a better immunogenicity and clinical protection.

Method: We conducted three prospective double-blind randomised controlled trial among the elderly and health care workers (HCWs), between 1 January 2015 and 31 December 2019. In study 1, elderly subjects ≥ 65 years in the Queen Mary Hospital were enrolled. In study 2, HCWs <60 years working in the Queen Mary Hospital were enrolled. In both studies, subjects were randomized into 3 groups (1:1:1). Group 1 received ID quadrivalent influenza with topical imiquimod (ID QIV + IMQ). Group 2 received ID QIV with topical placebo aqueous cream (ID QIV + AQ) and Group 3 received IM QIV with topical AQ (IM QIV + IMQ). In study 3, elderly subjects were randomized into 3 groups (1:1:1). Group 1 received ID 13-valent pneumococcal conjugated vaccine with topical imiquimod (ID PCV + IMQ). Group 2 received ID PCV with topical AQ (ID PCV + AQ) and Group 3 received IM PCV with topical AQ (IM PCV + IMQ). The primary endpoints for study 1 and 2, were the seroconversion rate at the end of the third year. The primary endpoint for study 3 was the proportion of strong responders at 6 months, as defined by ≥4-fold increase of pre and post-vaccination mean pneumococcal IgG ELISA antibody.

Results: Between 1 January 2015 and 31 December 2019, 286 elderly subjects were recruited for study1 and 280 HCWs were recruited for study 2. In both studies, the primary end-point, the seroconversion rate at 36 months for all 4 antigens were significantly higher in the ID QIV + IMQ groups when compared to the ID QIV + AQ and the IM QIV + AQ control groups. For study 3, 300 elderly subjects were recruited. The primary end-point, the proportion of strong responders at 6 months were significantly higher for serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in the ID PCV + IMQ groups when compared to the ID PCV + AQ and the IM PCV + AQ control groups. Adverse events were infrequent and self-limiting.

Conclusion: Topical pretreatment with TLR7 agonist imiquimod before ID QIV or ID PCV enhanced vaccine immunogenicity in the elderly subjects and also HCWs. Consecutive annual ID QIV with imiquimod pretreatment was not associated with hyporesponsiveness.

Project No.: HKM-15-M08

ID-29-29

Rapid Detection of cfiA metallo-β-lactamase-producing Bacteroides Fragilis by the Combination of MALDI-TOF MS and CarbaNP

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Introduction: Carbapenem resistance in Bacteroides fragilis is emerging and is mainly attributed to insertion sequence (IS)-mediated activation of the carbapenemase gene cfiA.

Project Objectives: To determine the prevalence of cfiA-positive B. fragilis among clinical isolates of B. fragilis group and to use MALDI-TOF-MS to distinguish cfiA-positive B. fragilis strains from cfiA-negative B. fragilis strains.

Methods: A collection of 424 B. fragilis isolates were included in this study. The isolates were recovered consecutively from clinical specimens submitted to two hospital-based, clinical microbiology laboratories (A and B) in Hong Kong during January-December 2015. ClinProTools software (V3.0 Bruker Daltonics) was used to develop a classification model by recognizing mass peaks that could differentiate B. fragilis cfiA-negative and cfiA-positive strains. The ability of the CarbaNP assay to detect IS-mediated activation of the cfiA gene was assessed and the results obtained by molecular analysis were used as reference methods.

Results: All 424 strains were confirmed as B. fragilis by species-specific PCR assays. Of the 424 B. fragilis strains, 81 (19.1%) were cfiA-positive. Prevalence of cfiA among isolates the two laboratories were similar, being 18.5% (49/265) for laboratory A and 20.1% (32/159) for laboratory B (P = 0.703). The support vector machine model generated by ClinProTools was found to be the most reliable algorithm for differentiation of cfiA-positive and cfiA-negative B. fragilis subgroups. Using the direct transfer method, all but one cfiA-negative isolates were correctly identified to the two subgroups by the model. The correct

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identification of the cfiA-negative isolate was obtained upon retesting by the extraction method. Of the 81 cfiA-positive isolates, PCR and sequencing showed that 30 had an IS element providing the promoter for activation of cfiA. CarbaNP test with reference to presence of IS element in cfiA upstream region had sensitivity, 100%; specificity, 80.4%; positive predictive value, 75.0% and negative predictive value, 100%.

Conclusion: The combination of MALDI-TOF MS and CarbaNP assay can be applied in diagnostic clinical laboratory for rapid identification of B. fragilis with IS-element activated cfiA gene.

Project No.: HKM-15-M10

ID-30-38
Persistence and Clearance of Oral Human Papillomavirus Infections: A Prospective Population-based Cohort Study

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Introduction and Project Objectives: This study aimed to evaluate the incidence of and factors associated with persistence and clearance of oral human papillomavirus (HPV) infections.

Method: A prospective cohort study invited 458 subjects (231 HPV-positive and 227 HPV-negative at baseline) to attend follow-ups at 12 months. Those 231 HPV-positive subjects and 10 new infections were invited to reassessment at 24 months. We used next-gen sequencing for detection and genotyping of HPV.

Results: α-HPV infections showed higher persistence rates than β/γ-HPV (22.7% vs 9.2% at 12 months [P < .05], 10.6% vs 6.8% at 24 months [P = .30]). Clearance rates of α-HPV were lower than β/γ-HPV at 12 months (31.8% vs 45.1%; P = .05) and higher at 24 months (7.6% vs 4.8%; P = .36). Persistence of β/γ-HPV was positively associated with males (crude odds ratio [COR] = 3.8, 95% confidence interval [CI] = 1.3-11.2), elderly (51-65 vs 16-50 years; COR = 5.1, 95% CI = 1.2-22.3), and smoking (COR = 4.3, 95% CI = 1.9-9.6). Drinking (COR = 0.5, 95% CI = 0.3-0.9), handwashing less than 90% of times before meals (COR = 0.6, 95% CI = 0.3-0.9), and using public bath more than once per month (COR = 0.5, 95% CI = 0.2-0.9) were risk factors hindering β/γ-HPV clearance.

Conclusion: This study identified factors associated with persistence and clearance of oral HPV infections among Chinese. Studies on other ethnogeographic groups may further inform prevention strategies of oral HPV infection and immunization programmes.

Project No.: CU-17-C20

ID-31-46
Factors Associated with TB Reactivation among HIV Patients on Antiretroviral Therapy

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Introduction and Project Objectives: TB reactivation rate among immunocompromised patients, including HIV-infected individuals, is higher than the general population. We aimed to determine the factors associated with TB reactivation among HIV patients in Hong Kong.

Methods: Baseline socio-demographics, longitudinal clinical and laboratory data of HIV patients attending a major HIV specialist clinic in Hong Kong were collected retrospectively. Patients who were diagnosed with HIV between 2002 and 2013, and were tuberculin skin test (TST) positive were included in the analysis. We defined TB reactivation as the diagnosis of TB at least one year after the first TST positive result. To examine the association of CD4 and CD4/CD8 ratio with TB reactivation, univariable and multivariable cox regression models adjusted by history of latent TB infection (LTBI) treatment were performed. Sub-analysis was performed after excluding TB reactivation before antiretroviral therapy (ART) initiation and ART naïve patients to examine the factors associated with TB reactivation in patients on ART.

Results: By 2017, 508 patients with 3203 person-years (PY) of follow-ups were selected for analysis. TB reactivation incidence from the last negative TST time-point was 4.68 cases per 1000 PY (95%C.I.=2.72-7.55) in general, and 2.93 cases per 1000 PY (95% C.I.= 1.43-5.38) after ART initiation. Low CD4 count and concurrent CD4≤200/μL and CD4/CD8 ratio≤0.5 were significantly associated with TB reactivation in both univariable and multivariable cox regression model. In the period between months 6-24 following ART initiation, CD4 ≤200/μL (aHR=5.01, p<0.05) and concurrent low CD4 and CD4/CD8 ratio (aHR=5.01, p<0.05) were significant factors. At the time of the first TST positive result, CD4 count (aHR=0.997, p<0.05), CD4/CD8 ratio (aHR=0.08, p<0.05) and ART status (aHR=0.18, p<0.05) were significant factors for TB reactivation. In sub-analysis, immunological markers remained significantly associated with TB reactivation in months 6-24 from ART and at the first positive TST.

Conclusion: TB reactivation incidence after ART initiation was lower than that for the overall HIV positive population. HIV patients with LTBI and who experienced very low CD4

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level were at higher risk of TB reactivation, and should receive screening for TB disease for timely diagnosis and treatment, and immediate ART initiation for immune recovery.

Project No.: CU-18-A17

ID-32-107

Cellular Mechanism of Reactivation of Lytic Cycle of Epstein – Barr Virus (EBV) by a Novel Compound, C7, in EBV-associated Epithelial Malignancies

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Introduction and Project Objectives: Pharmaceutical reactivation of Epstein–Barr virus (EBV) lytic cycle represents a potential therapeutic strategy against EBV-associated epithelial malignancies such as gastric carcinoma and nasopharyngeal carcinoma (NPC). A novel lytic-inducing compound, C7, which exhibits structural similarity to Dp44mT, a known intracellular iron chelator, was found to reactivate EBV lytic cycle in GC and NPC. This study aims to 1) delineate the mode of action of C7 and clinically available iron chelators in EBV lytic reactivation, and 2) to determine the cytopathic effect and synergism on EBV lytic reactivation by combining C7 with ganciclovir or other lytic inducers that possess distinct mechanism in EBV lytic reactivation such as histone deacetylase inhibitor (HDACi).

Methods and Results: Previous study showed the activation of the hypoxia signaling pathway upon C7/iron chelator treatment. We verified that the hypoxia signaling pathway was not the only pathway associated with EBV lytic reactivation induced by C7/iron chelators. Treatment with either the ERK1/2 or autophagy inhibitor significantly abolished C7-mediated EBV lytic reactivation but not in those induced by HDACi, suggesting the involvement of the ERK1/2-autophagy pathway in EBV lytic cycle reactivated only by C7/iron chelators. In addition, these two subclasses of lytic inducers imposed different cellular effects and led to distinct stages of cell cycle arrest in NPC cells. Furthermore, only the inhibition of autophagy initiation was required for EBV lytic reactivation. siRNA knockdown of various autophagic proteins of the early autophagy stages such as beclin-1, ATG3, ATG5, ATG7, LC3B, ATG10, AT12 and Rab9, revealed only the knockdown of ATG5 diminished EBV lytic reactivation, indicating a specific role of ATG5 in C7-reactivated EBV lytic cycle.

Conclusion: This study has introduced C7 and clinically available iron chelators as a new class of compounds for EBV lytic reactivation. They reactivate the viral lytic cycle through intracellular iron chelation and the activation of the ERK1/2-autophagy axis, which represent novel and distinct mechanism from that of the conventional lytic inducers. This supports the introduction of C7/iron chelators to the conventional drug reservoir to enhance the efficacy and explore possible drug combination in the lytic induction therapy against EBV-positive malignancies.

Project No.: 16150472

ID-33-114

Host Inflammatory Responses in Adults with Severe RSV Lower Respiratory Tract Infections

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Introduction and Project Objectives: Respiratory syncytial virus (RSV) is known to be an important cause of lower respiratory tract infection in infants and young children, leading to hospitalizations and death. Its impact in adults however, has only been appreciated in recent years. We aim to study the viral kinetics and host inflammatory response of RSV infection in older adults, and their correlation with disease severity.

Methods: We performed a prospective observational study in adults with RSV infection. We serially collected nasal-throat swabs for quantification of RSV-A and RSV-B viral load, and peripheral blood samples for measurement of cytokine/chemokine concentrations. The study endpoints were (i) requiring supplemental oxygen therapy, and (ii) non-invasive ventilation, intensive care, or died within 30 days of admission. We performed multivariable logistic regression models to identify independent variables for severe disease.

Results: We enrolled 71 hospitalized patients and 10 outpatients treated for RSV infection (median age 75 years, 51% male, and 74% with comorbidities). Among hospitalized patients, 61% required supplemental oxygen therapy, and 18% had severe disease requiring non-invasive ventilation or intensive care, or died within 30 days. Inflammatory cytokine/chemokines IL-6, CXCL8/IL-8, CXCL9/MIG and CXCL10/IP-10 increased significantly during the acute phase of illness. IL-6 concentration was independently associated with severe disease after adjusting for confounding factors. RSV viral load was not associated with disease severity throughout the course of illness.

Conclusion: Host inflammatory response is a major marker of severe disease in older adults with RSV infection.

Project No.: CU-16-A2

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ID-34-158
Novel Human Neutralizing Antibodies against HIV/AIDS

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Introduction and Project Objectives: Due to natural transmission of diverse HIV-1 subtypes in Hong Kong, we aim to discover novel broadly neutralizing antibodies (bnAbs) against HIV/AIDS in humans.

Methods: We have generated a panel of 40 Tier-2 HIV-1 pseudoviruses representing major subtypes throughout China to characterize human bnAbs. The potency and synergy of bnAbs were then tested against this panel of HIV-1 pseudotypes and some primary isolates in vitro and against live virus challenge in humanized mice.

Results: We have also established a diverse panel of 120 international HIV-1 pseudoviruses covering all major subtypes in the world. Using the pseudovirus assay, we screened 101 patient specimens out of 250 collected with focus on the identification of individuals with potent and broad anti-HIV-1 neutralizing antibodies. Meantime, we investigated the potency, synergy and breadth of an engineered bispecific broadly neutralizing antibody (bs-bnAb) as an innovative product for HIV-1 prophylactic and therapeutic interventions. We discovered that by preserving 2 single-chain variable fragment (scFv) binding domains of each parental bnAb, a single gene–encoded tandem bs-bnAb, BiIA-SG, displayed substantially improved breadth and potency. BiIA-SG neutralized the 40 and additional 84 collaborator's HIV-1– pseudotyped viruses tested, including global subtypes/recombinant forms, transmitted/founder viruses, variants not susceptible to parental bnAbs and to many other bnAbs with an average IC50 value of 0.073 μg/ml (range < 0.001–1.03 μg/ml). In humanized mice, an injection of BiIA-SG conferred sterile protection when administered prior to challenges with diverse live HIV-1 stains.

Conclusion: These results warrant the clinical development of BiIA-SG as a promising bs-bnAb–based biomedical intervention for the prevention and treatment of HIV-1 infection. Our outputs have served as one of the core technical platforms for one of the recent Innovation and Technology Commission funded HKU projects.

Project No.: 16150442

ID-35-159
Epidemiology of Human Papillomavirus (HPV) Infection among HPV-Vaccinated Young Adult Female in Hong Kong

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Introduction and Project Objectives: Human Papillomavirus (HPV) is a common viral infection with the extensive studies focused on exploring its prevalence and associated risk factors and health behaviour. HPV vaccine is one of the prevention strategies to prevent infection and reduce the risk of cervical cancer. However, study on the relationship between HPV prevalence, uptake rates of cervical cancer screening and other protective behaviour among HPV vaccinated women in Hong Kong is scanty. This study, therefore, not only to investigative the epidemiology of HPV infection among young adult women who have received HPV vaccination but also to explore the impact of introducing HPV DNA self-sampling on the uptake rate of cervical cancer screening in Hong Kong.

Methods: A mixed study design with a cross-sectional survey and laboratory HPV testing was adopted in which conducted in two phases accordingly. Young adult female aged ≥25 years who received HPV vaccine in the HPV Vaccination Campaign were recruited to have telephone interviews and collected their HPV self-sampling specimen if they agreed. Summary of participants' lifestyle behaviours and how past cervical cancer screening habit affected the current screening uptake using HPV self-sampling tool was reported. Prevalence and genotypes of HPV infection were also examined. Feedback on performing the HPV self-sampling test and future preference were recorded in the post-survey after the self-collected sampling procedure.

Results: A total of 651 respondents with a mean age of 30.4 (SD=1.8) were completed the telephone survey and 86 women who were successfully completed and returned the HPV self-sampling specimen for testing HPV infection in phase 2. The overall HPV infection was 1.2% (1/86) in which low-risk HPV (Lr-HPV 42) type was detected. Women who are elder, married and had sexual intercourse were more likely to have Pap smear screening before. The perception and acceptance of HPV self-sampling was very positive among the vaccinated young adult female and majority of them expressed that they would consider HPV self-sampling as a future preference of screening for cervical cancer prevention, especially to those who were under-screened.

Conclusion: This study provides a good insight to advance our knowledge on the evolution of HPV infection by evaluating the effectiveness of HPV vaccination in Hong Kong. The findings also provide a substantial information for policy formulation on cervical cancer prevention programme, especially the highly

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positive findings on acceptability and future preference of HPV self-sampling as an alternative cervical cancer screening in the health system in Hong Kong.

Project No.: CU-17-C19

ID-36-184

Comparative Benefit-cost Analyses of Health Interventions Using Human Papillomavirus Vaccination as a Case Study

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Introduction and Project Objectives: There is increasing interest in estimating the broader benefits of public health interventions beyond those captured in traditional cost-utility analyses. Cost-benefit analysis (CBA) in principle offers a way to capture such benefits, but a wide variety of methods have been used to monetise benefits in CBAs. This study aimed to understand the implications of different CBA approaches for capturing and monetising benefits and their potential impact on public health decision-making.

Methods: We conducted a CBA of human papillomavirus (HPV) vaccination in the United Kingdom using eight methods for monetising health and economic benefits, valuing productivity loss using either (1) the human capital or (2) the friction cost method, including the value of unpaid work in (3) human capital or (4) friction cost approaches, (5) adjusting for hard-to-fill vacancies in the labour market, (6) using the value of a statistical life, (7) monetising quality-adjusted life years and (8) including both productivity losses and monetised quality-adjusted life years. A previously described transmission dynamic model was used to project the impact of vaccination on cervical cancer outcomes. Probabilistic sensitivity analysis was conducted to capture uncertainty in epidemiologic and economic parameters.

Results: Total benefits of vaccination varied by more than 20-fold (£0.6–12.4 billion) across the approaches. The threshold vaccine cost (maximum vaccine cost at which HPV vaccination has a benefit-to-cost ratio above one) ranged from £69 (95% CI £56–£84) to £1417 (£1291–£1541).

Conclusion: Applying different approaches to monetise benefits in CBA can lead to widely varying outcomes on public health interventions such as vaccination. Use of CBA to inform priority setting in public health will require greater convergence around appropriate methodology to achieve consistency and comparability across different studies.

Project No.: HKS-17-E15

ID-37-205

The Clinical Severity Profile and Subclinical Infections of Enterovirus 71 in Children

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Introduction and Project Objectives: Hand-foot-and-mouth disease (HFMD) causes a substantial disease burden in Asian regions including Hong Kong, mainly in children below 5 years of age. Enterovirus 71 (EV-A71), coxsackievirus A16 (CV-A16) and the newly emerging coxsackievirus A6 (CV-A6) are the most common enterovirus serotypes causing HFMD in Hong Kong. However, EV-A71 is of particular interest as it is more likely to lead to severe outcomes including neurological complications. Only a small proportion of EV-A71 infections lead to severe disease. A larger proportion was mild or even subclinical cases. For EV-A71, the clinical severity pyramid has not been characterized. The proposed objective of this study is to characterize the risks of subclinical and clinical infections, and associated severe outcomes based on published evidence.

Methods: We obtained data on EV-A71 associated events and the prevalence of antibody titers against EV-A71 among healthy children aged 6-35 months from the published results of unvaccinated children reported by phase III clinical trials of EV71 vaccine candidates. Titer distribution and geometric mean titer (GMT) for unvaccinated children were also obtained from the trial reports. Case-severity risks of HFMD cases caused by EV-A71 were extracted from a large scale epidemiological study in China. Serological correlates of protection against EV-A71 associated disease were also extracted from the literature. We applied a hierarchical Bayesian model, which synthesized published evidence to reconstruct the severity profile of EV-A71 infections, including medically attended symptomatic disease, hospitalization, severe complications and death.

Results: We estimated that on average, 15.1% of children were infected by EV-A71 in a year. Most EV-A71 infections were mild, with about 10% symptomatic and seeking medical attention and 2.2% hospitalized. The model also suggested that 70% of children had ≥4-fold rises in antibody titers after infection.

Conclusion: The hierarchical Bayesian model provided a unified framework to synthesize evidence from multiple sources. Our model provided good estimates, consistent with other published studies and supported by simulation studies. Aggregated data on the serological correlates of protection against infection and the immune response were used, which are routinely reported by vaccine clinical trials. The approach can be applied to other diseases, allowing characterization of the severity profile which is important to the understanding of disease burden at the population level, transmission dynamics and guiding public health measures.

Project No.: HKS-18-E16

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ID-38-214

Comparative Analysis of Host Transcriptomic and Lipidomic Profile Induction by Human Enterovirus 71 and Human Coxsackievirus A16: Implications on Pathogenesis, Diagnosis, and Treatment

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Introduction and Project Objectives: Human enterovirus A71 (HEV-71) and coxsackievirus A16 (CV-A16) are major causes of hand, foot, and mouth disease (HFMD) which may be complicated by respiratory, neurological, cardiac, and systemic complications. This project aims to identify host factors which are biologically relevant in enterovirus infections through transcriptomics and lipidomics approaches, and exploit these host factors as novel antiviral strategies.

Methods: Transcriptomics and lipidomics analyses of enterovirus-infected human rhabdomyosarcoma cells were performed with RNA-Seq and ultra-high performance liquid chromatography-electrospray ionization-quadrupole-time of flight-mass spectrometry (UPLC-ESI-Q-TOF-MS), respectively. Integrative transcriptomic-lipidomic analysis and lipid modulator compound library screening were performed to identify host-targeting antivirals with broad-spectrum activities against enteroviruses and other human-pathogenic viruses.

Results: (i) Transcriptomics analysis identified growth arrest and DNA damage-inducible protein (GADD34) as a novel host dependency factor that facilitates HEV-71 replication. HEV-71 infection induces up-regulation of GADD34 expression, which reduces eIF-2α phosphorylation and promotes viral replication. The selective GADD34 inhibitor Sephin1 significantly inhibits HEV-71 and other picornaviruses in-vitro, in human small intestinal organoids, and/or induced pluripotent stem cells-derived human neural progenitor cells. (ii) UPLC-ESI-Q-TOF-MS-based lipidomics profiling reveals significant perturbations of intracellular lipid homeostasis in enterovirus-infected cells, with 47 lipids in 11 lipid classes being significantly perturbed after HEV-71 or CV-A16 infection. Four polyunsaturated fatty acids (PUFAs), namely, arachidonic acid (AA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and eicosapentaenoic acid (EPA), were consistently upregulated upon HEV-71 and CV-A16 infection. Exogenously supplying AA, DHA, and EPA in cell cultures significantly reduced viral replication. (iii) Integrative transcriptomic-lipidomic analysis and lipid library screening identified AM580, a retinoid derivative and RAR-α agonist, to be highly potent in interrupting the life cycle of diverse viruses including HEV-71. Using click chemistry, the overexpressed sterol regulatory element binding protein (SREBP) was shown to interact with AM580, which accounted for its broad-spectrum antiviral activity. Mechanistic studies pinpointed multiple SREBP proteolytic processes and SREBP-regulated lipid biosynthesis pathways that are indispensable for virus replication.

Conclusion: Our project has identified novel host factors with important biological relevance in HEV-71, CV-A16, and other picornavirus infections, including GADD34, PUFAs, and SREBP, that may serve as druggable targets. The effects of Sephin1, PUFAs, and AM580 against HEV-71 and other picornavirus infections should be further evaluated in animal models and/or clinical trials.

Project No.: HKM-15-M04

ID-39-216

Roles of the Chromatin Architectural Protein CTCF in Hepatitis B Virus Transcription

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Introduction and Project Objectives: Hepatitis B virus (HBV) infection is highly endemic in Hong Kong. Over 25% of HBV carriers will ultimately develop life-threatening liver diseases such as hepatocellular carcinoma (HCC). Although anti-HBV therapy has improved remarkably in the past decade, it is still not curative mainly due to the pool of covalently closed circular DNA (cccDNA), which serves as the template for HBV transcription, a key step in HBV replication. Thus, a clear understanding of how HBV transcription is regulated by host cell factors may provide novel therapeutic targets for the design of anti-HBV drugs.

Methods: We first employed both gain-of-function and loss-of-function approaches to define the roles of CTCF in HBV transcription using both transfection and acute infection model systems. The binding of CTCF to cccDNA and the location of CTCF binding sites were then determined using a combination of chromatin immunoprecipitation (ChIP), in vitro binding assay, electrophoretic mobility shift assay (EMSA), and site-directed mutagenesis. We also explored whether CTCF may regulate HBV transcription by altering HBV promoter activity, spatial interaction between HBV promoters and enhancers, and histone modifications. Finally, we created several site-specific mutations that could disrupt different CTCF post-translational modifications to examine the effect of such modifications on the ability of CTCF to regulate HBV transcription.

Results: HBV infection enhanced the expression of endogenous CTCF, suggesting that CTCF is involved in HBV biology and pathogenesis. Overexpression of CTCF stimulated the production of HBV pgRNA and cccDNA while its knockdown resulted in the opposite, which showed that CTCF has a positive role in HBV transcription. CTCF was recruited to all HBV promoters and enhancers, and two CTCF binding sites in enhancer I were first predicted using bioinformatics and then

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verified by biological experiments. Also, three mechanisms of how CTCF can stimulate HBV transcription were shown. The first mechanism was the activation of S1 and S2 promoters. The second mechanism was the formation of spatial interaction between enhancer I and the S1/S2 promoters potentially via chromatin looping. The third mechanism was the establishment of the active histone mark H3K4me3 at the S1 and S2 promoters. Finally, we showed that poly(ADP)-ribosylation and SUMOylation of CTCF, but not its phosphorylation, inhibited the stimulatory effect of CTCF on HBV transcription.

Conclusion: CTCF binds to at least two sites on HBV cccDNA, and thereby functions as an activator of HBV transcription by direct binding for activation of promoter activity, chromatin looping, and histone modifications.

Project No.: 16150342

ID-40-24

Ifd6p is An Aryl Alcohol Dehydrogenase Which Modulates Biofilm Matrix Production and Susceptibility to Stressors in Candida Dubliniensis Biofilms

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Introduction: The regulatory mechanisms of biofilm matrix production in Candida dubliniensis are ill defined. By virtue of the pivotal role of alcohol dehydrogenases in biofilm development in C. albicans and the close phylogenetic relationship between C. albicans and C. dubliniensis, we set to investigate the molecular and cellular bases of C. dubliniensis biofilm matrix production with special attention to alcohol dehydrogenases.

Project Objectives: (1) To create IFD6, CSH1, and ADH5 null and overexpression strains in C. dubliniensis; (2) To examine and compare the phenotypic properties of the null and overexpression strains in biofilm development; and (3) To evaluate the pathobiological significance of alcohol dehydrogenase activity in C. dubliniensis.

Methods: C. dubliniensis alcohol dehydrogenases null, complemented, and overexpression strains were created using PCR-based gene targeting techniques, and their phenotypic determinants were investigated using biochemical, cell-based, and microscopic approaches. In vitro models of Candida infections were employed to evaluate the pathobiological significance of alcohol dehydrogenases.

Results: C. dubliniensis IFD6, CSH1, and ADH5 null, complemented, and overexpression strains were created and verified by PCR and Southern hybridization. Biochemical, cell-based, and microscopic analyses indicated that IFD6 played key roles in C. dubliniensis biofilm matrix production. Overexpression of IFD6 gene reduced biofilm and matrix biomass and increased susceptibility to certain antifungal agents and stressors. However, alteration in virulence was negligible.

Conclusion: The findings suggest that biofilm matrix production in C. dubliniensis is modulated by IFD6.

Implications: Unravelling the regulatory mechanisms governing biofilm development provides key data to the understanding of the role of alcohol dehydrogenase in C. dubliniensis, and cast light on the design of anti-Candidal strategy by modulating alcohol dehydrogenase activity.

Project No.: 14131202

ID-41-62

Dissecting the Molecular Mechanism of Anvm-Mediated Signal Transduction during Pseudomonas Aeruginosa Infection

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Introduction and Project Objectives: Pseudomonas aeruginosa is one of the most common pathogens in hospital-acquired infection, which is tightly controlled by a multi-layered regulatory network including quorum sensing system (QS), type VI secretion system (T6SS) and host immune resistance. In response to infection, phagocytic cells in the human immune system produce high concentrations of reactive oxygen species (ROS). However, P. aeruginosa needs to overcome the high concentration of ROS before successfully infecting host cells. In previous work, we found 80 cysteines that are highly sensitive to oxidative stress. The most sensitive cysteine is Cys44 (sensitivity ratio = 0.09) in the functional unknown protein P. aeruginosa 3880 (PA3880), which was named AnvM (anaerobic and virulence regulator) in our research. In the current study, we attempted to fully characterize this protein and found that it plays important roles in response to oxidative stress and virulence and to host response.

Methods: In the process of project research, we used MEGA7 software, which constructed phylogenetic tree of AnvM-like proteins. The characterization of AnvM is detected by reverse transcription-polymerase chain reaction (RT-PCR), cytoplasm and membrane protein purification, minimum inhibitory concentration (MIC) and real-time quantitative PCR. RNA-seq was carried out and Glutathione S-transferase (GST) pulldown assay was performed to screen potential proteins

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interacting with AnvM. C12-HSL activity, bioassay of C4-HSL and PQS production were measured to test the levels of QS molecules. Mouse experiment and histological analysis was used to determine the functional role of AnvM in influencing the host immune response. Bacterial burdens in the lungs after homogenization in PBS. Superoxide production in AMs was detected by NBT assay and H2DCF assay. Phagocytosis assay and lipid peroxidation assay were performed, and myeloperoxidase assay was tested for determining the oxidative burst in primary alveolar macrophages from infected or control mice. Immune pathway was confirmed by immunoblotting.

Results: In this study, we discovered anvM, acted as a regulator of anaerobic metabolism, response to oxidative stress and virulence in P. aeruginosa. At the same time, we found more than 30 anvM homologues in other bacterial genomes, indicating that anvM was widely distributed in the bacterial kingdom. In addition, the deletion of anvM gene changed the expression of more than 700 genes, including a set of virulence genes under both aerobic and anaerobic conditions. In order to further study the mechanism of anvM-mediated signal transduction in virulence, we used the bacterial two-hybrid test and found that the AnvM protein directly interacted with the QS regulator MvfR and the anaerobic regulator Anr. Subsequently, we found that the lack of AnvM protein can attenuate the pathogenicity of P. aeruginosa, resulting in increased the survival rate of mice, decreased the burden of bacteria, muffled inflammatory response and reduced lung damage in mice. In terms of mechanism, we identified that Cys44 was a key site for full function of anvM to affect the phagocytosis of alveolar macrophages and bacterial clearance. We also found that AnvM directly interacted with the host receptors TLR2 and TLR5, which might lead to the activation of the host immune response. Overall, the current characterization of AnvM will help to uncover new targets and strategies for the treatment of P. aeruginosa infection.

Conclusion: As a newly discovered member of regulatory proteins, AnvM is important in regulating the interaction between bacteria and the host immune system. AnvM has a multi-layered adjustment function, such as combining with MvfR, Anr, TLR2 and TLR5. It may be a key regulator of bacterial physiology and host response, and therefore represents a potential therapeutic target. This work provides novel details about the bacterial response to oxidative stress, virulence, host response to inflammation and may provide new insights into the regulation and function of the interaction between Pseudomonas aeruginosa and host cells.

Project No.: 17160022

ID-42-80

Comparisons of Exhaled Air Dispersion during High Flow Nasal Cannula Oxygen Therapy and CPAP

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Introduction and Project Objectives: High flow nasal cannula (HFNC) is an emerging therapy for respiratory failure but the extent of exhaled air dispersion during treatment is unknown. We examined exhaled air dispersion during HFNC therapy versus CPAP on a human patient simulator (HPS) in an isolation room with 16 air changes/hr.

Methods: HPS was programmed to represent different severity of lung injury. CPAP was delivered at 5-20 cmH2O via nasal pillows (Respironics Gel or ResMed Swift FX) or oronasal mask (Quattro, ResMed). HFNC, humidified to 37°C, was delivered at 10-60 L/min to the HPS. Exhaled airflow was marked with intrapulmonary smoke for visualization and revealed by laser light-sheet. Normalized exhaled air concentration was estimated from the light scattered by the smoke particles. Significant exposure was defined when there was ≥20% normalized smoke concentration.

Results: In normal lung condition, exhaled air dispersion, along the sagittal plane, increased from 186 (34) [mean(SD)] to 264 (27) mm and from 207(11) to 332 (34) mm when CPAP was increased from 5 to 20 cmH2O via Respironics and ResMed nasal pillows, respectively. Leakage from the oronasal mask was negligible. Exhaled air distances increased from 65 (15) to 172 (33) mm when HFNC was increased from 10 to 60 L/min. Air leakage to 620 mm occurred laterally when HFNC and the interface tube became loose.

Conclusion: Exhaled air dispersion during HFNC therapy and CPAP via different interfaces is limited provided there is good mask interface fitting (Full article published in Eur Respir J 2019 Apr 11;53(4):1802339).

Project No.: 15140282

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ID-43-92

Inhalable Dry Powder Formulation of Naked Sirna Using Spray-Drying Technology for the Treatment of Respiratory Diseases

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Introduction and Project Objectives: Small interfering RNA (siRNA) holds great promise for the treatment of various lung diseases including respiratory infections. It induces specific gene silencing through RNA interference (RNAi). RNA is a macromolecule notorious for its poor stability, rendering its delivery a big challenge. Inhaled dry powder formulation is attractive due to the ease of administration and good stability. High local concentration of siRNA can be achieved with reduced systemic exposure and side effects. Inspired by the ability of siRNA to be transfected in the airways without a delivery vector, we propose to formulate naked siRNA as dry powder. Spray-drying was examined for the preparation of inhalable siRNA dry powder. It involves the atomisation of siRNA solution into hot gas to allow the evaporation of solvent. However, RNA molecules are inevitably exposed to high shear stress and temperature, increasing the risk of degradation. This study aimed to develop an inhalable dry powder formulation of siRNA by identifying an optimal spray-drying condition and employing suitable excipients to ensure good aerosol properties while maintaining RNA integrity.

Methods: Mannitol was used as bulking excipient in the preparation of spray-dried siRNA powder. Two dispersion enhancers, L-leucine and human serum albumin (HSA) were investigated to improve the aerosol performance. The physicochemical properties and biological activities of the dry powder were also evaluated.

Results: Spray-drying produced particles of siRNA with wrinkled surface. Both L-leucine and HSA tend to accumulate at the liquid-air interface of the atomised droplets during solvent evaporation due to its hydrophobicity (L-leucine is a hydrophobic amino acid) or low mobility (HSA is a macromolecular larger than siRNA). They were enriched and formed a shell on the particle surfaces. When the solvent exhausted during evaporation, the shell collapsed, forming corrugated particles. Particles with dispersion enhancer displayed a better performance, as reflected by the high emitted fraction (the fraction that exited the inhaler) and fine particle fraction (the fraction with aerodynamic diameter suitable for lung deposition) in the cascade impactor study. The gel-retardation assay demonstrated that the short double-stranded siRNA is physically robust with no sign of degradation observed following spray-drying. The biological activity of spray-dried powder was also successfully retained.

Conclusion: Spray-drying is suitable for preparing siRNA formulations for inhalation. Both L-leucine and HSA can improve the aerosol performance of the powder. To enable its translation to the clinic, the evaluation of its therapeutic efficacy in animal models and long-term stability are paramount.

Project No.: 15140962

ID-44-115

Treatment and Outcomes of Community-acquired Pneuomonia (CAP) in Hong Kong - A Prospective Cohort Study

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Introduction and Project Objectives: Understanding local epidemiology and etiologies of community-acquired pneumonia in hospitalized patients is crucial for determining the appropriateness of treatment guidelines. We aim to determine the etiologies, severity, and outcomes in adults hospitalized for community-acquired pneumonia, and to study the impact of empirical antibiotic therapy on patient outcomes.

Methods: We performed a prospective observational cohort study involving adults hospitalized for community-acquired pneumonia in Hong Kong. Sputum, nasopharyngeal aspirate, blood and urine were collected for bacterial culture, molecular tests for detection of viruses and atypical pathogens, and antigen tests. Multivariable logistic regression model and Cox proportional hazard models were performed to determine independent factors associated with prolonged hospitalization and mortality.

Results: From February 2017 to July 2018, 258 patients were enrolled. The median age was 73 (interquartile range 61 – 80) years, 66% were male, 57% had underlying chronic illnesses, 13% had CURB-65 score ≥3, and 1-year mortality 10%. Pathogens were identified in 45% of patients; 20% had viral, 15% bacterial, and 9% polymicrobial pneumonia. Streptococcus pneumoniae (12%), influenza virus (12%) and Mycoplasma pneumoniae (1.2%) were the most common bacterial, viral and atypical pathogens respectively. Non-adherence to local empirical antibiotic treatment guideline (primarily recommending beta-lactam and doxycycline) was observed in 25%, and was independently associated with prolonged hospitalization (≥7 days) and higher mortality, after adjustment for age, underlying chronic illness, and disease severity.

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Conclusion: Adherence to treatment guidelines was associated with shorter hospitalization and improved survival. We provided evidence for the use of doxycycline for coverage of atypical pathogens in non-severe pneumonia.

Project No.: CU-17-A16

ID-45-119

Development and Evaluation of Novel Synthetic Bacterial Ribosomal RNA Transcription Inhibitors as Antimicrobials Against Methicillin-Resistant Staphylococcus Aureus (MRSA)

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Introduction: The emergence of bacterial pathogen methicillin-resistant Staphylococcus aureus (MRSA) is a global public health burden. Dwindling financial incentives for the development of antibiotics underlies a diminishing drug pipeline and ultimately a lack of approved novel antimicrobials. The transcription factors NusB and NusE forms a highly conserved heterodimer vital to bacterial transcription, thus their protein-protein interaction (PPI) interface presented a rational target for the development of transcription-inhibiting antimicrobials. Here we report the identification of "nusbiarylins" – a first-in-class inhibitor of bacterial transcription with novel mechanisms of action achieved through pharmacophore-based drug design and antimicrobial activity testing.

Project Objectives:

1. To make chemical derivatives of the bacterial rRNA synthesis inhibitor CUHK4.
2. To evaluate the antimicrobial activities and cytotoxicity of the bacterial rRNA synthesis inhibitor derivatives.
3. To confirm the mechanism of the optimized bacterial rRNA synthesis inhibitors at the molecular level.

Methods: The lead compound CUHK4 and its chemical derivatives were chemically synthesised and biologically characterised to assess their antimicrobial activity against clinically significant S. aureus strains including MRSA by broth microdilution, determine host cell cytotoxicity by MTT assay, probe for resistance generation by serially passaging at sub-inhibitory concentrations and to explore possible drug synergism with existing antimicrobials by checkerboard assay. The molecular mechanisms of nusbiarylins were assessed by quantitative polymerase chain reaction (qPCR) of 16S and 23S ribosomal RNA expression, while PPI target and potency were ascertained by our novel in vitro split-luciferase protein-fragment complementation assay (PCA). Binding affinity between nusbiarylins and NusB was evaluated by isothermal calorimetry (ITC).

Results: Our mini-library of nusbiarylin derivatives were found to strongly and specifically disrupt their intended molecular target, leading to impacted rRNA expression in treated cells which ultimately arrested bacterial growth. Biological investigations also suggested good antimicrobial activity for nusbiarylins – comparable to existing chemotherapeutic compounds – against both wild type and drug-resistant S. aureus strains, as well as low cytotoxicity in host cells, low rate of resistance emergence, and absence of antagonistic effects when used in combination with existing drugs. This presents a potential antimicrobial candidate with promising aspects for further investigation at early pre-clinical stages of drug development.

Conclusion: In this proposal we validated the druggability of a key bacterial PPI. Our findings encourage further development of more potent and optimised compounds within this novel family of transcription inhibitors to meet the urgent clinical needs of novel treatment options for multi-resistance bacterial infections.

Project No.: 17160152

ID-46-163

Efficacy and Mechanistic Evaluation of Banana Lectin (BanLec) as a Novel Pan-coronavirus Antiviral Agent: In-vitro and Ex-vivo Evidence

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Introduction and Project Objectives: Coronaviruses (CoVs) have repeatedly crossed species barriers from animals to human. In the past two decades, three coronaviruses, namely severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, have emerged to cause epidemics or pandemics in humans. Effective anti-CoV treatment options remain scarce. The spike glycoprotein of CoVs is crucial for virus-cell membrane fusion and cell entry, and is a potential anti-CoV therapeutic target. Lectins are carbohydrate-binding proteins widely found in nature and some have potential antiviral activities. We have previously engineered a BanLec that has preserved broad-spectrum antiviral potency with significantly reduced mitogenicity by introducing a single amino acid substitution to replace histidine 84 with a threonine (H84T-BanLec). We hypothesized that H84T-BanLec may be a "pan-CoV" antiviral through binding with CoV spike glycoproteins. In this study, we aimed to study the anti-CoV activities of H84T-BanLec in in vitro, ex vivo, and in vivo models, and investigated the mechanism of H84T-BanLec's pan-CoV antiviral activity.

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Methods: The antiviral activity of H84T-BanLec against MERS-CoV, SARS-CoV-2, and other human-pathogenic CoVs was evaluated in in vitro, ex vivo, and/or in vivo models. In silico modelling, structural analyses, and mechanistic studies were performed to investigate H84T-BanLec's anti-CoV mechanism and virus-drug compound interactions.

Results: H84T-BanLec potently inhibited the highly virulent MERS-CoV, pandemic SARS-CoV-2 and its variants, and other human-pathogenic coronaviruses at nanomolar concentrations. MERS-CoV-infected human DPP4-transgenic mice treated by H84T-BanLec have significantly higher survival, lower viral burden, and reduced pulmonary damage. Time-of-drug-addition assay shows that H84T-BanLec targets virus entry. Structural analyses demonstrated binding of H84T-BanLec to multiple SARS-CoV-2 spike mannose sites with high affinity. Modelling experiments identify distinct high-mannose glycans in spike recognized by H84T-BanLec. The multiple H84T-BanLec binding sites on spike likely account for the activity against SARS-CoV-2 variants and the lack of resistant mutants.

Conclusion: The novel findings in this study provided the basis for further in vivo and clinical evaluation of H84T-BanLec as a pan-CoV antiviral compound for the ongoing MERS epidemic in the Middle East and the COVID-19 pandemic, as well as future emerging CoVs. The new mechanistic insights from the present study may facilitate the development of additional carbohydrate-binding agents as pan-CoV antiviral drug compounds.

Project No.: 15140762

ID-47-179
Sexual-related and Drug-related Risk on Depression and Suicidal Ideation among Young Women Engaging in Compensated Dating

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Introduction and Project Objectives: Women engaging in compensated dating were exposed to significant sexual and drug-related risk factors that could have adverse effect on their mental health. The present study examined the association between sexual-related risks (i.e. duration of engaging in compensated dating, number of clients per week, condomless sex, and history of sexually transmitted disease), drug-related risk (i.e. illicit drug use), depression, and suicidal ideation among young women taking part in compensated dating.

Methods: A total of 183 young women engaging in compensated dating were recruited from three sources (i.e. online outreach, organizations serving women engaging in compensated dating, and participant referral) and were invited to complete an online survey.

Results: A total of 75.5% of participants have scored above the cut-off for depression and 17.6% reported having had suicidal ideation in the past year. Results from structural equation modeling showed that sexual-related risks and illicit drug use were positively associated with depression which in turn, was associated with suicidal ideation.

Conclusion: Interventions that promote mental health and prevent suicidal risk for young women engaging in compensated dating are warranted and should minimize their sexual and drug-related risk.

Project No.: CU-16-C15

ID-48-183
Characterizing the Dynamics Underlying Global Spread of Emerging Infectious Diseases

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Introduction and Project Objectives: Over the past few decades, global metapopulation epidemic simulations built with worldwide air-transportation network (WAN) data have been the main tool for studying how epidemics spread from the origin to other parts of the world (e.g., for pandemic influenza, SARS, and Ebola). However, it remains unclear how disease epidemiology and the air-transportation network structure determine epidemic arrivals for different populations around the globe. This study aims to fill this knowledge gap by developing and validating an analytical framework that requires only basic analytics from stochastic processes.

Methods: We set up our framework by characterizing the probability distribution of epidemic arrival times (EATs) for all populations in three metapopulation networks with increasingly complex structure: (i) The two-population network which has the simplest metapopulation structure; (ii) the shortest-path-tree of the WAN (WAN-SPT) which is the dominant subnetwork driving global spread of epidemics; and (iii) the WAN. We build the global simulator using 2015 worldwide flight booking data from the Official Airline Guide (OAG) and the Gridded Population of the World Version 4 (GPWv4) data set from the NASA Socioeconomic Data and Applications Center (SEDAC) at Columbia University. The WAN in our global metapopulation epidemic model comprises 54,106 connections and 2309 populations and preserves more than 92% of the global air bookings. We apply the analytical framework retrospectively to the 2009 influenza pandemic and 2014 Ebola epidemic.

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Results: In the first case study of inferring the transmissibility of the 2009 pandemic influenza A/H1N1 virus, the reduction in computational complexity and requirement provided by our framework translates into substantial improvement for timeliness and efficiency in situational awareness. In the second case study of the 2014 West African Ebola epidemic, we estimate that the reporting proportion (and hence the total number of cases) would have been statistically identifiable and the results are robust against temporal variations in epidemic growth rate.

Conclusion: Our framework not only elucidates the dynamics underlying global spread of epidemics but also advances our capability in nowcasting and forecasting epidemics. The findings demonstrate that key epidemic parameters could be robustly estimated in real-time from public data on local and global spread at very low computational cost.

Project No.: HKS-17-E13

ID-49-185
Assessing the Impact of Respiratory Infections and Weather Conditions on Donor Attendance and Blood Inventory in Hong Kong

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Introduction and Project Objectives: Maintaining a stable, safe and sufficient blood supply is crucial to the healthcare system. Every year, seasonal influenza epidemics lead to substantial hospitalizations and pose intense pressure on blood transfusion service worldwide, especially in an ageing population of Hong Kong which often see bi-annual influenza outbreaks. However, limited quantitative studies have been performed to assess the impacts of influenza and other respiratory infections on blood supply.

Methods: We estimated the impacts of respiratory infections on donor attendance and blood inventory, considering the confounding effects of weather conditions. The method only required influenza-like illness data from the existing sentinel surveillance network, local weather data, donor attendance records from blood transfusion service and blood inventory levels from local healthcare system.

Results: We estimated the number of donor attendance dropped by 6–10% when the number of consultations with influenza-like illnesses (ILIs) reported by sentinel general outpatient clinics exceeded five per 1000 consultations, which is a moderate activity level and has been observed frequently in Hong Kong. Blood inventory decreased with increased ILI consultation rates reported by sentinel general outpatient clinics. Adverse weather conditions had negative impacts on both donor attendance and blood inventory.

Conclusion: Epidemics of influenza and other respiratory infections coupled with adverse weather conditions affected blood supply in Hong Kong. The pressure on blood transfusion service to maintain a stable and sufficient blood supply during influenza seasons should not be overlooked, especially in an ageing population of Hong Kong.

Project No.: HKS-18-E17

ID-50-218
Characterization of a Novel Transcript Isoform of STING that Negatively Regulates Innate Antiviral Response

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Introduction: STING plays a pivotal role in innate DNA sensing in human cells. It adapts the activation signal triggered by several different sensing pathways to cellular machinery of type I interferon (IFN) production. STING binds with and is activated by a novel second messenger termed 2'3'-cGAMP, which is a cyclic dinucleotide synthesized by the key DNA sensor cGAS and carries two mixed types of phosphodiester bonds.

Project Objectives: The overall goal of this project was to document fully a novel transcript isoform of STING termed STING-β and its function in cellular 2'3'-cGAMP signalling and DNA sensing.

Design: Subcellular localization was determined by confocal microscopy. Interaction of STING with 2'3'-cGAMP and partner proteins was analysed by affinity chromatography and co-immunoprecipitation. Activity of STING-β to perturb innate immune signalling was measured by reporter assays, RT-PCR and ELISA. Viral replication was monitored by plaque assays as well as viral RNA and protein detection.

Results: A novel transcript isoform of STING designated STING-β functioning as a dominant inhibitor of innate DNA and RNA sensing was identified and characterised. STING-β does not contain transmembrane domains and was found to express at low levels in many different types of human tissues and cells. Its mRNA was induced by viruses and an inverse correlation between its expression and IFN-β production was noted. In patients with systemic lupus erythematosus (SLE), which is an interferonopathy characterised by overproduction of type I interferons (IFNs), a decline in STING-β expression was observed. STING-β exerted a dominant suppressive effect

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on the activation of IFN production in response to all stimuli tested. On the contrary, when STING-β was specifically knocked down, the expression of IFNs, IFN-stimulated genes and other cytokines induced by cyclic dinucleotides, DNA, RNA and viruses was boosted. Mechanistically, STING-β antagonised STING-α through direct binding. STING-β was also capable of binding with TBK1 to impede the interaction of the latter with other protein partners including STING-α and TRIF. Finally, STING-β retained the complete 2'3'-cGAMP-binding domain of STING-α and was fully competent in binding with 2'3'-cGAMP, preventing it from binding with STING-α and thereby shutting down IFN-β transcription.

Conclusion: STING-β acts as a dominant inhibitor of innate DNA and RNA sensing by sequestering 2'3'-cGAMP cyclic dinucleotide and other transducer proteins.

Implications: Our study reveals another level of regulation for DNA and RNA sensing, with implications in rational design and developments of antivirals and immunomodulatory agents for combating viral and autoimmune diseases.

Project No.: 15140682