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Harvesting Convalescent Plasma for Hyperimmune Intravenous Globulin Production: A Multicentre, Randomised Double-Blind Controlled Trial for Treatment of Patients with Serious S-OIV H1N1 Infection

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Background: Experience from influenza pandemics suggested that convalescent plasma treatment given within 4 to 5 days of symptom onset might be beneficial. However, robust treatment data is lacking.

Methods: This is a multicentre prospective double-blind randomized controlled trial. Convalescent plasma from patients who recovered from the 2009 pandemic influenza [A(H1N1)pdm09] infection was fractionated to hyperimmune intravenous immunoglobulin (H-IVIG) by CSL Biotherapies, Australia. Patients with severe A(H1N1)pdm09 infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized to receive H-IVIG or normal IVIG manufactured before 2009 as control. Clinical outcome and adverse effects were compared.

Results: Between 2010 and 2011, thirty-five patients were randomized to receive H-IVIG (17 patients) or IVIG (18 patients). One defaulted patient was excluded from analysis. No adverse event related to treatment was reported. Baseline demographics and viral load before treatment were similar between the two groups. Serial respiratory viral load demonstrated that H-IVIG treatment was associated with significantly lower day 5 and 7 post-treatment viral load when compared to the control ($p=0.04$ and $p=0.02$ respectively). The initial serum cytokine level was significantly higher in the H-IVIG group but fell to similar level 3 days after treatment. Subgroup multivariate analysis of the 22 patients who received treatment within 5 days of symptom onset demonstrated that H-IVIG treatment was the only factor which independently reduced mortality [OR:0.14, 95% CI, 0.02-0.92; $p=0.04$].

Conclusions: Treatment of severe A(H1N1)pdm09 infection with H-IVIG within 5 days of symptom onset was associated with a lower viral load and reduced mortality.

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In Silico Structure-based Screening and Characterization of Inhibitors for Influenza A Virus Nucleoprotein

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The trend of drug resistance developed in different strains of influenza viruses is worrying, and it is of utmost importance and urgency to develop new drugs against this virus. The viral nucleoprotein (NP) is a major component of the ribonucleoprotein (RNP) complex for the transcription and replication of the virus. In order to maintain a stable RNP structure, NP forms homooligomers by inserting its tail-loop to the tail-loop insertion site of another NP. In this study, we have employed structure-based virtual screening on the influenza A NP tail loop insertion site and found two hit compounds number 7 and 16 that can subdue influenza RNP activities. Subsequently, two analogs from compound 16 were identified which inhibit RNP activities of various influenza A subtypes and viral growth at micromolar levels. These analogs were also shown to directly interact with NP at 12.0 ± 1.25 and 41.6 ± 1.93 μM respectively by surface plasmon resonance assay. These novel anti-influenza compounds would provide a template for designing drug candidates with higher potency.

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A Detailed Longitudinal Study of Infection Attack Rates among Healthy Adults in Hong Kong during the Epidemic of the Human Swine Influenza A/H1N1 Virus in 2009

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Background: In an emerging influenza pandemic, estimating severity (the probability of a severe outcome, such as hospitalization, if infected) is a public health priority. As many influenza infections are subclinical, sero-surveillance is needed to allow reliable real-time estimates of infection attack rate (IAR) and severity.

Methods and Results: We tested 14,766 sera collected during the first wave of the 2009 pandemic in Hong Kong using viral microneutralization. We estimated IAR and infection-hospitalization probability (IHP) from the serial cross-sectional serologic data and hospitalization data. Had our serologic data been available weekly in real time, we would have obtained reliable IHP estimates 1 wk after, 1-2 wk before, and 3 wk after epidemic peak for individuals aged 5-14 y, 15-29 y, and 30-59 y. The ratio of IAR to pre-existing seroprevalence, which decreased with age, was a major determinant for the timeliness of reliable estimates. If we began sero-surveillance 3 wk after community transmission was confirmed, with 150, 350, and 500 specimens per week for individuals aged 5-14 y, 15-19 y, and 20-29 y, respectively, we would have obtained reliable IHP estimates for these age groups 4 wk before the peak. For 30-59 y olds, even 800 specimens per week would not have generated reliable estimates until the peak because the ratio of IAR to pre-existing

seroprevalence for this age group was low. The performance of serial cross-sectional sero-surveillance substantially deteriorates if test specificity is not near 100% or pre-existing seroprevalence is not near zero. These potential limitations could be mitigated by choosing a higher titer cutoff for seropositivity. If the epidemic doubling time is longer than 6 d, then serial cross-sectional sero-surveillance with 300 specimens per week would yield reliable estimates when IAR reaches around 6%-10%.

Conclusions: Serial cross-sectional serologic data together with clinical surveillance data can allow reliable real-time estimates of IAR and severity in an emerging pandemic. Sero-surveillance for pandemics should be considered.

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P110-Ab0092

A Longitudinal Study of Infection Attack Rates among Hospital Outpatients in Hong Kong during the Epidemic of the Human Swine Influenza A/H1N1 Virus in 2009 by Tracking Temporal Changes in Age-specific Seroprevalence Rates

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Seroprevalence survey is the most practical method for accurately estimating infection attack rate (IAR) in an epidemic such as influenza. These studies typically entail selecting an arbitrary titer threshold for seropositivity (e.g. microneutralization [MN] 1:40) and assuming the probability of seropositivity given infection (infection-seropositivity probability, ISP) is 100% or similar to that among clinical cases. We hypothesize that such conventions are not necessarily robust because different thresholds may result in different IAR estimates and serologic responses of clinical cases may not be representative. To illustrate our hypothesis, we used an age-structured transmission model to fully characterize the transmission dynamics and seroprevalence rises of 2009 influenza pandemic A/H1N1 (pdmH1N1) during its first wave in Hong Kong. We estimated that while 99% of pdmH1N1 infections became MN1:20 seropositive, only 72%, 62%, 58% and 34% of infections among age 3-12, 13-19, 20-29, 30-59 became MN1:40 seropositive, which was much lower than the 90%-100% observed among clinical cases. The fitted model was consistent with prevailing consensus on pdmH1N1 transmission characteristics (e.g. initial reproductive number of 1.28 and mean generation time of 2.4 days which were within the consensus range), hence our ISP estimates were consistent with the transmission dynamics and temporal buildup of population-level immunity. IAR estimates in influenza seroprevalence studies are sensitive to seropositivity thresholds and ISP adjustments which in current practice are mostly chosen based on conventions instead of systematic criteria. Our results thus highlighted the need for reexamining conventional practice to develop standards for analyzing influenza serologic data (e.g. real-time assessment of bias in ISP adjustments by evaluating the consistency of IAR across multiple thresholds and with mixture models), especially in the context of pandemics when robustness and comparability of IAR estimates are most needed for informing situational awareness and risk assessment. The same principles are broadly applicable for seroprevalence studies of other infectious disease outbreaks.

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Effectiveness of School Closures for Pandemic Influenza

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Large-scale antiviral intervention is now a major component of influenza pandemic preparedness planning in many countries. The emergence and spread of antiviral resistance (AVR) can substantially attenuate the effectiveness of large-scale antiviral intervention (e.g. targeted prophylaxis) and worsen the prognosis of severe cases (because antivirals will not be efficacious for cases infected with resistant strains). Reliable and timely estimates of the transmissibility of resistant strains is a public health priority once AVR is detected during an influenza pandemic.

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Direct Identification and Quantification of Host and Viral Transcriptomes after Influenza Infection Using the Next Generation Ultra-High Throughput DNA sequencer

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Introduction: Highly pathogenic avian influenza H5N1 virus causes lethal disease in humans. This virus can trigger a rapidly progressive viral pneumonia leading to acute respiratory distress syndrome. Studies from clinical, in vivo and in vitro data suggest a role of virus induced cytokine dysregulation in contributing to the pathogenesis of human H5N1 disease, however, the precise mechanisms by which the H5N1 virus elicits the differential and unique host responses are still not well understood.

Methods: To better understand the molecular events at the earliest time points, we used RNA-Seq to quantify and compare the host and viral transcriptomes induced by highly pathogenic H5N1 (A/Vietnam/3212/04) or low virulent H1N1 (A/Hong Kong/54/98) influenza viruses in human monocyte-derived macrophages at different post infection time.

Results and Conclusions: Our data revealed that our samples contained a variable mix of two macrophage populations corresponding to the M1 (classically activated) and M2 (alternatively activated) macrophage subtypes, a distinction not possible with previous microarray studies. When this confounding variable is considered in our statistical model, a clear set of dysregulated genes and pathways emerges at 6 hour post infection specifically in H5N1-infected macrophages, but not with H1N1 infection. Furthermore, we mapped reads comprise annotated known miRNA and found a distinct cellular miRNA expression patterns in response to influenza virus infection. We analyzed a set of potential miRNA target genes based on an inversely correlated expression pattern between the target mRNA and miRNAs and highlighted that innate immunity pathways particularly RIG-I like receptor signaling is significantly enriched in response to infection. In addition to known miRNAs, we have also identified some novel human miRNA species which have not been reported previously, while no miRNA was found to be encoded by influenza viruses.

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