



COVID-19, Influenza and RSV: Surveillance-informed prevention and treatment – Meeting report from an isirv-WHO virtual conference

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ABSTRACT

The International Society for Influenza and other Respiratory Virus Diseases (isirv) and the WHO held a joint virtual conference from 19th-21st October 2021. While there was a major focus on the global response to the SARS-CoV-2 pandemic, including antivirals, vaccines and surveillance strategies, papers were also presented on treatment and prevention of influenza and respiratory syncytial virus (RSV). Potential therapeutics for SARS-CoV-2 included host-targeted therapies baricitinib, a JAK inhibitor, tocilizumab, an IL-6R inhibitor, verdinexor and direct acting antivirals ensovibep, S-217622, AT-527, and monoclonal antibodies casirivimab and imdevimab, directed against the spike protein. Data from trials of nirsevimab, a monoclonal antibody with a prolonged half-life which binds to the RSV F-protein, and an Ad26.RSV pre-F vaccine were also presented. The expanded role of the WHO Global Influenza Surveillance and Response System to address the SARS-CoV-2 pandemic was also discussed. This report summarizes the oral presentations given at this meeting for the benefit of the broader medical and scientific community involved in surveillance, treatment and prevention of respiratory virus diseases.

1. Introduction

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to evolve, the emergence of a succession of dominant variants of concern (VOCs) from Alpha to the most recent Omicron, raises fresh concerns regarding increased transmissibility, severity of disease and impact on the effectiveness of vaccines, as well as the impact of future COVID-19 epidemics in relation to management of (seasonal) respiratory virus diseases, in particular influenza and respiratory syncytial virus (RSV).

Many aspects of the WHO Global Influenza Surveillance and Response System (GISRS) have been leveraged to address the COVID-19 threat, in particular timely sharing of information. Global monitoring of SARS-CoV-2 genetic variation, as for influenza, is essential to help track antigenic variation in relation to vaccine effectiveness and the possible need to update vaccine composition, and to detect the emergence of resistance to antiviral and immune therapeutics.

The object of the joint ISIRV-WHO virtual conference was to review current information on the circulation and impact of SARS-CoV-2, influenza, RSV and other respiratory viruses, their epidemiological

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interrelationships, implications for surveillance and progress on measures to combat disease by vaccines and therapeutics, both antivirals and immune therapeutics, and explore preparedness for future pandemics of respiratory virus disease.

In addition to the 16 plenary and 18 short oral presentations, there were 183 e-posters and a final discussion on preparing for the “Next Event”. Of the 732 participants, 36% were members of GISRS or from LMICs. (Currently all registrants can access the conference presentations and posters at <https://isrv.org/site/index.php/special-interest-groups/antiviral-group-home>. Most will also become publicly available in early 2022).

In his Opening Address, WHO Director General Tedros Adhanom Ghebreyesus stressed that the over-arching lesson from the COVID-19 pandemic is to be better prepared for future events. In particular, he emphasized the need for an integrated approach for surveillance, prevention, control and response to respiratory viruses with epidemic and pandemic potential. GISRS, a first line of defence against influenza for more than 70 years, has provided critical support to the response to COVID-19, and sets an excellent example of the basis for such an approach, as elaborated by subsequent speakers. The pandemic has provided the opportunity to innovate advances in surveillance, prevention and treatment of respiratory virus infections and in working together towards a healthier, safer, and fairer future.

2. Pandemic response and surveillance

2.1. Keynote talk: COVID-19 pandemic: response and preparing for the future

Mike Ryan, WHO Geneva, Switzerland

To date, there have been nearly a quarter billion confirmed cases of COVID-19, which represents a gross underestimate of the actual number, and over 5 million deaths. Many countries have experienced repeated waves of infection, while others have experienced more sustained transmission. The SARS-CoV-2 virus has continued to adapt and evolve with the emergence of VOCs with increased transmissibility and potential for immune escape (WHO, 2021k). The most recently predominant delta variant is highly adapted with an estimated reproductive number approaching twice that of the original virus (Liu and Rocklöv, 2021).

In some countries vaccination has been successful in substantially reducing the risk of morbidity and mortality, but less successful in driving down onward transmission and insufficient to reduce the reproduction number $R_t < 1$, where relatively high levels of community transmission have accompanied relaxation of social distancing restrictions and other non-pharmaceutical interventions (NPIs), as well as infections in the unimmunized. In countries with high immunization coverage there appears to be decoupling of case numbers and hospitalizations or deaths. While population-level immunity, acquired by vaccination or natural infection, continues to increase, a large proportion of the global population remains susceptible to COVID-19. Seroprevalence varies widely, ranging, for example, from 1.2% in the Western Pacific region to 48.5% in the African region in March–April 2021 (Arora et al., 2021; COVID-19 Immunity Task Force, 2021).

The inequity in the availability of vaccines has been exacerbated by the recent focus on booster doses in many countries before initial vaccinations have been ‘completed’ in less developed parts of the world. Despite the efforts of various organizations, including GAVI and CEPI (WHO, 2021c), it will be difficult to achieve the COVAX objectives of 40% vaccine coverage of the world population by the end of 2021 or 70% by mid-2022 without greater vaccine equity. Indeed 60 countries did not reach 10% coverage by end September 2021.

Having leveraged the capacities of GISRS and experiences of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and now COVID-19, the return of recurrent seasonal influenza and RSV, and concerns about a future influenza pandemic, will require more integrated multi-

pathogen surveillance. Existing and modified tools, including open access to genetic sequence data (GSD), the WHO R&D blueprint for epidemics, and risk communication and community engagement (RCCE) action plans, were critical in the global response to the COVID-19 pandemic. It will be important to harness the experience and lessons learned from the COVID-19 pandemic in developing a broader integrated surveillance and response system for respiratory viruses that builds on existing mechanisms and systems, and harnesses new technologies and partnerships to facilitate collaborative public health intelligence (Telenti et al., 2021). In addition to sustained surveillance during inter-pandemic periods, scalable, resilient responses to new events are a priority, including rapid collection and characterization of samples and data from outbreak clusters and prompt sharing of the findings.

2.2. Leveraging GISRS in a pandemic response

Wenqing Zhang, WHO, Geneva, Switzerland

The GISRS, coordinated by WHO for 70 years, is a well-developed network, currently supported by 158 institutions in 127 countries, areas or territories, for sharing of epidemiological information, genetic data and influenza viruses for detailed virological characterisation (WHO, 2021f). Following its acknowledged effective performance during the 2009 H1N1 pandemic, the network continued to enhance its capabilities, for example in 2015 initiating the integration of RSV surveillance in some countries in all WHO regions and the monitoring of a panel of respiratory viruses as in the PAHO region (Pan American Health Organization, 2020). In 2018 WHO developed a forward-looking ‘Global Influenza Strategy 2019–2030’, which provided a roadmap for broader integrated surveillance of respiratory diseases and pandemic preparedness (WHO, 2021e).

Many of the GISRS capacities have been used in responding to the COVID-19 pandemic. For example, most of the National Influenza Centers incorporated or switched to surveillance of SARS-CoV-2, and GISAID, a platform for effective sharing of influenza genetic sequence data, promoted the rapid sharing of SARS-CoV-2 genetic sequence data. Other components adapted for response to the COVID-19 pandemic include surveillance data reporting platforms, mechanisms of special (H5) reference laboratories, and the influenza vaccine updating process, in place since 1973. Thus, GISRS’ strategy has involved integration of sentinel surveillance of both influenza and SARS-CoV-2, expanding the diverse functions of GISRS and building capacity to support evolving public health needs to be sustainable and scalable for the next pandemic. Future goals include development of a ‘GISRS Plus’ platform (WHO, 2021a)), to encompass other respiratory viruses and a capacity for generic pandemic response, while not disrupting the functioning of the existing system for influenza at the heart of GISRS. Global coordination is key and will be organised in a sustainable manner, focusing on quality, global standards and emphasizing country ownership. Other important considerations include implementation of the Pandemic Influenza Preparedness (PIP) Framework (WHO, 2021h), and public health implications associated with the implementation of the Nagoya Protocol and other national Access-and-Benefit Sharing systems.

2.3. SARS-CoV-2 evolution: implications for vaccine strain selection

Kanta Subbarao, WHO CC for Reference and research on influenza, Melbourne, Australia

A number of different SARS-CoV-2 vaccines have been rapidly developed and proven highly efficacious, especially against severe disease (Subbarao, 2021). However, the level of neutralizing antibody and vaccine effectiveness have been shown to decline gradually over about 6 months (Chemaitelly et al., 2021; Levin et al., 2021), such that booster vaccinations have been implemented in many countries.

SARS-CoV-2 has continued to evolve with the emergence and spread of a succession of VOCs, with the Delta variant currently dominant

worldwide (Nextstrain, 2021). Some mutations enhance ACE2 receptor binding, accounting in part for increased transmissibility. Some amino acid substitutions in the spike protein, e.g. E484K in the Beta and Gamma variants, may contribute to antigenic change and antibody escape, causing reduced effectiveness of some antibody cocktails and vaccines (Cerutti et al., 2021).

A Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) has been established to review information on the impact of emerging VOCs and assess the possible need to adjust vaccine composition to optimize the performance of COVID-19 vaccines (WHO, 2021i). The GISRS collaborative vaccine consultation mechanism provides an excellent example of a well-established process for updating the composition of influenza vaccines in response to antigenic change in circulating viruses. The technical advisors and WHO Global Influenza Program work closely with vaccine manufacturers and regulatory agencies to enact the biannual WHO recommendations and ensure the availability of effective vaccines for use in the northern and southern hemisphere influenza seasons.

The year-round process for influenza encompasses global virological surveillance, sharing of genetic sequence data, viruses, post-infection ferret sera and post-vaccination human sera for antigenic characterization, and includes predictive modelling and estimation of vaccine effectiveness (WHO, 2021i). Surveillance and response to SARS-CoV-2 might require a similar intensive global collaboration to control COVID-19 in future.

(Post conference update note: At the end of November, a new SARS-CoV-2 VOC, named Omicron, was recognized and reported to the WHO. The Omicron variant encodes a large number of mutations in the spike protein and phenotypic characterization is underway. An update of the vaccine may be warranted if the Omicron variant spreads globally and is associated with severe illness, altered antigenicity and reduced vaccine effectiveness.)

2.4. Influenza antiviral resistance and lessons for SARS-CoV-2

Larisa Gubareva, CDC, Atlanta, GA, USA

Monitoring antiviral resistance is also an integral part of virological surveillance by GISRS, and is an important component of therapeutic use. The WHO Antiviral Working Group provides guidance on methodologies, both *in vitro* assays and animal models, and reference materials for assessing antiviral susceptibility, as well as guidance on molecular markers and criteria for reporting reduced susceptibility to influenza antivirals (WHO, 2021g). More than 20,000 viruses are assessed in a typical year (Takashita et al., 2020).

An extensive network for monitoring antiviral susceptibility of influenza viruses in the USA employs a sequence-first approach, involving NGS analysis of resistance markers, with phenotypic testing of selected viruses. The CDC emphasizes three perspectives for antiviral susceptibility: 1) clinical laboratories: focus on the best treatment for the individual patient, which is regulated by national authorities; 2) surveillance laboratories: focus on early detection of resistant viruses and epidemiology from patient samples; and 3) public health agencies: focus on modifying treatment recommendations, policies, and national stockpiles.

Surveillance for variants with reduced susceptibility in those who have not been exposed to antivirals provides evidence for possible transmission events. For example, the circulation of oseltamivir-resistant A(H1N1)pdm09 viruses has occurred on multiple occasions followed by local or global spread (Takashita et al., 2015). In general, there are no commercial laboratories or approved point of care assays to assess influenza virus susceptibility and few laboratories offer antiviral testing for clinical care management of Influenza.

The experience in influenza provides lessons for monitoring SARS-CoV-2 variants for reduced susceptibility to the various anti-spike monoclonal antibodies that are currently in use and for the antiviral polymerase and protease inhibitors that will increasingly be used

clinically in the future (Gubareva and Fry, 2020). For example, monitoring susceptibility of SARS-CoV-2 variants with the L452R substitution in the spike protein led to revoking of Emergency Use Authorization (EUA) for bamlanivimab monotherapy in mild-moderate COVID-19 in the USA in April 2021 because of likely loss of effectiveness (FDA, 2021).

Interpreting the significance of phenotypic results and changes in genetic markers is however difficult due to insufficient data on laboratory correlates of clinically relevant resistance.

2.5. Animal reservoirs and future risks

Ron Fouchier, Erasmus MC, Rotterdam, The Netherlands

Dr Fouchier drew attention to the importance of a more holistic approach – One Health – in evaluating risk of zoonotic infection by different respiratory viruses and being better prepared to respond to a potential incipient pandemic (Herfst and Fouchier, 2014). Hendra and Nipah viruses are examples of zoonotic pathogens that have been curtailed through a One Health approach that encompasses socio-behavioral interventions to reduce interactions between zoonotic reservoirs (fruit bats) and ‘bridging’ hosts (horses and pigs, respectively), and thereby reduce spillover into human populations. The concurrent increase in populations of domestic pig and poultry and humans and their proximity to one another has exacerbated the frequency of zoonotic influenza infections from the animal virus reservoirs and may benefit from similar approaches. Detailed characterization of zoonotic respiratory viruses is essential to help assess their potential risk.

Observational and experimental studies of the many zoonotic infections by different influenza A subtypes have revealed certain common genotypic and phenotypic traits associated with adaptation to increased mammalian transmission – receptor specificity and stability of the hemagglutinin (HA) and properties of the RNA polymerase – which are useful in assessing risk. That such risk traits can be generalizable was shown in a study on adaptation of an avian influenza A(H10N7) virus to seals, reporting that the hemagglutinin had increased stability and receptor binding to the human-type sialic acid receptor, with preferential binding to α 2,6-linked sialic acids (Herfst et al., 2020). As a practical demonstration, in 2017 the recognition that the H7N9 influenza viruses causing extensive outbreaks in poultry in China and substantial concurrent infection in the human population possessed a number of these transmissibility traits led to wide spread vaccination of chickens and the abrogation of subsequent outbreaks of human infection (Zeng et al., 2018).

Because SARS in 2003, and MERS since 2012, primarily caused severe lower respiratory tract infection (LRTI) with limited transmissibility between humans, they were easily recognisable, and potential adaptation to humans was avoided by effective global collaboration based on public health measures. SARS-CoV-2, on the other hand, replicates effectively in the upper respiratory tract (URT) causing mainly mild or asymptomatic infections and is much more transmissible, even from asymptomatic and pre-symptomatic infection, such that infections are difficult to detect and trace. Studies of influenza A infection of ferrets has also shown a correlation between efficient airborne transmission and URT but not LRTI (Richard et al., 2020).

A more proactive surveillance of viruses in wild and domestic animals is essential to provide early signals to intervene and possibly forestall potential zoonotic outbreaks and information for the development of broadly reactive vaccines (Karesh et al., 2012). In this context, close collaboration between the OIE/FAO Network of Expertise on Animal Influenza (OFFLU) laboratories and GISRS supports the biannual update of influenza candidate vaccine viruses for pandemic preparedness (WHO, 2021b).

2.6. How do respiratory viruses cause disease?

Yoshi Kawaoka, University of Wisconsin-Madison, WI, USA

SARS-CoV-2 infectiousness of aerosols over distance and time has

received limited study (Fears et al., 2020; van Doremalen et al., 2020) although transmission is clearly enhanced under poorly ventilated conditions. Dr Kawaoka described 2 series of experiments, one relating to concern about possible transmission from infected corpses which demonstrated that infection could be transmitted from dead hamsters infected with SARS-CoV-2 to co-housed naïve animals and that sealing the oral, nasal and anal orifices of corpses effectively prevented transmission. The other studies showed that, in an experimental setup, infectivity of SARS-CoV-2 virus in an aerosol was stable for a long time and could be effectively inactivated in an aerosol or solution by irradiation using a 500 mW deep-UV(265µm) LED (light-emitting diode), more so than by a conventional 50 mW LED.

Studies with human ACE-2 transgenic mice were undertaken to better understand COVID-19 pathogenesis, in which a 2-photon microscopy *in vivo* imaging system was used to analyse changes in mouse lung following SARS-CoV-2 infection (Ueki et al., 2020). In addition to infection of type I and II alveolar cells, changes in neutrophils were observed. Studies examining the effects of anti-neutrophil and anti-platelet therapies are planned using the model.

3. Short presentations: virus genetic variations

3.1. RSV F amino acid mutation and neutralizing antibody evasion

David Marchant, University of Alberta, Edmonton, Alberta, Canada

Fundamental questions persist about how RSV causes significant morbidity and mortality in children and adults. The two sub-types of RSV, types A and B, share >95% sequence homology, but they differ in their growth and neutralization profiles, and their relative country-specific burden each season. Importantly, RSV type A isolates from patients are less susceptible to the monoclonal antibody palivizumab than RSV type B isolates *in vitro*, although it is unclear whether this results in different clinical effectiveness when palivizumab is administered to high-risk infants as prophylaxis against RSV disease. Marchant and colleagues investigated the divergence of RSV into these two types with distinct behaviours. Sequencing of isolates revealed that types A and B differ at residue 305: leucine in type A, and isoleucine in type B. Computational modelling suggested the amino acid substitution results in conformational change in the palivizumab binding site, as well as in the RSV F (fusion glycoprotein) protomer. By engineering the L305I mutation into the rgRSV reverse genetics system for RSV type A, they found that susceptibilities to palivizumab and D25 sera were significantly increased compared to those for wild type virus. To investigate how divergence may have occurred, RSV type A was grown in the presence of increasing titers of anti-RSV-A sera, and an RSV polymerase inhibitor; L305I mutations were observed to emerge at the experimental evolutionary bottlenecks that were created in this model. The investigators propose that RSV-B may have evolved from effective neutralization of a parental RSV approximately 350 years ago.

3.2. SARS-CoV-2 in South Africa

Cheryl Cohen, National Institute for communicable disease, Johannesburg, South Africa

Because community and household settings differ across different countries and continents, pathogen transmission and disease burden may also differ, potentially influenced by factors such as income levels and living conditions. Therefore, it's important to study the impact of SARS-CoV-2 in country-specific contexts. To estimate the burden and transmission of SARS-CoV-2 in South Africa, Cohen and colleagues modified an existing study: Prospective Household study of Influenza and RSV Transmission (PHIRST) (Cohen et al., 2021a) to study SARS-CoV-2 burden, transmission dynamics, and interactions with others RVIs. The PHIRST coronavirus study (PHIRST-C) (Cohen et al., 2021b) recruited approximately 100 households and 500 individuals in

each of two groups, one urban and one rural. Of the 1189 adults and children enrolled between July 2020 and March 2021, 60% were female, 15% were people living with HIV, and 69% were unemployed. Nasal swabs for SARS-CoV-2 RT-PCR were collected twice-weekly, irrespective of symptoms, and serum was collected every two months for SARS-CoV-2 antibodies. Two epidemic waves (wild-type and Beta, respectively) occurred during the study period and by the end of the second wave, over one third of individuals had been infected. Overall, 1% of participants had evidence of SARS-CoV-2 infection by RT-PCR alone. By RT-PCR and serology combined, 34% had evidence of at least one infection episode, and 3% had evidence of reinfection episodes; 73% of 222 households had at least one infection. Prior infection reduced risk of re-infection by 84% in the 2nd wave. Household cumulative infection risk, defined as the proportion of household members with infection following introduction of SARS-CoV-2 to the household, was 16%. The rate of asymptomatic infection was unexpectedly very high in PHIRST-C, compared to findings from studies of SARS-CoV-2 transmission performed elsewhere (Buitrago-Garcia et al., 2020). Of 254 RT-PCR-confirmed episodes of SARS-CoV-2 infections with data available, 211 (83%) did not report symptoms. This was also higher than the proportion of asymptomatic influenza infections in the original PHIRST study (44%). The reasons for these discrepancies require further investigation, but may include differences in study designs, or possibly factors specific to different countries and their populations.

3.3. Within hospital SARS-CoV-2 transmission

Benjamin Lindsey, University of Sheffield, Sheffield, UK

Transmission of SARS-CoV-2 within healthcare settings has been a significant problem in many countries during the COVID-19 pandemic. Lindsey and colleagues demonstrated how combining viral genomic sequencing data with epidemiological data can inform nosocomial outbreak investigations and subsequent public health measures to minimize nosocomial transmission. In a retrospective Bayesian modelling study, the investigators used Outbreaker 2 (Campbell et al., 2018) to reconstruct transmission chains amongst 2181 patients and healthcare workers in Sheffield, England, during two UK epidemic waves (March–July 2020, and Nov 2020–Jan 2021). The inputs for the model were SARS-CoV-2 whole genome sequence, date of symptom onset, patient movement data, staff location of work, and the proportion of unsampled cases. The outputs were ancestral case, time of infection, location where infection occurred, and the number of unsampled cases between a case and the sampled ancestral case. A key finding from the study was that staff-to-staff transmission was estimated to be the most frequent transmission type during Wave 1, accounting for 31.6% of observed hospital-acquired infections; this decreased to 12.9% in Wave 2. By contrast, patient-to-patient transmissions increased from 27.1% in Wave 1–52.1% in Wave 2, becoming the predominant transmission type. Transmission hotspots were also evident, with >50% of hospital-acquired infections concentrated in 8 of 120 locations in Wave 1 and 10 of 93 locations in Wave 2. Ninety-five percent of nosocomial transmissions resulted in ≤2 secondary cases, with a maximum of 6 secondary cases. Approximately 40%–50% of hospital-onset patient cases resulted in onward transmission, compared to <4% of cases where the investigators were confident that infection in an index case had been acquired in the community. It appears that the onward transmission risk from nosocomial cases may be under-appreciated, or harder to identify and prevent, at least in some healthcare facilities.

3.4. Epidemiological and whole genome sequence data to assess clinical impact of SARS-CoV-2 mutations

Kirstin Leslie, Public Health Scotland, Glasgow, UK

The COVID-19 pandemic has seen extensive use of viral genome sequencing across the globe, particularly to monitor SARS-CoV-2 evolution and the emergence and spread of novel variants. The UK, via the

COVID-19 Genomics UK consortium (COG-UK), commenced sequencing a proportion of SARS-CoV-2-positive samples relatively early in the pandemic and sequences from UK cases now account for a large proportion of sequences in global databases. Public Health Scotland (PHS) commenced its surveillance of SARS-CoV-2 VOCs in December 2020, describing the spread of the Alpha and then Delta variants within Scotland. Additionally, PHS continued to monitor further genetic evolution of these variants, linking sequencing data with epidemiological and case-investigation data. Leslie and colleagues described how they identified, tracked and monitored three mutation profiles: Alpha + L452R, Delta + P251L, and Delta + G446V. Surveillance of Alpha + L452R identified 220 cases between March and May 2021, geographically linked to the Lanarkshire region of Scotland. Eighty percent of cases were aged under 40 years and 65% were unvaccinated. Binomial logistic regression analysis indicated no significantly increased risk of infection with Alpha + L452R compared to dominant Alpha in partially vaccinated cases (OR 0.83; 25%–95% CI: 0.51–1.35). Surveillance of Delta + P251L between May and Aug 2021, with 81% occurring in the Lothian region, also found no significant risk of infection with Delta + P251L compared to dominant Delta in fully vaccinated individuals (OR: 0.86; 25%–95% CI: 0.62–1.19). Similarly, no increased risk of infection with Delta + G446V in fully vaccinated individuals was detected (OR: 1.19; 25%–95% CI: 0.92–1.56). For all three mutation profiles, there was also no indication of an increase in severity of illness. As variants transmit and continue to evolve around the world, it is clear that combined genomic and epidemiological surveillance has an essential role in identifying variants and understanding their impact.

3.5. SARS-CoV-2 VOCs and mutations associated with increased spike cleavage

Alba Escalera, Icahn school of Medicine at Mount Sinai, NY, USA

SARS-CoV-2 VOCs typically have mutations in the spike (S) protein-encoding region of the genome, and some mutations are particularly high-risk given their potential impact on efficient spike cleavage, virus transmission, and escape from antibodies induced by infection or immunization. Escalera and colleagues described how the S mutation H655Y was selected in mink after infection with the USA-WA1/2020 SARS-CoV-2 wild type isolate (Escalera et al., 2021). Moreover, they identified the H655Y polymorphism in SARS-CoV-2 isolates obtained from COVID-19 infected patients from New York as early as March 2020. Western blots, performed to assess the spike cleavage of these human isolates, showed that the variant encoding the H655Y mutation (NY7 virus) had an enhanced spike protein processing. To better understand the impact of this polymorphism, they used a panel of human and animal SARS-CoV-2 viruses all bearing H655Y to confirm that this mutation facilitates spike protein processing in both Vero-E6 and Vero-TMPRSS2 cell systems. To investigate whether H655Y polymorphism enhances transmission, viral competition experiments were performed in the Syrian hamster model. In each infector-infectee pair, the infectee was inoculated with a mixture of WA1 wild type and WA1-H655Y at a one-to-one ratio. Although there were no significant differences in weight loss or viral titers between the two groups, the variant with H655Y became dominant in both infectors and infectees. Other recently emerged variants (Alpha, Beta, Gamma, Kappa, Delta) also showed enhanced spike protein processing in Vero-TMPRSS2 cells, despite having different mutations in S and demonstrating different expression levels of furin cleavage peptide (shown to be most abundant in the H655Y variant, followed by the Beta variant). This suggests that mutations promoting spike protein processing are a common feature in SARS-CoV-2 variants that have gained transmission advantages in the human population over common predecessors.

3.6. Co-infection of chickens with H9N2 and H7N9 and emergence of reassortant H9N9 virus

Sushant Bhat, the Pirbright institute, Woking, Surrey, UK

Avian influenza A viruses are a persistent threat to both animal and human health. Several distinct A(H9N2) viruses have been identified in poultry in different regions of the world. They rarely infect humans, typically causing mild illness when they do. However, A(H9N2) viruses are of concern because of their ability to donate partial or entire cassettes of genes to other influenza A viruses, especially when they co-circulate. The exemplar is Asian lineage avian influenza A(H7N9), which acquired internal genes from A(H9N2) and infects humans following close contact with infected birds, often resulting in severe illness. Furthermore, reassortant A(H9N2) viruses have been identified in China since 2013. Therefore, studying reassortment potential in co-circulating viruses is of particular importance. Bhat and colleagues experimentally infected chickens with A/Anhui/1/2013/H7N9 (Anhui/13) virus and A/Chicken/Pakistan/UDL-01/2008/H9N2 (UDL/08) virus and analyzed the genetic composition of reassortants by RT-qPCR, and their phenotypic characteristics. Co-infection resulted in an A(H9N9) reassortant virus with selective enrichment of polymerase genes from A(H9N2). Compared to A(H9N2), the reassortant A(H9N9) virus demonstrated increased replication in human A549 cells, and significantly higher receptor binding to both $\alpha 2,6$ and $\alpha 2,3$ sialoglycans. Replication levels of the A(H9N9) reassortant virus in ferrets were similar to those seen with A(H7N9), and ferrets exposed to A(H9N9) aerosols seroconverted, unlike ferrets exposed to A(H7N9). These findings, combined with the possibility of future co-circulation of A(H7N9) with the A(H9N2) viruses of G1 lineage found in the Indian sub-continent and the Middle East, highlight the potential threat to human and animal health from novel reassortant avian influenza viruses.

4. Treatment

4.1. Keynote talk: severe COVID-19, influenza, and RSV pathogenesis: similarities and differences

Peter Openshaw, Imperial College, London, UK

Many factors affect the severity of viral lung disease. These include the virus and its variants, host genetics, recent history of infection, environment and microbiome. To understand the disease, all these need to be studied and integrated mechanistic models developed.

RSV infects ciliated epithelial cells in the respiratory tract. It infects in infancy and reinfects throughout life, affecting all ages but presenting with different clinical features. RSV is the most frequent cause of bronchiolitis in infants, but it also exacerbates pre-existing respiratory conditions in adults and may cause serious respiratory illness in the elderly. The ability of RSV to cause repeated infections despite its rather low genetic and antigenic variability relies on its capacity to modulate and/or evade innate and adaptive immune responses (Openshaw et al., 2017). In children, severe RSV bronchiolitis is paradoxically associated with lower nasal viral loads and reduced IP-10/CXCL10, CCL5 and gamma interferon (IFN- γ) levels compared to infants with mild or moderate illness (Thwaites et al., 2018). This curious finding suggests that neither uncontrolled viral replication nor an overly exuberant immune response explains the severe disease and that there is much to learn about the infant immune system. However, higher nasal viral load and increased mucosal IL-6 levels have been reported in hospitalized older adults with RSV disease when compared to outpatients (Walsh et al., 2013). Mouse studies have suggested that regulatory T cell (Treg) responses are important in limiting disease severity. The HIC-Vac human infection challenge program (www.hic-vac.org) demonstrated that neutrophilic inflammation in the respiratory mucosa in adult volunteers predisposes to RSV infection (Habibi et al., 2020). In recent studies, it seems that older adults have enhanced viral replication and symptoms when infected with RSV.

Influenza viruses also infect the respiratory epithelium but have a wider cell tropism than RSV. The MOSAIC consortium, assembled during the 2009–11 influenza pandemic, enabled a comprehensive study of the causes of severe pandemic influenza. By comparing 255 patients with influenza-like illness (ILI), 172 (65%) of whom with PCR-confirmed influenza, with matched healthy and ILI controls, the study demonstrated that increased levels of soluble mediators, such as IL-1 β , IL-6 and CXCL8, in nasopharyngeal aspirates, and to a lesser extent in serum samples, correlated with disease severity. Longitudinal analysis of whole-blood transcriptional signatures provided evidence of progression from IFN-induced to neutrophil-associated patterns in severe influenza (Dunning et al., 2018). Additionally, a splice variant of the IFITM3 gene was particularly enriched up to 5.7% in severe patients, compared to 0.3% in controls, suggesting a role for this allele in an increased propensity to severe disease (Everitt et al., 2012). Recent human challenge studies have shown that influenza has faster viral replication kinetics and associated symptoms compared to RSV.

SARS-CoV-2 infects the respiratory epithelium but, like other human coronaviruses, can also affect the gastrointestinal (GI) tract. The time course of SARS-CoV-2 infection and COVID-19 progression is quite different from influenza and RSV. A typical pattern consists of a virus-driven phase lasting approximately 1 week from symptom onset that, if not self-resolving, might evolve into an inflammatory phase associated with severe disease. Hospitalization typically occurs on about day 7, with clinical deterioration to acute respiratory disease syndrome (ARDS) by day 9 and the necessity of ventilation by day 10. Death, if it occurs, typically happens after the 3rd week. Patients who survive need a month –and often longer– for full recovery. To date, the ISARIC Coronavirus Clinical Characterisation Consortium has analyzed data from more than 240,000 patients, representing roughly 50% of total hospitalized patients in the UK. This enabled the rapid identification of GI and multi-organ manifestations of COVID-19 in addition to documenting the response in the respiratory tract. It has identified comorbidities acting as risk factors for severe disease and host genetic mechanisms associated with severity. The disease is largely immune-mediated and to some extent heritable. For example, causal links exist between low expression of IFNAR2 and high expression of TYK2 to life-threatening disease (Pairo-Castineira et al., 2021). Treatment with corticosteroids benefits those with respiratory failure but might harm milder cases. Moreover, blood IL-6 and D-dimer levels are increased in severe disease (though not to ARDS levels), the latter indicating the thrombotic manifestations observed in part of this population. GM-CSF is another hub of the inflammatory network, which is raised in COVID-19 but not in severe influenza.

In conclusion, these three lung viral infections have distinct methods by which they evade immune defences. Each is also different in the ways that they trigger immune responses and cause disease, and each needs a different approach to treatment based on a deep understanding of the mucosal and systemic responses to infection.

4.2. Lessons learned from coronavirus animal models

Timothy Sheahan, UNC, Chapel Hill, USA

Evaluation of antiviral therapeutics requires both *in vitro* and *in vivo* preclinical models. The original SARS-CoV-2 strain failed to infect and replicate in standard laboratory mice, highlighting the need to develop tailored mouse models. Based on structural analysis of the viral spike protein receptor binding domain (RBD), it was postulated that two residues (Q498 and P499) interfered with the binding to the mouse ACE2 receptor. Using reverse genetics, a SARS-CoV-2 MA (“mouse adapted”) virus harboring both Q498Y and P499T spike mutations was generated. This new virus infected and replicated efficiently in mice, causing mild disease (Dinnon et al., 2020). After ten more passages in BALB/c mice, a lethal mouse-adapted strain was obtained. The MA10 virus had seven amino acid changes compared to the parental strain (nsp4: T285I; nsp7: K2R; nsp8: E23G; S: Q498Y, Q493K, P499T; ORF6:

F7S) and caused higher replication in the lower respiratory tract and severe disease, including a temporary reduction of pulmonary function (Leist et al., 2020). Older (more than 1 year old) mice were much more susceptible to infection than the young (10-week-old), with higher mortality (80% when infected with 1000 plaque forming units (pfu) compared to 20% in young mice infected with 10,000 pfu), greater weight loss, increased loss of pulmonary function and delayed viral clearance.

When evaluating antiviral candidates, whether for novel or repurposed therapeutics, the timing of therapy initiation and how “meaningful” antiviral activity is defined need to be considered. Lopinavir, a protease inhibitor used in combination with ritonavir for the treatment of HIV, showed antiviral activity against SARS-CoV-2 *in vitro* at concentrations within the range of reported plasma concentration of the drug. However, inhibitory drug concentrations in cell culture are not directly comparable to those achieved in humans, as the drug is highly plasma protein bound (~99%). This would account for the failure of this treatment in COVID-19 clinical trials, in contrast to efficacy in treating the much more susceptible HIV-1.

Remdesivir (GS-5734) which targets the RNA-dependent RNA polymerase (RdRp), is a monophosphoramidate prodrug of an adenosine analog initially developed for treating Ebola virus. It has subsequently shown antiviral activity against different human and animal coronaviruses in various cell lines including primary human airway epithelial cells (hAE), with 50% inhibitory dose (EC₅₀) values lower than 1 μ M. Preventive (–12 h) or very early treatment (+12 h after infection) completely prevented weight loss of mice infected with SARS-CoV-2 and significantly reduced pulmonary viral titers to almost undetectable levels. Although significant viral reduction was observed when treatment was initiated 24 h post infection (hpi), this did not prevent weight loss. The therapeutic efficacy of remdesivir was abrogated when treatment was initiated 48 hpi during peak virus replication in the mouse lung. The disease course of SARS-CoV-2 in mice is compressed compared to that in humans, so the therapeutic window within which to treat with a direct acting antiviral is shorter in mice than in humans. Nonetheless, preclinical data obtained from hAE, mice and non-human primates supported the clinical evaluation of remdesivir and the consequent FDA approval of this drug in October 2020.

Molnupiravir (EIDD-2801) another RdRp inhibitor, is an orally available nucleoside analog with broad *in vitro* efficacy against influenza, RSV, Ebola and coronaviruses, including SARS-CoV-2 (Sheahan et al., 2020). In mice infected with SARS-CoV or MERS-CoV, both prophylactic and therapeutic administration of EIDD-2801 improved pulmonary function and reduced virus titer and body weight loss. Based on promising preclinical results it is now in Phase 3 clinical trials for SARS-CoV-2 treatment in outpatients. [Post conference update note: The Phase 3 trial has been stopped as a 30% reduction in hospitalization or death was shown, and EUA has been requested (Dyer, 2021)].

4.3. Current status of antiviral therapy for COVID-19 and influenza: WHO perspectives

Janet Diaz, WHO, Geneva, Switzerland

The WHO has developed “Living guidelines for COVID-19” aiming to convert incoming clinical evidence into therapeutic guidelines rapidly, yet rigorously. The 5-step process implemented by the WHO Steering Committee includes: i) clinical data scanning and prioritization, ii) meta-analysis and evidence grading, iii) guideline development group meetings, iv) recommendation writing and external review and v) guideline publication and dissemination. The actual timeline from full data availability to guideline publication is 8–10 weeks. Updates to the WHO Therapeutics and COVID-19: living guideline are published in the WHO website guideline (WHO, 2021j), and are also available through the partner British Medical Journal website (<http://www.bmj.com/content/370/bmj.m3379>), which includes an innovative interactive infographics-based format that enables the application of different

filters to retrieve the desired information.

The latest version of the guideline for patients with mild and moderate COVID-19 introduces a new conditional recommendation to use a combination of neutralizing mAbs (casirivimab and imdevimab) in non-severe patients at the highest risk of severe disease, in parallel with pulse oximetry monitoring. This recommendation is based on clinical data from 4722 patients with a baseline risk for hospitalization of 4.2% and an OR of 0.29 (95% CI: 0.17–0.48). The expected results of the intervention are a reduction in hospitalizations of 14, 35, and 101 per 1000 in lower, middle, and higher risk patients, respectively.

In the case of patients with severe or critical COVID-19, the guideline recommends proning plus supplemental oxygen support (severe) or advanced respiratory support (critical). Baseline treatment recommendation includes corticosteroids and IL-6 receptor blockers, both based on a moderate to strong degree of evidence, supported by many concordant clinical trials. The novelty is the recent addition of casirivimab/imdevimab for seronegative hospitalized patients. The expected results for this new casirivimab/imdevimab recommendation in seronegative hospitalized patients ($n = 2823/9785$; RR 0.85, 95%CI: 0.76–0.95) are an overall reduction in mechanical ventilation of 42 per 1000, and a reduction in mortality of 39 and 69 per 1000 in severe and critical patients, respectively.

The next steps contemplate the analysis of available clinical evidence on convalescent plasma, JAK inhibitors, sotrovimab, anticoagulants and molnupiravir for their potential inclusion in the COVID-19 therapeutics guideline by the end of the year.

4.4. Immune modulation and biomarkers in COVID-19

John Beigel, NIH, Rockville, MD, USA

An overview was given of anti-inflammatory and immunomodulating therapies, restricted to agents in the National Institutes of Health (NIH), World Health Organization (WHO) guidelines for the management of COVID-19, or with regulatory approval (or EUA) by FDA. The three leading therapeutic classes meeting this criteria, based on large trials or pivotal Phase 3 trial data are interleukin-6 receptor (IL-6R) antagonists, corticosteroids and JAK inhibitors. The RECOVERY trial randomized hospitalized patients to receive 6 mg dexamethasone for 10 days or until hospital discharge ($n = 2104$) or standard care alone ($n = 4321$). Dexamethasone was associated with 17% reduction of 28-day mortality (rate ratio 0.83 [95% CI 0.75–0.93]). Subgroup analysis showed the greatest benefit for those on mechanical ventilation, with little benefit for those on oxygen only and potential harm for those requiring no supplemental oxygen. A meta-analysis of 73 studies of 21,350 hospitalized COVID-19 patients (Cano et al., 2021) showed that corticosteroid therapy showed a mortality benefit mainly in severely ill COVID-19 patients (OR, 0.65; 95% CI, 0.51–0.83; $P = 0.0006$). No data supported a benefit in outpatients.

Baricitinib is an oral JAK inhibitor used in treating rheumatoid arthritis that targets both JAK1 and JAK2. The ACTT-2 trial (Kalil et al., 2021) was a multicenter double-blind, placebo-controlled randomized trial conducted in 67 centers across eight countries comparing remdesivir alone or with baricitinib on recovery time and mortality. This trial showed an improved rate of recovery (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32). The greatest benefits were observed in patients requiring non-invasive ventilation or high-flow oxygen at enrollment (median time to recovery 10 vs. 18 days, rate ratio 1.51). In contrast to dexamethasone, baricitinib treatment had more impact on the 28-day mortality in low-flow (1.9 vs 4.7%) and high-flow oxygen (7.5 vs 12.9%) subgroups. A systematic review and meta-analysis of JAK inhibitors in hospitalized patients with COVID-19 (Wijaya et al., 2021), found the use of JAK inhibitors was associated with a reduced risk of mortality (OR 0.51, 95% CI 0.28–0.93, $P = 0.02$; I²: 7.8%, $P = 0.354$). The NIAID-sponsored ACTT-4 trial aimed to determine if baricitinib plus remdesivir or dexamethasone plus remdesivir were more effective at preventing adults hospitalized with COVID-19 on supplemental oxygen

from progressing to requiring mechanical ventilation or death, but this trial was closed to enrollment because pre-defined futility criteria were met indicating that neither treatment regimen studied is likely significantly better than the other (NIH, 2021). With just over 1000 patients the trial will remain blinded and final analysis is ongoing. The COV-BARRIER was another multicenter double-blind, placebo-controlled randomized trial (1525 participants) conducted in 101 centers across 12 countries (Marconi et al., 2021) comparing baricitinib added to standard of care (SOC) to SOC alone (including dexamethasone and/or remdesivir). Although there was no significant reduction in the frequency of disease progression, mortality benefits were apparent in patients requiring non-invasive ventilation or high-flow oxygen at baseline (17.5% vs. 29.4%, hazard ratio 0.52 [95% CI 0.33–0.80]). Those already on corticosteroids or remdesivir had less benefit. An addendum trial to COV-BARRIER evaluated mortality of participants on mechanical ventilation. Treatment with baricitinib significantly reduced 28-day all-cause mortality compared to placebo (39.2% vs 58.0%; hazard ratio [HR] = 0.54 [95%CI 0.31–0.96]; $p = 0.030$), (Ely et al., 2021), although mortality was extremely high. Baricitinib monotherapy may not be sufficient for those on mechanical ventilation.

Tocilizumab is a humanized monoclonal antibody against the IL-6R. The UK RECOVERY trial compared tocilizumab plus SOC to SOC alone and found significant overall reduction in 28-day mortality for tocilizumab participants (31% vs 35% RR = 0.85 [0.76–0.94]) (RECOVERY Collaborative Group, 2021) with the greatest reduction for those not on invasive mechanical ventilation. No benefit was observed in those not on corticosteroids. The REMDACTA trial evaluated whether tocilizumab plus remdesivir in hospitalized patients provided greater benefit than remdesivir alone, but the combination did not shorten time to hospital discharge or reduce mortality (Rosas et al., 2021), although a WHO meta-analysis concluded that use of IL-6 antagonists reduced mortality (Shankar-Hari et al., 2021). Several hundred studies are underway with over 50 anti-inflammatory agents.

4.5. SARS-CoV-2 variants: implications for monoclonals

Tyler Starr, Fred Hutchinson cancer research center, Seattle, WA, USA

The most potent neutralizing antibodies to SARS-CoV-2 target the spike RBD, inhibiting binding to the ACE2 receptor. Mutations in the RBD that reduce binding by therapeutic and vaccine-elicited antibodies have recently emerged across multiple SARS-CoV-2 lineages, highlighting the need for antibodies and vaccines that are robust to viral escape.

Deep mutational scanning and yeast-surface display was used to express every possible amino acid mutation at each site in the RBD and measure effects of each mutation on the affinity of the domain for the ACE2 receptor (Starr et al., 2021b). Some sites like 488 cannot tolerate changes, while others like 493 can tolerate many different substitutions and some substitutions even improve affinity, like Y453F and N501Y seen in several VOCs. Using mixed populations of yeast, Starr and colleagues used FACS selection to identify those that did not bind to selected monoclonal or polyclonal antibodies (Greaney et al., 2021). Most sites allowing antibody escape correlated with those with minimal impact on ACE2 receptor binding. While antibody cocktails are designed to minimize escape, distribution of the bamlanivimab plus etesevimab was paused due to concern over their efficacy against VOCs. Although mutations leading to escape to neutralization by each of these antibodies are at orthogonal sites on the RBD (Starr et al., 2021c), some of the VOCs have evolved mutations leading to escape, e.g. E484K in both Beta and Gamma lineages, L452R in Delta and K417N/T in Beta, Gamma and Delta. E484 is one of the most dominant epitopes to which polyclonal sera bind, so the use of the MAb is not driving mutations, but rather global immunity is exerting pressure on the viruses at sites tolerant of diversity. Casirivimab plus imdevimab (REGEN-CoV) is another cocktail, with escape to each mapped at largely non-overlapping sites in the

RBD (Starr et al., 2021b). Although F486 is critical to casivirimb binding, it has a high tolerance for diversity; E406W escapes the cocktail of both antibodies, but slightly attenuates receptor binding. Unlike the other MABs which were raised against the virus, sotrovimab was derived from memory B cells from a convalescent SARS-CoV-1 infected patient and selected for cross-reactive binding to SARS-CoV-2. It binds at a distinct more conserved site compared to the other MABs, and the escape map shows mutations at sites not commonly seen to date in the evolution of the virus. Thus, in developing new therapeutic antibodies we may need to avoid immunodominant epitopes, target diverse epitopes and prioritize breadth of binding to other coronaviruses, which may be more robust to short term evolution of pandemic viruses (Starr et al., 2021a).

4.6. Long COVID: interventions to reduce risk or treat

Charlotte Summers, University of Cambridge/Addenbrooke's hospital, Cambridge, UK

Emerging data suggest that around 1 in 10 patients hospitalized with COVID-19 die and more than 1 in 5 develop new or worsened symptoms during the first three months after discharge from hospital. People with prolonged symptoms after recovery from the acute phase of infection are termed as having 'Long COVID'. In the UK, the PHOSP-COVID study of 1077 hospitalized patients surviving 5 months post-discharge, found only 29% had fully recovered, 20% had a new disability and 19% had changed working status predominately due to ill health (PHOSP COVID Collaborative Group et al., 2021). Another study showed that 3–4 months after hospital discharge that 29.6% had a new respiratory diagnosis, 4.8% a new cardiac diagnosis, and 4.9% a new diabetes diagnosis (Ayoubkhani et al., 2021). HEAL-COVID – Helping Alleviate the Longer-term consequences of COVID-19 - is a national platform trial in the UK. The primary objective is to determine whether interventions in the post-hospital (convalescent) phase of COVID-19 improve longer-term mortality/morbidity outcomes. Other objectives are to evaluate treatment-specific and patient-reported outcomes of COVID-19 and to estimate the cost-effectiveness of treatments. The target population of this trial is hospitalized patients 18 years or older approaching the end of their admission for whom SARS-CoV-2 infection was the cause of admission. The platform structure allows multiple different treatments to be evaluated simultaneously and new treatments to be added. Current treatments recommended for study by an independent advisory panel include apixaban to reduce the risk of venous thromboembolic events (2 mg BD for 2 weeks) and atorvastatin, as both a potential immune modulator and for reduction of vascular inflammation (40 mg OD for 12 months). The primary outcome of this study is hospital-free survival at 12 months. Secondary outcomes include all-cause mortality, hospital readmission, serious adverse reactions. The Atom™ digital platform is being used to quantify how a patient feels, functions and responds to treatment. So far 550 patients have been enrolled at 97 sites in the UK with 15 more sites in setup.

5. Short presentations: therapeutics

5.1. Ensovibep, a multi-specific DARPIn for SARS-CoV-2

Francesca Malvezzi, Molecular Partners AG, Schlieren, Switzerland

Ensovibep is a clinical candidate composed of five linked Designed Ankyrin Repeat Protein (DARPIn) units including three targeting the virus and two binding to human serum albumin to support a longer systemic half-life. One DARPIn has a total size of approximately 15 kDa, one tenth the size of a monoclonal antibody. They have high thermostability, are produced in high yields by microbial expression, and have good safety and low immunogenic potential. Ensovibep (MPO420) has 3 distinct DARPIn modules with subtle differences in sequence, each binding to a similar region on the SARS-CoV-2 RBD that spans amino acids 450–493. Cryo-EM shows DARPIn #2 binds to the RBD in the up

conformation, with high affinity, competing with ACE2 binding (Walser et al., 2021). Although the mono DARPins have K_d values of 30–90 pM for the spike protein, the three linked RBD-binding DARPins show a strong avidity effect resulting in net binding affinity in the sub pM range. Neutralization assays on lentivirus, VSV-based pseudovirus or authentic SARS-CoV-2 demonstrate EC₅₀ values from 1 to 8 ng/mL for ensovibep against all frequent variants to date, including Delta (Rothenberger et al., 2021). Although some mutations reduce binding of some of the mono DARPins, (e.g., E484K or Q493K), ensovibep remains potent due to cooperative binding. An exception is F486V, which reduces binding of each RBD-binding domain as well as of ensovibep. However, mutations of F486 also impair binding to the ACE2 receptor and are therefore detected at very low frequency and are not present in any emerging variant (GISAID database). SARS-CoV-2 was passaged in Vero E6 cells with increasing concentrations of ensovibep, DARPIn #2 only, single REGN monoclonal antibodies or the REGN antibody cocktail. The monomeric DARPIn #2 and the REGN monoclonal antibodies lost the ability to protect the cells from virus infection after 1 to 3 passages, while the single molecule ensovibep maintained protection after 4 passages, comparable to the REGN antibody cocktail. Two Phase 2/3 trials of intravenous ensovibep are ongoing (EMPATHY and ACTIV-3). [Post conference update note: The recruitment of patients in the ensovibep arm of ACTIV-3 in hospitalized patients was stopped because of futility (Molecular Partners, 2021)].

5.2. Antiviral and anti-inflammatory activity of verdinexor and selinexor

Yosef Landesman, Karyopharm Therapeutics, Newton, MA, USA

Verdinexor and selinexor are orally available small molecule inhibitors that covalently bind to Cys528 in the cargo pocket of the nuclear export protein exportin-1 (XPO-1). XPO-1 transports proteins involved in replication of RSV (M-protein), influenza (NEP), SARS-CoV-2 (ORF3b, 9B, nucleocapsid, ACE-2) as well as in inflammatory responses. In a plaque reduction assay in A549 cells, verdinexor inhibited replication of RSV with an EC₅₀ of 0.96 μM and a CC₅₀ of 44.9 μM. After *in vitro* exposure from 2 to 24 or 2–48 hpi, between 1.5 and 2-fold more M-protein was retained in the nucleus, correlating with an approximate 2.5-fold reduction in virus titer (Mathew et al., 2021).

In Vero E6 cells infected with SARS-CoV-2, selinexor exposure either prior to infection or at the time of infection reduced the plaque number by >50% at concentrations of ≥10 nM (CC₅₀ 434 nM). In addition, there was a ≥2 log₁₀ reduction in virus titers with ≥10 nM selinexor (Kashyap et al., 2021). In SARS-CoV-2-infected ferrets, oral treatment with selinexor decreased viral loads in lungs at day 4 as assessed by qPCR and reduced pathology in nasal tissues. [Post conference update note: A Phase 2 placebo-controlled trial of oral selinexor in hospitalized COVID-19 patients did not show significant differences in clinical outcomes (Karyopharm Therapeutics Inc, 2021)]

5.3. S-217622 a potential oral SARS-CoV-2 3C-like protease inhibitor

Yuki Tachibana, Shionogi & Co., Ltd, Osaka, Japan

The active site of the 3C-like protease (3CL^{PRO}) is well conserved across SARS-CoV-2 and MERS-CoV. All share a catalytic dyad of Cys145 and His41, with no human cell protease with similar specificity. It cleaves polyproteins pp1a and pp1ab at 11 sites. A corporate compound library was screened virtually and biologically, and after optimization of activity and DMPK compound S-217622 was selected for further development. It is a non-covalent, non-peptidic, orally bioavailable small molecule.

In a 3CL^{PRO} enzyme assay, the IC₅₀ was 0.013 μM, and in a cytopathic effect (cpe)-inhibition assay of SARS-CoV-2 infected VeroE6/TMPRSS2 cells, the EC₅₀ values were approximately 0.4 μM for both wild-type virus and Alpha, Beta, Gamma and Delta variants. EC₅₀ values for SARS-CoV and MERS-CoV were 0.21 and 1.4 μM respectively. The plasma half-life and fraction absorbed orally in rat/monkey/dog were

favourable for a once daily oral administration. In mice infected with the Gamma strain and dosed orally immediately and at 12 hpi, doses of 8, 16 or 32 mg/kg were associated with 2.7, 3.5 or 3.7 \log_{10} reductions in lung virus titer at 24 hpi, respectively. When treatment was delayed for 24 h, and then treatment was given three times daily there was a dose dependent decrease in virus lung titers, with a 4.2 \log_{10} reduction at day 3 with 64 mg/kg. In a Phase 1 human study a single oral administration (dose 20–1000 mg) was safe and well tolerated. The plasma concentration increased rapidly and was predicted to exceed the target concentration with once daily dosing. Phase 2/3 studies are underway in Japan.

5.4. Dependence of SARS-CoV-2 antiviral activity on cell culture and animal models

Helen Box, University of Liverpool, Liverpool, UK

Previous studies have reported that probenecid, a uricosuric gout treatment, has potent antiviral activity against SARS-CoV-2 *in vitro* with an EC_{50} of 0.7 μ M. In a hamster model of infection there was a 3–4 \log_{10} reduction in lung virus titer at day 3 pi with a single 2 or 200 mg/kg treatment either prophylactically or therapeutically (Murray et al., 2021). The current study pre-treated Vero E6 cells for 2 h prior to infection with SARS-CoV-2 at a multiplicity of infection (moi) of 0.05 pfu/cell, followed at 48 h by fixation and staining to quantify cpe spectrophotometrically. In contrast to the remdesivir control (EC_{50} 1.7 μ M), the probenecid EC_{50} was >10 μ M. Hamsters were inoculated with virus and treated starting at 24 hpi with probenecid, (i.p. 100 mg/kg BID) for 4 doses. By qPCR quantification at 3 days pi there were no differences in the levels of total or subgenomic RNA between treated and untreated animals. Both groups also had comparable weight losses. Differences between the two laboratories results *in vitro* could be affected by the treatment time (96 h vs 48 h), moi (0.01 vs 0.05), detection method (plaque number vs cpe). Differences in the hamster model could be related to dose (2 or 200 mg/kg single dose vs 100 mg/kg BID for 2 days), quantification of virus (pfu/ml vs qPCR for total and subgenomic RNA) and strain (Washington 2020 vs Delta strain). The differences in these results highlight the necessity for standardization of methods used for the assessment of antiviral activity of preclinical candidates. In any case, the current results do not support the use of probenecid in COVID-19 without further pre-clinical testing.

5.5. AT-527 phase 2 study in hospitalized patients

Daniel Kuritzkes, Brigham and Women's hospital, Boston, MA, USA

AT-527 is a 6-modified purine nucleotide prodrug being developed by Atea Pharmaceuticals, USA, which potently inhibits the RdRp of SARS-CoV-2 and hepatitis C virus (Good et al., 2021). After phosphorylation to its active triphosphate metabolite, it has a dual mechanism of action including chain termination and inhibition of the Nidovirus RdRp associated nucleotidyl transferase domain (NiRAN), thus enabling a potentially high barrier to resistance. Initial human studies have shown favourable PK and safety profiles. Interim results were presented from a Phase 2, randomized, double-blind, placebo-controlled study in high-risk hospitalized patients with moderate COVID-19 undertaken prior to the emergence of the Delta variant. Patients received oral AT-527 550 mg BID or placebo for 5 days. The primary endpoint was the proportion of patients requiring respiratory support within the 14-day study period, but there were too few patients meeting this endpoint among the first 70 enrolled (5–6%) of 190 planned patients to assess clinical efficacy. The virology endpoint was available for 58 patients with baseline data and showed a mean 0.7 \log_{10} greater reduction from baseline viral RNA load compared to placebo at day 2. Numerically greater reductions were seen through day 8, and virus RNA was cleared earlier in patients treated with AT-527. Median time to alleviation of symptoms for AT-527 treated patients with higher viral loads was 11

days vs 13 days for the placebo group, although not statistically significant. An amended protocol will explore a higher dose.

5.6. Casirivimab and imdevimab combination therapy for outpatients with SARS-CoV-2

Diana Rofail, Regeneron pharmaceuticals Inc., Tarrytown, NY, USA

REGEN-COV consists of two noncompeting, neutralizing human IgG1 antibodies, casirivimab and imdevimab, that target the RBD of the SARS-CoV-2 spike protein (Hansen et al., 2020). Outpatients with a positive RT-qPCR test and ≥ 1 risk factor for severe disease received 1200 mg IV of REGEN-COV (n = 748) or placebo (n = 736), and were asked to record their symptoms (23 listed) in a daily electronic diary for 29 days (Weinreich et al., 2021). Based on patient reported outcomes, median time to first day of symptom resolution was shorter for REGEN-COV-treated patients than the placebo group (10 vs 14 days, $p < 0.0001$). Furthermore, median time to resolution of symptoms sustained for ≥ 2 days and ≥ 3 days were also shorter for REGEN-COV compared with placebo (14 vs 17 days, $p < 0.0017$ and 17 vs 21 days, $p < 0.0046$, respectively). The median time to return to usual health (9 vs 12 days, $p = 0.0001$) and return to usual activities (8 vs 10 days, $p < 0.0003$) were also shorter in REGEN-COV-treated patients than placebo-treated patients. This study demonstrated that REGEN-COV 1200 mg significantly improves the experience of outpatients with COVID-19 compared with placebo by shortening the time to symptoms resolution and time to return to usual health and activities.

6. Prevention and response

6.1. Keynote talk: novel vaccines for COVID-19, influenza, and RSV

Barney Graham, NIH, Rockville, MD, USA

Dr. Barney Graham emphasized that the development of novel vaccines for respiratory virus infections (RVIs) has entered a new era where more things are possible because of advances in basic research, new delivery platforms, and manufacturing. Newer technologies including structure-based vaccine design, computationally designed nanoparticles, gene-based antigen delivery, ability to target specific antibody lineages, and rapid platform manufacturing will facilitate an engineering approach to vaccine development in the future. Class 1 viral fusion proteins are present in RSV, influenza, coronaviruses, and other enveloped viruses, and these share functional homology and shared motifs and domains, thus offering the potential for generalizable solutions for improved vaccine antigen design (Graham et al., 2019).

For RSV, the use of prefusion specific neutralizing antibody enabled an understanding of the two conformational forms of the F glycoprotein, the prefusion functional and postfusion inactive forms, that have dramatic differences in surface topology and associated exposure of relevant epitopes. A stabilized pre-F antigen is more representative of live RSV than F in its post-F conformation. Historically, the adverse effects associated with formalin-inactivated RSV vaccine were linked to its predominate presentation of postfusion F (Killikelly et al., 2016). Preserving the apical epitopes in the prefusion state is key to immunogenicity (Crank et al., 2019), and prefusion F preferring memory B cells from naturally infected adults make more potent neutralizing antibodies. One stabilized subunit vaccine candidate showed promising results in mice and macaques and more than 10-fold boost in neutralizing activity in adults (Crank et al., 2019). A large number of prefusion F-based vaccines are currently under clinical study (PATH, 2021).

The foundation for rapid COVID-19 vaccine development began with technical advances stemming from efforts to develop an HIV-1 vaccine starting some 40 years ago. Recent work on the prefusion structures and stabilization of HKU1-CoV spike proteins and subsequent development of a prototype mRNA vaccine for MERS-CoV enabled rapid progress in developing SARS-CoV-2 vaccines as soon as the spike protein sequence

became available. For example, the Moderna mRNA-1273 vaccine entered Phase 3 clinical studies within 6.5 months after sequence availability. For mRNA vaccines, protein expression and reducing adverse host responses are affected by the mRNA chemistry and manufacturing process (Nelson et al., 2020). Phase 3 trials and real-world observational data have demonstrated the remarkable effectiveness of the Pfizer-BioNTech and Moderna mRNA-based vaccines. In addition to mRNA vaccines, multiple other platforms have been used to develop candidates, including inactivated whole virion, recombinant vectors like adenovirus, recombinant proteins, nanoparticles displaying protein subdomains, and others. As of 27 September 2021, 194 vaccine candidates were undergoing pre-clinical evaluation and 121 were in clinical evaluation (>20 Phase 3) with 7 registered by WHO (WHO, 2021d). In addition, the availability of high quality prefusion conformation spike protein was fundamental in developing neutralizing monoclonals and diagnostic reagents.

For influenza, current vaccines are largely based on 1940's technology of inactivated virus grown in chicken eggs. Seasonal influenza vaccines are only 50–60% effective in good years, need to be reformulated annually to match circulating strains, and are not effective against new pandemic viruses. The need for broader spectrum, more durably protective vaccines is evident, but antigenic variation and genetic plasticity, especially in the HA head, and pre-existing immunity (e.g., immunodominance of serotype-specific epitopes and of antibody lineages with limited breadth; effects on B cell phenotypes) are particular challenges. The VRC Influenza Vaccine Development Program has used structure-based precision antigen design and epitope mapping, single-cell analysis of B cells, and strategies to define and target specific antibody lineages with cross-neutralization potential in conjunction with nanoparticle display of antigen arrays to increase potency and heterotypic antigens to elicit subdominant antibody responses. Universal vaccine work has focused on the HA stem region because of its low mutation rate and lower immunogenicity than the HA globular head. The development of self-assembling proteinaceous nanoparticle-based vaccines has progressed to a quadrivalent mosaic nanoparticle vaccine expressing 20 HA trimers in an array that avoids immunodominance and displays conserved sites like the HA stem and receptor binding domains (Boyoglu-Barnum et al., 2021). These confer protection against both seasonal influenza viruses and heterosubtypic H5N1 and H7N9 viruses (not contained in the vaccine) in animal models through antibodies that target a conserved HA stem supersite. Initial clinical evaluation of this vaccine began in May 2021.

6.2. Non-pharmaceutical interventions

Ben Cowling, University of Hong Kong, Hong Kong

In a future RVI pandemic, initial public health responses will rely primarily on NPIs including isolation of sick and quarantine of those exposed, other social distancing strategies (school and workplace closures, avoiding crowds), personal protection measures (hand washing, face masks, respiratory etiquette), environmental controls (ventilation, surface cleaning, UV lights), and travel-related measures (restrictions, screening, border closures).

Shortly before the COVID-19 pandemic, WHO undertook a review of multiple guidance documents and systematic analysis of the available literature to update its recommendations for the use of NPIs in mitigating pandemic and epidemic influenza (Fong et al., 2020; Ryu et al., 2020; WHO, 2019; Xiao et al., 2020). Several RCTs have examined the effectiveness of preventing influenza with hand hygiene with or without masking but in general have not identified major protective effects. For most other interventions, very low or no quality evidence was available to inform recommendations. Of note, more drastic interventions like “lockdowns” and “stay-at-home orders” were not even considered as an NPI in this earlier review.

SARS-CoV-2, especially recently emerging VOCs, are more transmissible than influenza virus. Containment by local eradication, not

thought to be feasible for pandemic influenza, has been at least temporarily effective in mainland China and some other locations like Singapore, Australia and New Zealand. However, because most infections have been mild and hence difficult to identify in the community and transmission has been highest around the time of symptom onset and sometimes occurred pre-symptomatically, isolation of cases is often too late to prevent onwards transmission. There has been unprecedented broad and prolonged use of NPIs in efforts to flatten and delay outbreak peaks to reduce rapid increases in cases requiring care that have threatened to overwhelm healthcare systems.

Several studies have attempted to estimate the impact of NPIs, particularly social distancing policies, on COVID-19 transmission. Determining the impact of individual interventions is difficult when many measures are applied at the same time, and changes in individual behaviors and virus transmissibility over time are important. The value of face mask use in the community to reduce contagiousness of those infected in addition to protecting susceptible wearers has been debated widely (Cowling and Leung, 2020). One Danish randomized trial of wearing facemasks in the community found a modest 14% relative reduction in risk (from 2.1% to 1.8%) in COVID-19 cases compared to those not assigned facemasks (Bundgaard et al., 2021). A very large cluster-randomized trial of community-level mask promotion in rural Bangladesh villages concluded that increase in mask use was associated with reduced symptomatic seroprevalence by 9.3% (control prevalence 0.76%; treatment prevalence 0.68%) (Abaluck et al., 2021).

Given the limited impact of any one NPI, except perhaps for strict lockdowns, the use of targeted layered interventions, the so-called “Swiss cheese” concept, will be necessary to enhance NPI effectiveness. One modelling study assessing the effect of major NPIs across 11 European countries early in the pandemic concluded that the interventions had driven R_t (the average number of infections generated at time t by each infected case over the course of their infection) below 1 to achieve control of the epidemic. Lockdowns had by far the greatest effects and accounted for over 80% of the estimated reduction in transmissibility (Flaxman et al., 2020). A modelling analysis of 17 NPIs in Europe's second wave found that business closures, educational institution closures, and gathering bans reduced transmission, but less than they did in the first wave (Sharma et al., 2021). This was attributed to interval increases in safety measures and individual protective behaviors, like social distancing, that made certain areas of public interaction safer and hence reduced the effect of stringent bans and closures. This analysis found that closures of nonessential businesses (including restaurants, pubs, nightclubs) were particularly effective, with an estimated combined effect in reducing R_t by 35% [95% CI: 29–41%], whereas closing educational institutions had an estimated 7% [95% CI: 4–10%] effect.

Several surveillance studies have shown the dramatic impact of COVID-19-related social distancing measures on circulation of other RVIs like influenza. In addition, an observational study in Guangdong Province, China found that combined NPIs instituted for COVID-19 prevention reduced not only respiratory diseases but also a range of non-respiratory infectious diseases including gastrointestinal, vector-borne, and sexually transmitted ones (Xiao et al., 2021), and similar reports on NPIs for COVID-19 reducing other RVIs and non-respiratory infections have come from other countries.

Given the experience with COVID-19, several questions have been raised regarding NPIs with regard to future RVI outbreaks. For example, is COVID-19 at the highest level of the influenza pandemic severity scale? Will there be more enthusiasm to use NPIs including facemasks and work-at-home policies for severe seasonal influenza epidemics? For pandemic events, how effective might earlier border closures and other travel restrictions prove? What are the consequences of interventions like prolonged school or business closures? The data being gathered during the current pandemic may help to provide answers to some of these and other questions.

6.3. Preventing RVIs in pregnant women and infants

Marta Nunes, Wits vaccines and infectious diseases Analytics, South Africa

RVIs are responsible for significant maternal, neonatal and young infant morbidity and mortality. Compared to non-pregnant women, pregnant women with influenza infection are at higher risk for hospitalization and death (Mertz et al., 2017; Tempia et al., 2015). Influenza illness during pregnancy has also been associated with an increased risk of preterm birth and of fetal death (Fell et al., 2017). In 3 RCTs conducted in LMICs, the efficacy of maternal influenza immunization against influenza illness ranged between 31 and 70% in the women and 30–63% in their infants up to 6 months of age (Nunes and Madhi, 2018). Moreover, a retrospective study, in 4 well-resourced countries, estimated a vaccine effectiveness of 40% (95% CI, 12–59%) against maternal influenza-associated hospitalizations (Thompson et al., 2019) while in infants born to vaccinated mothers a pooled analysis of observational studies estimated an overall 72% reduction in the risk of influenza-related hospitalizations (Nunes and Madhi, 2018). Another pooled analysis from the RCTs showed a 20% reduction in severe pneumonia episodes in infants born to mothers immunized during pregnancy (Omer et al., 2018). It is notable that offspring of influenza A-infected pregnant mice have increased susceptibility to viral and bacterial infections in early life (Jacobsen et al., 2021). Such observations strongly support current recommendations for influenza immunization during pregnancy.

While the adverse impact of RSV infection during pregnancy is less clear than for influenza, RSV burden is high in young infants and this has led to attempts at maternal RSV immunization. One RCT enrolling 4636 pregnant women found that an investigational RSV F-protein nanoparticle vaccine had a non-significant vaccine efficacy of 39.4% (95% CI, 5.3–61.2%) in preventing medically significant RSV-LRTI up to 90 days of age (Madhi et al., 2020). Other large-scale Phase 3 trials of maternal RSV immunization utilizing pre-fusion F vaccines, including the GSK GRACE Study (NCT04605159) and the Pfizer MATISSE study (NCT04424316), are ongoing. Although the efficacy of monthly palivizumab prophylaxis in certain high-risk infant groups in reducing the risk of RSV hospitalization is well established, the administration challenges and costs limit its wide clinical use. A RCT of single-dose nirsevimab (MED18897), a potent F-protein inhibitor with a prolonged plasma elimination half-life, in healthy preterm infants demonstrated reduced medically attended RSV-LRTI through 150 days after dosing with an efficacy of 70.1% (95% CI, 52.3–81.2%) and RSV-associated hospitalization with an efficacy of 78.4% (95% CI, 51.9–90.3%) (Griffin et al., 2020). Ongoing trials are investigating its efficacy in high-risk infants eligible to receive palivizumab (NCT03959488) and in healthy infants entering their first RSV season (NCT03979313).

COVID-19 in pregnant women is associated with increased risk of poor maternal outcomes (Zambrano et al., 2020). Severe COVID-19 during pregnancy has also been linked to increased risk of preterm birth and stillbirth (Wei et al., 2021). Following mRNA vaccine administration, serum SARS-CoV-2 binding and neutralizing antibody responses appear to be similar in pregnant and non-pregnant women and are detectable in cord blood and breast milk, albeit at lower concentrations than in serum (Collier et al., 2021). No pregnancy-related safety signals with mRNA vaccines have been detected to date (Falsa-perla et al., 2021).

In summary, maternal immunization can protect the mother against infection, reduce the risk of transmission to the newborn, and provide direct protection against infection in the infants through transplacental transfer of antibodies or via antibodies secreted in breast milk.

6.4. Media and risk communication

Glen Nowak, University of Georgia, Athens, GA, USA

Public health officials and others involved in communicating

outbreak policies and recommendations to the public need to understand how the different types of media operate and how they can exert influence (Nowak and Cacciatore, 2020; Nowak et al., 2020; Tumpey et al., 2019). The media environment is complex and varies across and within countries (e.g., media access and availability is greater in metropolitan and urban areas and less in rural areas). The term media is broad-ranging and encompasses physical (e.g., newspapers and magazines), broadcast (e.g., television and radio), and digital (e.g., online, internet, and mobile phones) modes of dissemination, as well as government-owned versus company-based outlets (e.g., paid advertising, donated public service announcements) and “earned” media time or space (e.g., articles written by journalists or reporters).

Optimally, the roles of the news and government-owned media in an infectious diseases outbreak are to inform about the risks of the outbreak and the importance of public health measures, educate about the pathogen and the rationale for the public health recommendations, and to encourage compliance with the measures. In reality, media including news media, often primarily operate to attract and hold as large an audience as possible, because this increases their influence and/or profitability. Consequently, information is often presented in ways that have a clear bias or viewpoint, often with focus on conflict, controversy, crisis, unexpected developments, and/or failure.

There are many ways media, particularly news media, can engage when it comes to a significant outbreak, such as shown during the COVID-19 pandemic (Table 1). News and social media can help government and public health officials and those involved in the outbreak response by quickly and broadly providing clear information to those at risk, including healthcare workers and the public at large. News and information media often have more credibility and trust with their audience members than government officials or experts. News and information media can enhance the visibility of public health recommendations and actions, including in ways that are more understandable (e.g., stories and examples that illustrate benefits, risks, and/or the value of certain actions). However, news media are necessary but likely insufficient to achieve and sustain the needed levels of compliance and support for public health actions and recommendations over the course of an extended outbreak.

In future events, multiple types of media likely will need to be used, particularly for large-scale, prolonged outbreaks. As COVID-19 and flu pandemics have shown, media, particularly large and influential news media outlets, need access to data and expertise from government agencies and those involved in formulating policies and recommendations. Engagement with journalists and media organizations needs to be sustained, despite the significant time and resources required. Infrequent or poor engagement with news media enables individuals and organizations willing to engage quickly and continually to provide and amplify misinformation or disinformation without rebuttal. Because it is very difficult to achieve extended media visibility for more than one

Table 1

Examples of news media roles during the COVID-19 pandemic.

- Data compilation, summaries, and tracking; monitoring and surveillance
- Providing daily and weekly updates, summaries, and assessments
- Making visible positive, negative, and notable individual experiences (e.g., with COVID-19 disease or vaccination)
- Increasing the understanding and utility of public health and scientific data and information through graphics, visuals, videos, and interactivity
- Advocacy (e.g., government and public health action; access and availability to diagnostic tests, vaccines, adoption of preventive measures; inclusion and equity; government investments in treatment, research, and prevention).
- Accountability, including examining the actions and interests of those involved in pandemic response efforts as well as the effects and effectiveness of public health actions and recommendations
- Countering misinformation and disinformation
- Questioning, challenging, and opposing assessments, actions, and recommendations from those involved in the outbreak responses
- Providing interpretation, perspectives, opinions, and differing or opposing viewpoints

health threat or outbreak at a time, there is the risk that other threats will achieve less media attention during a pandemic. In summary, information and messages disseminated by the news media are an essential part of an outbreak response but the increasing complexity of the media landscape needs to be taken into account in outbreak communication.

7. Short presentations: prevention

7.1. Global study of adults hospitalized with influenza, RSV and hMPV

Ann R. Falsey University of Rochester, Rochester, NY, USA, on behalf of the HARTI study group

This study examined the global burden (42 sites in 12 countries) of adult hospitalization with acute respiratory tract illness (ARTI) from influenza, human metapneumovirus (hMPV) and RSV. The study, conducted from 2017 to 2020 in hospitalized adults >18 years old, confirmed that all 3 viruses can cause severe disease requiring hospitalization with risk factors including older age, compromised immunity, and underlying cardiorespiratory diseases. The aetiology of the ARTI was either confirmed during normal clinical practice or as a study-specific procedure.

The primary endpoint of the main study assessed the distribution of influenza, RSV and hMPV virus in hospitalized adult patients. In a substudy the primary endpoint assessed the medical burden of these respiratory viruses in hospitalized adults, and the secondary endpoints assessed data on viral load, symptom kinetics as well as clinical outcomes up to 3 months after hospitalization. 3861 patients were enrolled of whom 16.7% (644 patients) had influenza, 6.4% had RSV and 2.8% had hMPV. Of 709 patients in the substudy 51.6% had influenza, 33.6% had RSV, and 14.1% had hMPV. Individuals were hospitalized within 3 days of ARTI. RSV and hMPV patients were older, hospitalized later, had more core risk factors (chronic cardiac or pulmonary disease) and greater length of stay (LOS) than influenza patients. Pneumonia was the most common clinical syndrome for all viruses. RSV and hMPV patients more often needed supplemental oxygen compared to influenza. Influenza patients had lower NEWS (severity) scores than RSV and hMPV patients. There was no statistically significant difference between viral load for influenza A and B patients, although influenza B patients had higher viral load if they were hospitalized for >3 days. A higher percentage of RSV (12%) patients required ICU stays compared to influenza (8%) and hMPV (8%). For RSV B patients, a higher viral load was associated with a greater LOS. In multivariate analysis, greater LOS was associated with abnormal chest X ray, the need for supplemental O₂, chronic kidney diseases and 10-year increase in age. The use of supplemental O₂ was significantly associated with RSV and hMPV infection, as well as a greater severity of illness, chronic obstructive pulmonary disease, female gender and older age. Interestingly, for influenza and RSV 40% of patients had not returned to their normal state of health after 3 months. Overall RSV-infected patients were older, had more comorbidities and required longer hospital stays than influenza, highlighting the importance of prevention strategies such as evaluation and licensing of RSV vaccines in older adults.

7.2. Impact of the COVID-19 NPIs on influenza and other respiratory viral infections in New Zealand

Sue Huang, WHO national influenza centre, Wellington, New Zealand

Data was presented from the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) network. SHIVERS was established with a grant from US CDC to conduct research to understand influenza disease burden, viral aetiologies of ILI-associated risk factors, as well as vaccine effectiveness (VE) and preventive measures to reduce the burden of respiratory disease. New Zealand has a good public health system allowing linking of health data

in a well characterized population. SHIVERS consists of hospital based severe acute respiratory illness (SARI) surveillance, sentinel general practice-based ILI surveillance and human longitudinal cohorts. Initially based in Auckland, the study has been extended to Wellington with adult, infant, and household cohorts. During the COVID-19 pandemic the SHIVERS studies were used to measure the rates of SARI, ILI and the impact of NPIs on reducing disease burden.

From the end of March 2020 to the end of April 2021 the national stringent lockdown in New Zealand with closed borders, family bubbles, and social distancing eliminated the SARS-COV-2 virus after the first pandemic wave. Multiple surveillance systems showed much lower SARI incidence after these stringent NPIs were implemented, with no influenza cases and lower health-seeking rates across mild, moderate and severe disease levels (Huang et al., 2021). In 2021 SARI rates were higher than 2020 but most cases were due to RSV and no circulating influenza was detected. RSV is suspected of having been imported from Australia after New Zealand opened its border to Australia around the end of April 2021 and did not require isolation of travellers; whole genome sequence data are pending. Only 11 cases of influenza were detected during Jan–October 2021 mainly in returning travellers, whereas RSV was found at 7 times higher than baseline in children from 2015 to 2019. Ongoing SHIVERS studies include surveillance utilizing an extended definition of ARI, enhanced traveller surveillance using left over swabs from routine COVID testing, and an expanded hospital-based network in Southern Auckland. These ongoing studies are being conducted to understand why New Zealand did not have any influenza in 2020–2021 and what happened to non-influenza respiratory viruses.

7.3. A universal mRNA influenza T-cell vaccine and protection against H7N9 challenge in ferrets

Jørgen de Jonge, RIVM, Utrecht, The Netherlands

Universal influenza vaccines are urgently needed to provide broader and longer lasting immunity to protect against both seasonal and pandemic influenza. The internal proteins of influenza are highly conserved between different influenza viruses and contribute to broader protection. Therefore, a new mRNA T-cell vaccine coding for the internal NP, M1 and PB1 proteins of pandemic influenza A(H1N1) virus was developed and tested in the ferret model. The model to measure respiratory T cells (van de Ven et al., 2020) to show heterosubtypic protection was developed previously. In the current study, a group of ferrets was first infected with A(H1N1) virus and then boosted with the mRNA vaccine 6 weeks later, resembling the adult human situation (boost group). Another group of naïve ferrets received a prime-boost mRNA vaccine, resembling naïve children (prime-boost group). Both groups had a significant boost in NP, M1 and PB1 specific IFN- γ secreting T cell responses in blood 4 weeks after boosting compared to a group that only received an A(H1N1) infection. Moreover, these responses were also reactive to heterosubtypic viruses. IFN- γ responses of CD4⁺ and CD8⁺ T-cells after stimulation with pools of peptides from NP, PB1 and M1 were increased in the boost group and were higher than in the prime-boost group and after two heterosubtypic infections as measured by flow cytometry. Furthermore, mRNA vaccination could boost the local existing T-cell response induced by previous A(H1N1) infection in nasal turbinates, lung tissue and the bronchoalveolar lavage (BAL). Strikingly, intramuscular prime-boost mRNA vaccination induced local T-cells in the nasal turbinates and lung tissue, but not in the BAL. Seronegative ferrets were challenged intratracheally with A(H7N9) to investigate T cell protection from severe pneumonia. The placebo group had up to 20% weight loss by day 5, whereas the boost group was protected from severe weight loss and had almost no clinical symptoms and less virus replication in the lungs. Singly infected animals had reduced weight loss, however, with similar clinical symptom scores as the placebos. Moreover, mRNA boosting of A(H1N1)-primed ferrets showed enhanced protection against severe pneumonia compared to only A(H1N1)-primed ferrets as was shown by a significant reduction in

lung oedema. Overall, the mRNA vaccination boosted existing systemic and local T-cell responses, reducing disease and viral replication. mRNA vaccination is a promising strategy to contribute to heterosubtypic protection.

7.4. Efficacy and immunogenicity of an Ad26.RSV.preF-based vaccine in older adults

Christy A. Comeaux, Janssen vaccines & prevention BV, Leiden, The Netherlands on behalf of the CYPRESS investigators

There are currently no licensed RSV vaccines. The burden of disease in older adults is substantial, and in the USA, 137 to 256 hospitalized RSV cases have been reported per 100,000 population in ≥ 65 -years old (Branche et al., 2021). Efficacy and immunogenicity data were presented for an adenovirus-based RSV vaccine in a randomized, double-blind, placebo-controlled Phase 2b trial in patients aged ≥ 65 years old (CYPRESS (NCT03982199)). The vaccine consists of two components: a replication-deficient adenovirus (Ad26) expressing the RSV prefusion F protein (preF) and soluble recombinant preF protein. Administered intramuscularly, the vaccine has previously been shown to induce robust humoral and cellular immunity (Williams et al., 2020) and the Ad26.RSV.preF component alone shown to provide protection in a controlled human challenge model (Sadoff et al., 2021).

The aim of the trial was to demonstrate the efficacy of Ad26.RSV.preF-based vaccine in preventing RSV-mediated lower respiratory tract disease (LRTD). Conducted in 40 sites in the US, the trial randomized older adults (≥ 65 years old) with stable health prior to the RSV season at 1:1 ratio of vaccine ($n = 2900$) or placebo ($n = 2900$). Acute respiratory infection (ARI) surveillance was conducted via smart phone up to March 2020 in the first season. After reporting an ARI, participants filled out a daily symptom questionnaire and performed nasal self-swabbing on ARI day 1 or 2. On ARI day 3, 4 or 5, participants attended the study site for a clinical visit and an additional collection of a nasal swab and optional sputum sample for RT-PCR-confirmation of RSV. The primary endpoint was RSV-mediated LRTD.

The participants were evaluated in age subgroups of whom 73.6% were aged 65–74 years, 23.7% were aged 75–84 years, and 2.6% were aged ≥ 85 years. The vaccine efficacy for RSV-mediated LRTD was statistically significant and ranged from 69.8% to 80.0% depending upon the case definition. Using the most severe case definition of ≥ 3 symptoms of LRTI, the vaccine efficacy was highest in the 65–74 years (81.7%) but still 75.1% in the 75–84 year-old adults, whereas there were no RSV-positive LRTI in patients ≥ 85 years during the RSV season. The vaccine was safe and well tolerated. Administration of the vaccine significantly increased RSV neutralizing antibodies, which were maintained over baseline at 6 months post-vaccination, and also induced durable IFN- γ -secreting T-cells across the different age groups. In summary, no impact of age on vaccine immunogenicity was observed. Overall, the Ad26.RSV.preF-based vaccine was highly efficacious in preventing RSV-mediated LRTD in adults aged ≥ 65 years.

7.5. Influenza vaccination and COVID-19

Seyed M Hosseini-Moghaddam, University of Toronto, Ontario, Canada

Results were presented of a large-scale retrospective cohort study to investigate the impact of influenza vaccination on SARS-CoV-2 infection, hospitalization, and mortality. Influenza vaccination has been reported to reduce the risk of COVID-19, perhaps through stimulating a non-specific immune response, vaccine-associated viral interference, or other immune-mediated effects. Alternatively, the reduction in COVID-19 events after influenza vaccination could be associated with improved health awareness, residual confounders or a selection bias.

The study was conducted in all community-dwelling adults aged > 66 years living in Ontario, Canada with the index event defined as influenza vaccination for two consecutive influenza vaccination campaigns from

1st October 2019–31st March 2020 and 1st October 2020–31st March 2021. The objective of the study was to evaluate the impact of influenza vaccination on laboratory-confirmed SARS-CoV-2 infection, hospitalization, and 30-day all-cause mortality death following a positive SARS-CoV-2 test. The primary outcome was laboratory-confirmed SARS-CoV-2 test ≥ 14 days after influenza vaccination. Exclusion criteria included pending or missing COVID-19 test results, missing or unknown birth date or sex, residents of long-term care facilities, no contact with health care systems during the last 3 years, or receipt of SARS-CoV-2 vaccines.

Overall, 2,279,805 individuals were included in the study. After adjusting for covariates, a multivariable Cox proportional hazards model was used to estimate adjusted hazards ratios [aHR] for the associations between influenza vaccination and SARS-CoV-2 outcomes. In each annual cohort, a significant negative association was observed between people who received influenza vaccine and SARS-CoV-2 infection [aHR: 0.78 in 2019–20 and 0.76 in 2020–21], in 14-day hospitalization rates [aHR: 0.68 in 2019–20 and 0.81 in 2020–21], and 30 day all-cause mortality [aHR: 0.73 in 2019–20 and 0.58 in 2020–21]. Because healthy vaccination user bias may have explained the differences observed, periodic health examinations were evaluated. Older people who had periodic health examinations had reduced risk of SARS-CoV-2 infection [aHR: 0.85], hospitalization [aHR: 0.79], and death [aHR: 0.82], but were less likely to be tested for COVID-19. There was a greater negative association in SARS CoV-2 outcomes in people who had regular health examinations than in those that did not, findings which suggest that the negative association found between influenza vaccination and SARS-CoV-2 outcomes may have been due to a healthy user bias.

7.6. Immunological imprinting of the antibody response in COVID-19 patients

Teresa Aydiillo Gomez, Icahn school of Medicine, NY, USA

Immunological imprinting is the ability of the body to preferentially recall immunological memory from an initial infection when experiencing a secondary exposure through infection or vaccination. The original phenomenon was first described for influenza viruses by Francis in 1960 as original antigenic sin. This phenomenon may exist for the four endemic human coronaviruses (CoV) (NL63, OC43, HKU1 and 229E) and the zoonotic ones (SARS-CoV-1 and SARS-CoV-2, as well as MERS-CoV). The aim of the study was to conduct longitudinal antibody profiling to investigate the role of pre-existing immunity and immunological imprinting on COVID-19 patients' antibody responses and disease outcomes. Thirty-seven hospitalized COVID-19 patients (30% severe, 70% mild) (Del Valle et al., 2020) were enrolled in Barcelona, Spain during the first wave of SARS-CoV-2. Nasopharyngeal swabs and blood were collected at days 0, 3, 7 and 46 post-hospital admission with a mean of 7 days after symptom onset. SARS CoV-2 IgG and IgM antibodies were tested in ELISA against the full-length spike, RBD and nucleoprotein (N), as well as neutralizing antibodies. Cross-reactive antibody responses against human seasonal CoVs, alpha-229E, and beta-OC43 and HKU1 (both full-length and S2 domain) were investigated by ELISA. All patients developed neutralizing and ELISA antibodies against SARS-CoV-2 by 7 days post hospitalization, and the convalescent antibodies persisted up to day 46. COVID-19 patients had a back-boosting of antibodies to the highly conserved S2 domain of human beta-CoV spike proteins (OC43, and HKU1), but not to that of alpha (229E) (Aydiillo et al., 2021). There was a negative correlation between pre-existing IgG against HKU1 and OC43 full length spike proteins and the induction of de novo antibodies against SARS-CoV-2. However, no correlation was found for pre-existing anti-229E S or HKU1 S1 domain IgG levels. There was a positive correlation between higher CT values by RT-PCR and higher SARS-CoV-2 antibody responses. However, no correlation was found between viral loads and antibodies against other human coronaviruses. Patients with severe disease had an earlier induction of S2 antibodies with higher ratios of S2/RBD antibodies

compared to moderately ill subjects. Overall, the back boosting effect to shared antigenic domains and conserved epitopes between SARS CoV-2 and beta seasonal coronaviruses occurs at the detriment of antibodies against the more divergent SARS-CoV-2 RBD.

8. ISIRV panel discussion: preparing for the Next Event: surveillance, clinical research, and prevention strategies

Chair: Michael Jacobs; panel: Ben Cowling, Peter Horby, Ann Moen, Vasee Moorthy, Maria Zambon

8.1. Building on past endeavors

Gains in preparedness since the 2009 pandemic included countries and NGOs, like WHO, strengthening their infrastructure for managing emergency responses. During this time GISRS has improved in the quality of reporting and geographic representativeness of surveillance for influenza. The GISRS system supported many of the early laboratory responses during the COVID 19 pandemic, highlighting its utility as a scalable system to test for SARS-CoV-2. The commitment within GISRS to sharing data and sequence information globally has underpinned the approach to sequence sharing for the COVID-19 pandemic. The implementation of the PIP framework in 2011 has supported equity in sharing and access to benefits of GISRS. Partnership contributions from industry have supported gains in pandemic preparedness for influenza, many of which have supported the current pandemic response.

8.2. Identification of gaps

Developing an information system to understand severity was a recommendation following the 2009 pandemic. WHO developed a Pandemic Influenza Severity Assessment (PISA) system to support countries in setting thresholds and understanding the magnitude of seasonal, and hopefully, pandemic influenza. Despite this, notable gaps in capabilities were highlighted, so that efforts to augment and build systems to understand severity early in such events need to continue.

8.3. Broadening surveillance

While the GISRS was built for influenza, influenza surveillance also suffered during the pandemic as efforts focused on SARS-CoV-2. A strategic view towards a broader array of respiratory pathogen threats will help build resilience and support the development of more agile systems. As detection technologies converge, they become pathogen agnostic, making it easier for laboratories to implement detection strategies that use the same principles for a wider range of target organisms. GISRS has proven an excellent network and efficient way to use the same samples to test for multiple respiratory pathogens. During the pandemic over 90% of National Influenza Centers in GISRS have already integrated SARS-CoV-2 testing on their GISRS platform.

Work had begun to incrementally expand the GISRS platform to include RSV in 2015. The WHO RSV program was developed to provide baseline, pre-intervention data, against which the impact of interventions could be judged. The surveillance program, integrating both lab and epidemiology, is an example of targeted systematic molecular surveillance designed to provide information to support vaccination/therapeutic programs. While RSV surveillance was affected by the pandemic, the work to establish capability in the countries participating has largely been implemented, despite the difficulties.

8.4. Future integrated surveillance

A more integrated syndromic surveillance platform for detection of multiple respiratory pathogens is the most rational way forward. Given the overlaps in case definitions and clinical presentations, similarity in some of the vaccine target populations and ability to use sentinel

surveillance to estimate burden, the concept of GISRS Plus, tracking influenza and SARS-CoV-2 jointly becomes a cost-effective approach to surveillance and generating data to inform policies for prevention and control. Efforts to build on established country capacities with a view toward tracking a broader range of respiratory pathogens will serve global surveillance well. This will mean all member states having a national level surveillance program for key respiratory viruses of public health importance, with strong encouragement to develop sentinel surveillance for systematically sampling specific segments of the population.

8.5. Diagnostics developments

Societal expectations on testing have changed, and vastly more testing has taken place during this pandemic than is routine. The diagnostics industry has responded by increasing the diversity of offerings, including antigen detection platforms for in-home use and the multiplex technologies to enable multiple pathogen testing on the same samples. The latter is both efficient and cost-effective in providing much more information from the same material at approximately the same cost, "more for less".

Such data also gives the opportunity to study the interplay between the circulation of different pathogens and will enable the linking of clinical, surveillance and genomic data to understand more about the viruses and the populations affected, including severity. Improvements to near patient testing and development of good biomarker-based systems are some innovations that we should strive for to support clinician decision-making and improve information from clinical trials.

8.6. Global sequence data sharing

The power of global sequence databases to track the molecular evolution of individual pathogens, the importance of systematic sequence sharing, and the value of these systems for early warning cannot be overestimated. Sharing of the first SARS-CoV-2 sequence on 10th January 2020 was instrumental in warning the world what was circulating and enabling the rapid development of specific diagnostics and vaccines. The importance of this capability has been amply demonstrated and will be the expected early warning response capability.

8.7. Importance of data linkage

An example of changes arising from the pandemic was the increased realization of the potential for data linkages to deliver added value and the benefit of collaborative sharing across clinical and public health domains. Linking laboratory, surveillance, sequence, and clinical data will lead to greater gains in understanding the virus and the host response and accelerating advances in prevention and treatment. Developing and instituting these systems now will provide greater evidence for assessing and managing epidemics of seasonal pathogens and future pandemic events.

8.8. Non-pharmaceutical interventions

There was unprecedented use of NPIs or public health and social measures (PHSM), although use varied greatly from country to country. An understanding of the utility of the various NPIs (e.g., total lockdown, restricting large gatherings, mask wearing) needs to be further studied to apply them more strategically in the future. Trying to tease out which NPIs were applied in various settings, which resulted in greater reductions in transmission, and which layered NPIs offered a cumulative effect needs to be understood based on evidence gathered through the pandemic. Work also needs to be done to make the most of data from COVID-19 on suppression of other infections and to start planning how to improve the evidence base on reducing influenza transmission

through school-based and workplace measures that fall short of complete facility closures.

8.9. Clinical trial networks

A ready and robust clinical trials network system is important for preparedness and response. Improving the generation of high-quality evidence to drive public health decisions that benefit the clinician and patient and the public at large, including clinical trials for new pharmaceutical interventions and information needed to support rapid evaluation for regulatory approval, should be a priority. Expanding clinical trials networks and driving home the importance of prioritizing randomized evidence will enable societal and government decisions to follow the science as much as possible. One panel member noted that we cannot assume that clinical trial expertise/capacity necessarily leads to use of evidence in decision-making. In the current pandemic, the evidence generated by large, adaptively designed platform trials, generally sponsored by the public sector and academia rather than industry, have been highly impactful for translation into decisions.

In preparing for the next pandemic links between non-communicable diseases (diabetes, cancer, hypertension etc.) and infectious diseases trials networks should be maintained/strengthened, and more emphasis placed on out-patient networks/capacity. Networks need to sustain investigative activities in the inter-pandemic period to both maintain functionality and address relevant questions.

As new decisions about resource allocation are made, an assessment of the networks already in place when the pandemic occurred and those launched in response, needs to be undertaken to determine which efforts led to success and yielded important information for public health. Such a review should take place before making decisions about resource allocation to strengthen clinical trials capacity/networks.

8.10. Future preparedness

A broader respiratory vision, to support country capacity in the future and understand the interplay between respiratory pathogens is needed. Harnessing the power of data of all types and building cross linkages between surveillance, genomics, patients and clinical trial networks will support improved public health decision making based on evidence and preparedness for the future.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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