Virus Infection and Systemic Inflammation: COVID-19 and Beyond

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Respiratory infections with newly emerging zoonotic viruses such as SARS-CoV-2, the etiological agent of COVID-19, often lead to the perturbation of the human innate and adaptive immune responses causing severe disease with high mortality. The responsible mechanisms are commonly virus-specific and often include either over-activated or delayed local interferon responses, which facilitate efficient viral replication in the primary target organ, systemic viral spread, and rapid onset of organ-specific and harmful inflammatory responses. Despite the distinct replication strategies, human infections with SARS-CoV-2 and highly pathogenic avian influenza viruses demonstrate remarkable similarities and differences regarding the mechanisms of immune induction, disease dynamics, as well as the long-term sequelae.

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1. Introduction

As zoonotic viruses with diverse reservoirs in their natural animal hosts, both, Influenza A viruses (IAV) and Coronaviruses (CoV) pose a constant and significant pandemic threat to the human population. While endemic strains of IAV and CoV cause recurring seasonal waves of respiratory disease with flu-like symptoms, ongoing intra-host evolution in animal reservoirs, the progressive destruction of natural habitats and climate change along with increased animal trade and consumption are critical factors that increase the chances of human infections with zoonotic viruses, such as highly pathogenic avian influenza A viruses (HPAIV) of the subtypes H5N1, H7N9, or H5N8 as well as the newly emerged pandemic severe acute respiratory syndrome coronavirus Type 2 (SARS-CoV-2), the causative agent of coronavirus disease-19 (COVID-19). Infections can occur by direct contact to infected animals or contaminated environments and can cause severe, often lethal disease.

Confrontation of such non-human-adapted viruses with the highly evolved and multilayered human immune system often leads to an inbalanced activation of the early innate immune response pathways, which facilitates a perturbation in the recruitment of immune cells and their activation [1][2].

2. Crossing the Species Barrier—Human Infection with Zoonotic Viruses

Zoonotic transmission and establishment of a robust infection by CoV and IAV are spontaneous and sporadic events that are majorly determined by the degree of adaptation to the human receptors, which provides the first species barrier. In addition, the duration and type of contact to the infected animal are decisive. While human–human transmission is still rarely observed in case of HPAIV [3][4][5][6][7] due to a persisting incompatibility of the viral receptor-binding protein Hemagglutinin (HA) to the human type α2-6-linked sialic acid [8][9], the newly emerged zoonosis SARS-CoV-2 already crossed this species barrier by harboring a spike (S) protein that is capable of utilizing the human angiotensin-converting enzyme 2 (ACE2) protein as a receptor [10]. Pre-symptomatic airborne transmission from the upper respiratory tract (URT) as well as the absence of pre-existing immunity within the human population and the unavailability of vaccines or approved antiviral treatments were additional factors that contributed to the rapid virus spread and high mortality in humans in the first months of the pandemic. In order to prevent the collapse of healthcare systems and interfere with viral transmission, rapid enforcement of non-pharmaceutical interventions such as face masks, strict social distancing, contact tracing, and isolation of infected individuals were utilized. Despite these drastic measures, SARS-CoV-2 caused devastatingly high numbers of infections worldwide with severe pneumonia and high mortality in the first months [11]. In an exceptional effort, only one year later, highly efficient mRNA and adenovirus-based vaccines encoding the SARS-CoV-2 S protein were available and together with the nucleoside analog remdesivir, the first antiviral drug with emergency use approval for COVID-19 patients, resulted in a remarkable reduction of fatal cases in countries with access to these measures [12][13]. However, the S protein has demonstrated a high plasticity for continuous evolution which resulted in the emergence of viral variants with improved binding capacities to ACE2, alternative entry mechanisms, and partial evasion from the adaptive immune responses that are evoked by natural infection or vaccination as well as therapeutically used antibodies [14][15][16][17]. These unpredictable developments have resulted in the emergence of numerous subdominant and also several dominant viral variants that displayed individual characteristics of transmissibility and pathogenicity, which still pose a challenge to the clinical management of COVID-19.

3. From Local to Systemic—Disease Course and Immune Responses

Disease severity and dynamics of the viral infections are majorly determined by the cell types that express the receptors and thereby dictate the tissue tropism of the virus. CoV and IAV are both airborne viruses that initiate the infection in cells of the human URT and lower respiratory tract (LRT) [18][19]. While seasonal CoV and IAV mainly infect the UTR, SARS-CoV-2 and HPAIV can also infect the LRT, which confers the higher pathogenicity of these viruses. Human lung biopsies of deceased infected individuals and ex vivo infections of human lung tissue have indicated that human lung stem cells in the LTR, known as alveolar type II pneumocytes (AT-II) are a preferred target of SARS-CoV-2 as well as IAV [19][20][21][22][23]. Other cells have also been shown to facilitate viral infection and replication, but infection of LTR cells is associated with severe disease [24][25]. Interestingly, classically activated M1 alveolar macrophages (AM) have been shown to be susceptible to infection by SARS-CoV-2 and contribute to viral spread. Supposedly the lower endosomal pH of activated M1 AMs promotes membrane fusion and virus replication. In contrast, activated AM of the M2 phenotype suppress viral replication by channeling the virus particles to lysosomal degradation [26]. Beyond the cells of the respiratory tract, SARS-CoV-2 replicates

systemically and also infects cells in several other organs, including intestinal epithelial cells, endothelial cells, and renal parenchymal cells ([27] and [28]), which contributes to the pathogenicity of COVID-19.

Clinical manifestation of COVID-19 is diverse, ranging from asymptomatic patients to severely affected patients and death. Infected individuals can shed virus particles even in a pre-symptomatic period with a peak of infectivity two days before and one day after symptom appearance [29]. Symptoms normally arise after an incubation time of five days and 14 days after exposure in symptomatic individuals [30]. The most common symptoms include fever, cough, fatigue, anosmia, and dyspnea [31][32]. Patients have also reported a sore throat, diarrhea, and nausea [33]. Interestingly, frequently reported symptoms differ between some of the SARS-CoV-2 variant strains. In general, studies suggest a similar symptom range for Alpha-, Beta-, and Delta-infected patients. Additional to the described symptoms for the initial SARS-CoV-2 strain, Alpha patients most commonly suffer from fatigue and headaches [34]. Delta causes a more rapid disease course with higher viral titers on top of specific auditory impairment and gangrene from blood clots [35][36]. In contrast to that, patients that are infected with Omicron suffer more likely from severe fatigue, sore throat, and hoarse voice, but significantly less from loss/altered smell, eye soreness, and sneezing, while hospital admission is also reduced in general [37]. A case study in Europe suggests two disease classifications: on the one hand, individuals with high viral loads in the respiratory tract without severe illness and on the other hand, a two-step progression with decreasing viral loads in the URT but significant worsening of symptoms after around 10 days [38], which develops into severe pneumonia and acute respiratory distress syndrome (ARDS). Severe COVID-19 correlates with systemic viral replication and high blood levels of inflammatory cytokines, which can turn into uncontrolled systemic inflammation that is associated with fever, tachycardia, tachypnea, and hypotension [39][40] as well as extrapulmonary manifestations such as acute kidney injury or thrombosis [41][42][43][44] resembling sepsis characteristics. Consequently, inflammatory manifestations of COVID-19 include cutaneous, hematological, neurological, cardiovascular, renal, pancreatic, endocrine, and ocular involvement additional to the pulmonary damage [45].

Interestingly, the clinical picture of human infections with HPAIV shares some striking similarities to COVID-19. Since the first human case in 1997, more than 1700 cases of human infections with HPAIV of the H5N1 subtype with a case fatality rate of approximately 50%, and more than 60 cases of H5N6 infections were reported globally. Only recently, the UK and USA each reported a case of human H5N1 infection in 2021 and 2022, respectively [46]. In addition, more than 1500 infections with low pathogenic avian influenza viruses (LPAIV) of the H7 subtypes (the majority being H7N9) along with H6N1, H9N2 and H10N3, H10N7, and H10N8 were reported until today with symptoms ranging from mild conjunctivitis to severe pneumonia [46]. Although the clinical data on human infections with HPAIV are still very limited, the reported symptoms, clinical manifestations, and risk factors resemble the clinical reports from severe COVID-19. Early symptoms include common flu-like features such as fever, cough, malaise, myalgia, headache, and sore throat, sometimes abdominal pain and diarrhea. Disease progression can be rapid as exemplified by a case report from a H5N6 infection that described how the appearance of fever above 38 °C was followed by hospitalization of the patient and transfer to intensive care unit (ICU) due to dyspnea in a time-frame of two days [47]. Most laboratory-confirmed H5N1 cases are already hospitalized patients with severe complications such as ARDS, pneumonia, and multi-organ failure [48]. In addition, leukopenia and lymphopenia, decreased platelet counts, and internal bleeding due to extensive organ damage, especially in lung tissue, were

reported. Other complications included encephalitis and septic shock which eventually lead to death within a median time of nine days post-symptom onset [3][49][50][51][52][53][54][55][56][57]. Similar symptoms were reported for human cases with other avian-derived influenza viruses [58][59]. Similar to COVID-19, several studies report that individuals with severe disease following infections with H5N1 presented elevated concentrations of circulating pro-inflammatory cytokines. These included Interleukin-6 (IL-6), Tumor necrosis factor alpha (TNF-α), Interferon gamma (IFN-γ), Interferon gamma-induced protein 10 (IP-10), and Monocyte chemoattractant protein-1 (MCP-1), which were not only higher compared to individuals that were infected with seasonal influenza viruses but also fatal cases demonstrated higher levels compared to the survivors [51][60][61]. While the number of case reports on human H5N1 infections is rather small compared to COVID-19, the immunopathology of H5N1 infections has been studied in diverse experimental models in vitro, ex vivo, and in vivo. Importantly, the results demonstrate a controversial role of cytokines for viral pathogenesis, which suggests that instead of a general over-activation, the induction of imbalanced inflammatory responses, mediated by virus-specific mechanisms, is one of the leading causes for the pathogenesis of HPAIV in humans [62][63][64][65][66][67]. In line with this, several studies demonstrated that anti-inflammatory therapeutic approaches alone were not sufficient to reduce lethality, suggesting that a combination of antiviral and anti-inflammatory treatments is more suitable [68][69], which has been revealed to be of similar importance for the treatment of COVID-19.

4. Biomarkers for the Prediction of Disease Progression in COVID-19 and Infections with HPAIV

Improved understanding of risk factors, prediction of individual disease trajectories, providing information on suitable and disease-targeted therapeutic interventions, as well as the identification of reliable biomarkers and clinical characteristics including immunological and inflammatory proteins, hematological, and organ-specific markers are still the most investigated fields in COVID-19 and IAV research. The description of host genetic and transcriptional markers in experimental infection is relatively common and has revealed promising candidates such as IFI27, which appears to be an early marker also for other respiratory virus diseases to facilitate early infection recognition [70][71]. However, the identification of reliable clinical conditions and biomarkers in patients is by far more complicated. A retrospective study could show an association between initial anemia and increased mortality as well as between a higher ferritin/transferrin ratio and the need for ICU admission with mechanical ventilation [72]. Lymphocytopenia seems to directly correlate with a fatal outcome. Lower lymphocyte counts were found in patients with ARDS, ICU patients, and non-survivors [73][74]. Similar to influenza patients, elevated levels of C-reactive protein (CRP) and also procalcitonin were found to serve as good predictors of severe outcomes [75][76][77]. Elevated levels of the pro-inflammatory cytokine IL-6 could be identified as an important marker for the severity and bilateral lung involvement as well as a predictor of mortality [78][79][80][81]. In addition, high blood levels of IL-1β, IL-2, IL-8, IL-17, G-CSF, GMCSF, IP-10, MCP-1, and TNF-α are indicative for severe COVID-19 [82]. Similarly, levels of D-dimer above 2.0 µg/mL on hospital admission and increased LDH levels were identified to predict mortality [73][83][84]. The results of the MYSTIC study found that the levels of endothelial and glycocalyx markers were indicative for substantial glycocalyx damage that was correlated with a more severe outcome during COVID-19 [85].

Due to the limited number of clinical cases with human HPIAV infections, the identification of solid biomarkers for severe Influenza is less robust. Nevertheless, increased levels of C-reactive protein (CRP) plus the pro-inflammatory cytokines IP-10, CXCL9 (MIG), IL-8, and MCP-1 were higher in patients with H5N1 infections compared to seasonal IAV and associated with severe outcomes [86]. Other manifestations include lymphocyte count, thrombocyte count, and elevated creatinine and aminotransferase levels. A retrospective study of 22 patients from Indonesia also reported elevated D-dimers, CRP, and ferritin levels, revealing impressive parallels to the proposed COVID-19 biomarkers [87][88].

5. The Contribution of PRRs to the Innate Immune Responses during COVID-19 and HPAIV Infections

As the first line of defense, the organ-specific innate immune responses are important determinants for the severity of the disease progression in COVID-19 as well as infections with HPAIV [89][90]. Perturbation of these early responses has been demonstrated to significantly contribute to the immunopathology during later disease stages. Increased age and genetic factors that lead to low or abnormal innate immune response are, therefore, considered as risk factors to develop severe disease [28].

The transcriptional programs that are initiated by the host innate immune response in infected cells lead to the expression and activation of cellular proteins that limit virus replication, induce cell death, and warn neighboring cells to curtail viral spread. Intracellular pattern recognition receptors (PRRs) in epithelial and immune cells identify pathogen-associated molecular patterns (PAMPs) at different steps during the virus life cycle and initiate signaling cascades that lead to the induction of interferons (IFNs) together with diverse mediators of inflammation [91]. The different families of PRRs, including RIG-I-like receptors (RLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and Toll-like receptors (TLRs) are expressed on the cell surfaces as well as intracellular compartments and display individual binding preferences for pathogen-derived nucleic acids or proteins. Downstream signaling involves the two major adaptor proteins, myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF) that further activate different transcription factors such as NFκB and interferon regulating factors (IRFs) that regulate the expression of pro-inflammatory cytokines such as IL-6, IL-1β, and IL-8, in addition to type I, II, and III IFNs and TNFs [92]. The nature of the induced antiviral responses in an infected cell is largely determined by the cellular equipment with PRRs, the type of PAMP, the affinity of their receptors, and the virus-specific mechanisms to counteract recognition and signaling [93]. Emerging data also suggest an important role of AMs in the pathogenesis of COVID-19. However, reports provide a mixed picture of the permissiveness and functional contribution of AM to COVID-19 and studies are difficult to compare due to the application of different experimental models or readouts. Nevertheless, there seem to be unique features of macrophages of the M0, M1, and M2 phenotypes during COVID-19. Using a model of human pluripotent stem cell -derived macrophages Lian et al. demonstrated that these cells are not permissive to SARS-CoV-2 but are activated in response to antibody-mediated uptake of infected cells. The differences in the activation were suggested to derive from the expression of unique sets of PRRs that react to the recognition of virus-associated PAMPs [94]. Some studies argue that M1 macrophages upregulate inflammatory factors upon infection

[94], while other studies showed that challenged macrophages from bronchoalveolar lavage fluid with SARS-CoV-2 are incapable of producing IFNs suggesting that viral RNA is not sensed [95]. During influenza infections, AMs are susceptible to abortive infection and efficiently sense the release and replicated cytoplasmic viral RNA and the M2 protein. Consequently, the production of Type I IFNs, CXCL5, CXCL9, CXCL10, CXCL11, TNF-α, and members of the IL-1 family is upregulated [96].

Recent studies provided evidence for the contribution of RLRs and some TLRs as cytoplasmic sensors of viral PAMPs for the development of severe COVID-19 and infections with HPAIV [97][98][99][100][101]. While RIG-I was identified as the major sensor for IAV RNAs [102], SARS-CoV-2 infection is preferentially sensed via the recognition of viral intermediates by melanoma differentiation-associated protein 5 (MDA5)and Laboratory of genetics and physiology 2 (LGP2) in epithelial cells [103]. These differences are determined by the individual viral replication strategies within different cellular compartments and the different nature of the viral genomes. The interaction of activated RIG-I with the protein mitochondrial antiviral signaling (MAVS) induces TNF receptor-associated factor (TRAF), IκB kinase (IKK), TANK-binding kinase 1 (TBK1), and finally the transcription factors IRF3, IRF7, and NFκB for the induction of type I and type III IFNs [104]. By autocrine and paracrine binding to their respective receptors, IFNs activate the Janus kinase (JAK)/signal transducer and activator of transcription protein (STAT) pathway, which leads to increased levels of PRRs and the expression of interferon-induced genes (ISGs), such as the viral restriction factors Myxovirus resistance protein 1 (MxA), 2′-5′-oligoadenylate synthetase 1 (OAS1), and ISG15 that inhibit virus replication [93].

The contribution of these mechanisms to the excessive induction of pro-inflammatory cytokines during HPAIV and SARS-CoV-2 infections is widely discussed. A recent report suggested that especially aberrant viral genomes, consisting of the 3′- and 5′-promoters but harboring large internal deletions, which are produced by the non-adapted viral polymerase of avian-derived IAV viruses in human cells act as potent immune stimulators that contribute to cytokine overexpression [105]. In a pre-published report, a similar mechanism was proposed to occur upon SARS-CoV-2 infection. Here, an incompatibility of the viral polymerase with the host transcriptional machinery was proposed to result in the production of higher levels of partially double-stranded small viral RNAs (svRNAs) encoding the 5′ ends of positive-sense genes compared to the human-adapted CoV OC43 and 229E. svRNAs were a potent ligand for RIG-I and resulted in the expression of IFN-β [106].

Interestingly, higher expression levels of TLR1, TLR4, TLR5, TLR8, and TLR9 and the TLR-adaptor protein MyD88 were also positively correlated with the severity of COVID-19 [107]. In addition, in vivo experiments in TLR2-deficient mice revealed that TLR2 activation occurred by the SARS-CoV-2 envelope (E) protein and contributed to IL-6 induction [107]. Accordingly, another study supported the importance of the TLR2 and NFκB axis during SARS-CoV-2 infection [108]. Thus far, the role of other TLRs in COVID-19 is still under investigation. TLRs, majorly TLR3 and TLR7, are also essential for the induction of the innate immune response against influenza viruses especially in immune cells, however, a distinct role in the sensing of HPAIV infections is not well established [109].

In addition to RLRs and TLRs, the RNA-dependent protein kinase R (PKR) plays an important role for the innate immune response during IAV infections. It is reported that PKR is activated during viral infection by sensing short

stretches of double-stranded viral RNAs, which leads to the inhibition of the cellular translation initiation factor eIF2-α and facilitates a host translational shut-off to restrict viral protein synthesis [110]. In contrast to this mechanism, other studies suggest a role of PKR in the induction of overshooting IFN and cytokine levels by HPAIV. Krischuns et al. demonstrated that the replication of HPAIV activates the signaling cascade PKR/p38/MSK1, which facilitates phosphorylation of the host transcriptional co-repressor TRIM28 at serine 473. Intriguingly, this modification alleviates the co-repressor function of TRIM28 and leads to increased levels of IFN-β, IL-6, and IL-8 in lung epithelial cells [63]. Whether PKR activation is facilitated by viral RNAs, possibly the discussed aberrant vRNAs of HPAIV, remains to be shown. While it was suggested that PKR activation during SARS-CoV-2 infection contributes to the delayed onset of the IFN response, it is unknown whether there are additional mechanisms of PKR that contribute to the high induction of pro-inflammatory cytokines [111].

6. Adaptive Immune Response against SARS-CoV-2

While T-cell responses are generally developed early within 6-10 days after exposure to primary SARS-CoV-2 infection and protect against severe disease, delayed onset of T-cell responses due to imbalanced innate immune reactions are associated with high levels of IFNs and other cytokines and are correlated with severe clinical outcomes and death [112][113]. Nevertheless, critically ill patients do not necessarily display a stronger T-cell response compared to patients with mild disease [114]. A number of studies report a dysregulation of B- and T-cells together with a strong T-cell lymphopenia in more severe cases of COVID-19 compared to moderate cases [113][115][116]. Although an increasing number of studies provide insights into adaptive immune responses during COVID-19 [117], there is still a need for a better understanding of the mechanisms underlying B- and T-cell activation. Although the development of new variants reduced the vaccine efficacy which facilitates increased risk of reinfections, the vaccine- and infection-induced T-cell responses seem to be widely retained over a long period of time and provide a protection against severe disease and death. Additionally, previous infection with SARS-CoV-2 provides 84% lower risk of reinfection for an average of seven months [118], enforcing the important role that the adaptive T-cell response plays for the protection against COVID-19.

7. Importance of Interferons for COVID-19

IFNs serve as the primary responders against virus infections. However, beyond the coordination of antiviral actions, induction and signaling of type I IFNs were also shown to play a crucial role for inflammation and pathology in COVID-19. Upon binding to their receptors (IFNAR1/R2) on the cell surface, they activate the JAK-STAT signaling and induce expression of ISGs, which orchestrate the antiviral innate-immune responses. Although during viral infections IFNs primarily exhibit an antiviral function, they also shape inflammatory responses by their immunomodulatory effects on the activation status of immune cells. Analysis of the systemic IFN signatures of hospitalized COVID-19 patients revealed that the cell-specific responses were associated with distinct IFNs [119]. While the transcript signatures in circulating immune cells reflected antiviral responses that were associated with IFN-α2 and IFN-γ signaling, the proteome signatures revealed patterns of platelet activation and endothelial damage that were closely correlated with responses that were induced by IFN-α6 and IFN-β. In addition, IFN-γ and

IFN-β levels were associated with high CRP levels as a prognostic marker for poor outcome as well as an increased ratio of neutrophils to lymphocytes as a marker of late severe disease, respectively [119]. The observed differences in the IFN landscape were linked to clinical implications such as seroconversion and hospitalization time, corroborating the importance of an intact IFN response to prevent the development of severe COVID-19 and death. Also, during infections with IAV an intact IFN response is crucial [50][89].

Individuals with inborn errors of type I IFN innate-immunity impacting IFN secretion or IFN response were reported to suffer from severe viral diseases in either childhood or early adulthood [120]. Three inborn errors of immunity: the functional deficiencies of transcription factors IRF7, IRF9, as well as the RNA receptor TLR3, were shown to promote influenza-associated pneumonia [121][122][123][124]. New insights were provided by the COVID Human Genetic Effort (COVID-HGE), which revealed that more than 3.5% of patients with severe COVID-19-associated pneumonia carried previously described deficiencies in *IRF7* and *IFNAR1*, or *TLR3*, *TICAM1*, *TBK1*, and *IRF3* [125]. In addition, this identified several novel genetic mutations in *UNC93B1*, *IRF7*, *IFNAR1*, and *IFNAR2* leading to life-threatening deficiencies in the IFN response [125]. A chromosome-wide genetic approach uncovered X-linked recessive TLR7 deficiency as a risk-factor for life-threatening severe COVID-19 in <60 years old men [126]. While endosomal TLR7 is long known to sense single-stranded RNA (ssRNA) [127], and its coding sequence has been under strong negative selection [128], its exact roles in human innate immunity remained enigmatic for years [124]. These recent discoveries highlight the essential roles of double-stranded RNA sensor TLR3, ssRNA sensor TLR7, and type I IFN innate immunity in restricting SARS-CoV-2 infection. Interestingly, none of the patients with specific deficiencies of the type III IFN cascade (IL10RB deficiency) suffered from life-threatening viral infections, including COVID-19 pneumonia [125].

7.1. Type I IFN Autoantibodies in COVID-19

Autoimmune B-cell phenotypes in humans exhibiting inborn errors of cytokine immunity can produce neutralizing autoantibodies (Auto-Abs) against IFNs such as IFN-α,β,ω (favoring viral diseases), IFN-γ (favoring mycobacterial diseases), or against cytokines such as IL-6 (favoring staphylococcal diseases) and IL-17A, IL-17F (favoring mucocutaneous candidiasis), that resemble the clinical phenotypes of mutations encoding these defective cytokines and/or their receptor subunits [129]. Type I IFN Auto-Abs were initially reported in patients that were diagnosed with systemic lupus erythematosus, myasthenia gravis, thymic abnormalities, as well as in IFN recipients [107]. While these type I IFN Auto-Abs received little attention due to the absence of negative clinical reports [124][129] the COVID-19 pandemic has put a new spotlight on the immunopathological implications of type I IFN Auto-Abs for human susceptibility to viral infections and disease progression. More than 10% of patients with severe COVID-19-associated pneumonia tested positive for neutralizing Auto-Abs against IFN-α2 and/or IFN-ω [130]. Around 94% of infected carriers were men, and almost half of them aged 65+ years, thereby establishing first-line evidence that the higher prevalence of type I IFN Auto-Abs in males and older individuals explain their high risk to severe COVID-19. These observations were successively replicated via autonomous cohorts by other studies [131][132][133][134][135][136][137][138][139][140][141][142][143][144][145]. Further immunogenetic analysis revealed that all carriers of IFN-α2 Auto-Abs also had Auto-Abs against the other IFN-α subtypes (IFN-α1, 2, 4, 5, 6, 7, 8, 10, 13, 14, 16, 17, 21), while only two of these carriers had Auto-Abs against IFN-β, one against IFN-κ, and two against IFN-ε [130].

The carriers of neutralizing Auto-Abs against the IFN-α subtypes had low or undetectable plasma-levels of the 13 IFN-α subtypes during the disease course [130][146][147]. Interestingly, type III IFN Auto-Abs are only rarely detected in the severe COVID-19 cohort [130][148]. Not surprisingly, SARS-CoV-2-infected individuals with known preexisting Autoimmune Polyglandular Syndrome type I (APS-1) and type I IFN Auto-Abs had a high risk of progressing to severe COVID-19 [130][149][150]. In a clinical study of 22 APS-1 patients, 19 patients progressed to severe COVID-19, of which four died, while other patients presented asymptomatic or paucisymptomatic infections, likely due to earlier medical intervention [151]. Interestingly, another clinical report described four young APS-1 patients with type I IFN Auto-Abs that only presented mild-to-moderate COVID-19 [152]. However, a large cohort with 34,000 individuals aged between 20 and 100 years revealed a striking prevalence of neutralizing Auto-Abs against IFN-α and/or IFN-ω with increasing age also in the normal population [130][145]. Type I IFN Auto-Abs were shown to not only diminish the circulating levels of type I IFNs but also to reduce their early local expression in the nasal epithelium leading to compromised antiviral barrier in the URT [153]. It is highly likely that type I IFN Auto-Abs also affect other viral infections, such as HPAIV infections. A recent report suggested that type I IFN Auto-Abs contributed to the development of adverse reactions following immunization with live attenuated yellow fever virus vaccine [154], thereby qualifying their presence/absence as a decisive factor for the safety evaluation of prophylactics and therapeutics.

Taken together, these new insights have important real-life implications and recommend close monitoring and early vaccination of individuals with known defects in the IFN responses to reduce the risk of severe COVID-19 and other similar virus diseases. In addition, such patients should be restrained from donating convalescent sera for clinical studies and therapeutic applications as the transfer of type I IFN Auto-Abs could have severe consequences [130][155]. These findings further help in fine-tuning prophylactic and therapeutic strategies, including plasmapheresis, plasmablast-depleting monoclonal Abs, and targeted inhibition of type I IFN-responsive B-cells [130][156]. Furthermore, as early treatment with IFN-α2 is likely not beneficial to this patient cohort, the therapeutic potential of nebulized IFN-β could be evaluated, as anti-IFN-β Auto-Abs are rarely reported in individuals with type I IFN Auto-Abs.

7.2. Therapeutic Application of IFNs for COVID-19 and HPAIV Infections

Type I and type III IFNs exert strong antiviral activities by inducing ISG-mediated antiviral effectors at the cellular level. In addition, they enhance the functions of monocytes and macrophages, promote $CD4^+$ and $CD8^+$ T-cell and B-cell responses, and enhance the actions of dendritic cells and natural killer cells. Recombinant IFN-α2 is the only clinically-approved subtype for antiviral treatment against chronic hepatitis B and hepatitis C virus infections, while IFN-β is licensed for treatment of Multiple Sclerosis [157][158]. On the other hand, type I IFNs can exert strong immunopathological activities, by either inducing immunosuppressive effects that interfere with antiviral responses, or by promoting histopathological inflammation that aggravates disease [159]. At the systemic level, type I IFN treatment induces common side-effects such as chills, fever, myalgia, and headache, which are rarely dose-limiting unlike the other uncommon adverse side-effects such as hematotoxicity and neurotoxicity [160]. Despite these risks, the reported virus-induced delay of the IFN response and the high sensitivity of SARS-CoV-2 to exogenously applied type I IFNs encouraged several clinical trials to be conducted during the early pandemic [161][162]. However,

the outcome of systemically applied type I IFNs in severely ill COVID-19 patients was rather disappointing and suffered from the lack of a clear benefit as well as the application of additional co-treatments which hampered the analysis of IFN-only benefits. In contrast, the data for the therapeutic use of IFN-λ are more promising. As IFN-λ receptors are localized only along the gastrointestinal and respiratory epithelium, IFN-λ subtypes exhibit lesser inflammatory effects but stronger antiviral activities than the other IFNs, which may provide an explanation for their greater therapeutic benefit [163]. The antiviral potential of IFN-λ subtypes against SARS-CoV-2 were shown in vitro, and were evident from the ILIAD trial (NCT04354259) in ambulatory uncomplicated COVID-19 patients [164][165][166][167]. As part of the TOGETHER trial, recent results using a single subcutaneous shot of pegylated IFN-λ (type III IFN) in vaccinated, non-hospitalized patients within the first seven days after symptoms onset demonstrated up to 50% protection against hospitalization and 60% against death [168]. However, publication of the results is still awaited.

The current knowledge on the exogenous administration of recombinant IFNs for prophylaxis/therapy against HPAIV infections is only limited. A single-time low-dose IFN-α2 pretreatment significantly reduced the pulmonary viral titers in H5N1-infected mice, while the antiviral effect was improved with multiple pre-treatments, indicating that even a low-dose IFN-α treatment induces a potent antiviral program that reduces virus titers in lungs [169]. To date, only one double-blind, placebo-controlled Phase-II clinical trial (NCT00895947) investigated the prophylactic effects of oral, low-dose IFN-α administration against respiratory diseases, including influenza, in healthy adults, and reported that the treatment alleviated disease symptoms, especially in vaccinated individuals, though it was ineffective in preventing virus-infections [170]. These studies strongly support the high potential of IFN-α for prophylaxis or therapeutic treatments against IAV infection. However, solid and comprehensive research to determine the antiviral properties of human IFN-α subtypes against seasonal and highly pathogenic influenza viruses in a human study model is not available and needs to be performed to enable clinical applications. The suboptimal therapeutic effects of IFN-α2 and IFN-β encouraged researchers to explore the functional diversity of IFN-α subtypes for antiviral treatment against SARS-CoV-2 and influenza viruses [171][172][173][174]. These reports demonstrate the induction of distinct and subtype-specific transcriptomic landscapes which translate into virus-specific antiviral properties in different tissues, further suggesting their individual therapeutic potential [175].

8. Antiviral and Immunomodulatory Treatments for COVID-19

The therapeutic approaches against COVID-19, to a great extent, resemble the strategies that are employed against infections with seasonal IAV and HPAIV and include the inhibition of viral entry, blocking of the viral enzymes, and targeting of virus supportive host factors to restrict viral replication. In addition, immunomodulatory strategies to reduce or rebalance the exaggerated and uncontrolled immune responses were widely investigated. As for IAV, a high risk of resistance development is associated with use of direct-acting antivirals during COVID-19, which needs to be tightly controlled. Due to the unavailability of approved antivirals, the use of neutralizing antibodies from convalescent sera was one of the first approaches to be investigated for antiviral therapy of COVID-19 [176]. This technique provides immediate short-term immunization against infectious agents by transferring virus-specific neutralizing antibodies and has been successfully applied for other highly infectious viral

diseases such as the Spanish flu, SARS in 2003, pandemic influenza A (H1N1) in 2009, HPAIV, and Ebola by limiting virus replication in the acute phase of infection and enabling rapid recovery [177][178]. While the Food and Drug Administration (FDA) granted emergency use for convalescent plasma therapy for COVID-19 in August 2020, this decision was revised on 4 February 2021, only recommending plasma with high neutralizing antibody titers for use in hospitalized patients in early disease phases or in patients with humoral disorders [179]. In the past, convalescent plasma therapy was mostly only used in epidemics and pandemics. Its effectiveness can be correlated to the pathogen as well as the timing and dosage of the treatment [180]. More controlled studies are required to fully evaluate the clinical effectiveness of convalescent plasma including its use in immunocompetent patients with severe disease. In addition to convalescent therapy, neutralizing monoclonal antibodies (mAbs) targeting the receptor-binding site of the SARS-CoV-2 S protein were rapidly identified [181] and tested in clinical studies (RECOVERY, REGEN-COV), either alone or in combination [182][183]. Similar to convalescent sera, the use of neutralizing mAbs is preferably useful in immunocompromised hospitalized COVID-19 patients but not recommended for broad applications due to the high risk of resistance developments. In addition, the effectiveness of mAbs suffers from rapid evolution of SARS-CoV-2 variants, which present diverse degrees of immune escape from infection and vaccine-elicited antibodies along with reduced sensitivity towards the available therapeutic mAbs. While the mAB sotrovimab demonstrates stable neutralizing activity against Omicron BA.1 and BA.1.1, it's in vitro activity against the Omicron BA.2 subvariant is already significantly reduced. Currently, bebtelovimab retains high in vitro activity against circulating Omicron subvariants. Treatment guidelines recommend mAb therapy only if paxlovid or remdesivir is unavailable [184].

8.1. Direct-Acting Antivirals for Treatment of COVID-19

Remdesivir is a nucleoside analog prodrug, which is metabolized intracellularly to an adenosine triphosphate (ATP) analog that inhibits the activity of the viral RNA polymerase (sold under the brand name Veklury, Gilead) [185]. Its function as a broad-spectrum viral RNA-dependent RNA polymerase (RdRp) inhibitor is well studied and it is effective against several positive and negative-sense RNA viruses including Ebola, hepatitis C virus, respiratory syncytial virus, as well as SARS-CoV-2 in vitro and in vivo [186][187]. In contrast, it only shows low antiviral activity against the segmented negative-sense RNA viruses IAV, Lassa Virus, and Crimean-Congo hemorrhagic fever virus, which is likely facilitated by differences in the structural architecture of the polymerase active sites which disfavors remdesivir as a substrate for RNA synthesis [188][189][190]. So far, remdesivir is effective against all SARS-CoV-2 variants and the only antiviral drug that is approved for COVID-19 treatment by the FDA for hospitalized patients with a high risk to develop severe COVID-19 [184]. Only recently, the FDA has extended the approval of remdesivir also for the treatment of non-hospitalized adults and pediatric patients with mild to moderate disease that are at high risk to develop COVID-19 based on a randomized, placebo-controlled clinical trial (NCT04501952) [191]. Alternatively, the orally available nucleoside analog molnupiravir (sold as Lagevrio, Merck) has received emergency use approval by the FDA in December 2021 for non-hospitalized adults with mild to moderate COVID-19 at high risk to develop severe disease within five days of symptom onset in the absence of access to different antivirals (EUA 108 Merck Molnupiravir FS for HCPs FS Lagevrio 03232022 (fda.gov)). In contrast to remdesivir, molnupiravir is an orally available drug that reduces viral replication by a mutagenesis mechanism, which fosters the general concern of enhanced resistance development and putative integration into the human DNA [192].

Therefore, relevant guidelines recommend that molnupiravir is only used in the absence of access to alternative antivirals such as remdesivir and should be restricted to five consecutive days [184]. Despite the substantial differences in the virus biology, the effectiveness of other nucleoside analogs to inhibit the activity of viral polymerases and restrict viral replication was also shown against several other viruses, including the 2009 H1N1 pandemic influenza virus and subtypes H5N1, and H7N9 [193][194]. In vivo studies show that the drug favipiravir improved the survival of HPAIV-infected mice [195] and was also considered as an antiviral against COVID-19 with ongoing clinical trials. Unfortunately, no significant improvement of the clinical parameters or recovery rate could be observed yet, neither in mild nor in moderate cases of COVID-19 [196][197]. Nevertheless, treated patients showed a tendency to resolve earlier from fever and cough [196]. In light of additional emerging zoonoses with high pandemic potential, the virus and disease-specific applications of nucleoside analogs should be intensively studied.

Main protease (Mpro or 3CLpro) and papain-like protease (PLpro) are viral proteases that are required for the replication of SARS-CoV-2. However, targeting these crucial steps by lopinavir/ritonavir and darunavir/cobicistat did not provide convincing clinical benefit in patients with COVID-19 [198]. In contrast, nirmatrelvir, an orally-administered C3-like protease inhibitor that is sold in combination with ritonavir under the brand name Paxlovid, is recommended for use in high-risk, non-hospitalized COVID-19 patients from the age of 12 within five days after symptoms onset. However, due to extensive drug interactions, the application of this drug is restricted [184][199]. Unfortunately, studies using recombinant Mpro have shown that certain amino acid substitutions are associated with reduced activity (G15S, H164N, H172Y, and Q189K; 4- to 233-fold reduction) [200]. P132H mutation in nsp5 (Mpro) has been reported in the novel Omicron variant, harboring the risk of resistance [201].

8.2. Immunomodulatory Strategies to Alleviate Immunopathology in COVID-19

About 10-20% of COVID-19 patients develop severe symptoms with systemic inflammation as the second stage of disease, severe lung infection, multi-organ failure, and diffuse/disseminated intravascular coagulation following severe pneumonia [202][203]. Previous experiences from influenza pandemics suggested that therapeutic approaches for COVID-19 require antiviral as well as anti-inflammatory strategies. Although the peripheral blood cytokine profiles are not identical, the key mediators of immunopathology are common to both lethal H5N1 influenza infection and COVID-19. Especially the pro-inflammatory cytokines IL-6, IL-1β, TNF-α, IL-10, and IP-10 have been shown to correlate with disease severity in both infections, thus indicating that similar host signaling processes are involved in the disease development. Hence, the immunomodulatory strategies for both viral infections share high similarity. Beyond broad immunosuppressive strategies using corticosteroids that have demonstrated contradictory benefits during progressed and severe IAV infections and COVID-19, more targeted strategies to block or redirect cytokine-specific immune response pathways are intensively investigated and demonstrated promising effects. Especially strategies to reduce the concentration and signaling of harmful cytokines such as IL-6, IL-1, and TNF-α have been intensively investigated in clinical studies for COVID-19.

The IL-6 receptor-directed mAb tocilizumab is specifically directed to the membrane-bound IL-6 receptor (mIL6R) and soluble IL-6 receptor (sIL6R). Clinical studies have shown conflicting results regarding the use of tocilizumab in the treatment of severe COVID-19 [204][205]. However, it has been reported that tocilizumab reduces mortality and

the need for mechanical ventilation in severe COVID-19 patients [206][207]. IL-6 is involved in a number of essential anti-viral defenses, including $CD8^+$ T cell function and differentiation, T-cell responses, macrophage activation, and migration. Therefore, it should be noted that the use of these drugs targeting IL-6 in the early stages of COVID-19 may result in inhibition of the following antiviral defense steps [208]. Although the risk of bacterial infection due to this immunosuppression is considered, WHO and NIH guidelines recommend the use of IL-6 receptor blockers for the treatment of COVID-19. IL-1α is quickly expressed upon lung cell necrosis and triggers the synthesis of IL-6, TNF-α, Granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-17, thus the IL-1 blocker anakinra was suggested as an alternative treatment for patients in which corticosteroid treatment, also combined with tocilizumab, was not beneficial. Mortality rates and hospitalization time could indeed be reduced [209][210].

TNF-α triggers the cytokine release syndrome and facilitates the interaction of ACE2 with SARS-CoV-2. The studies on the use of TNF-α inhibitors for the treatment of severe influenza have been a guide for the treatment of COVID-19. High TNF-α serum concentration is associated with severe COVID-19 disease, and it has been speculated that anti-TNF therapy can be used in high-risk elderly patients with COVID-19 [113][211]. Interestingly, COVID-19 patients who regularly use anti-TNF agents due to inflammatory bowel diseases (Crohn's disease or ulcerative colitis) generally had a mild disease. This suggests that anti-TNF therapy indirectly reduces the overshooting response of the immune system in patients with COVID-19 [212][213][214]. However, the time of administration, dose, and stage of the disease are critical for TNF-α blockers, and early use may accelerate viral replication and worsen the clinical course of the disease, as in other immunomodulatory treatments [215][216]. Anti-TNF strategies have not been useful in the treatment of inflammatory conditions, such as sepsis, and clinical trials were not conducted in humans neither for HPAIV infections nor for COVID-19 [215].

JAK inhibitors such as baricitinib or tofacitinib are recommended as a treatment for COVID-19 as they can prevent the phosphorylation of key proteins (IL-6 and STAT3) that are involved in signal transduction leading to immune activation and inflammation. The WHO has made a strong recommendation for JAK inhibitors, specifically baricitinib, in patients with severe and critical COVID-19 [217]. Moreover, due to its affinity to a regulator of endocytosis, AP2-associated kinase 1 (AAK1), it has been reported to act as an antiviral by reducing SARS-CoV-2 endocytosis [218].

TLR pathway inhibitors were appearing on the horizon of promising therapeutics after revealing the correlation between high levels of several TLRs and severe COVID-19 [107]. Especially TLR3, TLR4, TLR7, and TLR8 were shown to induce cytokine production, so targeting these specific TLRs could reduce the risk of an hyperinflammatory response during COVID-19 [219]. A Phase II clinical trial of the TLR7/8 inhibitor M5049 (NCT04448756) in COVID-19 patients suffering from pneumonia was completed without providing conclusive data. Similar to other immunomodulatory treatments, TLRs with their key role in innate immunity should not be completely blocked to maintain an antiviral barrier. Nevertheless, targeting specified TLR subtypes with an optimized dose and duration of the treatment could be an effective strategy for the treatment of COVID-19 [220][221]. Additionally, in vitro and in vivo studies have shown that the TLR4 antagonist FP7 significantly reduces the production of lethal lipopolysaccharide (LPS)-mediated cytokines during influenza infection [222].

Although it is debated whether single anti-cytokine therapies are beneficial in COVID-19, the involvement of many cytokines in cytokine storm suggests that the effect of combined therapies may be clinically better [223]. In the current NIH guideline, the recommended treatment for severe COVID-19 patients who need oxygen support is remdesivir plus dexamethasone, and tocilizumab can be added to this treatment in people with more critical disease (hospitalized and requiring ECMO). Depending on the clinical condition and progression of the patient, the treatment regimen can be changed [184][224].

It is reported that ARDS was treated using systemic corticosteroids in France during the 2009 H1N1 influenza pandemic and in China during the 2013 H7N9 avian influenza pandemic. However, there is insufficient evidence to support the use of corticosteroids in severe influenza [225]. The anti-inflammatory and immunosuppressive effects of glucocorticosteroids are based on three mechanisms; (I) the direct effects on gene expression by the binding of glucocorticoid receptors to glucocorticoid-responsive elements, (II) the indirect effects on gene expression through the interactions of glucocorticoid receptors with other transcription factors i.e., NFκB and activator protein 1, and (III) the glucocorticoid receptor-mediated effects on second-messenger cascades [217]. The use of corticosteroids in COVID-19 disease was not routinely recommended by the WHO because it inhibits the immune response, which has a key role in the defense of the host against viruses, reduces viral clearance, and increases the risk of secondary infection. However, multiple randomized studies show that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who need supplemental oxygen by reducing the systemic inflammatory response that is induced by COVID-19 [226][227]. Importantly, this demonstrates again the importance of monitoring the patient's disease state and clinical parameters. Whereas the described antivirals such as nucleoside analogs should be given to a patient in a rather early phase of the disease for optimal outcome, patients with already progressed disease including a hyperinflammation benefit from immunomodulation such as glucocorticosteroids and also possibly kinase inhibitors and cytokine inhibitors.

References

1. Yu, H.; Peng, C.; Zhang, C.; Stoian, A.M.M.; Tazi, L.; Brennan, G.; Rothenburg, S. Maladaptation after a virus host switch leads to increased activation of the pro-inflammatory NF-κB pathway. Proc. Natl. Acad. Sci. USA 2022, 119, e2115354119.
2. Rouse, B.T.; Sehrawat, S. Immunity and immunopathology to viruses: What decides the outcome? Nat. Rev. Immunol. 2010, 10, 514–526.
3. Kandun, I.N.; Wibisono, H.; Sedyaningsih, E.R.; Yusharmen; Hadisoedarsuno, W.; Purba, W.; Santoso, H.; Septiawati, C.; Tresnaningsih, E.; Heriyanto, B.; et al. Three Indonesian Clusters of H5N1 Virus Infection in 2005. N. Engl. J. Med. 2006, 355, 2186–2194.
4. Koopmans, M.; Wilbrink, B.; Conyn, M.; Natrop, G.; van der Nat, H.; Vennema, H.; Meijer, A.; van Steenbergen, J.; Fouchier, R.; Osterhaus, A.; et al. Transmission of H7N7 avian influenza A virus

to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet 2004, 363, 587–593.

5. Olsen, S.J.; Ungchusak, K.; Sovann, L.; Uyeki, T.M.; Dowell, S.F.; Cox, N.J.; Aldis, W.; Chunsuttiwat, S. Family Clustering of Avian Influenza A (H5N1). Emerg. Infect. Dis. 2005, 11, 1799–1801.
6. Ungchusak, K.; Auewarakul, P.; Dowell, S.F.; Kitphati, R.; Auwanit, W.; Puthavathana, P.; Uiprasertkul, M.; Boonnak, K.; Pittayawonganon, C.; Cox, N.J.; et al. Probable Person-to-Person Transmission of Avian Influenza A (H5N1). New Engl. J. Med. 2005, 352, 333–340.
7. Hien, T.T.; Liem, N.T.; Dung, N.T.; San, L.T.; Mai, P.P.; Chau, N.V.V.; Suu, P.T.; Dong, V.C.; Mai, L.T.Q.; Thi, N.T.; et al. Avian Influenza A (H5N1) in 10 Patients in Vietnam. New Engl. J. Med. 2004, 350, 1179–1188.
8. Rogers, G.N.; Paulson, J.C. Receptor determinants of human and animal influenza virus isolates: Differences in receptor specificity of the H3 hemagglutinin based on species of origin. Virology 1983, 127, 361–373.
9. Stevens, J.; Blixt, O.; Glaser, L.; Taubenberger, J.K.; Palese, P.; Paulson, J.C.; Wilson, I.A. Glycan Microarray Analysis of the Hemagglutinins from Modern and Pandemic Influenza Viruses Reveals Different Receptor Specificities. J. Mol. Biol. 2006, 355, 1143–1155.
10. Nova, N. Cross-Species Transmission of Coronaviruses in Humans and Domestic Mammals, What Are the Ecological Mechanisms Driving Transmission, Spillover, and Disease Emergence? Front. Public Health 2021, 9, 717941.
11. Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L.; et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020, 579, 270–273.
12. Harder, T.; Koch, J.; Vygen-Bonnet, S.; Külper-Schiek, W.; Pilic, A.; Reda, S.; Scholz, S.; Wichmann, O. Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: Interim results of a living systematic review, 1 January to 14 May 2021. Eurosurveillance 2021, 26, 2100563.
13. Remdesivir and three other drugs for hospitalised patients with COVID-19: Final results of the WHO Solidarity randomised trial and updated meta-analyses. Lancet 2022, 399, 1941–1953.
14. Cameroni, E.; Bowen, J.E.; Rosen, L.E.; Saliba, C.; Zepeda, S.K.; Culap, K.; Pinto, D.; VanBlargan, L.A.; De Marco, A.; di Iulio, J.; et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. Nature 2022, 602, 664–670.
15. McCallum, M.; Czudnochowski, N.; Rosen, L.E.; Zepeda, S.K.; Bowen, J.E.; Walls, A.C.; Hauser, K.; Joshi, A.; Stewart, C.; Dillen, J.R.; et al. Structural basis of SARS-CoV-2 Omicron immune evasion and receptor engagement. Science 2022, 375, 864–868.

16. Starr, T.N.; Greaney, A.J.; Addetia, A.; Hannon, W.W.; Choudhary, M.C.; Dingens, A.S.; Li, J.Z.; Bloom, J.D. Prospective mapping of viral mutations that escape antibodies used to treat COVID-19. Science 2021, 371, 850–854.
17. Greaney, A.J.; Loes, A.N.; Crawford, K.H.; Starr, T.N.; Malone, K.D.; Chu, H.Y.; Bloom, J.D. Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell Host Microbe 2021, 29, 463–476.e6.
18. Murphy, K. SARS CoV-2 Detection From Upper and Lower Respiratory Tract Specimens. Chest 2020, 158, 1804–1805.
19. Nicholls, J.M.; Chan, M.C.W.; Chan, W.Y.; Wong, H.K.; Cheung, C.Y.; Kwong, D.L.W.; Wong, M.P.; Chui, W.H.; Poon, L.; Tsao, S.W.; et al. Tropism of avian influenza A (H5N1) in the upper and lower respiratory tract. Nat. Med. 2007, 13, 147–149.
20. Weinheimer, V.K.; Becher, A.; Tönnies, M.; Holland, G.; Knepper, J.; Bauer, T.T.; Schneider, P.; Neudecker, J.; Rückert, J.C.; Szymanski, K.; et al. Influenza A Viruses Target Type II Pneumocytes in the Human Lung. J. Infect. Dis. 2012, 206, 1685–1694.
21. Shinya, K.; Ebina, M.; Yamada, S.; Ono, M.; Kasai, N.; Kawaoka, Y. Influenza virus receptors in the human airway. Nature 2006, 440, 435–436.
22. Hou, Y.; Okuda, K.; Edwards, C.E.; Martinez, D.R.; Asakura, T.; Dinnon, K.H.; Kato, T.; Lee, R.E.; Yount, B.L.; Mascenik, T.M.; et al. SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract. Cell 2020, 182, 429–446.e14.
23. Ortiz, M.E.; Thurman, A.; Pezzulo, A.A.; Leidinger, M.R.; Klesney-Tait, J.A.; Karp, P.H.; Tan, P.; Wohlford-Lenane, C.; McCray, P.B.; Meyerholz, D.K. Heterogeneous expression of the SARS-Coronavirus-2 receptor ACE2 in the human respiratory tract. eBioMedicine 2020, 60, 102976.
24. Lakdawala, S.S.; Jayaraman, A.; Halpin, R.A.; Lamirande, E.W.; Shih, A.R.; Stockwell, T.B.; Lin, X.; Simenauer, A.; Hanson, C.T.; Vogel, L.; et al. The soft palate is an important site of adaptation for transmissible influenza viruses. Nature 2015, 526, 122–125.
25. Lee, I.T.; Nakayama, T.; Wu, C.-T.; Goltsev, Y.; Jiang, S.; Gall, P.A.; Liao, C.-K.; Shih, L.-C.; Schürch, C.M.; McIlwain, D.R.; et al. ACE2 localizes to the respiratory cilia and is not increased by ACE inhibitors or ARBs. Nat. Commun. 2020, 11, 5453.
26. Lv, J.; Wang, Z.; Qu, Y.; Zhu, H.; Zhu, Q.; Tong, W.; Bao, L.; Lv, Q.; Cong, J.; Li, D.; et al. Distinct uptake, amplification, and release of SARS-CoV-2 by M1 and M2 alveolar macrophages. Cell Discov. 2021, 7, 24.
27. Chertow, D.; Stein, S.; Ramelli, S.; Grazioli, A.; Chung, J.-Y.; Singh, M.; Yinda, C.K.; Winkler, C.; Dickey, J.; Ylaya, K.; et al. SARS-CoV-2 Infection and Persistence Throughout the Human Body and Brain National Institutes of Health. 2021. Available online: https://www.researchsquare.com/article/rs-1139035/v1 (accessed on 18 May 2022).

28. Flerlage, T.; Boyd, D.F.; Meliopoulos, V.; Thomas, P.G.; Schultz-Cherry, S. Influenza virus and SARS-CoV-2: Pathogenesis and host responses in the respiratory tract. Nat. Rev. Genet. 2021, 19, 425–441.

29. He, X.; Lau, E.H.Y.; Wu, P.; Deng, X.; Wang, J.; Hao, X.; Lau, Y.C.; Wong, J.Y.; Guan, Y.; Tan, X.; et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat. Med. 2020, 26, 672–675.

30. Bi, Q.; Wu, Y.; Mei, S.; Ye, C.; Zou, X.; Zhang, Z.; Liu, X.; Wei, L.; Truelove, S.A.; Zhang, T.; et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: A retrospective cohort study. Lancet Infect. Dis. 2020, 20, 911–919.

31. Alimohamadi, Y.; Sepandi, M.; Taghdir, M.; Hosamirudsari, H. Determine the most common clinical symptoms in COVID-19 patients: A systematic review and meta-analysis. J. Prev. Med. Hyg. 2020, 61, E304–E312.

32. Brann, D.H.; Tsukahara, T.; Weinreb, C.; Lipovsek, M.; Van Den Berge, K.; Gong, B.; Chance, R.; Macaulay, I.C.; Chou, H.-J.; Fletcher, R.B.; et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci. Adv. 2020, 6, eabc5801.

33. Burke, R.M.; Killerby, M.E.; Newton, S.; Ashworth, C.E.; Berns, A.L.; Brennan, S.; Bressler, J.M.; Bye, E.; Crawford, R.; Morano, L.H.; et al. Symptom Profiles of a Convenience Sample of Patients with COVID-19—United States, January–April 2020. MMWR. Morb. Mortal. Wkly. Rep. 2020, 69, 904–908.

34. Klaser, K.; Molteni, E.; Graham, M.S.; Canas, L.S.; Osterdahl, M.F.; Antonelli, M.; Chen, L.; Deng, J.; Murray, B.; Kerfoot, E.; et al. COVID-19 due to the B.1.617.2 (Delta) variant compared to B.1.1.7 (Alpha) variant of SARS-CoV-2: Two prospective observational cohort studies. medRxiv 2021.

35. Hagen, A. How Dangerous Is the Delta Variant (B.1.617.2)? Available online: https://asm.org/Articles/2021/July/How-Dangerous-is-the-Delta-Variant-B-1-617-2 (accessed on 20 June 2022).

36. Shiehzadegan, S.; Alaghemand, N.; Fox, M.; Venketaraman, V. Analysis of the Delta Variant B.1.617.2 COVID-19. Clin. Pract. 2021, 11, 778–784.

37. Menni, C.; Valdes, A.M.; Polidori, L.; Antonelli, M.; Penamakuri, S.; Nogal, A.; Louca, P.; May, A.; Figueiredo, J.C.; Hu, C.; et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: A prospective observational study from the ZOE COVID Study. Lancet 2022, 399, 1618–1624.

38. Spiteri, G.; Fielding, J.; Diercke, M.; Campese, C.; Enouf, V.; Gaymard, A.; Bella, A.; Sognamiglio, P.; Moros, M.J.S.; Riutort, A.N.; et al. First cases of coronavirus disease 2019 (COVID-19) in the

WHO European Region, 24 January to 21 February 2020. Eurosurveillance 2020, 25, 2000178.

39. Sinha, P.; Matthay, M.A.; Calfee, C.S. Is a “Cytokine Storm” Relevant to COVID-19? JAMA Intern. Med. 2020, 180, 1152–1154.
40. England, J.T.; Abdulla, A.; Biggs, C.; Lee, A.Y.; Hay, K.; Hoiland, R.L.; Wellington, C.L.; Sekhon, M.; Jamal, S.; Shojania, K.; et al. Weathering the COVID-19 storm: Lessons from hematologic cytokine syndromes. Blood Rev. 2021, 45, 100707.
41. Nadim, M.K.; Forni, L.G.; Mehta, R.L.; Connor, M.J., Jr.; Liu, K.D.; Ostermann, M.; Rimmelé, T.; Zarbock, A.; Bell, S.; Bihorac, A.; et al. COVID-19-associated acute kidney injury: Consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat. Rev. Nephrol. 2020, 16, 747–764.
42. Yang, X.; Yu, Y.; Xu, J.; Shu, H.; Xia, J.; Liu, H.; Wu, Y.; Zhang, L.; Yu, Z.; Fang, M.; et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir. Med. 2020, 8, 475–481.
43. Robbins-Juarez, S.Y.; Qian, L.; King, K.L.; Stevens, J.S.; Husain, S.A.; Radhakrishnan, J.; Mohan, S. Outcomes for Patients With COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. Kidney Int. Rep. 2020, 5, 1149–1160.
44. Poissy, J.; Goutay, J.; Caplan, M.; Parmentier-Decrucq, E.; Duburcq, T.; Lassalle, F.; Jeanpierre, E.; Rauch, A.; Labreuche, J.; Susen, S.; et al. Pulmonary Embolism in Patients With COVID-19. Circulation 2020, 142, 184–186.
45. Ramos-Casals, M.; Brito-Zerón, P.; Mariette, X. Systemic and organ-specific immune-related manifestations of COVID-19. Nat. Rev. Rheumatol. 2021, 17, 315–332.
46. Centers for Disease Control and Prevention. Reported Human Infections with Avian Influenza A V. Available online: https://www.cdc.gov/flu/avianflu/reported-human-infections.htm (accessed on 6 May 2022).
47. Yang, L.; Zhao, X.; Li, X.; Bo, H.; Li, D.; Liu, J.; Wang, D. Case report for human infection with a highly pathogenic avian influenza A(H5N6) virus in Beijing, China 2019. Biosaf. Health 2020, 2, 49–52.
48. Yuen, K.-Y.; Chan, P.; Peiris, J.S.M.; Tsang, D.; Que, T.; Shortridge, K.; Cheung, P.; To, W.; Ho, E.; Sung, R.; et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 1998, 351, 467–471.
49. Yu, H.; Gao, Z.; Feng, Z.; Shu, Y.; Xiang, N.; Zhou, L.; Huai, Y.; Feng, L.; Peng, Z.; Li, Z.; et al. Clinical Characteristics of 26 Human Cases of Highly Pathogenic Avian Influenza A (H5N1) Virus Infection in China. PLoS ONE 2008, 3, e2985.

50. Koutsakos, M.; Kedzierska, K.; Subbarao, K. Immune Responses to Avian Influenza Viruses. J. Immunol. 2019, 202, 382–391.

51. To, K.-F.; Chan, P.K.; Chan, K.-F.; Lee, W.-K.; Lam, W.-Y.; Wong, K.-F.; Tang, N.L.; Tsang, D.N.; Sung, R.Y.; Buckley, T.A.; et al. Pathology of fatal human infection associated with avian influenza A H5N1 virus. J. Med Virol. 2001, 63, 242–246.

52. Le, M.T.Q.; Wertheim, H.F.L.; Nguyen, H.D.; Taylor, W.; Hoang, P.V.M.; Vuong, C.D.; Nguyen, H.L.K.; Nguyen, H.H.; Nguyen, T.Q.; Nguyen, T.V.; et al. Influenza A H5N1 Clade 2.3.4 Virus with a Different Antiviral Susceptibility Profile Replaced Clade 1 Virus in Humans in Northern Vietnam. PLoS ONE 2008, 3, e3339.

53. Kandun, I.N.; Tresnaningsih, E.; Purba, W.H.; Lee, V.; Samaan, G.; Harun, S.; Soni, E.; Septiawati, C.; Setiawati, T.; Sariwati, E.; et al. Factors associated with case fatality of human H5N1 virus infections in Indonesia: A case series. Lancet 2008, 372, 744–749.

54. Oner, A.F.; Bay, A.; Arslan, S.; Akdeniz, H.; Sahin, H.A.; Cesur, Y.; Epcacan, S.; Yilmaz, N.; Deger, I.; Kizilyildiz, B.; et al. Avian Influenza A (H5N1) Infection in Eastern Turkey in 2006. N. Engl. J. Med. 2006, 355, 2179–2185.

55. Chotpitayasunondh, T.; Ungchusak, K.; Hanshaoworakul, W.; Chunsuthiwat, S.; Sawanpanyalert, P.; Kijphati, R.; Lochindarat, S.; Srisan, P.; Suwan, P.; Osotthanakorn, Y.; et al. Human Disease from Influenza A (H5N1), Thailand. Emerg. Infect. Dis. 2005, 11, 201–209.

56. Buchy, P.; Mardy, S.; Vong, S.; Toyoda, T.; Aubin, J.-T.; Miller, M.; Touch, S.; Sovann, L.; Dufourcq, J.-B.; Richner, B.; et al. Influenza A/H5N1 virus infection in humans in Cambodia. J. Clin. Virol. 2007, 39, 164–168.

57. Uyeki, T.M. Human Infection with Highly Pathogenic Avian Influenza A (H5N1) Virus: Review of Clinical Issues. Clin. Infect. Dis. 2009, 49, 279–290.

58. Pan, M.; Gao, R.; Lv, Q.; Huang, S.; Zhou, Z.; Yang, L.; Li, X.; Zhao, X.; Zou, X.; Tong, W.; et al. Human infection with a novel, highly pathogenic avian influenza A (H5N6) virus: Virological and clinical findings. J. Infect. 2016, 72, 52–59.

59. Chen, H.; Yuan, H.; Gao, R.; Zhang, J.; Wang, D.; Xiong, Y.; Fan, G.; Yang, F.; Li, X.; Zhou, J.; et al. Clinical and epidemiological characteristics of a fatal case of avian influenza A H10N8 virus infection: A descriptive study. Lancet 2014, 383, 714–721.

60. Peiris, J.; Yu, W.; Leung, C.; Cheung, C.; Ng, W.; Nicholls, J.; Ng, T.; Chan, K.; Lai, S.; Lim, W.; et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet 2004, 363, 617–619.

61. De Jong, M.D.; Simmons, C.P.; Thanh, T.T.; Hien, V.M.; Smith, G.J.D.; Chau, T.N.B.; Hoang, D.M.; Chau, N.V.V.; Khanh, T.H.; Dong, V.C.; et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. Nat. Med. 2006, 12, 1203–1207.

62. Chan, M.C.; Cheung, C.Y.; Chui, W.H.; Tsao, S.W.; Nicholls, J.M.; Chan, Y.O.; Chan, R.W.; Long, H.T.; Poon, L.L.; Guan, Y.; et al. Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells. Respir. Res. 2005, 6, 135.

63. Krischuns, T.; Günl, F.; Henschel, L.; Binder, M.; Willemsen, J.; Schloer, S.; Rescher, U.; Gerlt, V.; Zimmer, G.; Nordhoff, C.; et al. Phosphorylation of TRIM28 Enhances the Expression of IFN-β and Proinflammatory Cytokines During HPAIV Infection of Human Lung Epithelial Cells. Front. Immunol. 2018, 9, 2229.

64. Cheung, C.; Poon, L.; Lau, A.; Luk, W.; Lau, Y.; Shortridge, K.; Gordon, S.; Guan, Y.; Peiris, J. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: A mechanism for the unusual severity of human disease? Lancet 2002, 360, 1831–1837.

65. Lipatov, A.S.; Andreansky, S.; Webby, R.J.; Hulse, D.J.; Rehg, J.E.; Krauss, S.; Perez, D.R.; Doherty, P.C.; Webster, R.G.; Sangster, M.Y. Pathogenesis of Hong Kong H5N1 influenza virus NS gene reassortants in mice: The role of cytokines and B- and T-cell responses. J. Gen. Virol. 2005, 86, 1121–1130.

66. Sakabe, S.; Iwatsuki-Horimoto, K.; Takano, R.; Nidom, C.A.; Le, M.T.Q.; Nagamura-Inoue, T.; Horimoto, T.; Yamashita, N.; Kawaoka, Y. Cytokine production by primary human macrophages infected with highly pathogenic H5N1 or pandemic H1N1 2009 influenza viruses. J. Gen. Virol. 2011, 92, 1428–1434.

67. Mok, K.P.; Wong, C.H.K.; Cheung, C.Y.; Chan, M.C.W.; Lee, S.M.Y.; Nicholls, J.M.; Guan, Y.; Peiris, J.S.M. Viral Genetic Determinants of H5N1 Influenza Viruses That Contribute to Cytokine Dysregulation. J. Infect. Dis. 2009, 200, 1104–1112.

68. Salomon, R.; Hoffmann, E.; Webster, R.G. Inhibition of the cytokine response does not protect against lethal H5N1 influenza infection. Proc. Natl. Acad. Sci. USA 2007, 104, 12479–12481.

69. Xu, T.; Qiao, J.; Zhao, L.; He, G.; Li, K.; Wang, J.; Tian, Y.; Wang, H. Effect of dexamethasone on acute respiratory distress syndrome induced by the H5N1 virus in mice. Eur. Respir. J. 2009, 33, 852–860.

70. Gupta, R.K.; Rosenheim, J.; Bell, L.C.; Chandran, A.; Guerra-Assuncao, J.A.; Pollara, G.; Whelan, M.; Artico, J.; Joy, G.; Kurdi, H.; et al. Blood transcriptional biomarkers of acute viral infection for detection of pre-symptomatic SARS-CoV-2 infection: A nested, case-control diagnostic accuracy study. Lancet Microbe 2021, 2, e508–e517.

71. Tang, B.M.; Shojaei, M.; Parnell, G.P.; Huang, S.; Nalos, M.; Teoh, S.; O'Connor, K.; Schibeci, S.; Phu, A.L.; Kumar, A.; et al. A novel immune biomarker IFI27 discriminates between influenza and bacteria in patients with suspected respiratory infection. Eur. Respir. J. 2017, 49, 1602098.

72. Bellmann-Weiler, R.; Lanser, L.; Barket, R.; Rangger, L.; Schapfl, A.; Schaber, M.; Fritsche, G.; Wöll, E.; Weiss, G. Prevalence and Predictive Value of Anemia and Dysregulated Iron Homeostasis in Patients with COVID-19 Infection. J. Clin. Med. 2020, 9, 2429.

73. Terpos, E.; Ntanasis-Stathopoulos, I.; Elalamy, I.; Kastritis, E.; Sergentanis, T.N.; Politou, M.; Psaltopoulou, T.; Gerotziafas, G.; Dimopoulos, M.A. Hematological findings and complications of COVID-19. Am. J. Hematol. 2020, 95, 834–847.

74. Huang, I.; Pranata, R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): Systematic review and meta-analysis. J. Intensive Care 2020, 8, 36.

75. Huang, I.; Pranata, R.; Lim, M.A.; Oehadian, A.; Alisjahbana, B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: A meta-analysis. Ther. Adv. Respir. Dis. 2020, 14, 1753466620937175.

76. Smilowitz, N.R.; Kunichoff, D.; Garshick, M.; Shah, B.; Pillinger, M.; Hochman, J.S.; Berger, J.S. C-reactive protein and clinical outcomes in patients with COVID-19. Eur. Hearth J. 2021, 42, 2270–2279.

77. Hu, R.; Han, C.; Pei, S.; Yin, M.; Chen, X. Procalcitonin levels in COVID-19 patients. Int. J. Antimicrob. Agents 2020, 56, 106051.

78. Liu, T.; Zhang, J.; Yang, Y.; Ma, H.; Li, Z.; Zhang, J.; Cheng, J.; Zhang, X.; Zhao, Y.; Xia, Z.; et al. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. EMBO Mol. Med. 2020, 12, e12421.

79. Chen, H.; Wang, J.; Su, N.; Bao, X.; Li, Y.; Jin, J. Simplified immune-dysregulation index: A novel marker predicts 28-day mortality of intensive care patients with COVID-19. Intensiv. Care Med. 2020, 46, 1645–1647.

80. Giannakodimos, I.; Gkountana, G.-V.; Lykouras, D.; Karkoulias, K.; Tsakas, S. The Role of Interleukin-6 in the Pathogenesis, Prognosis and Treatment of Severe COVID-19. Curr. Med. Chem. 2020, 28, 5328–5338.

81. Liu, F.; Li, L.; Xu, M.; Wu, J.; Luo, D.; Zhu, Y.; Li, B.; Song, X.; Zhou, X. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J. Clin. Virol. 2020, 127, 104370.

82. Qin, C.; Zhou, L.; Hu, Z.; Zhang, S.; Yang, S.; Tao, Y.; Xie, C.; Ma, K.; Shang, K.; Wang, W.; et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin. Infect. Dis. 2020, 71, 762–768.

83. Zhang, L.; Yan, X.; Fan, Q.; Liu, H.; Liu, X.; Liu, Z.; Zhang, Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J. Thromb. Haemost. 2020, 18, 1324–1329.

84. Yao, Y.; Cao, J.; Wang, Q.; Shi, Q.; Liu, K.; Luo, Z.; Chen, X.; Chen, S.; Yu, K.; Huang, Z.; et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: A case control study. J. Intensiv. Care 2020, 8, 49.

85. Rovas, A.; Osiaevi, I.; Buscher, K.; Sackarnd, J.; Tepasse, P.-R.; Fobker, M.; Kühn, J.; Braune, S.; Göbel, U.; Thölking, G.; et al. Microvascular dysfunction in COVID-19: The MYSTIC study. Angiogenesis 2021, 24, 145–157.

86. Vasileva, D.; Badawi, A. C-reactive protein as a biomarker of severe H1N1 influenza. Agents Actions 2019, 68, 39–46.

87. Beigel, J.H.; Farrar, J.; Han, A.M.; Hayden, F.G.; Hyer, R.; de Jong, M.D.; Lochindarat, S.; Nguyen, T.K.T.; Nguyen, T.H.; Tran, T.H.; et al. Avian influenza A (H5N1) infection in humans. N. Engl. J. Med. 2005, 353, 1374–1385.

88. Soepandi, P.Z.; Burhan, E.; Mangunnegoro, H.; Nawas, A.; Aditama, T.Y.; Partakusuma, L.; Isbaniah, F.; Ikhsan, M.; Swidarmoko, B.; Sutiyoso, A.; et al. Clinical Course of Avian Influenza A(H5N1) in Patients at the Persahabatan Hospital, Jakarta, Indonesia, 2005. Chest 2010, 138, 665–673.

89. Diamond, M.S.; Kanneganti, T.-D. Innate immunity: The first line of defense against SARS-CoV-2. Nat. Immunol. 2022, 23, 165–176.

90. Ramos, I.; Fernandez-Sesma, A. Innate Immunity to H5N1 Influenza Viruses in Humans. Viruses 2012, 4, 3363–3388.

91. Thompson, M.R.; Kaminski, J.J.; Kurt-Jones, E.A.; Fitzgerald, K.A. Pattern Recognition Receptors and the Innate Immune Response to Viral Infection. Viruses 2011, 3, 920–940.

92. Kanneganti, T. Intracellular innate immune receptors: Life inside the cell. Immunol. Rev. 2020, 297, 5–12.

93. Ivashkiv, L.B.; Donlin, L.T. Regulation of type I interferon responses. Nat. Rev. Immunol. 2014, 14, 36–49.

94. Lian, Q.; Zhang, K.; Zhang, Z.; Duan, F.; Guo, L.; Luo, W.; Mok, B.W.-Y.; Thakur, A.; Ke, X.; Motallebnejad, P.; et al. Differential effects of macrophage subtypes on SARS-CoV-2 infection in a human pluripotent stem cell-derived model. Nat. Commun. 2022, 13, 2028.

95. Dalskov, L.; Møhlenberg, M.; Thyrsted, J.; Blay-Cadanet, J.; Poulsen, E.T.; Folkersen, B.H.; Skaarup, S.H.; Olagnier, D.; Reinert, L.; Enghild, J.J.; et al. SARS-CoV-2 evades immune detection in alveolar macrophages. EMBO Rep. 2020, 21, e51252.

96. Wang, J.; Nikrad, M.P.; Travanty, E.A.; Zhou, B.; Phang, T.; Gao, B.; Alford, T.; Ito, Y.; Nahreini, P.; Hartshorn, K.; et al. Innate Immune Response of Human Alveolar Macrophages during Influenza A Infection. PLoS ONE 2012, 7, e29879.

97. Cuevas, A.M.; Clark, J.M.; Potter, J.J. Increased TLR/MyD88 signaling in patients with obesity: Is there a link to COVID-19 disease severity? Int. J. Obes. 2021, 45, 1152–1154.
98. Sohn, K.M.; Lee, S.-G.; Kim, H.J.; Cheon, S.; Jeong, H.; Lee, J.; Kim, I.S.; Silwal, P.; Kim, Y.J.; Paik, S.; et al. COVID-19 Patients Upregulate Toll-like Receptor 4-mediated Inflammatory Signaling That Mimics Bacterial Sepsis. J. Korean Med Sci. 2020, 35, e343.
99. Zhao, Y.; Kuang, M.; Li, J.; Zhu, L.; Jia, Z.; Guo, X.; You, F. Publisher Correction: SARS-CoV-2 spike protein interacts with and activates TLR4 (Cell Research, (2021), 31, 7, (818-820), 10.1038/s41422-021-00495-9). Cell Res. 2021, 31, 825.
100. Yamada, T.; Sato, S.; Sotoyama, Y.; Orba, Y.; Sawa, H.; Yamauchi, H.; Sasaki, M.; Takaoka, A. RIG-I triggers a signaling-abortive anti-SARS-CoV-2 defense in human lung cells. Nat. Immunol. 2021, 22, 820–828.
101. Hui, K.P.Y.; Lee, S.M.Y.; Cheung, C.-Y.; Mao, H.; Lai, A.K.W.; Chan, R.W.Y.; Chan, M.C.W.; Tu, W.; Guan, Y.; Lau, Y.-L.; et al. H5N1 Influenza Virus–Induced Mediators Upregulate RIG-I in Uninfected Cells by Paracrine Effects Contributing to Amplified Cytokine Cascades. J. Infect. Dis. 2011, 204, 1866–1878.
102. Kato, H.; Takeuchi, O.; Sato, S.; Yoneyama, M.; Yamamoto, M.; Matsui, K.; Uematsu, S.; Jung, A.; Kawai, T.; Ishii, K.; et al. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature 2006, 441, 101–105.
103. Yin, X.; Riva, L.; Pu, Y.; Martin-Sancho, L.; Kanamune, J.; Yamamoto, Y.; Sakai, K.; Gotoh, S.; Miorin, L.; De Jesus, P.D.; et al. MDA5 Governs the Innate Immune Response to SARS-CoV-2 in Lung Epithelial Cells. Cell Rep. 2021, 34, 108628.
104. Rehwinkel, J.; Gack, M.U. RIG-I-like receptors: Their regulation and roles in RNA sensing. Nat. Rev. Immunol. 2020, 20, 537–551.
105. Te Velthuis, A.J.W.; Long, J.C.; Bauer, D.L.V.; Fan, R.L.Y.; Yen, H.-L.; Sharps, J.; Siegers, J.Y.; Killip, M.J.; French, H.; Oliva-Martín, M.J.; et al. Mini viral RNAs act as innate immune agonists during influenza virus infection. Nat. Microbiol. 2018, 3, 1234–1242.
106. Watanabe, Y.; Arai, Y.; Yamanaka, I.; Okomato, T.; Isobe, A.; Nakai, N.; Kamimura, N.; Suzuki, T.; Daidoji, T.; Ono, T.; et al. Stimulation of Dysregulated IFN- β Responses by Aberrant SARS-CoV-2 Small Viral RNAs Acting as RIG-I Agonists. 2022. Available online: https://assets.researchsquare.com/files/rs-1271053/v2/b9e39a7d-71a8-46e9-b293-e1334e366176.pdf?c=1647456052 (accessed on 6 May 2022).
107. Zheng, M.; Karki, R.; Williams, E.P.; Yang, D.; Fitzpatrick, E.; Vogel, P.; Jonsson, C.B.; Kanneganti, T.-D. TLR2 senses the SARS-CoV-2 envelope protein to produce inflammatory cytokines. Nat. Immunol. 2021, 22, 829–838.

108. Khan, S.; Shafiei, M.S.; Longoria, C.; Schoggins, J.W.; Savani, R.C.; Zaki, H. SARS-CoV-2 spike protein induces inflammation via TLR2-dependent activation of the NF-κB pathway. eLife 2021, 10, e68563.

109. Iwasaki, A.; Pillai, P.S. Innate immunity to influenza virus infection. Nat. Rev. Immunol. 2014, 14, 315–328.

110. Dey, M.; Cao, C.; Dar, A.C.; Tamura, T.; Ozato, K.; Sicheri, F.; Dever, T.E. Mechanistic Link between PKR Dimerization, Autophosphorylation, and eIF2α Substrate Recognition. Cell 2005, 122, 901–913.

111. Li, Y.; Renner, D.M.; Comar, C.E.; Whelan, J.N.; Reyes, H.M.; Cardenas-Diaz, F.L.; Truitt, R.; Tan, L.H.; Dong, B.; Alysandratos, K.D.; et al. SARS-CoV-2 induces double-stranded RNA-mediated innate immune responses in respiratory epithelial-derived cells and cardiomyocytes. Proc. Natl. Acad. Sci. USA 2021, 118, e2022643118.

112. Sette, A.; Crotty, S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 2021, 184, 861–880.

113. Chen, G.; Wu, D.; Guo, W.; Cao, Y.; Huang, D.; Wang, H.; Wang, T.; Zhang, X.; Chen, H.; Yu, H.; et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J. Clin. Investig. 2020, 130, 2620–2629.

114. Oja, A.E.; Saris, A.; Ghandour, C.A.; Kragten, N.A.; Hogema, B.M.; Nossent, E.J.; Heunks, L.M.; Cuvalay, S.; Slot, E.; Linty, F.; et al. Divergent SARS-CoV-2-specific T- and B-cell responses in severe but not mild COVID-19 patients. Eur. J. Immunol. 2020, 50, 1998–2012.

115. Diao, B.; Wang, C.; Tan, Y.; Chen, X.; Liu, Y.; Ning, L.; Chen, L.; Li, M.; Liu, Y.; Wang, G.; et al. Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19). Front. Immunol. 2020, 11, 827.

116. Mathew, D.; Giles, J.R.; Baxter, A.E.; Oldridge, D.A.; Greenplate, A.R.; Wu, J.E.; Alanio, C.; Kuri-Cervantes, L.; Pampena, M.B.; D'Andrea, K.; et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. Science 2020, 369, 6508.

117. Moss, P. The T cell immune response against SARS-CoV-2. Nat. Immunol. 2022, 23, 186–193.

118. Hall, V.J.; Foulkes, S.; Charlett, A.; Atti, A.; Monk, E.J.M.; Simmons, R.; Wellington, E.; Cole, M.J.; Saei, A.; Oguti, B.; et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: A large, multicentre, prospective cohort study (SIREN). Lancet 2021, 397, 1459–1469.

119. Galbraith, M.D.; Kinning, K.T.; Sullivan, K.D.; Araya, P.; Smith, K.P.; Granrath, R.E.; Shaw, J.R.; Baxter, R.; Jordan, K.R.; Russell, S.; et al. Specialized interferon action in COVID-19. Proc. Natl. Acad. Sci. USA 2022, 119, e2116730119.

120. Meyts, I.; Casanova, J. Viral infections in humans and mice with genetic deficiencies of the type I IFN response pathway. Eur. J. Immunol. 2021, 51, 1039–1061.

121. Ciancanelli, M.J.; Huang, S.X.L.; Luthra, P.; Garner, H.; Itan, Y.; Volpi, S.; Lafaille, F.G.; Trouillet, C.; Schmolke, M.; Albrecht, R.A.; et al. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. Science 2015, 348, 448–453.

122. Hernandez, N.; Melki, I.; Jing, H.; Habib, T.; Huang, S.S.; Danielson, J.; Kula, T.; Drutman, S.; Belkaya, S.; Rattina, V.; et al. Life-threatening influenza pneumonitis in a child with inherited IRF9 deficiency. J. Exp. Med. 2018, 215, 2567–2585.

123. Lim, H.K.; Huang, S.X.; Chen, J.; Kerner, G.; Gilliaux, O.; Bastard, P.; Dobbs, K.; Hernandez, N.; Goudin, N.; Hasek, M.L.; et al. Severe influenza pneumonitis in children with inherited TLR3 deficiency. J. Exp. Med. 2019, 216, 2038–2056.

124. Bastard, P.; Zhang, Q.; Zhang, S.-Y.; Jouanguy, E.; Casanova, J.-L. Type I interferons and SARS-CoV-2: From cells to organisms. Curr. Opin. Immunol. 2022, 74, 172–182.

125. Zhang, Q.; Bastard, P.; Liu, Z.; Le Pen, J.; Moncada-Velez, M.; Chen, J.; Ogishi, M.; Sabli, I.K.D.; Hodeib, S.; Korol, C.; et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020, 370, eabd4570.

126. Zhang, S.-Y.; Zhang, Q.; Casanova, J.-L.; Su, H.C.; Abel, L.; Bastard, P.; Cobat, A.; Jouanguy, E.; Notarangelo, L.; Covid The COVID Team. Severe COVID-19 in the young and healthy: Monogenic inborn errors of immunity? Nat. Rev. Immunol. 2020, 20, 455–456.

127. Yang, K.; Puel, A.; Zhang, S.; Eidenschenk, C.; Ku, C.-L.; Casrouge, A.; Picard, C.; von Bernuth, H.; Senechal, B.; Plancoulaine, S.; et al. Human TLR-7-, -8-, and -9-Mediated Induction of IFN-α/β and -λ Is IRAK-4 Dependent and Redundant for Protective Immunity to Viruses. Immunity 2005, 23, 465–478.

128. Barreiro, L.B.; Ben-Ali, M.; Quach, H.; Laval, G.; Patin, E.; Pickrell, J.K.; Bouchier, C.; Tichit, M.; Neyrolles, O.; Gicquel, B.; et al. Evolutionary Dynamics of Human Toll-Like Receptors and Their Different Contributions to Host Defense. PLoS Genet. 2009, 5, e1000562.

129. Puel, A.; Bastard, P.; Bustamante, J.; Casanova, J.L. Human autoantibodies underlying infectious diseases. J. Exp. Med. 2022, 219, e20211387.

130. Bastard, P.; Rosen, L.B.; Zhang, Q.; Michailidis, E.; Hoffmann, H.-H.; Zhang, Y.; Dorgham, K.; Philippot, Q.; Rosain, J.; Béziat, V.; et al. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020, 370, eabd4585.

131. Abers, M.S.; Rosen, L.B.; Delmonte, O.M.; Shaw, E.; Bastard, P.; Imberti, L.; Quaresima, V.; Biondi, A.; Bonfanti, P.; Castagnoli, R.; et al. Neutralizing type-I interferon autoantibodies are associated with delayed viral clearance and intensive care unit admission in patients with COVID-19. Immunol. Cell Biol. 2021, 99, 917–921.

132. Acosta-Ampudia, Y.; Monsalve, D.M.; Rojas, M.; Rodríguez, Y.; Gallo, J.E.; Salazar-Uribe, J.C.; Santander, M.J.; Cala, M.P.; Zapata, W.; Zapata, M.I.; et al. COVID-19 convalescent plasma composition and immunological effects in severe patients. J. Autoimmun. 2021, 118, 102598.

133. Vazquez, S.E.; Bastard, P.; Kelly, K.; Gervais, A.; Norris, P.J.; Dumont, L.J.; Casanova, J.-L.; Anderson, M.S.; DeRisi, J.L. Neutralizing Autoantibodies to Type I Interferons in COVID-19 Convalescent Donor Plasma. J. Clin. Immunol. 2021, 41, 1169–1171.

134. Wang, E.Y.; Mao, T.; Klein, J.; Dai, Y.; Huck, J.D.; Jaycox, J.R.; Liu, F.; Zhou, T.; Israelow, B.; Wong, P.; et al. Diverse Functional Autoantibodies in Patients with COVID-19. Nature 2021, 595, 283–288.

135. Ziegler, C.G.; Miao, V.N.; Owings, A.H.; Navia, A.W.; Tang, Y.; Bromley, J.D.; Lotfy, P.; Sloan, M.; Laird, H.; Williams, H.B.; et al. Impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19. Cell 2021, 184, 4713–4733.e22.

136. Troya, J.; Bastard, P.; Planas-Serra, L.; Ryan, P.; Ruiz, M.; de Carranza, M.; Torres, J.; Martínez, A.; Abel, L.; Casanova, J.-L.; et al. Neutralizing Autoantibodies to Type I IFNs in >10% of Patients with Severe COVID-19 Pneumonia Hospitalized in Madrid, Spain. J. Clin. Immunol. 2021, 41, 914–922.

137. Zhang, Q.; Bastard, P.; Karbuz, A.; Gervais, A.; Tayoun, A.A.; Aiuti, A.; Belot, A.; Bolze, A.; Gaudet, A.; Bondarenko, A.; et al. Human genetic and immunological determinants of critical COVID-19 pneumonia. Nature 2022, 603, 587–598.

138. Carapito, R.; Li, R.; Helms, J.; Carapito, C.; Gujja, S.; Rolli, V.; Guimaraes, R.; Malagon-Lopez, J.; Spinnhirny, P.; Lederle, A.; et al. Identification of driver genes for critical forms of COVID-19 in a deeply phenotyped young patient cohort. Sci. Transl. Med. 2022, 14, abj7521.

139. Chang, S.E.; Feng, A.; Meng, W.; Apostolidis, S.A.; Mack, E.; Artandi, M.; Barman, L.; Bennett, K.; Chakraborty, S.; Chang, I.; et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. Nat. Commun. 2021, 12, 5417.

140. Chauvineau-Grenier, A.; Bastard, P.; Servajean, A.; Gervais, A.; Rosain, J.; Jouanguy, E.; Cobat, A.; Casanova, J.-L.; Rossi, B. Autoantibodies Neutralizing Type I Interferons in 20% of COVID-19 Deaths in a French Hospital. J. Clin. Immunol. 2022, 42, 459–470.

141. Goncalves, D.; Mezidi, M.; Bastard, P.; Perret, M.; Saker, K.; Fabien, N.; Pescarmona, R.; Lombard, C.; Walzer, T.; Casanova, J.; et al. Antibodies against type I interferon: Detection and association with severe clinical outcome in COVID-19 patients. Clin. Transl. Immunol. 2021, 10, e1327.

142. Koning, R.; Bastard, P.; Casanova, J.-L.; Brouwer, M.C.; van de Beek, D.; van Agtmael, M.; Algera, A.G.; Appelman, B.; van Baarle, F.; Bax, D.; et al. Autoantibodies against type I interferons

are associated with multi-organ failure in COVID-19 patients. Intensiv. Care Med. 2021, 47, 704–706.

143. Raadsen, M.P.; Gharbharan, A.; Jordans, C.C.E.; Mykytyn, A.Z.; Lamers, M.M.; van den Doel, P.B.; Endeman, H.; van den Akker, J.P.C.; Geurtsvan Kessel, C.H.; Koopmans, M.P.G.; et al. Interferon-α2 Auto-antibodies in Convalescent Plasma Therapy for COVID-19. J. Clin. Immunol. 2022, 42, 232–239.

144. Solanich, X.; Rigo-Bonnin, R.; Gumucio, V.-D.; Bastard, P.; Rosain, J.; Philippot, Q.; Perez-Fernandez, X.-L.; Fuset-Cabanes, M.-P.; Gordillo-Benitez, M.; Suarez-Cuartin, G.; et al. Pre-existing Autoantibodies Neutralizing High Concentrations of Type I Interferons in Almost 10% of COVID-19 Patients Admitted to Intensive Care in Barcelona. J. Clin. Immunol. 2021, 41, 1733–1744.

145. Van der Wijst, M.G.P.; Vazquez, S.E.; Hartoularos, G.C.; Bastard, P.; Grant, T.; Bueno, R.; Lee, D.S.; Greenland, J.R.; Sun, Y.; Perez, R.; et al. Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19. Sci. Transl. Med. 2021, 13, eabh2624.

146. Trouillet-Assant, S.; Viel, S.; Gaymard, A.; Pons, S.; Richard, J.-C.; Perret, M.; Villard, M.; Brengel-Pesce, K.; Lina, B.; Mezidi, M.; et al. Type I IFN immunoprofiling in COVID-19 patients. J. Allergy Clin. Immunol. 2020, 146, 206–208.e2.

147. Hadjadj, J.; Yatim, N.; Barnabei, L.; Corneau, A.; Boussier, J.; Smith, N.; Péré, H.; Charbit, B.; Bondet, V.; Chenevier-Gobeaux, C.; et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020, 369, 718–724.

148. Credle, J.J.; Gunn, J.; Sangkhapreecha, P.; Monaco, D.R.; Zheng, X.A.; Tsai, H.J.; Wilbon, A.; Morgenlander, W.R.; Dong, Y.; Jayaraman, S.; et al. Neutralizing IFNL3 Autoantibodies in Severe COVID-19 Identified Using Molecular Indexing of Proteins by Self-Assembly. bioRxiv 2021.

149. Beccuti, G.; Ghizzoni, L.; Cambria, V.; Codullo, V.; Sacchi, P.; Lovati, E.; Mongodi, S.; Iotti, G.A.; Mojoli, F. A COVID-19 pneumonia case report of autoimmune polyendocrine syndrome type 1 in Lombardy, Italy: Letter to the editor. J. Endocrinol. Investig. 2020, 43, 1175–1177.

150. Carpino, A.; Buganza, R.; Matarazzo, P.; Tuli, G.; Pinon, M.; Calvo, P.L.; Montin, D.; Licciardi, F.; De Sanctis, L. Autoimmune Polyendocrinopathy–Candidiasis–Ectodermal Dystrophy in Two Siblings: Same Mutations but Very Different Phenotypes. Genes 2021, 12, 169.

151. Bastard, P.; Orlova, E.; Sozaeva, L.; Lévy, R.; James, A.; Schmitt, M.M.; Ochoa, S.; Kareva, M.; Rodina, Y.; Gervais, A.; et al. Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. J. Exp. Med. 2021, 218, e20210554.

152. Meisel, C.; Akbil, B.; Meyer, T.; Lankes, E.; Corman, V.M.; Staudacher, O.; Unterwalder, N.; Kölsch, U.; Drosten, C.; Mall, M.A.; et al. Mild COVID-19 despite autoantibodies against type I

IFNs in autoimmune polyendocrine syndrome type. J. Clin. Investig. 2021, 131, e150867.

153. Lopez, J.; Mommert, M.; Mouton, W.; Pizzorno, A.; Brengel-Pesce, K.; Mezidi, M.; Villard, M.; Lina, B.; Richard, J.-C.; Fassier, J.-B.; et al. Early nasal type I IFN immunity against SARS-CoV-2 is compromised in patients with autoantibodies against type I IFNs. J. Exp. Med. 2021, 218, e20211211.
154. Bastard, P.; Michailidis, E.; Hoffmann, H.-H.; Chbihi, M.; Le Voyer, T.; Rosain, J.; Philippot, Q.; Seeleuthner, Y.; Gervais, A.; Materna, M.; et al. Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. J. Exp. Med. 2021, 218, e20202486.
155. Klein, S.L.; Pekosz, A.; Park, H.-S.; Ursin, R.L.; Shapiro, J.R.; Benner, S.E.; Littlefield, K.; Kumar, S.; Naik, H.M.; Betenbaugh, M.J.; et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. J. Clin. Investig. 2020, 130, 6141–6150.
156. Wang, T.T.; Ravetch, J.V. Functional diversification of IgGs through Fc glycosylation. J. Clin. Investig. 2019, 129, 3492–3498.
157. Paul, F.; Pellegrini, S.; Uzé, G. IFNA2: The prototypic human alpha interferon. Gene 2015, 567, 132–137.
158. Severa, M.; Farina, C.; Salvetti, M.; Coccia, E.M. Three Decades of Interferon-β in Multiple Sclerosis: Can We Repurpose This Information for the Management of SARS-CoV2 Infection? Front. Immunol. 2020, 11, 1459.
159. McNab, F.; Mayer-Barber, K.; Sher, A.; Wack, A.; O'Garra, A. Type I interferons in infectious disease. Nat. Rev. Immunol. 2015, 15, 87–103.
160. Reder, A.T.; Feng, X. How Type I Interferons Work in Multiple Sclerosis and Other Diseases: Some Unexpected Mechanisms. J. Interf. Cytokine Res. 2014, 34, 589–599.
161. Mantlo, E.; Bukreyeva, N.; Maruyama, J.; Paessler, S.; Huang, C. Antiviral activities of type I interferons to SARS-CoV-2 infection. Antivir. Res. 2020, 179, 104811.
162. Kumar, S.; Çalışkan, D.M.; Janowski, J.; Faist, A.; Conrad, B.C.G.; Lange, J.; Ludwig, S.; Brunotte, L. Beyond Vaccines: Clinical Status of Prospective COVID-19 Therapeutics. Front. Immunol. 2021, 12, 752227.
163. Stanifer, M.L.; Guo, C.; Doldan, P.; Boulant, S. Importance of Type I and III Interferons at Respiratory and Intestinal Barrier Surfaces. Front. Immunol. 2020, 11, 608645.
164. Vanderheiden, A.; Ralfs, P.; Chirkova, T.; Upadhyay, A.A.; Zimmerman, M.G.; Bedoya, S.; Aoued, H.; Tharp, G.M.; Pellegrini, K.L.; Manfredi, C.; et al. Type I and Type III Interferons Restrict SARS-CoV-2 Infection of Human Airway Epithelial Cultures. J. Virol. 2020, 94, e00985-20.
165. Feld, J.J.; Kandel, C.; Biondi, M.J.; Kozak, R.A.; Zahoor, M.A.; Lemieux, C.; Borgia, S.M.; Boggild, A.K.; Powis, J.; McCready, J.; et al. Peginterferon lambda for the treatment of outpatients with

COVID-19: A phase 2, placebo-controlled randomised trial. Lancet Respir. Med. 2021, 9, 498–510.

166. Metz-Zumaran, C.; Kee, C.; Doldan, P.; Guo, C.; Stanifer, M.L.; Boulant, S. Increased Sensitivity of SARS-CoV-2 to Type III Interferon in Human Intestinal Epithelial Cells. J. Virol. 2022, 96, e0170521.
167. Stanifer, M.L.; Kee, C.; Cortese, M.; Zumaran, C.M.; Triana, S.; Mukenhirn, M.; Kraeusslich, H.-G.; Alexandrov, T.; Bartenschlager, R.; Boulant, S. Critical Role of Type III Interferon in Controlling SARS-CoV-2 Infection in Human Intestinal Epithelial Cells. Cell Rep. 2020, 32, 107863.
168. EIGER Biopharmaceuticals. Eiger's Single-Dose Peginterferon Lambda for COVID-19 Reduced Risk of Hospitalization or ER Visits by 50% in a Predominantly Vaccinated Population in Phase 3 TOGETHER Study. Available online: https://www.prnewswire.com/news-releases/eigers-single-dose-peginterferon-lambda-for-covid-19-reduced-risk-of-hospitalization-or-er-visits-by-50-in-a-predominantly-vaccinated-population-in-phase-3-together-study-301504827.html (accessed on 4 May 2022).
169. Haasbach, E.; Droebner, K.; Vogel, A.B.; Planz, O. Low-Dose Interferon Type I Treatment Is Effective Against H5N1 and Swine-Origin H1N1 Influenza A Viruses In Vitro and In Vivo. J. Interf. Cytokine Res. 2011, 31, 515–525.
170. Bennett, A.L.; Smith, D.W.; Cummins, M.J.; Jacoby, P.A.; Cummins, J.M.; Beilharz, M.W. Low-dose oral interferon alpha as prophylaxis against viral respiratory illness: A double-blind, parallel controlled trial during an influenza pandemic year. Influ. Other Respir. Viruses 2013, 7, 854–862.
171. Sutter, K.; Dickow, J.; Dittmer, U. Interferon α subtypes in HIV infection. Cytokine Growth Factor Rev. 2018, 40, 13–18.
172. Matos, A.D.R.; Wunderlich, K.; Schloer, S.; Schughart, K.; Geffers, R.; Seders, M.; De Witt, M.; Christersson, A.; Wiewrodt, R.; Wiebe, K.; et al. Antiviral potential of human IFN-α subtypes against influenza A H3N2 infection in human lung explants reveals subtype-specific activities. Emerg. Microbes Infect. 2019, 8, 1763–1776.
173. Guo, K.; Shen, G.; Kibbie, J.; Gonzalez, T.; Dillon, S.M.; Smith, H.A.; Cooper, E.H.; Lavender, K.; Hasenkrug, K.J.; Sutter, K.; et al. Qualitative Differences Between the IFNα subtypes and IFNβ Influence Chronic Mucosal HIV-1 Pathogenesis. PLOS Pathog. 2020, 16, e1008986.
174. Chen, J.; Li, Y.; Lai, F.; Wang, Y.; Sutter, K.; Dittmer, U.; Ye, J.; Zai, W.; Liu, M.; Shen, F.; et al. Functional Comparison of Interferon-α Subtypes Reveals Potent Hepatitis B Virus Suppression by a Concerted Action of Interferon-α and Interferon-γ Signaling. Hepatology 2021, 73, 486–502.
175. Schuhenn, J.; Meister, T.L.; Todt, D.; Bracht, T.; Schork, K.; Billaud, J.-N.; Elsner, C.; Heinen, N.; Karakoese, Z.; Haid, S.; et al. Differential interferon-α subtype induced immune signatures are

associated with suppression of SARS-CoV-2 infection. Proc. Natl. Acad. Sci. USA 2022, 119, e2111600119.

176. Hung, I.F.N.; To, K.; Lee, C.-K.; Lee, K.-L.; Chan, K.K.C.; Yan, W.-W.; Liu, R.; Watt, C.-L.; Chan, W.-M.; Lai, K.-Y.; et al. Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection. Clin. Infect. Dis. 2011, 52, 447–456.
177. Xu, Z.; Zhou, J.; Huang, Y.; Liu, X.; Xu, Y.; Chen, S.; Liu, D.; Lin, Z.; Liu, X.; Li, Y. Efficacy of convalescent plasma for the treatment of severe influenza. Crit. Care 2020, 24, 469.
178. Marano, G.; Vaglio, S.; Pupella, S.; Facco, G.; Catalano, L.; Liumbruno, G.M.; Grazzini, G. Convalescent plasma: New evidence for an old therapeutic tool? Blood Transfus. 2016, 14, 152–157.
179. Nitesh, J.; Kashyap, R.; Surani, S.R. What we learned in the past year in managing our COVID-19 patients in intensive care units? World J. Crit. Care Med. 2021, 10, 81–101.
180. Brown, B.L.; McCullough, J. Treatment for emerging viruses: Convalescent plasma and COVID-19. Transfus. Apher. Sci. 2020, 59, 102790.
181. Bertoglio, F.; Meier, D.; Langreder, N.; Steinke, S.; Rand, U.; Simonelli, L.; Heine, P.A.; Ballmann, R.; Schneider, K.-T.; Roth, K.D.R.; et al. SARS-CoV-2 neutralizing human recombinant antibodies selected from pre-pandemic healthy donors binding at RBD-ACE2 interface. Nat. Commun. 2021, 12, 1577.
182. Gavriatopoulou, M.; Ntanasis-Stathopoulos, I.; Korompoki, E.; Fotiou, D.; Migkou, M.; Tzanninis, I.-G.; Psaltopoulou, T.; Kastritis, E.; Terpos, E.; Dimopoulos, M.A. Emerging treatment strategies for COVID-19 infection. Clin. Exp. Med. 2021, 21, 167–179.
183. Majumder, J.; Minko, T. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. AAPS J. 2021, 23, 14.
184. National Institutes of Health. COVID-19 Treatment Guidelines; Anti-SARS-CoV-2 Antibody Products. Available online: https://www.covid19treatmentguidelines.nih.gov/ (accessed on 4 May 2022).
185. Ader, F.; Bouscambert-Duchamp, M.; Hites, M.; Peiffer-Smadja, N.; Poissy, J.; Belhadi, D.; Diallo, A.; Lê, M.-P.; Peytavin, G.; Staub, T.; et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): A phase 3, randomised, controlled, open-label trial. Lancet Infect. Dis. 2022, 22, 209–221.
186. Williamson, B.N.; Feldmann, F.; Schwarz, B.; Meade-White, K.; Porter, D.P.; Schulz, J.; Van Doremalen, N.; Leighton, I.; Yinda, C.K.; Pérez-Pérez, L.; et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 2020, 585, 273–276.

187. Tanni, S.E.; Silvinato, A.; Floriano, I.; Bacha, H.A.; Barbosa, A.N.; Bernardo, W.M. Use of remdesivir in patients with COVID-19: A systematic review and meta-analysis. J. Bras. Pneumol. 2022, 48, e20210393.

188. Mulangu, S.; Dodd, L.E.; Davey, R.T., Jr.; Tshiani Mbaya, O.; Proschan, M.; Mukadi, D.; Lusakibanza Manzo, M.; Nzolo, D.; Tshomba Oloma, A.; Ibanda, A.; et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N. Engl. J. Med. 2019, 381, 2293–2303.

189. Cho, A.; Saunders, O.L.; Butler, T.; Zhang, L.; Xu, J.; Vela, J.E.; Feng, J.Y.; Ray, A.S.; Kim, C.U. Synthesis and antiviral activity of a series of 1′-substituted 4-aza-7,9-dideazaadenosine C-nucleosides. Bioorganic Med. Chem. Lett. 2012, 22, 2705–2707.

190. Lo, M.K.; Jordan, R.; Arvey, A.; Sudhamsu, J.; Shrivastava-Ranjan, P.; Hotard, A.L.; Flint, M.; McMullan, L.; Siegel, D.; Clarke, M.O.; et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci. Rep. 2017, 7, srep43395.

191. U.S. Food & Drug Administration. FDA Takes Actions to Expand Use of Treatment for Outpatients with Mild-to-Moderate COVID-19. Available online: https://www.fda.gov/news-events/press-announcements/fda-takes-actions-expand-use-treatment-outpatients-mild-moderate-covid-19 (accessed on 4 May 2022).

192. Zhou, S.; Hill, C.S.; Sarkar, S.; Tse, L.V.; Woodburn, B.M.D.; Schinazi, R.F.; Sheahan, T.P.; Baric, R.S.; Heise, M.T.; Swanstrom, R. β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 Through Lethal Mutagenesis But Is Also Mutagenic To Mammalian Cells. J. Infect. Dis. 2021, 224, 415–419.

193. Furuta, Y.; Gowen, B.B.; Takahashi, K.; Shiraki, K.; Smee, D.F.; Barnard, D.L. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antivir. Res. 2013, 100, 446–454.

194. Duwe, S. Influenza viruses—Antiviral therapy and resistance. GMS Infect. Dis. 2017, 5, Doc04.

195. Sidwell, R.W.; Barnard, D.L.; Day, C.W.; Smee, D.F.; Bailey, K.W.; Wong, M.-H.; Morrey, J.D.; Furuta, Y. Efficacy of Orally Administered T-705 on Lethal Avian Influenza A (H5N1) Virus Infections in Mice. Antimicrob. Agents Chemother. 2007, 51, 845–851.

196. Chen, C.; Zhang, Y.; Huang, J.; Yin, P.; Cheng, Z.; Wu, J.; Chen, S.; Zhang, Y.; Chen, B.; Lu, M.; et al. Favipiravir Versus Arbidol for Clinical Recovery Rate in Moderate and Severe Adult COVID-19 Patients: A Prospective, Multicenter, Open-Label, Randomized Controlled Clinical Trial. Front. Pharmacol. 2021, 12, 683296.

197. Bosaeed, M.; Alharbi, A.; Mahmoud, E.; Alrehily, S.; Bahlaq, M.; Gaifer, Z.; Alturkistani, H.; Alhagan, K.; Alshahrani, S.; Tolbah, A.; et al. Efficacy of favipiravir in adults with mild COVID-19: A randomized, double-blind, multicentre, placebo-controlled clinical trial. Clin. Microbiol. Infect. 2022, 28, 602–608.

198. Smith, P.O.; Jin, P.; Rahman, K.M. Strategies for drug repurposing against coronavirus targets. Curr. Res. Pharmacol. Drug Discov. 2022, 3, 100072.

199. Extance, A. Covid-19: What is the evidence for the antiviral Paxlovid? BMJ 2022, 377, o1037.

200. Lamb, Y.N. Nirmatrelvir Plus Ritonavir: First Approval. Drugs 2022, 82, 585–591.

201. Hung, Y.-P.; Lee, J.-C.; Chiu, C.-W.; Lee, C.-C.; Tsai, P.-J.; Hsu, I.-L.; Ko, W.-C. Oral Nirmatrelvir/Ritonavir Therapy for COVID-19: The Dawn in the Dark? Antibiotics 2022, 11, 220.

202. Azkur, A.K.; Akdis, M.; Azkur, D.; Sokolowska, M.; Van De Veen, W.; Brüggen, M.-C.; O'Mahony, L.; Gao, Y.; Nadeau, K.; Akdis, C.A. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020, 75, 1564–1581.

203. Rizk, J.G.; Kalantar-Zadeh, K.; Mehra, M.R.; Lavie, C.J.; Rizk, Y.; Forthal, D.N. Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs 2020, 80, 1267–1292.

204. Kennedy, G.A.; Varelias, A.; Vuckovic, S.; Le Texier, L.; Gartlan, K.H.; Zhang, P.; Thomas, G.; Anderson, L.; Boyle, G.; Cloonan, N.; et al. Addition of interleukin-6 inhibition with tocilizumab to standard graft-versus-host disease prophylaxis after allogeneic stem-cell transplantation: A phase 1/2 trial. Lancet Oncol. 2014, 15, 1451–1459.

205. Sheng, F.S.F.; Han, M.H.M.; Huang, Z.H.Z.; Zhang, L.Z.L. Interleukin 6 receptor inhibitor tocilizumab suppresses cytokine expression, inflammasome activation and phagocytosis in a cell model of sepsis. Pharmazie 2016, 71, 636–639.

206. Abani, O.; Abbas, A.; Abbas, F.; Abbas, M.; Abbasi, S.; Abbass, H.; Abbott, A.; Abdallah, N.; Abdelaziz, A.; Abdelfattah, M.; et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2021, 397, 1637–1645.

207. Alzghari, S.K.; Acuña, V.S. Supportive Treatment with Tocilizumab for COVID-19: A Systematic Review. J. Clin. Virol. 2020, 127, 104380.

208. Morris, G.; Bortolasci, C.C.; Puri, B.K.; Marx, W.; O'Neil, A.; Athan, E.; Walder, K.; Berk, M.; Olive, L.; Carvalho, A.F.; et al. The cytokine storms of COVID-19, H1N1 influenza, CRS and MAS compared. Can one sized treatment fit all? Cytokine 2021, 144, 155593.

209. Kyriazopoulou, E.; Huet, T.; Cavalli, G.; Gori, A.; Kyprianou, M.; Pickkers, P.; Eugen-Olsen, J.; Clerici, M.; Veas, F.; Chatellier, G.; et al. Effect of anakinra on mortality in patients with COVID-19: A systematic review and patient-level meta-analysis. Lancet Rheumatol. 2021, 3, e690–e697.

210. Kyriazopoulou, E.; Poulakou, G.; Milionis, H.; Metallidis, S.; Adamis, G.; Tsiakos, K.; Fragkou, A.; Rapti, A.; Damoulari, C.; Fantoni, M.; et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: A double-blind, randomized controlled phase 3 trial. Nat. Med. 2021, 27, 1752–1760.

211. Feldmann, M.; Maini, R.N.; Woody, J.N.; Holgate, S.T.; Winter, G.; Rowland, M.; Richards, D.; Hussell, T. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 2020, 395, 1407–1409.

212. Okeke, F.; Mone, A.; Swaminath, A. The Course of SARS-COV2 Infection Was Not Severe in a Crohn's Patient Who Administered Maintenance Anti-TNF Therapy Overlapping the Early Pre-Symptomatic Period of Infection. Antibodies 2020, 9, 42.

213. Duret, P.-M.; Sebbag, E.; Mallick, A.; Gravier, S.; Spielmann, L.; Messer, L. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. Ann. Rheum. Dis. 2020, 79, 1251–1252.

214. Abdullah, A.; Neurath, M.F.; Atreya, R. Mild COVID-19 Symptoms in an Infliximab-Treated Ulcerative Colitis Patient: Can Ongoing Anti-TNF Therapy Protect against the Viral Hyperinflammatory Response and Avoid Aggravated Outcomes? Visc. Med. 2020, 36, 338–342.

215. Darwish, I.; Mubareka, S.; Liles, W.C. Immunomodulatory therapy for severe influenza. Expert Rev. Anti-infective Ther. 2011, 9, 807–822.

216. Guo, Y.; Hu, K.; Li, Y.; Lu, C.; Ling, K.; Cai, C.; Wang, W.; Ye, D. Targeting TNF-α for COVID-19: Recent Advanced and Controversies. Front. Public Health 2022, 10, 833967.

217. Alijotas-Reig, J.; Esteve-Valverde, E.; Belizna, C.; Selva-O'Callaghan, A.; Pardos-Gea, J.; Quintana, A.; Mekinian, A.; Anunciacion-Llunell, A.; Miro-Mur, F.A. Immunomodulatory therapy for the management of severe COVID-Beyond the anti-viral therapy: A comprehensive review. Autoimmun. Rev. 2020, 19, 102569.

218. Richardson, P.; Griffin, I.; Tucker, C.; Smith, D.; Oechsle, O.; Phelan, A.; Rawling, M.; Savory, E.; Stebbing, J. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020, 395, e30–e31.

219. Safaei, S.; Karimi-Googheri, M. Letter to the Editor: Toll-Like Receptor Antagonists as a Potential Therapeutic Strategy Against Cytokine Storm in COVID-19-Infected Patients. Viral Immunol. 2021, 34, 361–362.

220. Manik, M.; Singh, R.K. Role of toll-like receptors in modulation of cytokine storm signaling in SARS-CoV-2-induced COVID-19. J. Med Virol. 2022, 94, 869–877.

221. Patra, R.; Das, N.C.; Mukherjee, S. Targeting human TLRs to combat COVID-19: A solution? J. Med Virol. 2021, 93, 615–617.

222. Perrin-Cocon, L.; Aublin-Gex, A.; Sestito, S.E.; Shirey, K.A.; Patel, M.C.; André, P.; Blanco, J.; Vogel, S.N.; Peri, F.; Lotteau, V. TLR4 antagonist FP7 inhibits LPS-induced cytokine production and glycolytic reprogramming in dendritic cells, and protects mice from lethal influenza infection. Sci. Rep. 2017, 7, srep40791.

223. Harrison, C. Focus shifts to antibody cocktails for COVID-19 cytokine storm. Nat. Biotechnol. 2020, 38, 905–908.

224. Feuillet, V.; Canard, B.; Trautmann, A. Combining Antivirals and Immunomodulators to Fight COVID-19. Trends Immunol. 2021, 42, 31–44.

225. Liu, Q.; Zhou, Y.-H.; Yang, Z.-Q. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell. Mol. Immunol. 2016, 13, 3–10.

226. Xiang, Z.; Liu, J.; Shi, D.; Chen, W.; Li, J.; Yan, R.; Bi, Y.; Hu, W.; Zhu, Z.; Yu, Y.; et al. Glucocorticoids improve severe or critical COVID-19 by activating ACE2 and reducing IL-6 levels. Int. J. Biol. Sci. 2020, 16, 2382–2391.

227. Keller, M.J.; Kitsis, E.A.; Arora, S.; Chen, J.-T.; Agarwal, S.; Ross, M.J.; Tomer, Y.; Southern, W. Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19. J. Hosp. Med. 2020, 15, 489–493.

228. Honigsbaum, M.; Krishnan, L. Taking pandemic sequelae seriously: From the Russian influenza to COVID-19 long-haulers. Lancet 2020, 396, 1389–1391.

229. Sellers, S.A.; Hagan, R.S.; Hayden, F.G.; Fischer, W.A. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. Influ. Other Respir. Viruses 2017, 11, 372–393.

230. Kumar, K.; Guirgis, M.; Zieroth, S.; Lo, E.; Menkis, A.H.; Arora, R.C.; Freed, D.H. Influenza Myocarditis and Myositis: Case Presentation and Review of the Literature. Can. J. Cardiol. 2011, 27, 514–522.

231. Aranda, J.; Oriol, I.; Martín, M.; Feria, L.; Vázquez, N.; Rhyman, N.; Vall-Llosera, E.; Pallarés, N.; Coloma, A.; Pestaña, M.; et al. Long-term impact of COVID-19 associated acute respiratory distress syndrome. J. Infect. 2021, 83, 581–588.

232. Chopra, V.; Flanders, S.A.; O'Malley, M.; Malani, A.N.; Prescott, H.C. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Ann. Intern. Med. 2021, 174, 576–578.

233. Martin-Villares, C.; Molina-Ramirez, C.P.; Bartolome-Benito, M.; Bernal-Sprekelsen, M.; Perez-Fernandez, A.; Alcantara-Armenteros, S.; Monjas-Cánovas, I.; Sancho-Mestre, M.; Alemán-Lopez, O.; Deola-Trasserra, M.D.; et al. Outcome of 1890 tracheostomies for critical COVID-19 patients: A national cohort study in Spain. Eur. Arch. Oto-Rhino-Laryngol. 2021, 278, 1605–1612.

234. Zhao, Y.-M.; Shang, Y.-M.; Song, W.-B.; Li, Q.-Q.; Xie, H.; Xu, Q.-F.; Jia, J.-L.; Li, L.-M.; Mao, H.-L.; Zhou, X.-M.; et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. eClinicalMedicine 2020, 25, 100463.

235. Shaw, B.; Daskareh, M.; Gholamrezanezhad, A. The lingering manifestations of COVID-19 during and after convalescence: Update on long-term pulmonary consequences of coronavirus disease 2019 (COVID-19). La Radiol. Med. 2021, 126, 40–46.

236. Van Gassel, R.J.J.; Bels, J.L.M.; Raafs, A.; van Bussel, B.C.T.; van de Poll, M.C.G.; Simons, S.O.; van der Meer, L.W.L.; Gietema, H.A.; Posthuma, R.; van Santen, S. High Prevalence of Pulmonary Sequelae at 3 Months after Hospital Discharge in Mechanically Ventilated Survivors of COVID-19. Am. J. Respir. Crit. Care Med. 2021, 203, 371–374.

237. Huang, C.; Huang, L.; Wang, Y.; Li, X.; Ren, L.; Gu, X.; Kang, L.; Guo, L.; Liu, M.; Zhou, X.; et al. 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. Lancet 2021, 397, 220–232.

238. Méndez, R.; Latorre, A.; González-Jiménez, P.; Feced, L.; Bouzas, L.; Yépez, K.; Ferrando, A.; Zaldívar-Olmeda, E.; Reyes, S.; Menéndez, R. Reduced Diffusion Capacity in COVID-19 Survivors. Ann. Am. Thorac. Soc. 2021, 18, 1253–1255.

239. Carfì, A.; Bernabei, R.; Landi, F. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020, 324, 603–605.

240. Carvalho-Schneider, C.; Laurent, E.; Lemaignen, A.; Beaufils, E.; Bourbao-Tournois, C.; Laribi, S.; Flament, T.; Ferreira-Maldent, N.; Bruyère, F.; Stefic, K.; et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin. Microbiol. Infect. 2021, 27, 258–263.

241. Puntmann, V.O.; Carerj, M.L.; Wieters, I.; Fahim, M.; Arendt, C.; Hoffmann, J.; Shchendrygina, A.; Escher, F.; Vasa-Nicotera, M.; Zeiher, A.M.; et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020, 5, 1265.

242. Garrigues, E.; Janvier, P.; Kherabi, Y.; Le Bot, A.; Hamon, A.; Gouze, H.; Doucet, L.; Berkani, S.; Oliosi, E.; Mallart, E.; et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J. Infect. 2020, 81, e4–e6.

243. Taquet, M.; Luciano, S.; Geddes, J.R.; Harrison, P.J. Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021, 8, 130–140.

244. Nordvig, A.S.; Fong, K.T.; Willey, J.Z.; Thakur, K.T.; Boehme, A.K.; Vargas, W.S.; Smith, C.J.; Elkind, M.S. Potential Neurologic Manifestations of COVID-19. Neurol. Clin. Pr. 2021, 11, e135–e146.

245. Heneka, M.T.; Golenbock, D.; Latz, E.; Morgan, D.; Brown, R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimer's Res. Ther. 2020, 12, 69.

246. Kaseda, E.T.; Levine, A.J. Post-traumatic stress disorder: A differential diagnostic consideration for COVID-19 survivors. Clin. Neuropsychol. 2020, 34, 1498–1514.

247. Ritchie, K.; Chan, D.; Watermeyer, T. The cognitive consequences of the COVID-19 epidemic: Collateral damage? Brain Commun. 2020, 2, fcaa069.

248. Patell, R.; Bogue, T.; Koshy, A.; Bindal, P.; Merrill, M.; Aird, W.C.; Bauer, K.A.; Zwicker, J.I. Postdischarge thrombosis and hemorrhage in patients with COVID-19. Blood 2020, 136, 1342–1346.

249. Weng, J.; Li, Y.; Li, J.; Shen, L.; Zhu, L.; Liang, Y.; Lin, X.; Jiao, N.; Cheng, S.; Huang, Y.; et al. Gastrointestinal sequelae 90 days after discharge for COVID-19. Lancet Gastroenterol. Hepatol. 2021, 6, 344–346.

250. Rubino, F.; Amiel, S.A.; Zimmet, P.; Alberti, G.; Bornstein, S.; Eckel, R.H.; Mingrone, G.; Boehm, B.; Cooper, M.E.; Chai, Z.; et al. New-Onset Diabetes in Covid-19. N. Engl. J. Med. 2020, 383, 789–790.

251. Stevens, J.S.; King, K.L.; Robbins-Juarez, S.Y.; Khairallah, P.; Toma, K.; Verduzco, H.A.; Daniel, E.; Douglas, D.; Moses, A.A.; Peleg, Y.; et al. High rate of renal recovery in survivors of COVID-19 associated acute renal failure requiring renal replacement therapy. PLoS ONE 2020, 15, e0244131.

252. Phetsouphanh, C.; Darley, D.R.; Wilson, D.B.; Howe, A.; Munier, C.M.L.; Patel, S.K.; Juno, J.A.; Burrell, L.M.; Kent, S.J.; Dore, G.J.; et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat. Immunol. 2022, 23, 210–216.

253. Schultheiß, C.; Willscher, E.; Paschold, L.; Gottschick, C.; Klee, B.; Henkes, S.S.; Bosurgi, L.; Dutzmann, J.; Sedding, D.; Frese, T.; et al. The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. Cell Rep. Med. 2022, 3, 100663.

254. Luyt, C.-E.; Combes, A.; Becquemin, M.-H.; Beigelman-Aubry, C.; Hatem, S.; Brun, A.-L.; Zraik, N.; Carrat, F.; Grenier, P.A.; Richard, J.-C.M.; et al. Long-term Outcomes of Pandemic 2009 Influenza A(H1N1)-Associated Severe ARDS. Chest 2012, 142, 583–592.

255. Melms, J.C.; Biermann, J.; Huang, H.; Wang, Y.; Nair, A.; Tagore, S.; Katsyv, I.; Rendeiro, A.F.; Amin, A.D.; Schapiro, D.; et al. A molecular single-cell lung atlas of lethal COVID-19. Nature 2021, 595, 114–119.

256. Schneider, C.; Nobs, S.P.; Kurrer, M.O.; Rehrauer, H.; Thiele, C.; Kopf, M. Induction of the nuclear receptor PPAR-γ by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages. Nat. Immunol. 2014, 15, 1026–1037.

257. Wang, P.; Nair, M.S.; Liu, L.; Iketani, S.; Luo, Y.; Guo, Y.; Wang, M.; Yu, J.; Zhang, B.; Kwong, P.D.; et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1. Nature 2021, 593, 130–135.

258. Sudre, C.H.; Murray, B.; Varsavsky, T.; Graham, M.S.; Penfold, R.S.; Bowyer, R.C.; Pujol, J.C.; Klaser, K.; Antonelli, M.; Canas, L.S.; et al. Attributes and predictors of long COVID. Nat. Med. 2021, 27, 626–631.

259. Arnold, D.T.; Hamilton, F.W.; Milne, A.; Morley, A.J.; Viner, J.; Attwood, M.; Noel, A.; Gunning, S.; Hatrick, J.; Hamilton, S.; et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: Results from a prospective UK cohort. Thorax 2021, 76, 399–401.

260. Halpin, S.J.; McIvor, C.; Whyatt, G.; Adams, A.; Harvey, O.; McLean, L.; Walshaw, C.; Kemp, S.; Corrado, J.; Singh, R.; et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J. Med. Virol. 2021, 93, 1013–1022.

261. Thompson, E.J.; Williams, D.M.; Walker, A.J.; Mitchell, R.E.; Niedzwiedz, C.L.; Yang, T.C.; Huggins, C.F.; Kwong, A.S.; Silverwood, R.J.; Di Gessa, G.; et al. Risk factors for ongoing symptomatic COVID-19 and post-COVID-19 syndrome: Analyses of 10 lon-gitudinal studies and electronic health records in the UK. medRxiv 2021.

262. Strain, W.D.; Sherwood, O.; Banerjee, A.; Van der Togt, V.; Hishmeh, L.; Rossman, J. The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID. Vaccines 2021, 10, 652.

263. Kuodi, P.; Gorelik, Y.; Zayyad, H.; Wertheim, O.; Wiegler, K.B.; Jabal, K.A.; Dror, A.A.; Nazzal, S.; Glikman, D.; Edelstein, M. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: A cross-sectional study of patients tested between March 2020 and November 2021. medRxiv 2022.

264. Rahman, M.; Imam, H.; Nahar, N.; Chowdhury, F.U.H. Third dose vaccine With BNT162b2 and its response on Long COVID after Breakthrough infections. medRxiv 2021.

265. Al-Aly, Z.; Bowe, B.; Xie, Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat. Med. 2022, 1–7.

266. Yasuhara, J.; Kuno, T.; Takagi, H.; Sumitomo, N. Clinical characteristics of COVID-19 in children: A systematic review. Pediatr. Pulmonol. 2020, 55, 2565–2575.

267. Castagnoli, R.; Votto, M.; Licari, A.; Brambilla, I.; Bruno, R.; Perlini, S.; Rovida, F.; Baldanti, F.; Marseglia, G.L. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents. JAMA Pediatr. 2020, 174, 882.

268. Pierce, C.A.; Sy, S.; Galen, B.; Goldstein, D.Y.; Orner, E.; Keller, M.J.; Herold, K.C.; Herold, B.C. Natural mucosal barriers and COVID-19 in children. JCI Insight 2021, 6, e148694.

269. Loske, J.; Röhmel, J.; Lukassen, S.; Stricker, S.; Magalhães, V.G.; Liebig, J.; Chua, R.L.; Thürmann, L.; Messingschlager, M.; Seegebarth, A.; et al. Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. Nat. Biotechnol. 2022, 40, 319–324.

270. Yoshida, M.; Worlock, K.B.; Huang, N.; Lindeboom, R.G.H.; Butler, C.R.; Kumasaka, N.; Conde, C.D.; Mamanova, L.; Bolt, L.; Richardson, L.; et al. Local and systemic responses to SARS-CoV-2 infection in children and adults. Nature 2022, 602, 321–327.

271. Riphagen, S.; Gomez, X.; Gonzalez-Martinez, C.; Wilkinson, N.; Theocharis, P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020, 395, 1607–1608.

272. Viner, R.M.; Whittaker, E. Kawasaki-like disease: Emerging complication during the COVID-19 pandemic. Lancet 2020, 395, 1741–1743.

273. Ahmed, M.; Advani, S.; Moreira, A.; Zoretic, S.; Martinez, J.; Chorath, K.; Acosta, S.; Naqvi, R.; Burmeister-Morton, F.; Burmeister, F.; et al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine 2020, 26, 100527.

274. Hoste, L.; Van Paemel, R.; Haerynck, F. Multisystem inflammatory syndrome in children related to COVID-19: A systematic review. Eur. J. Pediatr. 2021, 180, 2019–2034.

275. Nakamura, A.; Ikeda, K.; Hamaoka, K. Aetiological Significance of Infectious Stimuli in Kawasaki Disease. Front. Pediatr. 2019, 7, 244.

276. Banday, A.Z.; Arul, A.; Vignesh, P.; Singh, M.P.; Goyal, K.; Singh, S. Kawasaki disease and influenza—New lessons from old associations. Clin. Rheumatol. 2021, 40, 2991–2999.

277. Gruber, C.N.; Patel, R.S.; Trachtman, R.; Lepow, L.; Amanat, F.; Krammer, F.; Wilson, K.M.; Onel, K.; Geanon, D.; Tuballes, K.; et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). Cell 2020, 183, 982–995.e14.

278. McArdle, A.J.; Vito, O.; Patel, H.; Seaby, E.G.; Shah, P.; Wilson, C.; Broderick, C.; Nijman, R.; Tremoulet, A.H.; Munblit, D.; et al. Treatment of Multisystem Inflammatory Syndrome in Children. New Engl. J. Med. 2021, 385, 11–22.

279. Stephenson, T.; Pereira, S.M.P.; Shafran, R.; de Stavola, B.L.; Rojas, N.; McOwat, K.; Simmons, R.; Zavala, M.; O'Mahoney, L.; Chalder, T.; et al. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): A national matched cohort study. Lancet Child Adolesc. Health 2022, 6, 230–239.

280. Molteni, E.; Sudre, C.H.; Canas, L.S.; Bhopal, S.S.; Hughes, R.C.; Antonelli, M.; Murray, B.; Kläser, K.; Kerfoot, E.; Chen, L.; et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. Lancet Child Adolesc. Health 2021, 5, 708–718.

281. Schreiber, A.; Viemann, D.; Schöning, J.; Schloer, S.; Zambrano, A.M.; Brunotte, L.; Faist, A.; Schöfbänker, M.; Hrincius, E.; Hoffmann, H.; et al. The MEK1/2-inhibitor ATR-002 efficiently blocks SARS-CoV-2 propagation and alleviates pro-inflammatory cytokine/chemokine responses. Cell. Mol. Life Sci. 2022, 79, 65.

282. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.-H.; Nitsche, A.; et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020, 181, 271–280.e8.

283. Günl, F.; Mecate-Zambrano, A.; Rehländer, S.; Hinse, S.; Ludwig, S.; Brunotte, L. Shooting at a Moving Target—Effectiveness and Emerging Challenges for SARS-CoV-2 Vaccine Development. Vaccines 2021, 9, 1052.

284. Alwan, N.A. The teachings of Long COVID. Commun. Med. 2021, 1, 15.

285. Alwan, N.A. Lessons from Long COVID: Working with patients to design better research. Nat. Rev. Immunol. 2022, 22, 201–202.